THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (November–December 2017) 67(6):432–441
DOI 10.1007/s13224-017-1009-0

ORIGINAL ARTICLE

Serous Tubal Carcinogenesis: The Recent Concept of Origin of Ovarian, Primary Peritoneal and Fallopian Tube High-Grade Serous Carcinoma

Tushar Kar[1] · Asaranti Kar[2] · Ipsita Dhal[3] · Sasmita Panda[4] · Priyadarshini Biswal[5] · Bhagyalaxmi Nayak[6] · Niranjan Rout[4] · Sagarika Samantray[4]

Received: 12 March 2017 / Accepted: 15 May 2017 / Published online: 1 June 2017

About the Author

Tushar Kar Vice President, FOGSI-2010; Chairperson, FOGSI (Oncology) 2004–2009; Academic Adviser, SCB Medical College, Cuttack; National Corresponding Editor, FOGSI Journal (2014–2016); Peer Reviewer, IJOG, Indian Edition; Executive committee member, ICOG (2015–2017); Executive committee member, IAGE (2015–2017); Faculty & Resource personnel in national, international conferences, seminars & workshops; Contributed many chapters in many text books; Published many articles in National & International journals; Published two text books "Do's & Don'ts in OBGYN" & "Safe Surgical Practice". Awards: Adarsa Chikitshaka Award-2007, Mani Manika Award-2010, Dharanidhar Award-2010, Best Medical Publication D.C. Dutta Award, 2011, TARINI PRATIVA SAMMANA, 2015. Overall a very good person, good teacher, brilliant academician, efficient administrator and organizer.

Tushar Kar is a Professor and HOD in VIMSAR, Burla, India; Asaranti Kar is a Associate Professor in the Department of Pathology, S.C.B. Medical College, Cuttack, India; Ipsita Dhal is a SR, Lady Hardinge Medical College, New Delhi, India; Sasmita Panda is a Assistant Professor, in the Department of Oncopathology, AHRCC, Cuttack, India; Priyadarshini Biswal is a Assistant Professor in the S.C.B. Medical College, Cuttack, Odisha, India; Bhagyalaxmi Nayak is a Assistant Professor in the Department of Gynecologic Oncology, AHRCC, Cuttack, Odisha, India; Niranjan Rout is a Professor & Dean, Dept. of Oncopathology, AHRCC, Cuttack, India; Sagarika Samantray is a Associate Professor in Department of Oncopathology, AHRCC, Cuttack, India.

✉ Asaranti Kar
asarantikar@yahoo.co.in

[1] Department of Obstetrics & Gynecology, VIMSAR, Burla, Odisha, India

[2] Department of Pathology, S.C.B. Medical College, Cuttack, India

[3] SR, Lady Hardinge Medical College, New Delhi, India

[4] Department of Oncopathology, AHRCC, Cuttack, India

[5] Department of Pathology, S.C.B. Medical College, Cuttack, Odisha, India

[6] Department of Gynecologic Oncology, AHRCC, Cuttack, Odisha, India

Abstract

Background Pelvic (non-uterine) high-grade serous carcinomas (PHGSC) including ovarian, tubal and primary peritoneal serous carcinomas have increased death: incidence ratio due to presentation at advanced stage, rapid progression, poor prognosis and high morbidity. Ambiguity regarding their pathogenesis and lack of a proper screening method is the cause of their late detection and high fatality rate. This study was undertaken to assess the fallopian tube for the presence of precursor lesions in pelvic serous carcinoma.

Methods This was a prospective case–control study carried out in a tertiary care center. Consecutive specimens of 55 cases of pelvic high-grade serous carcinoma and 41 controls inclusive of 21 low-grade serous carcinoma, 10 benign adnexal masses and 10 normal adnexa were included in the study. Both side fallopian tubes in each case were subjected to histopathological examination and p53, Ki67 immunohistochemistry.

Results There were 55 cases of PHGSC comprising of 50 cases of ovarian HGSC, two cases of primary peritoneal carcinoma (PPC) and three cases of tubal carcinoma. Serous tubal intraepithelial carcinoma (STIC) was detected in 14 cases (28%), p53 signature in 13 cases (26%) and tubal intraepithelial lesion in transition in 10 cases (20%) of ovarian HGSC. One case (50%) of PPC and one (33%) case of tubal carcinoma revealed the presence of STIC. None of the controls exhibited any precursor lesion except ovarian low-grade serous carcinoma where p53 was detected in 20% of cases.

Conclusion This revelation concludes that fallopian tubes are the sites of precursors of PHGSC to a large extent. In the absence of a proper screening method of HGSC, prophylactic bilateral salpingectomy at hysterectomy for benign diseases can achieve ultimate goal of reduction in incidence of PHGSC.

Keywords Ovarian · Tubal · Primary peritoneal carcinoma · Pelvic high-grade serous carcinoma · Prophylactic salpingectomy · Serous tubal intraepithelial carcinoma · p53 · Ki67

Introduction

Pelvic high-grade serous carcinomas (PHGSCs), including ovarian carcinoma (OC), tubal carcinoma (TC) and primary peritoneal carcinomas (PPC), receive much attention from clinicians and researchers because of their usually advanced stage at presentation, rapid progression, extra-ovarian disease at the time of diagnosis, poor prognosis and high fatality rate. Lack of a proper screening method in these cases is the cause of their late detection. Despite considerable efforts aimed at elucidating the molecular mechanisms of these cancers, their pathogenesis is still unknown. Recent evidence suggests that these tumors may follow a defined precursor that has been present for a prolonged interval. Recently, the distal fallopian tube has been documented as a common (80%) site of tumor origin in BRCA+ve (BRCA1 or BRCA2) women undergoing risk reducing salpingo-oophorectomy [1, 2]. Examination of prophylactically removed tubes has shown serous tubal intraepithelial carcinoma (STIC) of the fimbriated end between 57 and 100% [3–8]. The p53 signature and the tubal intraepithelial lesion in transition (TILT) are regarded as precursor lesions of STIC [1, 9]. Given the complexities involved about the origin of pelvic serous cancers, it is important to investigate the roles of fallopian tubes with regard to the occurrence of p53 signature, TILT and STIC. Again, the precursor lesions in both fallopian tubes remain undetected and their clinical significance and role in pelvic serous carcinogenesis is yet to be clearly established.

So, in this project we studied the association of tubal precancerous lesions in a consecutive series of OC, TC and PPC and controls comprising of low-grade OC, benign adnexal masses and normal adnexa. We compared the frequency and distribution of the precursor lesions. The precursor lesions were detected by examining the fallopian tube samples by both histomorphologically and immunohistochemically with p53 and Ki 67.

Methods

The study was carried out in Department of Obstetrics & Gynaecology, Department of Pathology and Department of Oncopathology within a period of 2 years. Institutional ethical committee clearance was obtained from two centers (vide letter no-AHRCC-IEC/32 dt.25.11.2013 & SCB-IEC-108/22.11.2014). The diagnosis of OC, TC and PPC was done (irrespective of original clinical diagnosis) as per the standard criteria like tumor distribution and the presence or absence of a precursor lesion. Occurrence of intraepithelial carcinoma is mandatory for a diagnosis of tubal carcinoma but not for ovarian or peritoneal carcinoma. Depending on tumor distribution like large ovarian mass with parenchymal involvement are considered to be of ovarian origin and tumors without ovarian surface involvement and/or large tubal mass are classified as primary peritoneal carcinoma [10, 11]. A group of control patients were taken which included normal adnexa, benign ovarian adnexal masses and low-grade ovarian serous carcinomas.

After recording clinical and investigation findings and personal and family history from the patients, the specimens were subjected to histotechniques and examined by two separate histopathologists. In case of disparity, third pathologist was consulted. Both sides fallopian tubes were grossed according to "SEE-FIM" protocol (sectioning and extensively examining the fimbriated end) [12]. By this method, multiple longitudinal sections of the distal two cm of the tube were taken (usually 2–3 sections). Serial transverse sections (every 2–3 mm) were taken from the isthmus and ampulla (6–8 sections). The sections were examined histopathologically for detection of various precursor lesions. Paraffin blocks of each tube which were most representative were chosen for

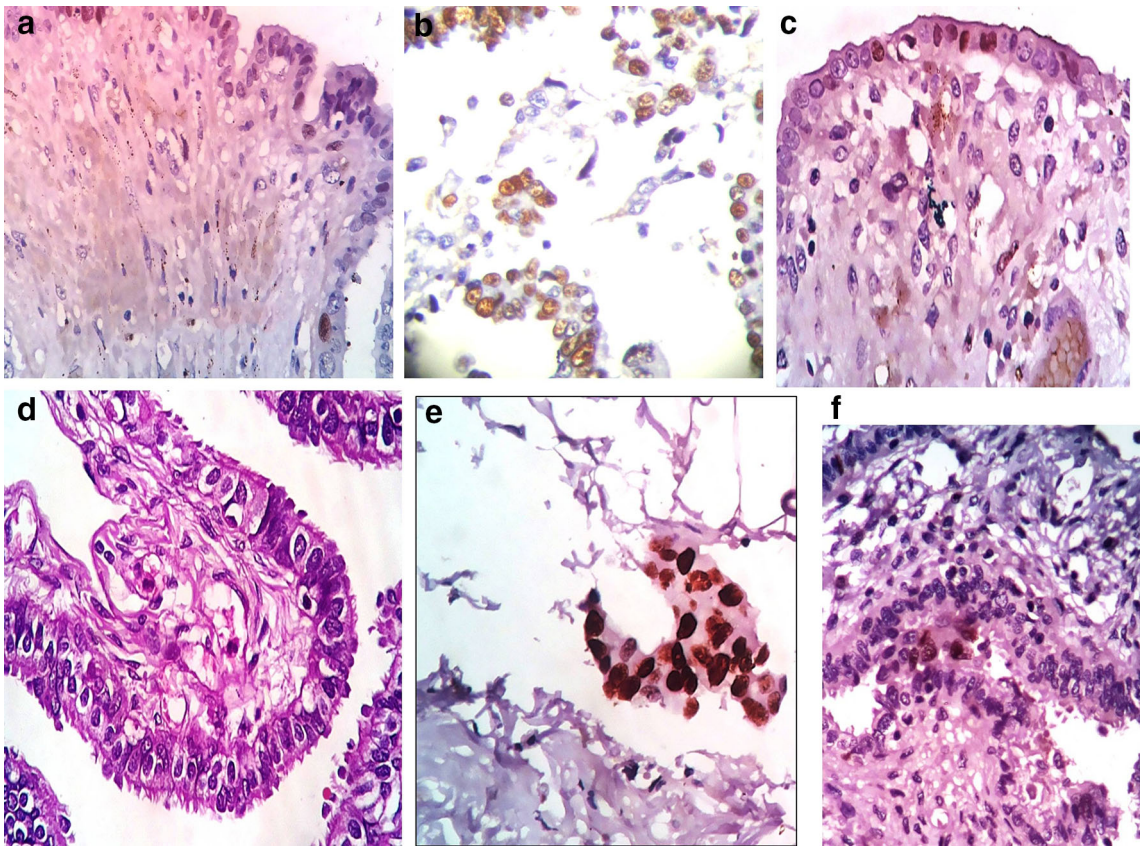

Fig. 1 **a–c** Histomorphology and immunohistochemical findings in p53 signature, **a** H & E stainx 400, p53 IHCx400, **c** Ki 67 × 400. **d–f** Histomorphology and immunohistochemical findings in STIL, **d** H & E stainx400, **e** p53 IHCx400, **f** Ki67 IHCx400

immunohistochemical staining with p53 and Ki67. Biogenex ready-to-use mouse monoclonal antibodies were utilized for this purpose. The results of histopathology and immunohistochemistry were noted down in tabulated manner. The paired t test and one-way ANOVA were employed to find out the correlation between desired variables. The result was considered statistically significant if p value was less than 0.05.

For morphological analysis of different steps in serous carcinogenesis in fallopian tube, the histopathological and immunohistochemical features are put forth by Lee et al. and Crum et al. [13, 14]. Diagnostic algorithm proposed by Vang et al. [15] was utilized for the diagnosis of precursor lesions incorporating results of morphology and immunohistochemical findings. p53 signature is characterized by low proliferative index (<10% nuclei positive for Ki67) with mild cytologic atypia and secretory cell outgrowth. p53 immunostaining shows accumulation of p53 in linear stretch of 12 or more consecutive secretory cell nuclei (Fig. 1a–c). STIC is diagnosed by stratification of secretory cells, loss of polarity, architectural distortion, atypia and strong staining of many nuclei with p53 and high proliferative index (>10% nuclei positive for Ki67) (Fig. 2c–e). TILT is the intermediate lesion with features in between the above two extreme conditions (Fig. 1d–f).

Results

Total 96 cases were included in the study, out of which 55 cases belonged to pelvic HGSC categorized into different groups based on the conventional criteria of diagnosis as devised by WHO [10, 11]. Accordingly, they were classified into ovarian (50 or 90.9% cases), PPC (3 or 5.5% cases) and tubal (2 or 3.6% cases) Control group included 21 cases of low-grade serous carcinoma (LGSC) of ovary and 10 cases of benign adnexal masses (6 serous and 4 mucinous cystadenomas, 10 normal adnexas removed with hysterectomy for benign causes like adenomyosis, leiomyoma and endometrial polyp). Age of the PHGSC patients ranged from 29 to 72 years; mean ± SD was 47 ± 9.89 years (Table 1). Controls age ranged from 32 to 60 years, and mean ± SD was 42 ± 5.46 years. Majority were detected in fourth decades of life (36%). Predominantly, the patients were of parity 2–4 (36 cases, 65.4%), followed by P1 in 13 cases (23.6%), and least number of

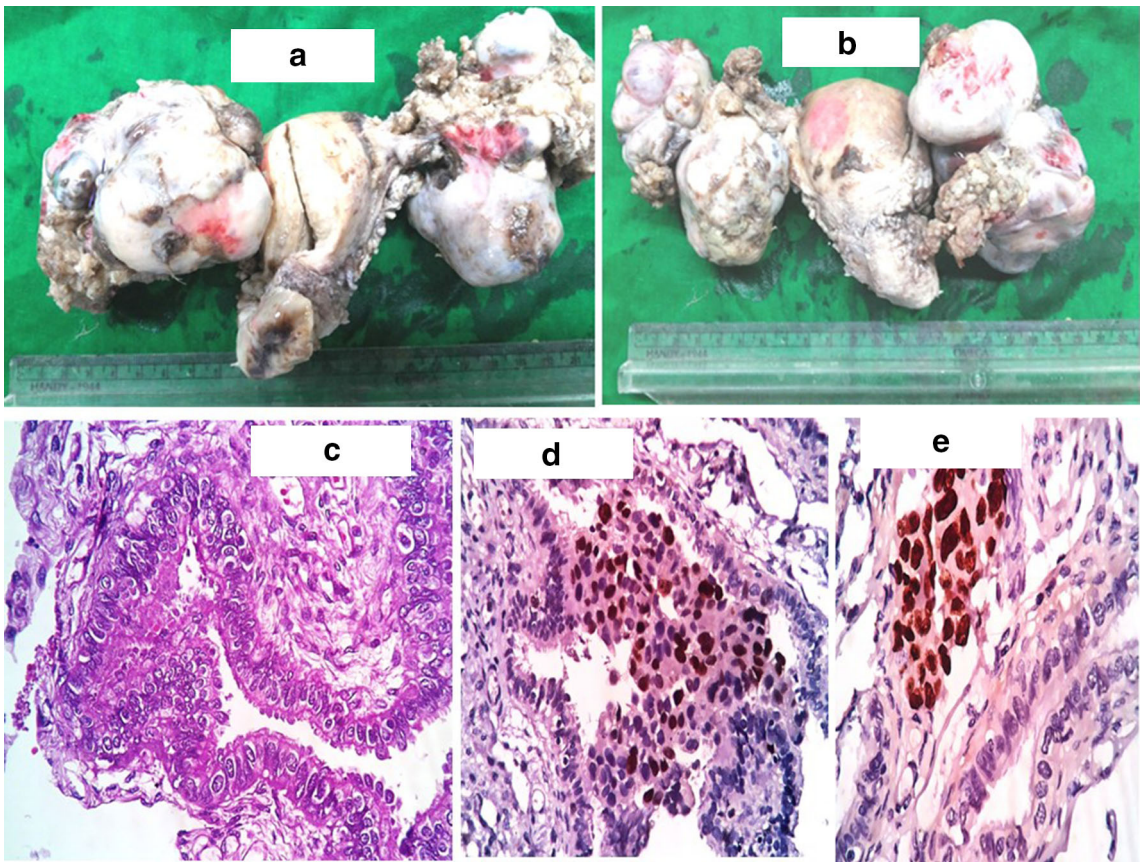

Fig. 2 **a**, **b** Gross picture of bilateral solid ovarian serous carcinoma. **c**–**e** Histomorphology and immunohistochemical findings in STIC, **c** H&E stainx400, **d** p53 IHCx400, **e** Ki67 IHCx400

Table 1 Group wise distribution of cases ($n = 96$)

Groups	Number	Age range	Parity			Menopausal status	
			0	1	2–4	Pre	Post
I-Normal ovaries	10	40–60	0	2	8	3	7
II-Benign adnexal mass	10	30–60	2	4	4	2	8
III-Low-grade serous tumor	21	32–55	3	7	11	8	13
IV-High-grade serous carcinoma	55	29–72	6	13	36	32	23

cases were nullipara (10.9%). Out of them, 32 (58.1%) were premenopausal and 23 (41.9%) were postmenopausal (p value was nonsignificant = 0.579). Most of the controls were postmenopausal (28 patients, 68.3%) belonging to para 2–4 (23 patients, 56.1%) (Table 1). Family history of pelvic carcinoma was present in 29 PHGSC (53%) and 17 (41.5%) of the controls.

Commonest clinical presentation was bleeding per vaginum (26 cases = 47%) followed by pain abdomen and abdominal swelling (Table 2). Among ovarian carcinomas, majority had bilateral involvement (24 cases = 44%). 29% of them were solid with very significant p value (0.0093) (Table 2; Fig. 2a, b). Twenty-seven patients had ascites at the time of presentation, out of which malignant cells were found in 5 cases (majority being ovarian-4 cases) and 21 (38%) had omental deposits from which 17 cases (80.95%) belonged to ovarian HGSC. Most common size was between 4 and 6 cm, and mean ± SD was 4.97 ± 1.52 cm (p value was significant = 0.0329). Most of the women (36 = 66%) were in stage II and III (p value was 0.0002 = extremely significant) (Table 3). Majority of the tumors (29 cases, 53%) were predominantly solid, and least were predominantly cystic in consistency (9 cases 16%). High-grade pelvic tumors mostly belonged to FIGO stage II and III (36 cases, 66%) with least number of cases (6 cases or 11%) in stage I. Ovarian tumors predominantly

Table 2 Demographic factors of patients with pelvic high-grade serous carcinoma-

Factor	Result
Mean age of presentation	47 ± 9.89 years
+ve Family history of breast/ovarian carcinoma	29 (53%)
−ve Family history of breast/ovarian carcinoma	26 (47%)
Presenting complaint of bleeding P/V	26 (47%)
Presenting complaint of pain abdomen	15 (27%)
Presenting complaint of abdominal swelling	14 (26%)
Right-sided ovarian mass	16 (31%)
Left-sided ovarian mass	13 (25%)
Bilateral ovarian mass	23 (44%)

were stage III (16 cases), followed by stage II (15 cases), stage IV (13 cases) and stage I (6 cases), respectively. Out of the 3 cases of tubal carcinoma, 2 were of stage II and out of the 2 cases of PPC one each was of stage II and stage III. In one-way ANOVA, p value was found to be 0.0002 which was extremely significant.

Evidence of various precursor lesions in fallopian tube was detected in 40 cases (72.72%). Precursor lesions like p53 signature, TILT and STIC were most commonly encountered in OHGSC (37/55 cases-67.27%) (Table 2). The commonest tubal intraepithelial lesion was STIC, seen in 16/55 cases (29.09%). Out of 50 cases of OHGSC, 13 cases showed p53 signature (26%), 10 (20%) showed TILT and 14 cases (28%) were STIC positive with significant p value (0.0474). Both cases of tubal serous carcinoma had shown the presence of STIC (Fig. 3a–d). And out of primary peritoneal serous carcinoma, one case each had the presence of p53 signature and STIC in one side tube (Fig. 4a–c). But none of the control cases showed positivity for any precursor lesions except low-grade ovarian serous carcinoma where 2 cases (20%) revealed the presence of p53. Unilateral OHGSC had ipsilateral TIC (56%), and bilateral TIC was most frequent in fimbrial region (80.2% cases).

Among the ovarian tumors, correlation was done between grade and stage of tumor with the presence/absence of precursor lesions in fallopian tubes. Significant correlation was seen between grade and TIC (p value 0.0474), and tubal intraepithelial lesions (p value 0.0374) but no significant correlation could be seen between stage of ovarian tumor with precursor lesions (p value 0.5417).

Discussion

Salpingectomy is a prophylactic or preventive surgery to remove the entire fallopian tubes with all hysterectomies for women at high risk of ovarian, tubal and peritoneal serous cancers. For last few decades, the fallopian tube is being targeted as a future method of prevention of such malignancies since screening and early detection are unsuccessful. It has been suggested that one-third to nearly half of pelvic serous carcinomas have the presence of tubal intraepithelial carcinoma in association. This leads to the belief that a subset of carcinomas which appear to be primary ovarian or peritoneal HGSCs may be of fallopian tube origin besides the invasive tubal carcinoma which arise from tubal intramucosal carcinoma. Therefore in the present study, we have tried to document the presence of precursor lesions of pelvic serous carcinoma, i.e., STIC,

Table 3 Characteristics of ovarian, peritoneal and tubal high-grade serous carcinoma

Factor	Ovarian	Tubal	Peritoneal	Total
Presence of ascites	24	2	1	27 (49.09%)
Malignant cells in ascitic fluid	4	0	1	5 (9.09%)
Omental deposits present	17	2	2	21 (38%)
Size of tumor ≤4 cm	11	1	2	14 (25.4%)
Size of tumor >4 ≤ 8 cm	36	3	2	38 (69.2%)
Size of tumor >8 cm	3	0	0	3 (5.4%)
Mostly solid in consistency	25	2	2	29 (53%)
Mostly cystic in consistency	9	0	0	9 (16%)
Mixed consistency	16	1	0	17 (31%)
FIGO stage I tumors	6	0	0	6 (11%)
FIGO stage II tumors	15	2	1	18 (33%)
FIGO stage III tumors	16	1	1	18 (33%)
FIGO stage IV tumors	13	0	0	13 (23%)
Occurrence of p53 signature	13	0	1	14 (25.45%)
Occurrence of TILT	10	0	0	10 (18.18%)
Occurrence of STIC	14	1	1	16 (29.09%)

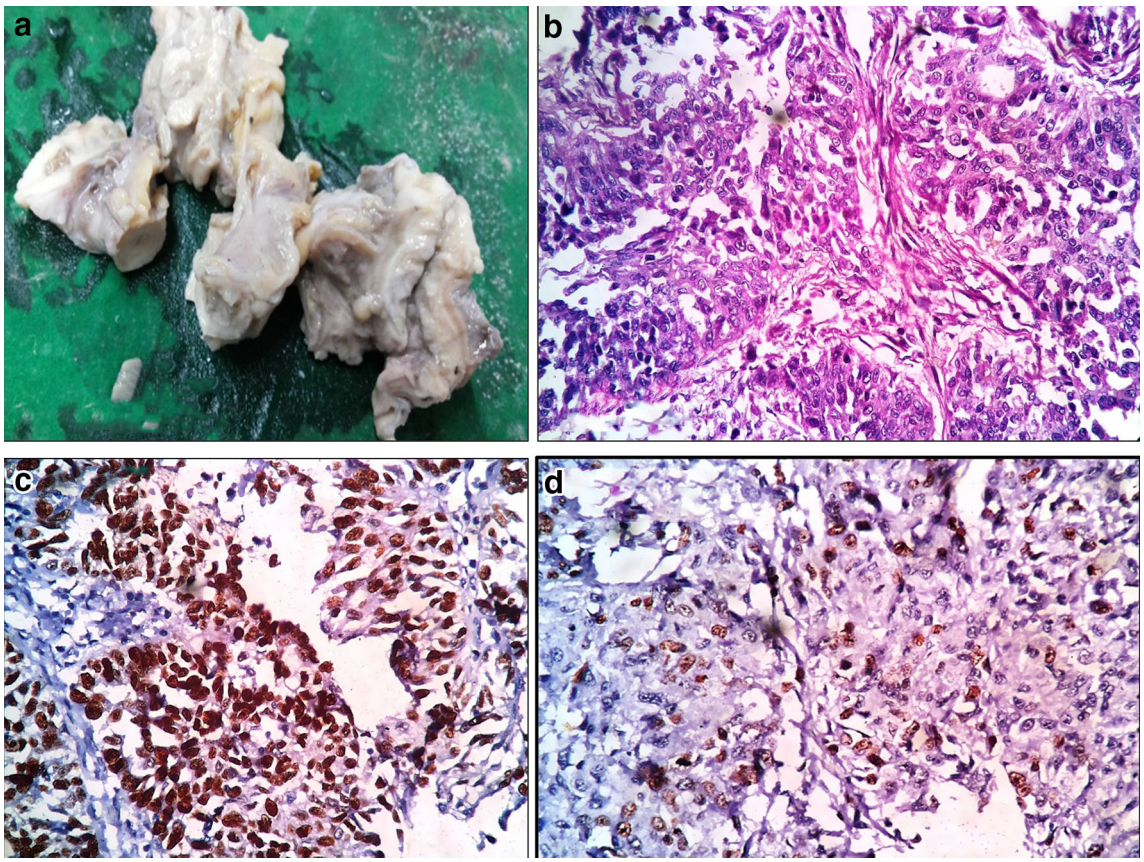

Fig. 3 **a–d** **a** Gross picture of tubal carcinoma, **b** H & E stain x400, **c** p53 IHCx400, **d** Ki67 IHCx400

TILT and p53 signature in a series of consecutive cases of ovarian, tubal and peritoneal carcinomas.

This study was conducted on 55 consecutive cases of high-grade pelvic serous carcinoma along with 21 low-grade ovarian serous carcinoma, 10 benign ovarian tumors and 10 normal ovaries removed for benign causes like adenomyosis, leiomyoma and endometrial polyps. Percentage of ovarian serous carcinoma out of total pelvic serous carcinomas was 90.9%, peritoneal carcinoma was 5.5%, and tubal carcinoma was 4.6%. Christopher G et al. studied 52 cases of pelvic non-uterine carcinomas and got ovarian origin in 37 (71%), peritoneal in 8 (15%) and tubal origin in 7 (13%) cases. Among the high-grade serous carcinomas (total number = 47), there were 33 (70.21%) ovarian, 8 (17.02%) primary peritoneal and 6 (12.77%) tubal type [16]. Kindelberger et al. [4] also studied 55 cases of pelvic serous carcinoma and divided them into two groups: those with TIC (41 cases) and those without it (14 cases). Forty-one cases of pelvic serous carcinoma comprised of 30 ovarian, 5 tubal and 6 peritoneal carcinoma, and out of 14 cases, there were 13 ovarian carcinoma and one peritoneal carcinoma. In the study of 300 gynecological malignancies done by Shangguo T et al. [17], 68 cases of HGSC were analyzed which comprised of 32 of ovarian, 28 endometrial, 7 peritoneal and one of cervical origin. Mittal et al. studied 32 high-grade pelvic serous carcinoma and found ovarian in 62.5% cases, tubal in 6.25% of cases, and peritoneal in 31.25% of cases as per existing criteria of WHO which changed later basing on revised criteria of origin of pelvic serous carcinoma [10, 11, 18]. In comparison, there is increased incidence of ovarian HGSC in this series which needs larger studies to establish it and also rigorous screening, prophylaxis and management protocols are necessary to reduce this high incidence in this region.

Out of 50 cases of ovarian HGSC, 13 (26%) showed p53 signature, 10 (20%) had TILT positivity and 14 (28%) were STIC positive. Tang et al. [17] had detected STIC in 6 out of 32 cases of HGSC of ovary and 2 out of 7 cases of PPC. Kindelberger et al. [4] detected STIC in 29 of 41 (71%) cases of pelvic serous carcinoma. This is comparable with our data as in present study precursor lesions were seen in 40 of 55 cases (72%). Tubal p53 signature was observed in 29 out of 75 (38%) cases of HGSC of ovary which is similar to our findings (26%). Above study showed p53 signature, TILT and STIC in 26, 20 and 28% in HGSC, 50, 0 and 50% in TC and 0, 0 and 33% in PPC, respectively. This observation is well supported by Leonhardt K et al. where frequency of p53 signature, TILT and STIC was

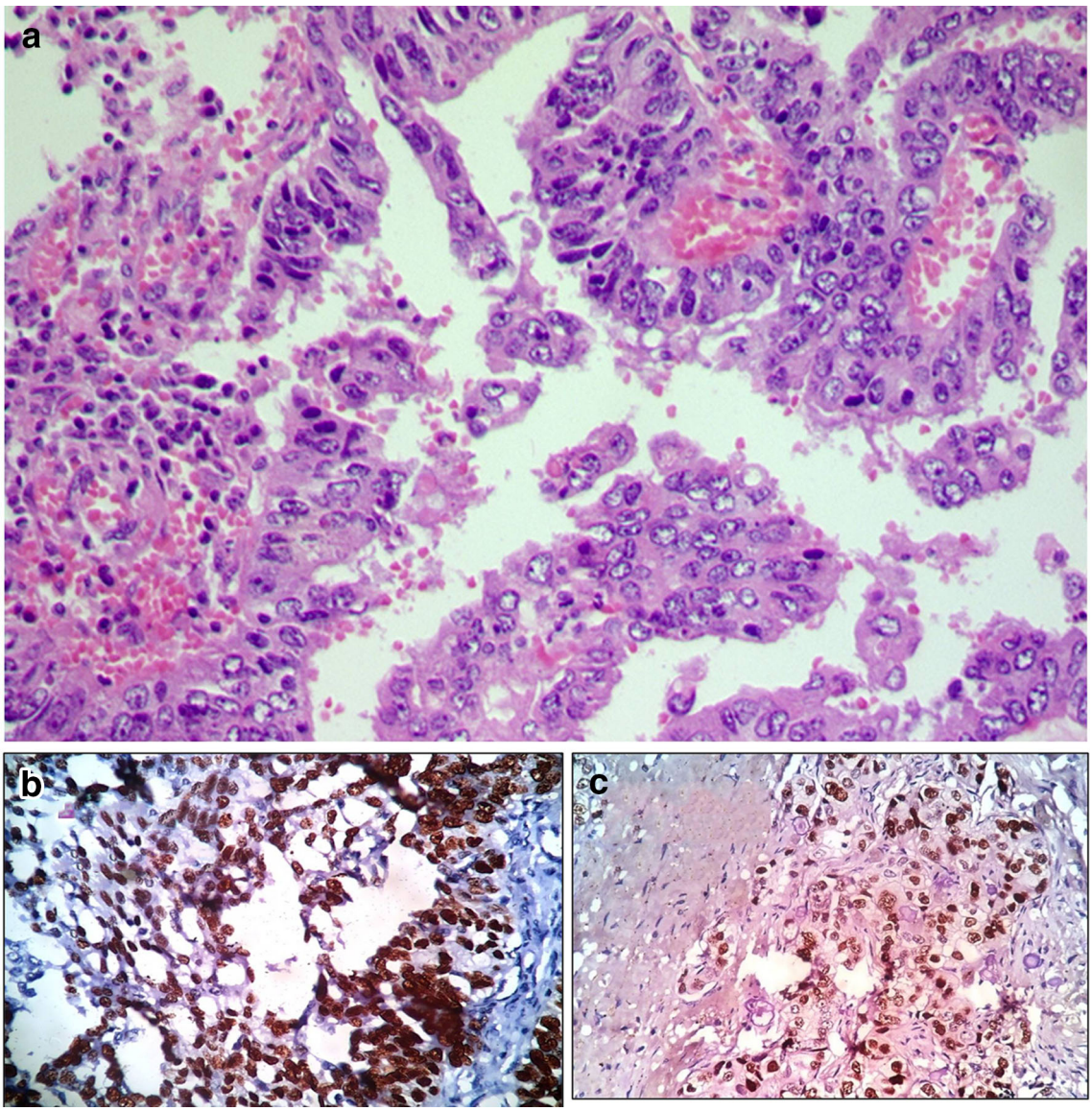

Fig. 4 **a–c** Primary peritoneal carcinoma. **a** H & E stain x400, **b** p53 IHCx400, **c** Ki67 IHCx400

35.7, 7.1 and 0% in cases of prophylactic BSO, 18.2%. 9.1% and 18.2% in TC and 11.1, 0 and 33.3% in PPC [19]. STIC was seen only in fimbrial end of tube which is supported by Mittal N et al. who also got in all cases of STIC [14]. Kindelberger et al. [4] and Przybycin et al. [16] got STIC in fimbrial end in 92–93% of patients. Laterality of TIC was more ipsilateral and unilateral with one-sided ovarian tumors and predominantly bilateral in bilateral ovarian tumors. This was also obtained in the study of Mittal et al. [18].

Statistically significant data (0.0351) were obtained when the tumor size was correlated with the presence of precursor lesions. Out of 40 cases having precursor lesions at their tubal end, 19 cases (9 cases STIC +ve, 7 cases TILT +ve and 3 cases p53 signature +ve) belonged to tumor size between 4 and 6 cms, that constitutes around 48%. Similarly in 11 cases (28%), tumor size was between 2 and 4 cms, followed by 8 cases (20%) in which size was between 6 and 8 cms. The association of tumor size with p53 signature positivity was statistically significant with a *p* value of 0.0351, but due to the small sample size it might be a biased value. So larger sample size should be taken to further evaluate its statistical significance. This finding was comparable with the study of Christopher et al. [16] who found that mean tumor size was 5.5 cms in 23 STIC +ve cases and 6.4 cms in 17 STIC -ve cases.

Correlation of grade of ovarian tumor with the presence of precursor lesions was done, and out of the 50 cases of

Table 4 Correlation of grade of ovarian tumor with the presence of precursor lesions

Ovarian lesions	Precursor lesions			
	Number of cases studied	"P53 signature" +ve cases(%)	TILT +ve cases (%)	STIC +ve cases (%)
Cases				
High-grade papillary serous carcinoma	50	13 (26%)	10 (20%)	14 (28%)
Controls				
Low-grade papillary serous carcinoma	20	2 (20%)	0 (0%)	0 (0%)
Benign adnexal tumors of ovary	10	0 (0%)	0 (0%)	0 (0%)
Normal ovaries	10	0 (0%)	(0%)	(0%)

high-grade ovarian carcinoma, 26% showed P^{53} signature positivity, 20% had TILT positivity and 28% were STIC positive. Out of the control cases, only two of low-grade ovarian serous carcinoma showed positivity for any precursor lesion, i.e., p53 (Table 4). Paired *t* test result between cases and controls for-P^{53} signature (p value = 0.0560) and TILT (p value = 0.0806) were not significant. But it was seen that STIC positivity was significantly associated with high-grade ovarian serous carcinoma cases (p value = 0.0474). Our finding was consistent with that of Tang et al. [17] who have mentioned that no STIC was identified among 90 cases of benign adnexal masses and in 15 cases of ovarian borderline tumors. They have found STIC in 6 (18.8%) out of 32 cases of high-grade ovarian serous carcinoma and in 2 (28.6%) out of 7 cases of peritoneal serous carcinoma. P53 signatures were detected in 29 of 75 cases (38%) of high-grade ovarian tumors and in none of the benign ovarian cysts studied by Folkins et al. [3]. Leonhardt et al. [19] had studied 14 cases of high-grade ovarian serous carcinoma and 10 cases of serous ovarian borderline tumor. According to their study, the frequency of p53 signature, TILT and STIC was 35.7, 7.1 and 0% in cases of high-grade tumors. None of the borderline tumors showed evidence of any precursor lesion. Singer et al. [20] also found p53 signature in 50.8% of high-grade tumors and in none of the low-grade and borderline tumors.

Correlating the tumor stage with the presence of precursor lesions, in the present study it was found that 24 (60%) out of the 40 precursor positive high-grade pelvic tumors were of stage III/IV in which 9 cases were p53 signature positive, 8 were TILT positive and 7 cases were STIC positive. Similarly, 11 (28%) out of 40 were of stage II and 5 (12%) were stage I tumors. However, no significant correlation was found between tumor stage and the presence of precursor lesions. Our study was in concordance with the study done by Gao et al. [21] who also found 94 stage III/IV tumors out of 116 cases (81%). Seidman et al. [22] found that patients with STIC were significantly more likely to have FIGO stage IV as compared to those without STIC (42 vs. 12.5%, respectively; $p = 0.037$). In the study by Reitsma et al. [23], most of the STIC positive cases were of FIGO stage I/II. These studies were all done in small sample size cases and have resulted in variation in findings. However, overall the findings suggest that there is no significant correlation between tumor stage and the presence of precursor lesions and needs larger sample size taken for more definitive results.

The mean age of presentation of PHGSC was 47 years with a standard deviation of 9.89 (47 ± 9.89). Reitsma et al. [23] studied cases ranging from 30 to 90 years and found median age to be 44 years. Leeper et al. [6] had studied 30 cases of ovarian HGSC with a mean age of 46 years (30–55 years). Majority (44%) of the ovarian tumors were bilateral at the time of presentation. This was in concordance with study of Gao et al. [21] in which 66% cases had bilateral adnexal masses, 20% were right sided and 14% left sided. High parity (para 2 in 36% women), premenopausal age group(58.1%), family history of pelvic carcinoma (53%), ascites at presentation (27 women) with demonstration of malignant cells in 5 patients most of which had ovarian HGSC, omental carcinomatous deposits (in 38% out of which 80.95% were ovarian HGSC) were observed during the study. But all of them were non-significant after paired *t* test. However, predominantly solid component of tumor (53%, p value 0.0093), mean tumor size ± SD of 4.97 ± 1.52 cm (p value 0.0329), higher staging (stage II/III) of high-grade pelvic tumors of (p value 0.0002) were found statistically significant. But it is not sure what message do these findings give and further research is necessary to substantiate these findings and utilize these data toward patient management and benefits.

Conclusion

Based on the results of this study and of multiple other studies reported in the literature, it can be concluded that TIC acts as a precursor lesion for most of the ovarian, fallopian tube and primary peritoneal HGSCs. Their similar

histogenesis has led to a common staging system in all the pelvic carcinomas (FIGO, Rome 2012) [24]. The current WHO, TNM and FIGO classification of serous carcinoma follows the similar staging system for tumors of the ovary, fallopian tube and peritoneum [19]. Also, according to the International Consortium for Cancer Reporting recommendations for reporting of ovarian, fallopian tube and primary peritoneal carcinoma, the histological sites of tumor involvement and the primary site of origin of tumor should be recorded as it is necessary for staging [25].

Thus, prophylactic salpingectomy while performing hysterectomy and doing fimbriectomy as opposed to tubal ligation for tubal sterilization can be adopted as a screening and preventive method for these lethal entities. These initiatives have already been taken at some places of the world, like Vancouver General Hospital and British Columbia Cancer Agency [15]; however, future clinical trials are necessary.

Strength

This study includes all types of non-uterine pelvic serous carcinomas with analysis and correlation with most of the demographic factors associated with these tumors. The cases are randomly selected, and chemotherapy treatment has been included as one of the variables. Strict criteria have been followed including IHC for diagnosis and confirmation of tubal precursor lesions. There are only a few studies which have evaluated sporadic pelvic serous carcinomas to document the involvement of the ovaries, tubes and the junctional epithelia by the putative precursor lesions.

Limitations of the Study

The small sample size may account for the discrepancies with other studies which have been observed during the comparison of various parameters.

- The BRCA mutation status of patients is not known. Due to economical constraints, BRCA1 and p53 mutation analysis could not be done in the patients, which would have helped us to characterize the tumors of familial and non-familial nature.

Acknowledgement We sincerely acknowledge the technical staff of S.C.B. Medical College, Cuttack, and AHRCC, Cuttack, for their effort and timely help.

Compliance with Ethical Standards

Conflict of interest All the authors express that there is no conflict of interest.

Ethical committee approval was obtained from 2 centers (1) Name of Institutional ethics committee (IEC)/Institutional review board (IRB)-Institutional ethics committee, S.C.B.Medical College, Cuttack, Orissa. Ethics Committee Regd. No. ERC/84/Inst/OR//2013 Issued under rule 122DD of the Drugs & Cosmetics Rules 1945. Ref.No-108 dated 22.11.2014. (2) Name of Institutional ethics committee (IEC)/Institutional review board (IRB)-Acharya Harihar Regional Cancer Centre Institutional ethics committee (AHRCC-IEC). Ethics Committee Regd. No. ERC/297/Inst/OR//2013 Issued under rule 122DD of the Drugs & Cosmetics Rules 1945. Ref.No-AHRCC-IEC/32 dated 25.11.2013.

Informed Consent Informed consent—taken.

Human and Animal Consent Animal studies should be clearly indicated—not done.

References

1. Crum CP. Intercepting pelvic cancer in the distal fallopian tube: theories and realities. Mol Oncol. 2009;3:165–70.
2. Herrington CS, Mc Cluggage WG. The emerging role of the distal Fallopian tube and p53 in pelvic serous carcinogenesis. J Pathol. 2010;220:5–6.
3. Folkins AK, Jarboe EA, Roh MH, et al. Precursors to pelvic serous carcinoma and their clinical implications. Gynecol Oncol. 2009;113:391–6.
4. Kindelberger DW, 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.
5. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 2007;25:3985–90.
6. Leeper K, Garcia R, Swisher E, et al. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecol Oncol. 2002;87:52–6.
7. 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.
8. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingooophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol. 2005;23:127–32.
9. Jarboe E, Folkins A, Nucci MR, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. Int J Gynecol Pathol. 2008;27:1–9.
10. Benedet JL, Ngan HYS, Hacker NF. For the FIGO committee on gynecologic oncology staging classifications and clinical practice guidelines of gynecologic cancers. Int J Gynecol Obstet. 2000;70:209–62.
11. Lee KR, Tavassoli FA, Prat J, et al. Surface epithelial–stromal tumors. In: Tavassoli FA, Deville P, editors. World Health Organization classification of tumors pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003. p. 117–45.
12. 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.
13. 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.
14. Crum CP, Drapkin R, Kindelberger D, et al. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res. 2007;5:35–44.

15. Vang R, Shih I, Kurman RJ. Fallopian tube precursors of ovarian low- and high-grade serous neoplasms. Histopathology. 2013;62:44–58.
16. Przybycin CG, Kurman RJ, Ronnett BM, et al. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol. 2010;34:1407–16.
17. Tang S, Onuma K, Deb P, et al. Frequency of serous tubal intraepithelial carcinoma in various gynecologic malignancies: a study of 300 consecutive cases. Int J Gynecol Pathol. 2012;31(2):103–10.
18. Mittal N, Srinivasan R, Gupta N, et al. Secretory cell outgrowths, p53 signatures, and serous tubal intraepithelial carcinoma in the fallopian tubes of patients with sporadic pelvic serous carcinoma. Indian J Pathol Microbiol. 2016;59:481–8.
19. Leonhardt K, Einenkel J, Sohr S, et al. 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.
20. Singer G, Sto R, Cope L, et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis. Am J Surg Pathol. 2005;29:218–24.
21. Gao F, Bhargava R, Yang H, et al. Clinicopathologic study of serous tubal intraepithelial carcinoma with invasive carcinoma: Is serous tubal intraepithelial carcinoma a reliable feature for determining the organ of origin? Hum Pathol. 2013;44:1534–43.
22. Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. Gynecol Oncol. 2011;120:470–3.
23. Reitsma W, de Bock GH, Oosterwijk JC, et al. Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. Eur J Cancer. 2013;49:132–41.
24. Jaime P, FIGO Committee on Gynecological Oncology. FIGO's staging classification for cancer of ovary, fallopian tube and peritoneum: abridged republication. J Gynecol Oncol. 2015;26:87–9.
25. McCluggage WG, Judge MJ, Clarke BA, et al. Data set for reporting of ovarian, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). Mod Pathol. 2015;28:1101–22.