Expression of Estrogen Receptor and Progesterone Receptor in Malignant Epithelial Ovarian Tumors

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Abstract

Background: Malignant epithelial ovarian tumors are a significant cause of cancer-related deaths in women. The expression of estrogen and progesterone receptors (ER and PR) in these tumors has been studied extensively, as they play a critical role in the pathogenesis and treatment of ovarian cancer. ER and PR expression levels in ovarian tumors can impact treatment decisions and patient outcomes. Therefore, understanding the frequency and distribution of ER and PR expression in different types of ovarian tumors is crucial in improving patient care.

Method: This cross-sectional observational study was conducted at the Department of Pathology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. The study duration was 2 years, from January 2018 to December 2019. During this period, a total of 45 adult female patients with histopathologically diagnosed malignant epithelial ovarian tumors by H&E staging were selected for the study.

Results: In this study, the majority of participants were aged 41-60 years and reported irregular menstrual cycles or being post-menopausal. Most were nulliparous, and the mean CA125 level was 149.51. Serous cystadenocarcinoma was the most common diagnosis (68.89%). ER was positive in 51.11% of cases, with a higher proportion in serous cystadenocarcinoma (64.52%) compared to mucinous cystadenocarcinoma. PR was positive in 80% of cases, with the highest proportion in endometrioid carcinoma (50%). ER expression was significantly higher in serous tumors compared to non-serous tumors (p=0.002), but the association between tumor type and PR expression was not significant (p=0.192).

Conclusion: The study found that the majority of participants were aged 41-60 years, had irregular menstrual cycles, or were post-menopausal. Serous cystadenocarcinoma was the most common diagnosis. A significant difference in ER positivity was observed between serous and mucinous cystadenocarcinoma, as well as other subtypes. PR positivity was observed in the majority of participants, but no significant association was observed with histopathological subtypes or serous types.

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Introduction

Ovarian cancer is the deadliest gynecological malignancy among women, accounting for a significant proportion of cancer diagnoses and deaths worldwide. According to the World Ovarian Cancer Coalition (2018) and Globocan estimates, ovarian cancer was responsible for 7.1% of all new cancer diagnoses and 4.1% of all cancer deaths in women in 2020.[1,2] In Bangladesh, ovarian cancer accounted for 2% of cancer-related deaths in 2018.[3] The median age of ovarian cancer diagnosis is 63 years, and this older age is associated with more advanced disease and lower survival rates.[4] Various factors, such as geography, ethnicity, and economic development, contribute to the different distribution of ovarian cancer occurrence worldwide. The most common risk factors for ovarian cancer include age, marital status, menstrual history, obstetric history, hormonal status, and family history.[5] Ovarian malignancies arise primarily from the ovarian surface epithelium (OSE), which is a single layer of epithelial cells that lines the ovary. Approximately 90% of ovarian malignancies originate from the epithelial layer, while other possible sites of origin include the fallopian tube epithelium and peritoneal mesothelium.[6] In epithelial ovarian tumors, hormones and growth factors play a crucial role in regulating cell proliferation, differentiation, and apoptosis. The dysregulation of these processes allows cells with mutations in proto-oncogenes and tumor suppressor genes to survive and expand clonally. Pituitary gonadotropins, such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), androgens, estrogens, progesterones, and insulin-like growth factor I (IGF-I) have all been implicated in ovarian cancer development.[7] The secretion of steroid hormones, estrogen and progesterone, from the ovaries is associated with the pathogenesis of malignancies, including breast, endometrial, and ovarian cancers.[8] There is a strong association between the pathogenesis and progression of ovarian cancer and estrogen.[9] After binding to their specific receptors (estrogen receptor, ER and progesterone receptor, PR), estrogen promotes the physiological actions of cell survival and proliferation. ER expression in human epithelial ovarian carcinoma varies, and ER-positive cases are higher in malignant and borderline tumors compared to benign tumors.[10,11] On the other hand, progesterone plays a critical role in follicle maturation and works in concert with estrogen to promote ovulation and the formation of the corpus luteum. Increased PR expression is associated with a better survival rate for epithelial ovarian cancer and PR-positive cases are higher in borderline tumors compared to malignant tumors.[11,12] However, some studies have suggested that ER and PR positivity in epithelial ovarian cancer is associated with better clinical outcomes.[10] Despite the conflicting results, identifying the expression of estrogen and progesterone receptors in malignant epithelial ovarian tumors is important for several reasons. Furthermore, knowledge of the hormone receptor status of the tumor can help guide treatment decisions, such as the choice of hormone therapy or targeted therapy.

Objectives

We aimed to investigate the expression of estrogen and progesterone receptors in malignant epithelial ovarian tumors. Our findings might be able to contribute to a better understanding of the biology of ovarian cancer.

Methods

This cross-sectional observational study was conducted at the Department of Pathology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. The study duration was 2 years, from January 2018 to

December 2019. During this period, a total of 45 adult female patients with histopathologically diagnosed malignant epithelial ovarian tumors were selected for the study. Any patients being treated with radiotherapy or chemotherapy, and patients declining consent were excluded from the study. Informed written consent was obtained from each participant, and ethical approval was also obtained from the ethical review committee of the study hospital prior to data collection. Participants were ensured complete anonymity and the right to withdraw from the study at any time. Estrogen Receptor (ER) and Progesterone Receptor (PR) immunostained sections were examined under light microscope. ER and PR-positive cells were subjected to manual counting. ER, PR expression was evaluated by the Allred system of scoring (semi-quantitative method).[13,14] Data was collected using a premade data collection sheet, and statistical analysis was done by using Fisher's Exact test, with a 95% confidence interval and a p-value of <0.05 was considered significant.

Results

The mean age of the participants was 51.29 years, and the age range was from 35 to 70 years. Most participants were aged 41-60 years, with 73.33% reporting irregular menstrual cycles and 24.44% being post-menopausal. The mean age at menarche was 10.86 years, with 71.11% having an age at menarche of >10 years old. The majority of participants (86.67%) were nulliparous, and only 13.33% reported being multiparous. The mean CA-125 level was 149.51, and 88.89% of the participants had a level in the range of 101-299.

Table I: Distribution of participants by baseline characteristics (n=45)

Variables	Frequency	Percentage
Age		
≤40	4	8.89%
41-50	21	46.67%
51-60	15	33.33%
61-70	5	11.11%
Mean±SD	51.29±7.9	
Range(min-max)	(35-70)	
Menstrual Status		
Regular	1	2.22%
Irregular	33	73.33%
Post-menopausal	11	24.44%
Age at Menarche		
≤10	13	28.89%
>10	32	71.11%
Mean±SD	10.8 6±0.91	
Range(min-max)	(9 -13)	
Parity		
Nulliparity	39	86.67%
Multiparity	6	13.33%
CA-125 level		
61-100	5	11.11%
101-299	40	88.89%
Mean±SD	149.51±42.58	
Range (min-max)	(80-250)	

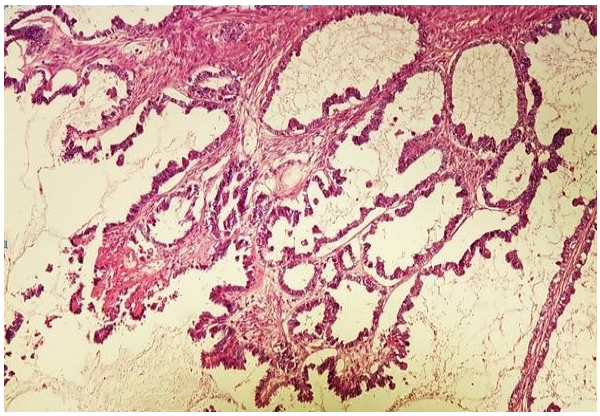

Figure 1. Photograph showing a case of histopathological section of papillary serous cystadenocarcinoma (H & E X 10x)

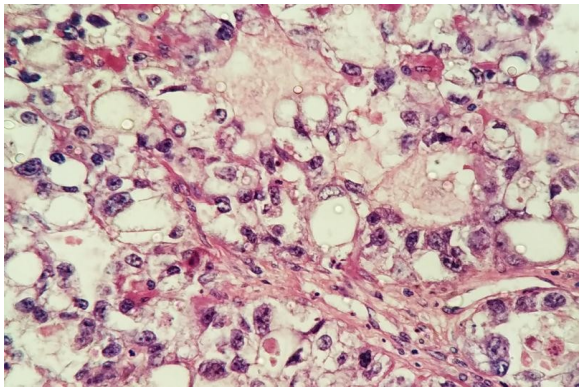

Figure 2. Photomicrograph showing histopathological section of serous cystadenocarcinoma (Grade-3). (H & E X 40X)

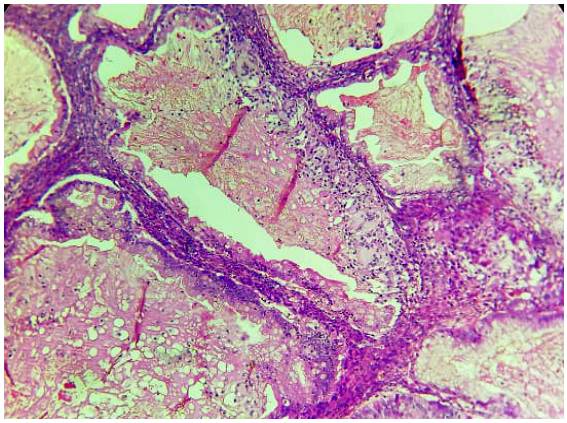

Figure 3. Photograph showing a case of histopathological section of mucinous cystadenocarcinoma (H & E X 10x)

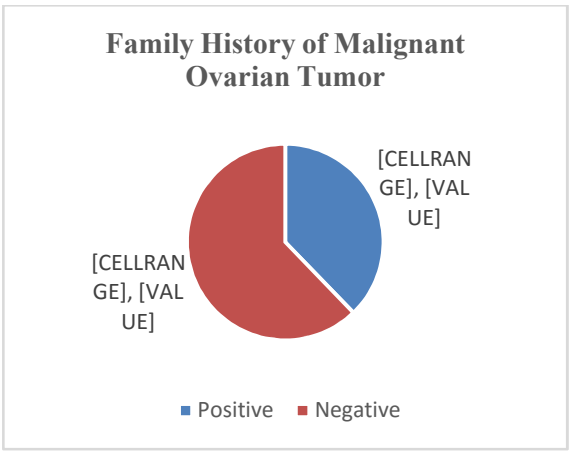

Figure 4. Family History of malignant ovarian tumor (n=45)

Among the participants of the present study, 37.78% of the participants had a family history of malignant ovarian tumor, while 62.22% of participants had no such family history.

Table II: Distribution of the study patients according to histopathological diagnosis (n=45)

Histopathological Diagnosis	Frequency	Percentage
Serous Cystadenocarcinoma	31	68.89%
Mucinous Cystadenocarcinoma	8	17.78%
Endometrioid Carcinoma	4	8.89%
Clear Cell Carcinoma	2	4.44%

Out of the total number of cases, 31 (68.89%) were diagnosed with serous cystadenocarcinoma, 8 (17.78%) with mucinous cystadenocarcinoma, 4 (8.89%) with endometrioid carcinoma, and 2 (4.44%) with clear cell carcinoma.

Table III: Distribution of the study patients according to USG finding (n=45)

USG Findings	Frequency	Percentage
Complex adnexal mass	25	55.56%
Multiloculated cystic lesion	4	8.89%
Solid mass	16	35.56%

Among the patients, 55.56% had a complex adnexal mass, 35.56% had a solid mass, and 8.89% had a multiloculated cystic lesion.

Table IV: Distribution of the study patients with ascites (n=45)

Ascites	Frequency	Percentage
Absent	32	71.11%
Present (Malignant Cell positive)	10	22.22%
Present (Malignant Cell Negative)	3	6.67%

Out of the 45 participants, ascites was absent in 32 (71.11%) of them, while it was present in 13 (28.89%) participants. Of those with ascites, 10 (22.22%) had malignant cells detected in the ascitic fluid and 3 (6.67%) had no malignant cells detected.

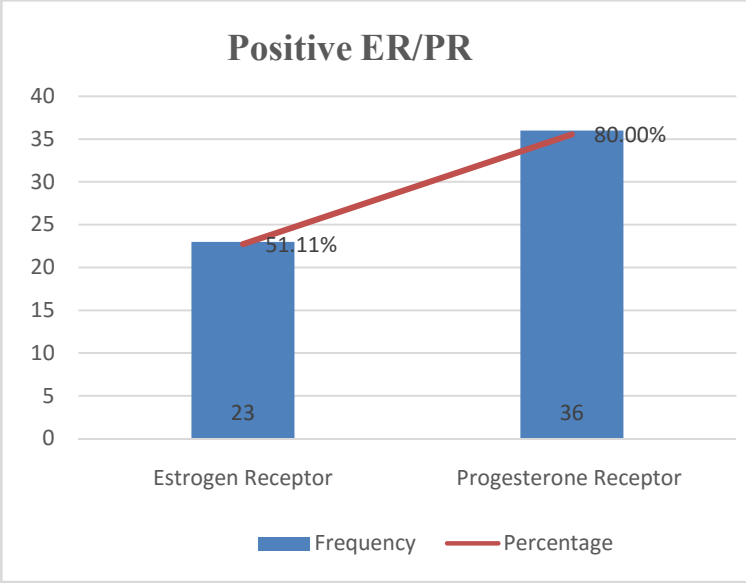

Figure 5. Prevalence of Estrogen and Progesterone receptor expression among participants (n=45)

Out of the 45 participants, 23 (51.11%) were positive for ER, while 36 (80.00%) were positive for PR.

Table V: Distribution of the different histopathological diagnoses according to estrogen receptor (ER) status (n=45)

Estrogen receptor (ER)	Serous cystadAAFAAWenocarcinoma (n=31)		Mucinous cystadenocarcinoma (n=8)		Endometrioid carcinoma (n=4)		Clear cell carcinoma (n=2)		P value
	n	%	n	%	n	%	n	%	
Positive	20	64.52%	0	0.00%	2	50.00%	0	0.00%	0.001s
Negative	11	35.48%	8	100.00%	2	50.00%	2	100.00%	

Among the 31 cases of serous cystadenocarcinoma, 20 (64.52%) were positive for ER, while none of the 8 cases of mucinous cystadenocarcinoma were positive. For the 4 cases of endometrioid carcinoma, 2 (50.00%) were positive, and for the 2 cases of clear cell carcinoma, none were positive for ER. The difference in ER positivity between serous and mucinous cystadenocarcinoma, as well as other subtypes was statistically significant (P=0.001).

Table VII: Distribution of the different histopathological diagnoses according to progesterone receptor (PR) status (n=45)

Progesterone receptor (PR)	Serous cystadenocarcinoma (n=31)		Mucinous cystadenocarcinoma (n=8)		Endometrioid carcinoma (n=4)		Clear cell carcinoma (n=2)		P-value
	n	%	n	%	n	%	n	%	
Positive	5	16.13%	2	25.00%	2	50.00%	0	0.00%	0.303ns
Negative	26	83.87%	6	75.00%	2	50.00%	2	100.00 %	

The results indicate that the percentage of patients with positive PR status was highest in endometrioid carcinoma (50%) followed by mucinous cystadenocarcinoma (25%) and serous cystadenocarcinoma (16.13%), with no patients with clear cell carcinoma having positive PR status. However, the P-value of 0.303 suggests that this difference is not statistically significant.

Table VII: Correlation of estrogen receptor (ER) expression with serous and non-serous tumor type (n=45)

Tumor type	Positive ER (n=22)		Negative ER (n=23)		P value
	N	%	N	%	
Serous	20	90.91%	11	47.83%	0.002s
Non-serous	2	9.09%	12	52.17%	

Among the 45 cases studied, 22 (48.89%) had positive ER expression, while 23 (51.11%) had negative ER expression. The majority of patients with serous tumors (90.91%) had positive ER expression, while less than half of the patients with non-serous tumors (9.09%) had positive ER expression. The difference between the two groups was statistically significant, with a p-value of 0.002.

Table VIII: Correlation of progesterone receptor (PR) expression with serous and non-serous tumor type (n=45)

Tumor type	Positive PR (n=9)		Negative PR (n=36)		P value
	N	%	n	%	
Serous	5	55.56%	26	72.22%	0.192ns
Non serous	4	44.44%	10	27.78%	

Of the total 45 patients, 9 (20%) showed positive PR expression while 36 (80%) showed negative expression. Among the serous tumor types, 5 patients (55.56%) had positive PR expression, whereas 26 patients (72.22%) had negative expression. Among the non-serous tumor types, 4 patients (44.44%) had positive PR expression, while 10 patients (27.78%) had negative expression. However, the association between tumor type and PR expression was not found to be statistically significant (P value = 0.192, not significant).

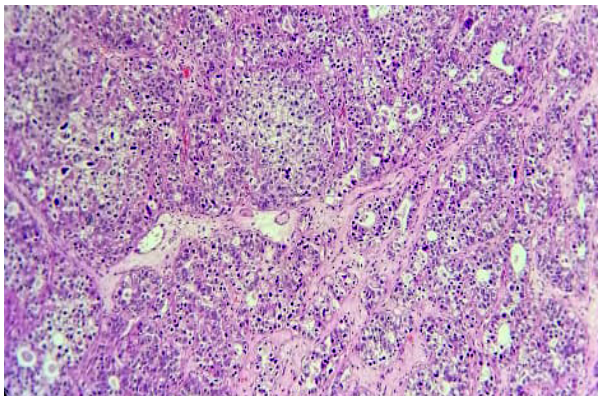

Figure 6. Photograph showing a case of the histopathological section of clear cell carcinoma (Grade 2) (H & E X 10x)

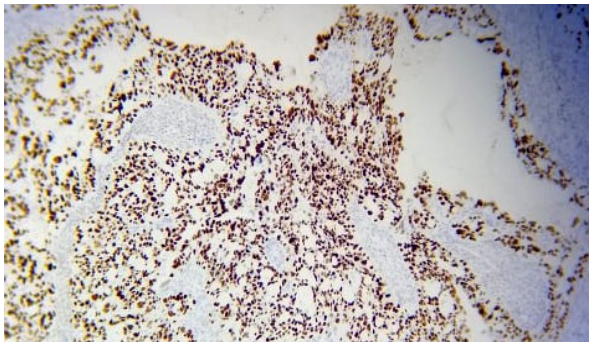

Figure 7. Photograph showing positive ER expression in serous cystadenocarcinoma (H & E X 10x)

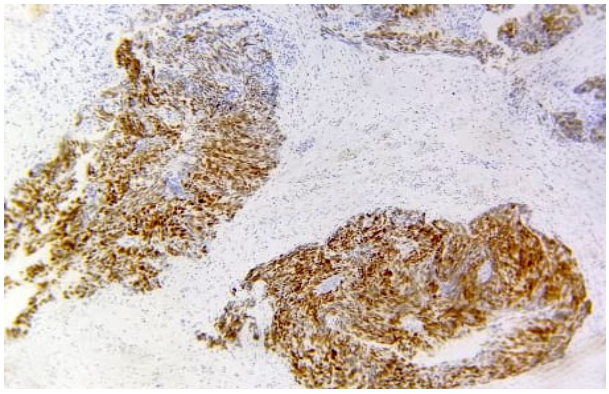

Figure 8. Photograph showing positive PR expression in serous cystadenocarcinoma (H & E X 10x)

Discussion

Currently, debulking surgery and platinum-based chemotherapy are the mainstays of ovarian cancer treatment. In spite of this optimal therapy, 5-year survival in stage III and IV is only 18-47%.[1] Recurrence is common problem after complete remission. Therefore, a need for more effective therapy such as hormonal therapy would be appealing in this setting.[16] The epidemiological evidence strongly suggests the steroid hormones, primarily estrogen and progesterone are implicated in carcinogenesis of epithelial ovarian tumors.[17] The present study focused on such hormones and their expression in patients with malignant epithelial ovarian tumor. In this study, most of patients (21, 46.7%) belonged to age 41-50 years. The mean age was 51.29±7.91 years. Advancing age is recognized as a risk factor for this malignancy, as majority of studies have found patients suffering from this ailment to be over 40 years of age.[17,18] Regarding menstrual status, it was observed that 71.1% patients were post-menopausal, which is considered as a high-risk marker for ovarian cancer, observed in the findings of other studies.[20,21] Higher incidence of malignant tumors were found in naliparous women in this study. Cirlio PM et al., also found association of ovarian cancer with nulliparity.[20] In the present study, the mean CA125 was significantly higher in patients with malignant tumors (149.51±42.58U/ml) compared to non-malignant cases. This finding was consistent with a previous study by Chen et al., where the mean CA125 level in malignant tumors was 184.62 U/ml.[23] Family history is a significant risk factor for ovarian cancer, as it can be hereditary in nature. In fact, around 5% to 10% of ovarian cancer cases are attributed to family cancer syndromes.[4] In the current study, 17 out of the total participants with malignant ovarian tumors (37.8%) had a positive family history of ovarian cancer. According to histopathological diagnosis, it

was observed that the majority of the patients had serous cystadenocarcinoma (51.67%), followed by mucinous cystadenocarcinoma (13.3%), endometrioid carcinoma (6.7%), and clear cell carcinoma (3.3%). This high prevalence of serous neoplasm was supported by the findings of other studies.[24] In terms of USG findings, 55.5% of the study patients had complex adnexal mass, 35.7% had solid mass, and 8.8% had multiloculated cystic lesion. Van Nagell JR et al., also found same findings, similar with this study.[25] The result of cytological examination of ascitic fluid is an important parameter and positive cytological finding represents an important predictive factor in diagnosis and recurrence. In the present study, 13 patients (28.9%) had ascites and among them 10 (22.22%) had malignant cells in ascitic fluid. Sangisetty et al., also found similar finding with present study.[29] Among the 45 patients of the present study, 23 patients were ER positive, and 36 patients were PR positive. In the present study, the expression of estrogen receptor (ER) was analyzed and it was observed that 64.5% of patients with serous carcinoma and 50% of patients with endometrioid carcinoma showed ER positivity.

However, none of the patients with mucinous carcinoma and clear cell carcinoma exhibited ER positivity. This difference in ER expression among various histopathological types was statistically significant with a p-value of 0.001. These findings support the previous studies that have also shown an association between ER and ovarian cancer.[30,31] The study findings on progesterone receptor expression showed that 5 (16.13%) patients with serous carcinoma, 2(25%) patients with mucinous carcinoma, and 2 (50%) patients with endometrioid carcinoma had PR positivity, while none of the clear cell carcinoma patients showed PR positivity. However, the difference was statistically not significant (p=0.303). Tangjitgamol S et al., also found this non significance finding with present study[28]. The study examined the distribution of patients according to serous and non-serous types and their correlation with estrogen and progesterone receptor expression. Among the serous carcinoma patients, 20 (90.9%) were estrogen receptor positive, while only 2 (9.1%) from the non-serous type were positive. The difference was statistically significant (p=0.002). For progesterone receptor expression, 5 (55.6%) patients with serous carcinoma and 4 (44.4%) with non-serous carcinoma had positivity, but the difference was not statistically significant (p=0.192). Similar findings were reported by Tangjitgamol S et al., which found no significant correlation between progesterone receptor expression and serous, non-serous tumor types.[28] Tangjitgamol S et al., also found estrogen receptor expression significantly higher in patients with serous carcinoma, while no significant difference was found for progesterone receptor expression.[28]

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion

The study found that the majority of participants were aged 41-60 years, had irregular menstrual cycles, or were post-menopausal. Serous cystadenocarcinoma was the most common diagnosis. A significant difference in ER positivity was observed between serous and mucinous cystadenocarcinoma, as well as other subtypes. PR positivity was observed in the majority of participants, but no significant association was observed with histopathological subtypes or serous types.

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