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Original Article

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A Case Control Study on Histomorphological Changes of Fallopian Tube in Surface Epithelial Tumors of Ovary at a Tertiary Care Center

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Abstract

Background: Ovarian cancer, specifically high-grade serous carcinoma, is among the top causes of cancer-related mortality in women, and there is no reliable screening test for its early detection. New evidence indicates that the fallopian tube, and more precisely its fimbrial part, may be the origin of most ovarian serous carcinomas, thereby going against the conventional belief placing the site of origin in the ovarian surface epithelium. ***Aim and objective:*** The aim of this research was to examine the relationship of histomorphological changes in the epithelium of the fallopian tubes with ovarian surface epithelial tumors. The main objective was to compare the epithelial changes in the Fallopian tube from panhysterectomy specimen of cases with different types of surface epithelial ovarian tumors (benign, borderline, or malignant) and cases with benign uterine lesions. ***Material and Methods:*** A case-control study was done during November 2020 to November 2021 at Lakeshore Hospital and Research Center, Kochi. Forty-eight patients were recruited: 24 cases of epithelial ovarian tumors (10 benign, 5 borderline, 9 malignant) and 24 controls of benign uterine lesions. Fallopian tubes from panhysterectomy specimens were graded for tubal involvement, epithelial stratification, atypia, mitosis, intraepithelial vacuoles, and other changes histologically. Statistical significance was determined using a p-value cut-off of 0.05. ***Results:*** The case group had significantly greater frequencies of epithelial stratification (37.5% vs. 4.2%, $p<0.05$), atypia (12.5% vs. 0.0%, $p<0.05$), mitosis (20.8% vs. 0.0%, $p<0.05$), and intraepithelial vacuoles (12.5% vs. 0.0%, $p<0.05$) compared with the control group. Tube involvement occurred in 4 of 9 malignant cases (44.4%), and serous tubal intraepithelial carcinoma (STIC) occurred in one high-grade serous carcinoma case (11.1%). No secretory cell outgrowth occurred in either group. ***Conclusion:*** The research establishes a significant correlation between histomorphological changes in the epithelium of the fallopian tube and ovarian serous carcinomas and thereby supports the postulate that the fallopian tube (fimbrial end) is a potential site of origin of the neoplasms. The research emphasizes the importance of examining fallopian tubes in the context of ovarian cancer and has preventive surgical implications such as salpingectomy.

Keywords: ***ovarian cancer, fallopian tube, serous carcinoma, histomorphological changes, epithelial stratification, serous tubal intraepithelial carcinoma, fimbrial end.***

Introduction

The ovarian neoplasms are ranked as eight most common of all the female genital tract neoplasms universally. Among them the commonest histopathological category is high grade serous carcinoma (Hohn AK et al, 2021). The majority of ovarian cancers were detected after they metastasized beyond ovary resulting in an increased death rate. At present no screening methods are available for the early detection of ovarian tumours.

The inception of epithelial tumours of ovary was always a subject of prolonged debate. Conventionally the epithelial tumours of ovary were considered to be originate from the ovarian surface epithelium which undergoes metaplastic changes leading to the development of different cell types such as serous, endometrioid, clear cell, mucinous and Brenner tumours of the surface epithelium of the ovary. These tumours share histomorphological similarities with the epithelia of the fallopian tube, endometrium, gastrointestinal tract, endocervix and urinary bladder (Dubeau L, 2008). In the normal ovary there are no structures that resemble these tumours. The cervix, endometrium and fallopian tubes are derived from the Mullerian ducts while the ovaries develop from mesodermal epithelium on the urogenital ridge distinct from the Mullerian ducts. Therefore an alternative theory suggests that tumours with a Mullerian phenotype such as serous, endometrioid and clear cell arise from Mullerian-type tissue rather than mesothelium (Dubeau L, 2008).

Recent researches have shown that origin of serous tumours of ovary, particularly high-grade serous carcinoma are primarily the

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epithelium of fallopian tube mainly fimbrial end (Diniz PM et al, 2011; Crum CP et al, 2007). In serous carcinomas some epithelial variations were exhibited at the fimbrial end of fallopian tube that includes epithelial stratification 2-5 layers (focal / diffuse pattern) secretory outgrowth, epithelial atypia, increase in mitotic counts, nuclear pleomorphism, detached tumour cells and glandular complexity (Diniz PM et al, 2011; Vang R et al, 2009; Liang Y et al, 2011; Crum CP, 2009; Jarboe E et al, 2008; Sehdev AS et al, 2010). Recent studies have demonstrated a positive association between immunohistochemical markers such as ki67 p53 and pax8 in the epithelial lining of the fimbrial region of the fallopian tube in patients with ovarian serous carcinoma. Most of serous tubal intraepithelial carcinomas (STIC) have an increased ki67 value. PAX8 was expressed in serous tumours as well as its fallopian tube epithelium. A gradual increase in p53 positivity occurs during the secretory cell outgrowth serous tubal intraepithelial carcinoma high grade serous carcinoma sequence (Sehdev AS et al, 2010; Gilks CB, Prat J, 2009; Kobayashi H et al, 2017; Neel BG et al, 2018).

In addition fallopian tubes of patients with BRCA mutations were studied, it was noted that 1-5 % of patients already had an early tubal malignancy at the time of their risk-reducing surgery (Callahan MJ et al, 2007; Cass I et al, 2005). The majority of these malignancies were early intraepithelial lesions and the most of them were presented in the distal fimbriated end of the fallopian tube the detection of occult malignancies and dysplastic changes showing that these patients had a higher risk for serous carcinoma ovary derived from the fallopian tube (Leeper K et al, 2002). Fallopian tube carcinoma thus became part of the spectrum of BRCA-associated diseases (Leeper K et al, 2002, Piek JM et al, 2001). The prophylactic salpingo-oophorectomy in BRCA positive patients helped to look for any premalignant lesions for serous carcinoma of ovary (Shaw PA et al, 2009).

The main challenge faced while explaining the pathogenesis of ovarian neoplasm lies in the fact that it is a heterogeneous condition composed of different tumour types with different characteristics and behaviour. Based upon its morphologic and molecular genetic studies the tumours of ovary is classified into two major category type I and type II (Kurman RJ, Shih IM, 2011). Type I ovarian neoplasms are less aggressive and generally present at the initial stage of disease they display a shared lineage between benign neoplasms and the corresponding carcinomas through an intermediate (borderline) phase which supports the histomorphological continuity of cancer evolution in these neoplasms. This stepwise progression of events is similar to the adenoma-carcinoma sequence that occurs in colorectal carcinoma (Kurman RJ, Shih IM, 2011). Type I tumours include low- grade serous low-grade endometrioid clear cell and mucinous carcinomas. Type II tumours have papillary complex glandular and solid patterns and are diagnosed as high-grade serous. Type II tumours are highly aggressive and almost always present in the late stage.

This new paradigm of ovarian carcinogenesis has important clinical implications by shifting the early events of ovarian carcinogenesis to fallopian tube and endometrium. Ovary prevention approaches for example salpingectomy with conservation of ovaries have the potential to reduce the burden of ovarian cancer without compromising hormonal function and fertility (Kurman RJ, Shih IM, 2011).

Methodology

The study was a case control, comparative, and observational study of fallopian tube epithelium in panhysterectomy specimen received for different surface epithelial tumors of ovary (including benign, borderline, and malignant) and panhysterectomy done in cases for benign uterine lesions. The data was collected at Lakeshore Hospital and Research Center, Nettoor, Kochi which is a tertiary care referral center from November 2020 to November 2021

General information regarding the patient was collected based on a pre-formed proforma

Inclusion Criteria

1. All cases of epithelial ovarian tumors (benign, borderline and malignant) and the corresponding fallopian tubes submitted for histopathological examination in the Department of Pathology were taken as cases.
2. Panhysterectomy specimen from women undergoing surgery for benign lesions of uterus were taken as control.

Exclusion Criteria

1. Ovarian epithelial tumors that have already been treated with neoadjuvant chemotherapy or radiotherapy were excluded
2. Salpingo-oopherectomy specimen, where fallopian tubes are incorporated to ovary and specimens where tubes were not submitted in toto for histological examination were excluded

Data Collection

A total of 48 (24 cases and 24 control) patients were selected based on the inclusion and exclusion criteria and their fallopian tubes were evaluated for

- Tubal involvement
- 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

Results

In this study, the majority of the patients in the case group fell into the age group of more than 50 years and the patients in the control group fall into 40-50 years. The minimum age was 29 (high grade serous carcinoma) and maximum age was 68 years (mucinous borderline tumor). The study included 24 cases, of which 10 cases were benign, 5 cases were borderline and 9 cases were malignant (**Figure 1**). About 24 patients with benign lesions of uterus were included in the control group, of which leiomyomas were the most common diagnosis (54.2%) (**Table 1**).

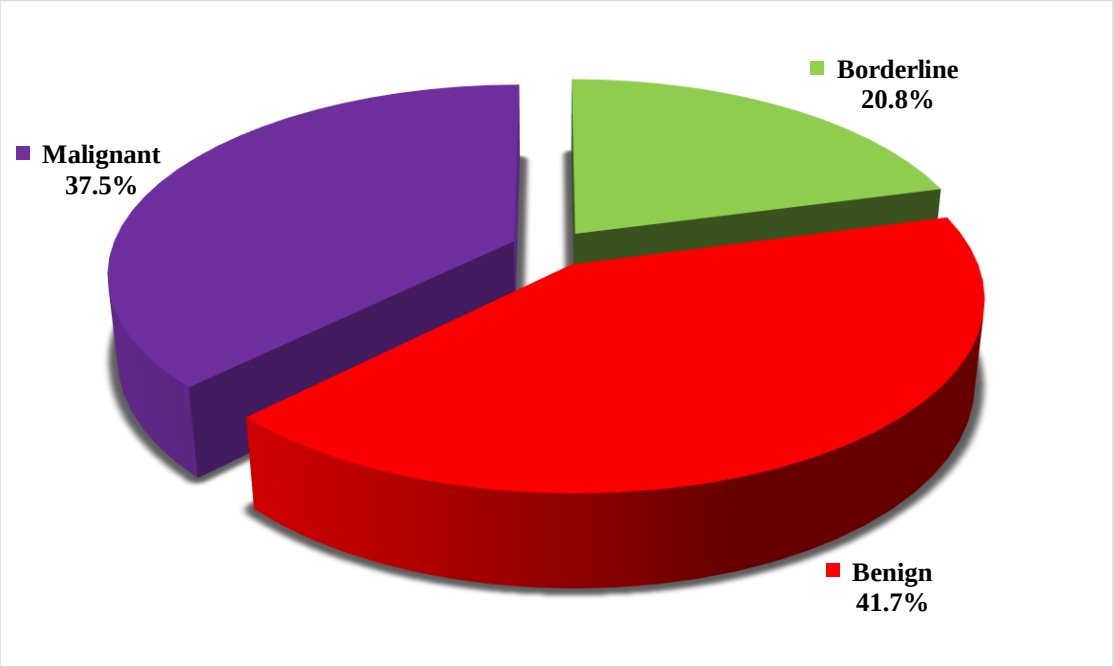

Figure 1: Distribution of Nature of Neoplasm in case group

Gross Images

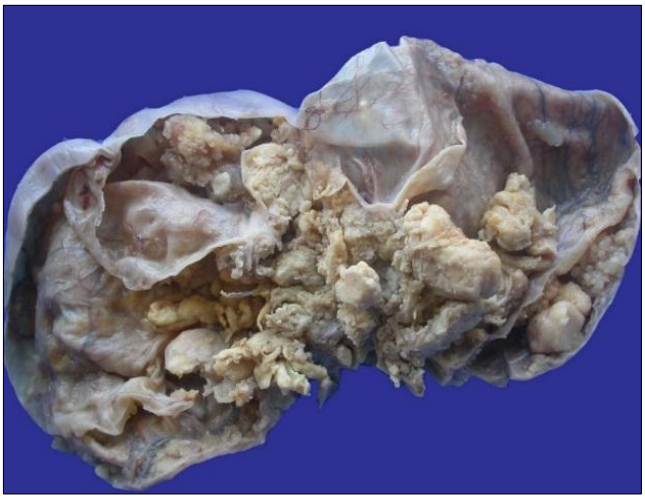

Image 1 a): High grade serous carcinoma ovary

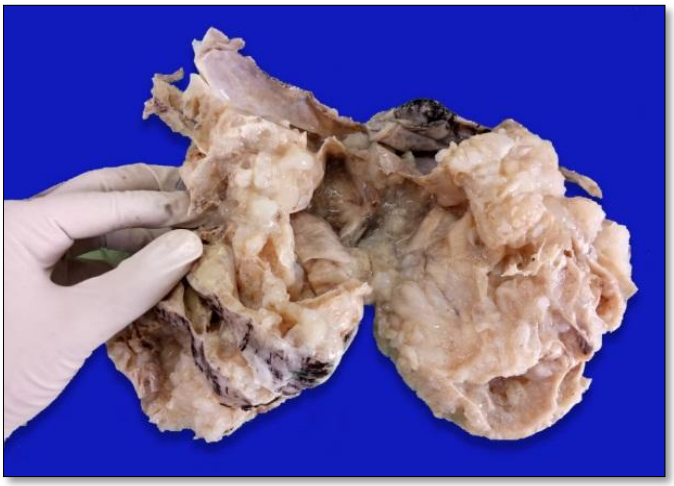

Image 1 b): Mucinous carcinoma ovary

Table 1: Distribution of Diagnosis in Case and Control Group

Diagnosis for Case Group (n=24)	**High Grade Serous Carcinoma**	**7(29.20%)**
	Serous Borderline Tumor	3(12.50%)
	Serous Cystadenoma	3(12.50%)
	Mucinous cystadenoma	3(12.50%)
	Mucinous Borderline Tumor	2(8.30%)
	Brenner Tumor	1(4.20%)
	Clear cell carcinoma	1(4.20%)
	Mucinous Cystadenocarcinoma	1(4.20%)
	Serous Cyst adenofibroma	1(4.20%)
	Serous Cystadenoma Fibroma	1(4.20%)
	Serous mucinous Cyst adenofibroma	1(4.20%)
Diagnosis for Control Group (n=24)	Leiomyoma Uterus	13(54.20%)
	Adenomyosis	5(20.80%)
	Adenomyoma	2(8.30%)
	Leiomyoma cervix	2(8.30%)
	Benign Endometrial Polyp	1(4.20%)
	Leiomyoma Uterus and Adenomyosis	1(4.20%)

In the study, case group consisted of 41.7% benign neoplasms, 20.8% borderline neoplasms and 37.7% malignant neoplasms. Most of the cases were unilateral with left side predominance. Tubal involvement by malignant neoplasm was noted in 4 out 9 malignant cases in the case group (**Image 2 a**) (**Table 2**).

Table 2: Distribution of Tubal Involvement in Malignant Cases

Tubal Involvement	Frequency	Percent
Involved	4	44.4%
Not Involved	5	55.6%

The p-value was less than the significance level 0.05 during the comparison between case and control group for epithelial stratification; the difference in epithelial stratification between cases and control is significant in the present study (Image 2 b). The table revealed that the epithelial stratification is significantly higher in case (37.5%) compared to control group (4.2%). The p-value was less than the significance level 0.05 while comparing atypia between case and control group; the difference in atypia between cases and control is significant (Image 2 c). The table revealed that the atypia is significantly higher in case (12.5%) compared to control group (0.0%). The p-value was less than the significance level 0.05 as well in the comparison of mitosis between case and control group; the difference in mitosis between cases and control is significant. The table reveals that the mitosis is significantly higher in case (20.8%) compared to control group (0.0%). No secretory cell outgrowth cases were noted. In case of comparison between intra epithelial vacuoles between case and control groups, the p-value came out to be less than the significance level 0.05; the difference in intra epithelial vacuoles between cases and control is significant. The table reveals that the intra epithelial vacuoles is significantly higher in case (12.5%) compared to control group (0.0%) (Image 2 d). While comparing tufting between case and control group, the p-value came out to be greater than the significance level 0.05; the difference in tufting between cases and control was not significant. The table reveals that the tufting was almost the same in case (4.2%) and control (0.0%) (Table 3, Figure 2). In our study, we observed serous tubal intraepithelial carcinoma in one (11.1%) out of nine malignant cases, which is lower than the previously mentioned study (Image 2 e). Some incidental findings were observed in the fallopian tubes of case and control groups as well in our study (**Table 4**).

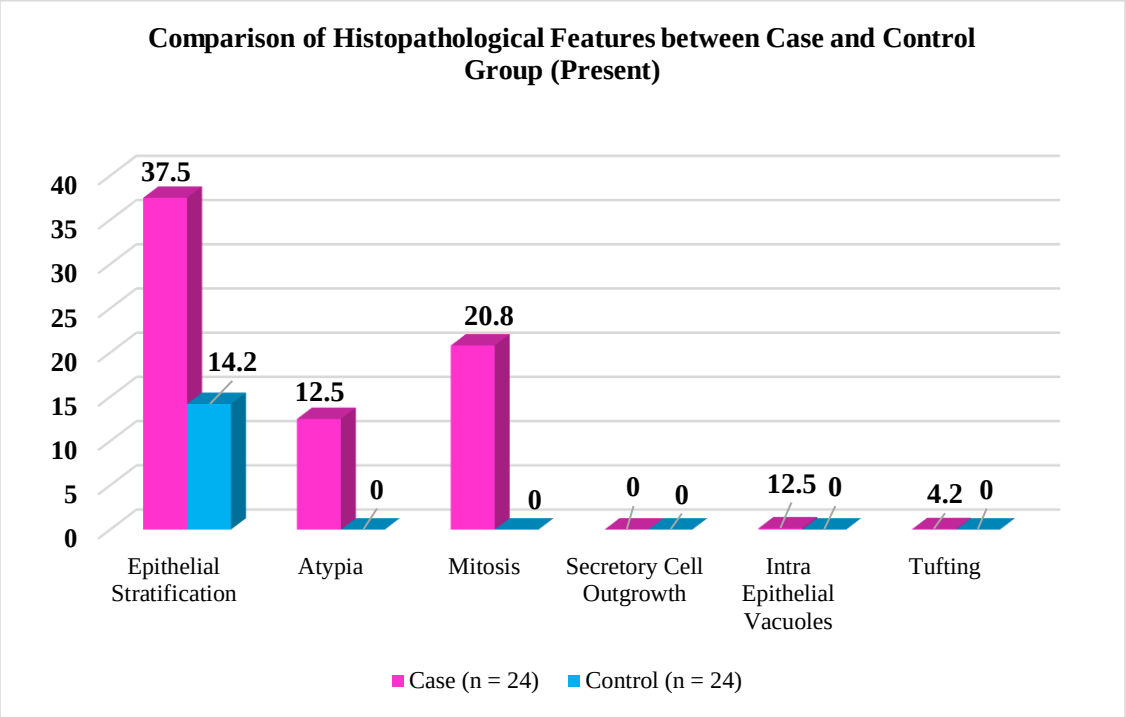

Figure 2: Comparison of histopathological features between case and control group (present)

Table 3: Comparison of Various Histopathological Features between Case and Control Group

Histopathological Features	Observation	Case (N = 24)	Control (N = 24)	P Value
Epithelial Stratification	Present	9 (37.5%)	1 (4.2%)	0.003
	Absent	15 (62.5%)	23 (95.8%)	
Atypia	Present	3 (12.5%)	0 (0.0%)	0.037
	Absent	21 (87.5%)	24 (100.0%)	
Mitosis	Present	5 (20.8%)	0 (0.0%)	0.006
	Absent	19 (79.2%)	24 (100.0%)	
Secretory Cell Outgrowth	Present	0 (0.0%)	0 (0.0%)	0
	Absent	24 (100.0%)	24 (100.0%)	
Intra Epithelial Vacuoles	Present	3 (12.5%)	0 (0.0%)	0.037
	Absent	21 (87.5%)	24 (100.0%)	
Tufting	Present	1 (4.2%)	0 (0.0%)	0.235
	Absent	23 (95.8%)	24 (100.0%)	

Microscopic images of histopathological findings observed in the case group (H&E Stain)

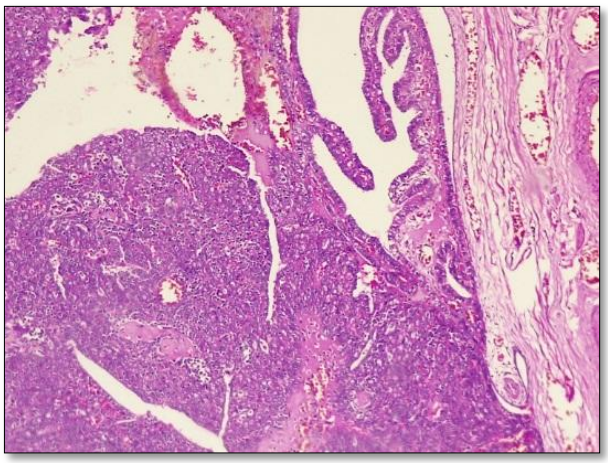

Image 2 a) Tubal involvement by malignant neoplasm

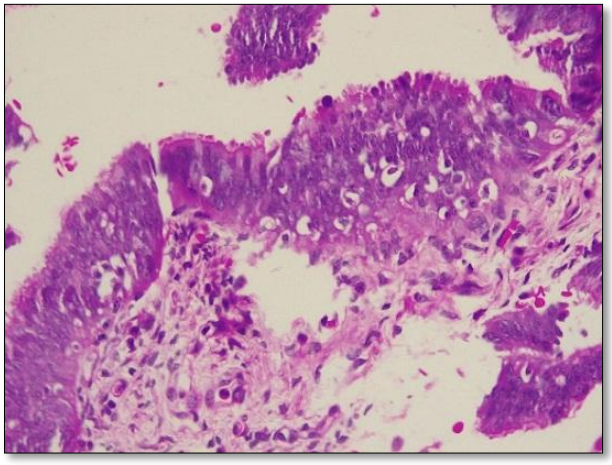

Image 2 b): Tubal epithelial stratification

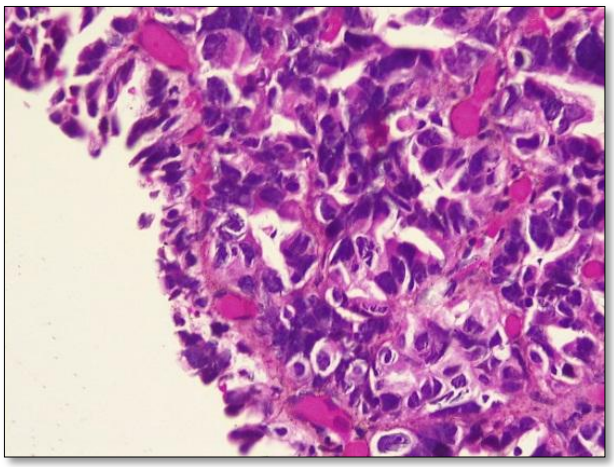

Image 2 c): Tubal epithelial atypia

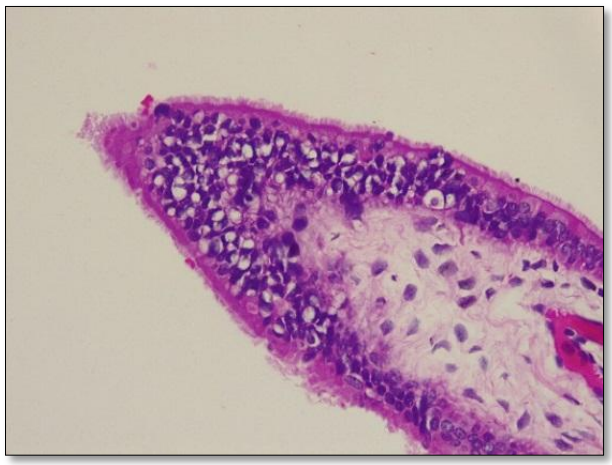

Image 2 d): Intraepithelial vacuoles

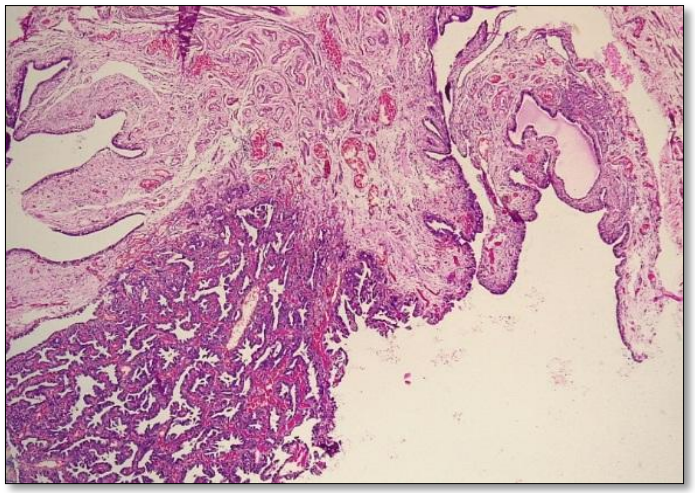

Image 2 e): Serous tubal intraepithelial carcinoma

Table 4: Distribution of Incidental Findings

Incidental Findings	Frequency	Percent
Paratubal Cyst	5	10.4%
Walthard Cell Nest	4	8.3%
Salphigitis	2	4.2%
Hematosaplhinx	1	2.1%
Calcification	1	2.1%
Endometriosis	1	2.1%
Endosalphingiosis Lymphnode	1	2.1%
Hydrosalphinx	1	2.1%

Discussion

Ovarian cancer (OC) is one of the most common and fatal outcome gynecological malignancies in women. So far, there has been no screening method for early detection of this disease. In fact, several studies have proven that the distal fallopian tube is the most frequent site of early serous cancer in women with history of inherited ovarian cancer risk (Semmel DR et al, 2009). The tubal intraepithelial carcinoma associated with high grade serous carcinoma supports Fallopian tube as the site of origin (Bergsten et al, 2020). Early diagnosis and timely treatment could be improved in ovarian carcinoma once the precursor lesion is identified.

A total of 96 fallopian tubes were obtained from females (between 29-68 years) and grouped into control (50 %) and case (50 %) groups. In the case group, there were: 10 (41.7%) benign, 5 (20.8%) borderline and 9 (37.5%) malignant ovarian tumours. Of the 24 cases, 11 were left sided (LT) (45.8%), 6 (25%) were right sided (RT) and 7 (29.1%) were bilateral tumours with respect to side of ovarian tumours. This observation, indicating a high prevalence of left side ovarian tumors has also been confirmed and expanded upon by an author (Aslani FS et al, 2019) in a separate study.

A notable correlation was observed between the case and control groups regarding premalignant changes, including epithelial stratification, epithelial atypia, mitotic rate, and intraepithelial vacuoles, in this study. Most of these changes were found at the fimbrial end of the fallopian tubes, particularly in cases of serous carcinomas.

Involvement of the fallopian tubes by carcinoma was identified in five out of nine (55.6%) malignant cases. The findings of this study were lower than those reported by an author (Diniz PM et al, 2011), who found that 6 out of 9 cases (66.7%) of ovarian carcinoma demonstrated concurrent involvement of the fallopian tube.

In our study, we observed a higher incidence of epithelial stratification in the case group (37.5%) compared to the control group (4.2%). This change was predominantly seen in cases of serous carcinoma. Although our study identified a diffuse stratification of the fallopian tube epithelium exclusively in the fallopian tube epithelium, this finding was also noted in serous carcinomas in the research conducted by an author (Jarboe et al, 2008).

Epithelial atypia, characterized by pleomorphism, a high nucleus-to-cytoplasm (N/C) ratio, loss of polarity, hyperchromasia, and enlarged nucleoli, was identified in the fimbriated ends of fallopian tubes in cases of high-grade serous tumors.

Similar findings were reported in another study (Vang R et al, 2009). A p-value for atypia less than the significance level of 0.05 was observed in our study, with a slightly elevated incidence in the case group (12.5%) compared to the control group (0%).

Tubal intraepithelial carcinoma was identified in 44% of 34 cases as reported by another author among individuals with high-grade pelvic serous carcinomas, whereas it was absent in all control cases (Liang Y et al, 2011).

A higher number of mitotic figures in the fimbrial end of the case group was observed compared to the control group ($p<0.05$). There was a significant difference in mitotic activity between the case and control groups (20.8% in cases versus 0.0% in controls). Moreover, an increase in mitotic figures in the fallopian tube epithelium in high-grade serous carcinoma cases was also reported by (Vang R et al, 2009). Our study similarly noted alterations in the fallopian tube epithelium of serous carcinoma cases.

Epithelial vacuolization exhibited a p-value below the significance threshold of 0.05, indicating significant differences in the number of intraepithelial vacuoles between the case and control groups. Specifically, epithelial vacuoles were found to be significantly more prevalent in the case group (12.5%) compared to the control group (0.0%). Two authors (Hunt JL, Lynn AA, 2002; Li J 2012) examined 287 non-tumoral fallopian tubes and discovered vacuolization in approximately 6.6% of the specimens, with a noted increase in frequency among older individuals. However, our study did not establish a correlation between age and vacuolization.

No secretory cell outgrowth was observed in the fimbrial end of both the case and control groups. One author indicated that serous carcinoma of the ovary, both low and high grade, originates from the distal end of the fallopian tube due to clonal expansions of secretory cells in that area (Hankinson SE et al, 1993). Mesonephric duct remnants were found in 10.4% of incidental findings, showing no correlation with age; however, two authors reported these remnants in only 4.5% of cases with a higher prevalence among older individuals also reported in another study. This study included mesonephric, paramesonephric, and mesothelial cysts, while the previously mentioned study noted only mesothelial cysts (Hunt JL, Lynn AA, 2002).

In the present study, walthard nests (transitional metaplasia) were seen in solid and cystic form in subserosa of fallopian tube (8.3%). There was no association between ovarian serous tumor and metaplasia on the same side. Salpingitis were observed in few of the cases (4.24%). These latter findings are comparable with the results of the two authors which were echoed in our study where endosalpingiosis was detected in a 2.1% of cases, as compared to 2.4% of their observations (Hunt JL, Lynn AA, 2002). Besides, postoperative pathology revealed endometriosis in 2.4% of our specimens, while this was not found in their study.

Conclusion

Ovarian carcinoma has been noted as one of the leading causes of cancer deaths in the females. However, no screening methods exist until now for the prior detection of the condition. It has been reported by many studies that fallopian tube is the principal site of early serous cancer in the female population along with a hereditary risk of ovarian cancer.

Our study focused on the aim to evaluate the histomorphological changes in the fallopian tube epithelium by comparing 24 cases of epithelial ovarian tumors with 24 benign uterine lesion cases.

There was a noticeable statistically significant association between the case and control group in epithelial stratification, epithelial atypia, mitosis and intraepithelial vacuoles. These findings were found mostly in the cases of serous carcinomas of ovary. Serous Tubal Intraepithelial Carcinoma (STIC) was found in one case of high-grade serous carcinoma. Therefore, fallopian tube epithelium could be one of site of origin of serous carcinoma ovary.

In our study secretory cell out growth was not found in the fimbrial end of case/control group. It was observed that mesonephric duct remnants were a more frequent incidental finding in the fallopian tubes.

To conclude, a study with more cases coupled with immunohistochemistry and molecular study will be helpful to confirm the tubal histogenesis of epithelial tumors of ovary.

Strengths and Limitations of the Study

The major strength of the study was that it was conducted at a tertiary care referral center benefiting from access to diverse cases and high-quality histopathological facilities increasing the reliability of the

findings. Multiple histomorphological parameters were evaluated like epithelial stratification, atypia mitosis, intraepithelial vacuoles, and tufting and secretory cell overgrowth in the fallopian tube epithelium. This thorough examination provided a detailed understanding of changes associated with ovarian tumors, particularly at the fimbrial end. However, the study has its own limitations. The sample size in this study was small. The study period was one year. A retrospective and prospective study over a longer study period would have helped in the identification and assessment of more cases and more variables. The study also lacked immunohistochemical analysis.

Declarations

Ethical Considerations

The study was evaluated and approved by the ethics committee conducted in our hospital, Lakeshore Hospital and Research Centre, Kochi, on 15.04.2021.

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Conflicts of Interests

The authors report no conflict of interest.

Article Category

Retrospective and Prospective study

Acknowledgement

None

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