

Fallopian Tube Epithelial Changes in Ovarian Serous Tumors Compared with Control Group: A Single-Center Study

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Abstract

Background: Recent studies have hypothesized that distal end of fallopian tube is a possible origin of ovarian serous carcinoma. This study investigated histopathological changes in fallopian tube epithelium (FTE) of the patients with ovarian serous tumors compared with control group. **Materials and Methods:** In a prospective cross-sectional study, fallopian tubes (right and left) of 34 cases with ovarian serous tumors were collected from patients who underwent surgery in two major gynecological centers affiliated to Shiraz University of Medical Sciences, Shiraz, Iran (2012–2015). They are composed of 21 (61.8%) high-grade serous carcinomas (HGSCs), 5 (14.7%) borderline ones, and 8 (23.5%) benign serous tumors. As control group, fallopian tubes of 72 hysterectomy cases without ovarian tumor were added to the study. Both tubes of all of the cases were submitted entirely, according to the protocol of sectioning and extensively examining the fimbriated end. The results were statistically analyzed using SPSS-PC windows and Chi-square tests. **Results:** Significant differences were found between the cases and control group in tubal epithelial cell stratification (especially >3 cell layers thickness), atypia, mitosis, glandular complexity, tufting, and detached epithelial cells ($P < 0.05$). These findings particularly atypia and mitosis were more frequently seen in the ampulla and fimbriated end of high-grade ovarian serous carcinomas. **Conclusion:** Our results showed that premalignant epithelial changes of the ampulla and the distal end of FTE were seen in some of the patients with ovarian HGSCs. Therefore, FTE could be one of the sources of ovarian serous carcinoma.

Keywords: Borderline serous tumor, fallopian tube, ovarian serous carcinoma

INTRODUCTION

Epithelial ovarian carcinomas are the most common gynecologic cancers and the fifth cause of death.¹⁻⁴ High grade serous carcinoma is the most common type of ovarian cancers, accounting for approximately 70% of ovarian cancers.⁵ Serous carcinoma is more common in women over 40 years.^{6,7} Most ovarian serous carcinomas show bilateral involvement.¹ Low-grade serous carcinomas are uncommon (<5% of all ovarian cancers). The borderline tumors account for 25% to 33% of the nonbenign serous tumors, and 70% in Stage I at the time of diagnosis.¹ It is shown in some of recent studies that most of these ovarian serous tumors, especially HGSC, are originated from fallopian tube epithelium (FTE), particularly the fimbriated end.^{1,6-12} In serous carcinomas, some epithelial alterations are present in the fimbriated end of a fallopian tube composed of 2–5 layers with focal or diffuse pattern, secretory outgrowth, some degrees of atypia, variable mitotic counts, nuclear pleomorphism, detached tumor cells, and glandular complexity.^{1,4,7,13,14}

One of the recent studies revealed dualistic origin (FTE and ovarian surface epithelium) for ovarian HGSC. They suggested the cell of origin could influence therapeutic response.¹⁵ Clarifying the exact origin of HGSC will improve the early detection and prevention of ovarian cancer, and reduce ovarian cancer mortality.¹⁶

Some recent studies have demonstrated immunohistochemical (IHC) alteration, by markers such as Ki67, p53, and PAX8, in the fimbriated end epithelium of fallopian tubes, removed due to ovarian serous carcinoma. An elevated Ki67 ($\geq 10\%$) was found in the majority of serous tubal intraepithelial carcinomas (STIC). PAX8 was considerably expressed in

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serous tumors and FTE samples, while it did not happen in ovarian serous epithelium samples. p53 was gradually increased during the secretory outgrowth-p53 signature-STIC-HGSC sequence.^{3,14,16,17}

Our goal was to study histological changes of FTE, especially fimbriated end in benign, borderline, and malignant serous ovarian tumors, in comparison with control group matched by age.

MATERIALS AND METHODS

Patient selection

This prospective cross-sectional study was performed on fallopian tube specimens of the women who underwent transabdominal hysterectomy and salpingo-oophorectomy (TAH and BSO) due to the ovarian serous tumor in 2012–2015. The specimens were collected mainly in two major gynecological centers affiliated to Shiraz University of Medical Sciences. Some other specimens were collected as control group. The protocol of the study was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. IR.sums.rec. 1392.5744).

A total of 212 fallopian tubes were collected, consisting of the right and left tubes for each case and control groups. There were 34 cases of the ovarian serous tumor (8 benign serous tumors, 5 borderline, and 21 serous carcinomas). Benign serous tumors consisted of unilocular cysts lined by cuboidal or columnar epithelium without atypia and mitosis. Borderline tumors were those with solid-cystic gross appearance, and/or papillary or polypoid structures. Microscopic criteria were stratified columnar epithelium with mild-to-moderate atypia without stromal invasion. Malignant serous tumors included high grades which were predominantly solid tumors. Microscopic criteria were marked variation in nuclear size (>3-fold), mitotic activity >12/10 high-power fields, with areas of hemorrhage and necrosis.¹⁸ No low-grade serous tumor was found during the study due to the low rate of occurrence (<5% of all cases of ovarian carcinoma). Control group included 72 patients whose tubes were removed due to nonneoplastic reasons. Case and control groups were matched for age. Exclusion criteria were the specimens of fallopian tubes without intact fimbriated end, previous tubal ligation, absence of one of the tubes, pregnant women, and TAH and BSO specimens due to other tumors. Seventy specimens were excluded. The number of samples in the control group was almost twice that of the case group, which increases the power of the study.

Methods

Both right and left fallopian tubes from case and control groups were submitted entirely, according to the protocol of sectioning and extensively examining the fimbriated end.¹⁹ The specimens were fixed in 10% formalin buffered solution for at least 24 h. The distal 2 cm of the fimbriated end is cut out, and the mucosa of fimbriae is sectioned longitudinally into four segments. The remainder was sectioned transversely with 2–3-mm thickness. All cut sections were totally submitted.²⁰ They were processed by

paraffin-embedding. Thereafter, they were cut and stained with H and E for light microscopy. The slides were evaluated by an expert gynecologic pathologist, and any morphologic changes were noted. For the case and control groups, data including age, normal variations, and any accidental findings of fallopian tube, especially fimbriated end were recorded. In the case group, side of the ovarian tumor, involvement of tube by tumors, tubal epithelial changes including epithelial stratification, focal or diffuse pattern, number of epithelial layer including 1 to >4 layers, atypia (pleomorphism, high nucleo-cytoplasmic [N/C] ratio, hyperchromasia), mitosis, secretory cell outgrowth (discrete area uninterrupted by ciliated cells which comprises >30 secretory cells), intraepithelial vacuoles, tufting, and hobnailing were investigated.²⁰ A few cases were reviewed in consultation with another expert to confirm the diagnosis.

Statistical analysis

Comparison of the results between two groups and also the frequency of nontumoral histologic findings were statistically analyzed using SPSS software for Windows, version 17 (SPSS Inc. Released 2008, Chicago, IL, USA) and Chi-square test.

RESULTS

A total of 212 fallopian tubes from women with a mean age of 55 ± 10 years were collected and were classified into two groups of control (68%), and cases with serous tumor (32%). Case group included 8 (23.5%) benign, 5 (14.7%) borderline, and 21 (61.8%) HGSCs. Side of ovarian tumors included Left (LT) 17 (50%), Right (RT) 11 (32.4%), and bilateral 6 (17.6%). Side of tubal involvement by tumors included LT 1 (2.9%), bilateral 6 (17.6%), and no involvement 27 (79.4%). From 21 serous carcinomas, 14 cases were in stage 3C, 6 in 2B, and 1 in 1C3. Ovarian capsular involvement was seen in 18 out of 21. None of the cases showed endometrial involvement by cancer. All parts of fallopian tubes were microscopically evaluated for any morphological changes.

From 21 HGSCs, 6 had bilateral ovarian involvement, and all of them had bilateral tubal involvement.

Comparison of secretory cell dominance (outgrowth) between case and control groups showed significant difference; for right and left fimbriated ends ($P = 0.012$) and ($P = 0.004$), and for right and left ampulla (LA) ($P = 0.012$) and ($P = 0.000$), respectively. All significant epithelial changes of the left fimbriated end (LF) and right fimbriated end (RF) in case and control group are presented in Table 1.

Due to the low rate of mitosis and atypia in right fimbriae in our study, this comparison was suboptimal for P value calculation. Stratification and atypia in the fimbriated end are shown in Figure 1a LA showed stratification of 2–3 cell layer in 61.8% and ≥ 4 layers in 54.1% of case group but showed 29.4% of 2–3 and 2.8% ≥ 4 layers in control group ($P < 0.05$). LA also showed mitosis in three cases (2.8%) and moderate atypia in 11 cases (10.4%). The comparison of these data with the control group showed significant differences ($P < 0.05$). In the

case group, 23.5% of LA had glandular structure ($P < 0.05$). In addition, comparison of vacuolization in case and control groups showed significant differences ($P < 0.05$).

Right ampulla's (RA's) epithelium showed 50% stratification of 2–3 cell layer and 41.2% of ≥ 4 layers in case group and 26.9% of 2–3 cell layers and non with ≥ 4 layers in control. Mitosis was noted in 3 (2.8%) and 5 (5.7%) showed moderate atypia. All cases with mitotic figure were HGSC and were located on the same side of ovarian tumor. Stratification in fimbriae was focal, but in ampulla, some cases were both focal and diffuse. Diffuse stratification in the ampullae of case group was more common than control group ($P < 0.05$). Detached cell was noted in the ampullary region, 3 specimens (2.8%) of LA, and 3 specimens (2.8%) of RA [Figure 1b]. None

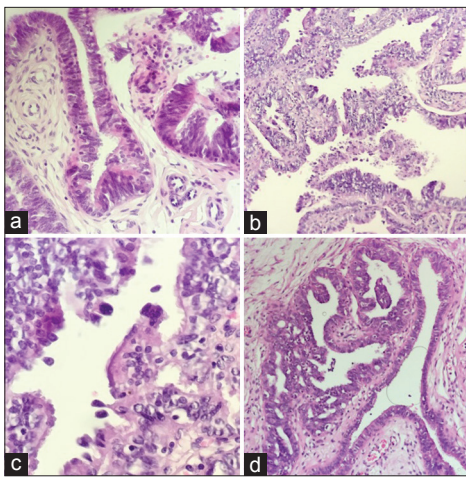


Figure 1: (a) Fimbriated end shows epithelial stratification (≥ 4), pleomorphism and nuclear hyperchromasia (H and E $\times 200$), (b) Ampulla shows secretory outgrowth, stratification, hobnailing, tufting, and sloughing of the epithelium (H and E $\times 100$), (c) Ampulla shows hobnailing and nuclear atypia (H and E $\times 400$), (d) Fimbriated end shows glandular structure and complexity

of the control group exhibited detached cells ($P = 0.0001$). Frequency of intraepithelial vacuolization, clear cell changes of RA epithelium were higher in the case than the control group ($P < 0.05$) [Figure 2]. RA also showed 17.6% glandular structure in the case group, and no evidence in the control group ($P < 0.05$). Glandular structure and complexity of the epithelium are shown in Figure 1d.

Hobnailing was seen in 2 cases (1.9%) in the left tube with bilaterality in 3 cases (2.8%) [Figure 1b and c]. Comparison with the control group showed a significant difference ($P < 0.05$). Tufting was found in RA, 5 (4.7%), LA 6 (5.7%), bilateral, 3 (2.8%) in case group, and none of control group ($P = 0.001$).

Comparison of metaplasia between case and control group showed no significant difference ($P = 0.101$). RF and LF showed glandular structures in the cases, but none of the patients in the control group showed this structure ($P < 0.05$). Incidental and morphological findings in the fallopian tubes of both case and control group are presented in Table 2.

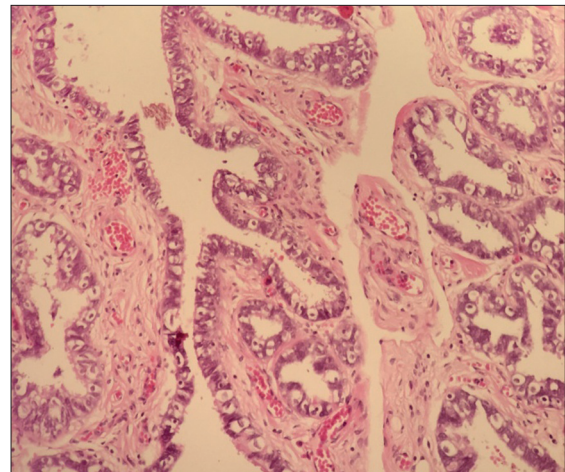


Figure 2: Fimbriated end epithelium with clear cell change (H and E, $\times 200$)

Table 1: Comparison of case and control group in epithelial cell proliferation status in the left and right fimbriated end

Epithelial alteration	LF			RF		
	Case frequency, n (%)	Control, n (%)	P	Case, n (%)	Control, n (%)	P
Stratification and number of layers						
1-2	16 (47.1)	71 (98.6)	0.000	24 (70.6)	72 (100)	0.000
2-3	16 (47.1)	1 (1.4)		8 (23.5)	0	
≥ 4 and (tufting)	2 (5.9)	0		2 (5.9)	0	
Atypia						
No	31 (91.2)	72 (100)	0.031	33 (97.1)	72 (100)	0.321
Moderate	3 (8.8)	0		1 (2.9)	0	
Sever	0	0		0	0	
Mitosis						
No	33 (97.1)	72 (100)	0.321	34 (100)	72 (100)	>0.05
Yes	1 (2.8)	0		0	0	
Glandular structure and complexity						
No	27 (79.4)	71 (98.6)	0.001	26 (76.4)	72 (100)	0.005
Yes	7 (10.6)	1 (1.4)		8 (12.1)	0	

LF – Left fimbriated end; RF – Right fimbriated end

Table 2: Incidental and usual morphologic findings in left ampulla, right ampulla, left fimbriated end, and right fimbriated end of both case and control group

Variables	Levels of variable	LA, n (%)	RA, n (%)	LF, n (%)	RF, n (%)
Psammomatous calcification	No	105 (99.1)	105 (99.1)	105 (99.1)	105 (99.1)
	Yes	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Endometriosis	No	103 (97.2)	104 (98.1)	106 (100)	106 (100)
	Yes	3 (2.8)	2 (1.9)	0	0
Hemangioma	No	105 (99.1)	105 (99.1)	105 (99.1)	105 (99.1)
	Yes	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Endosalpingiosis	No	104 (98.1)	102 (96.2)	106 (100)	106 (100)
	yes	2 (1.9)	4 (3.8)	0	0
Salpingitis	No	104 (98.1)	104 (98.1)	106 (100)	106 (100)
	yes	2 (1.9)	2 (1.9)	0	0

LA – Left ampulla; RA – Right ampulla; LF – Left fimbriated end; RF – Right fimbriated end

Single cysts in wall of the tubes were seen in 45.3% and 41.5% of the left and RA. Nevertheless, multiple cysts were found in 4.7% and 7.5% left and RA. However, this occurred at lower frequencies of 11.3% and 10.4% in the left and RF ends, respectively. Comparison with control group showed no significant difference.

The most common incidental finding was mesonephric (Wolffian duct) remnants, 89 (84%) of left and 86 (81%) of the right tube. This structure was found with relatively equal frequency in case and control groups ($P > 0.1$). We had only one psammomatous carcinoma (low-grade serous carcinoma) with psammomatous calcification in both left and right fallopian tubes. Hydrosalpinx was found in 2.8% and 3.8% of the left and RA, respectively. Comparison with the control group showed no significant association ($P = 0.3$). Marked hypervascularity was seen in 10 specimens (9.4%) of 106 tubes. This finding had higher frequency in younger women.

DISCUSSION

The distal of FTE is introduced to be the main source of HGSC of ovary in some studies of the last decade. In these studies, it is proposed that ovarian serous carcinomas are originated from premalignant lesion of the distal end of the fallopian tube which is termed serous intraepithelial carcinoma.^{1,7,20-22} Among the studies presenting the role of FTE in serous tumors, a few of them have studied the morphologic changes in fallopian tubes in known cases of benign, borderline, low- and high-grade ovarian serous carcinoma.

Our study focused on morphologic changes of fallopian tubes, in ovarian serous tumors and compared them with the control group. We found a significant correlation between HGSC and premalignant changes among 21 cases of serous carcinoma. Seven (33%) cases showed fallopian tube involvement by serous carcinoma, which is lower than the results presented by Patricia Diniz *et al.*¹ In their study, it was shown that the involvement of fallopian tube by ovarian carcinoma is very common: (6/9 cases; 66.7%). In the current study, stratification (especially cell layer thickness ≥ 4) occurred in a considerable number of cases of serous

carcinoma, which was different from benign serous tumors and nontumoral specimens ($P < 0.05$). Most of them showed focal pattern of stratification. However, in 21 HGSCs cases diffuse stratification was observed in the left (17.1%) and in RA (15.7%). Our findings were mostly in line with the study done by Jarboe *et al.*¹⁴

We found secretory cell outgrowth mostly in the fimbriated end and ampullas of case group ($P < 0.05$). Epithelial atypia consists of pleomorphism, high N/C ratio, loss of polarity, hyperchromasia, and enlarged nucleoli was found in the left and right tubes (fimbriated end and ampulla) of borderline and high-grade serous tumors. These findings were in line with the findings of Vang *et al.*⁴ In their study, most cases of HGSCs had variable form of enlarged round or oval nuclei, irregular chromatin distribution, irregular nuclear membranes, large nucleoli, hyperchromasia, and mitotic figures.

Our results were similar to Reade *et al.* study.²³ Glandular structure and complexity were observed in the fimbriated end and ampulla of fallopian tubes of serous carcinomas. None of the specimens from the control group exhibited glandular complexity, which is consistent with the results of Vang *et al.*'s study.⁴ They concluded that the glands with irregular slit-like spaces, extensive solid architecture, complexity, and micropapillary formation are highly in favor of HGSCs. In the current study, epithelial stratification ≥ 4 layers and tufting was observed in the fimbriated end of left (4.7%) and right (5.7%) tubes. LA showed stratification ≥ 4 layers in 54.1% of the case group. Significant epithelial alteration such as stratification ≥ 4 and tufting, mitosis, and moderate degree of atypia were observed in HGSC. In our study, we found significant atypia in the tubal epithelium of both ampulla (16.1%) and fimbriated end (11.7%) of HGSC cases, whereas Liang *et al.* identified TIC neoplasia in 44% of 34 cases with high-grade pelvic serous carcinomas, and all of them were in the fimbria only, while none of TIC was found in control cases.⁷ In another study, Hunt JL and Lynn worked on 287 nontumoral fallopian tubes and reviewed their hematoxylin and eosin slides, with an average of 3 complete cross-sections per specimen.²⁴ They found vacuolization in

about 6.6% of the specimens and showed that this finding had a higher frequency in old patients, while we observed no relationship between age and vacuolization.

Jie Li *et al.* showed that both low grade and HGSCs originated from the distal end of the fallopian tube due to clonal expansions of secretory cells of the fallopian tube.²⁵ The study also showed high frequency of secretory cell outgrowth in the case group.

Among incidental findings, mesonephric duct remnants (84% in the left and 81% in the right tube) were more frequent. These findings showed no relation with age, while in the study of Hunt and Lynn these remnants were reported in only 4.5% and more common in older women.²⁴ Mucinous and eosinophilic metaplasia were not found in our study, but cyst formation was observed mostly as a single cyst in the wall of the tubes, especially ampullae (left 45.3% and right 41.5%). The cysts included mesonephric, paramesonephric, mesothelial inclusion and cystic changes in transitional metaplasia. In the above-mentioned study, cyst (only mesothelial) was noted in 7.7% of cases.

In our study, Walt hard nests (transitional metaplasia) in solid and cystic forms were found in subserosa of 9.4% of LF end and 6.6% of RF end. There was no relation between ovarian serous tumor and metaplasia in the same side. Salpingitis was noted in minority of the cases with higher frequency in younger ages. These findings were comparable to the study of Hunt and Lynn.²⁴ In our study, 5.6% of the specimens showed endosalpingiosis, while it was noted in 2.4% of their study. We also found 4.7% endometriosis in all of our specimens, while not reported in their study.

Limitations of this study included lack of IHC staining.

CONCLUSION

Fallopian tube epithelial changes at both the ampulla and fimbriated end showed a significant difference between cases with and without ovarian serous tumors. Premalignant changes of FTE were observed in some of the cases with ovarian HGSC. Therefore, FTE could be one of the sources of ovarian serous carcinoma. In incidental findings, mesonephric duct remnant was the most common one with a high rate of occurrence, while this is reported in much lower rates in similar previous studies. Future study with more cases together with IHC study is advised to confirm the relationship between histologic premalignant changes of FTE and ovarian serous carcinoma.

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Conflicts of interest

There are no conflicts of interest.

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