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Estrogen and Progesterone Receptor Expression in Surface Epithelial Ovarian Tumors and Their Clinicopathological Correlation: A Cross-Sectional Study in Tertiary Care Hospital of Northern India

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ABSTRACT

Background: Ovarian tumors pose major health problem among women worldwide. Ovaries being a source of estrogen and progesterone are also the targets for these hormones. Therefore, Estrogen and Progesterone receptors are considered to be involved in the ovarian carcinogenesis.
Aim: To study ER, PR expression in surface epithelial ovarian tumors and their clinicopathological correlation.
Methods: The present study was conducted on 50 cases of ovarian tumors, 31 benign and 19 malignant. Estrogen and progesterone expression was studied by immunohistochemistry and correlated with various clinicopathological parameters such as, menopausal status, histological type, WHO grade and FIGO stage.
Results: In total, ER expression was seen in 22 (44%) and PR expression was seen in 19 (38%) cases. Out of 50 cases, 26 (52%) were ER, PR negative, 17 (34%) were ER, PR positive, 10% were ER positive, PR negative and 4% were PR positive, ER negative. There was a statistically significant ER expression in malignant tumors (p value <0.05) in comparison to benign and borderline tumors. Among histological type, ER, PR expression was higher in serous and high grade tumors which was statistically significant (p value <0.05). No significant association was found among ER, PR expression and age, menopausal status, grade and FIGO stage. Therefore, identification of these biological prognostic markers can help to select patients for endocrine therapy and to improve treatment planning.

Key words: Estrogen Receptor, Progesterone Receptor, Ovarian tumors, Immunohisto-chemistry, FIGO stage.

INTRODUCTION

Ovarian tumours are one of the major health problems among women globally. [1] A female at any time in her life has 6-7% risk of ovarian tumor, 1.5% risk of ovarian cancer and 1% mortality due to ovarian cancer. [2] Increasing age, early menarche, late menopause, nulliparity and delayed child bearing are associated with increased risk of ovarian cancer. [3] Cytosolic oestrogen and progesterone receptors are present in many organs including the breasts, endometrium, myometrium, cervix, fallopian tubes and ovaries. The ovaries in addition to being a source of estrogens and progesterone are also the targets for these hormones. [4] Since patients with similar clinicopathological characteristics experience different clinical outcome [5] therefore identification of biological factors (Estrogen and

progesterone receptor) related to tumor aggressiveness is relevant in order to identify high risk patients needing more aggressive therapy and a closer follow up. [6] The aim of the present study is to evaluate ER, PR expression in surface epithelial ovarian tumours and its correlation with various clinicopathological parameters.

MATERIAL AND METHODS

A hospital based cross sectional study was conducted on 60 specimens of ovarian neoplasms received in the Department of Pathology, Indira Gandhi Medical College, Shimla. Metastatic ovarian neoplasms were excluded. Relevant clinical details including age, menopausal status and FIGO stage were obtained from patient's records. The specimens were grossed and the sections were immersed in 10% neutral buffered formalin for 24-48 hrs. The tissue was processed manually, paraffin embedded and 2-3 microns thick sections were cut and stained with Haematoxylin & Eosin stain.

Immunohistochemical staining:

Representative sections that had an adequate area of cancer cells were selected for ER, PR staining. 3-4 microns thin sections were mounted on poly-1-lysine coated slides. Slides were placed in fully automated IHC machine, where the slides were heated at 80 degree Celsius for 15-20 minutes. De waxing was done for 3 cycles of 3 minutes each and washed with IHC buffer solution. Antigen retrieval was done by applying micro reagent: EZAR 2 (HX0032) for ER and PR, the slides were heated to 80 degree Celsius for 20-25 minutes and were washed with IHC buffer. Peroxide block was applied (HX0026) and the slides were incubated for about 10 minutes. Antibody was added for ER/PR. Slides were heated, incubated at 37 deg Celsius for 1 hour and washed with IHC buffer and deionised water. Polymer HRP was added to slides will be heated at 30 degree Celsius and incubated for 30 minutes. DAB working solution was added; slides were incubated for 8-10 minutes and then washed with deionised water and IHC buffer. Counter staining was done with haematoxylin and slides incubated for 5 minutes, then washed with deionised water and IHC buffer. Mounting was done using DPX. Positive control sections were taken from breast carcinoma and negative controls were provided by omission of primary antibody. At least ten random high-power fields were counted with a minimum of 1000 cells. Original H & E sections were reviewed in conjunction with the immunohistochemical stained section to obtain the final results. Allred scoring system was used for ER PR. Score 0-5 is given to the cells depending on the proportion of cells which are stained (proportion score [PS]) and score 0-3 is given depending on the intensity of staining (intensity score [IS]). By adding the PS and IS, we calculated the final Allred score (PS + IS = AS). Total score 0 to 2 was taken as negative and >=3 was taken as positive.

Data was entered in Microsoft Excel spreadsheet, cleaned for errors and analyzed using Epi Info software version 7.0. Quantitative variables were presented as means and their standard deviations. Qualitative variables were presented as proportions and their 95% confidence intervals. Chi square test were used for significance testing of qualitative variables. A two-sided p-value of < 0.05 was taken as statistically significant.

RESULTS

Clinical and Histological Data:

Age of the patients varied from 11-90 years with mean age of 50.5 $\pm$ 16.3 years. Most of the patients (38%) were in the 18- 39 years age group followed by 34% in 40-59 years and 28% in $\geq$60years. Of these 36% were premenopausal followed by perimenopausal and menopausal (32% each). Unilateral ovarian tumors were more common (68%) in comparison to bilateral ovarian tumors (32%) in the present study. Gross morphology of the ovarian tumors revealed 56% cystic tumors, 8% solid and 36% with both solid and cystic character.

However, uniloculated and multiloculated cysts were equal in number, 50% each.

On histological examination, majority of epithelial ovarian tumors were benign (54%), followed by malignant tumors (38%) and borderline tumors (8%).There was no significant difference in the Mean age of benign (40.4± 13.2 years) and borderline tumors (39±8.6 years), however the mean age of malignant ovarian tumors (60.9±13.5years) was significantly higher (p<0.001) in comparison to benign and borderline tumors. Out of 50 cases, majority were FIGO stage III (42.1%), followed by stage I (26.3%), stage II (21.1%), and stage IV (10.5%) tumors.

Table 1:- Clinical profile of patients (n=50)

Parameters	Number	Percentage (%)	95% CI
Menopausal status			
Premenopausal(<40 years)	18	36	22.9-50.8
Perimenopausal(40-55)	16	32	19.5-46.7
Menopausal(>55)	16	32	19.5-46.7
Laterality			
Unilateral	34	68	53.3-80.5
Bilateral	16	32	19.5-46.7
Tumor Type			
Benign	27	54	39.3-68.2
Borderline	4	8	2.2-19.2
Malignant	19	38	24.7-52.8
Figo stage			
I	5	26.3	9.1-51.2
II	4	21.1	6.0-45.6
III	8	42.1	20.2-66.5
IV	2	10.5	1.3-33.1

Histologically, the most common tumors were serous tumors followed by mucinous tumors. Among serous tumors, benign serous cystadenoma were most common (26%) followed by 22% of serous carcinoma (malignant) and one case of APST (borderline). Among the mucinous tumors, mucinous cystadenomas (benign) were most common followed by (20%), mucinous carcinomas constituting 10% and APMT (6%). Other tumors included endometrioid carcinoma (4%), Brenner tumor (4%) and Clear cell carcinoma (2%). Among malignant surface epithelial tumors 84.2% were high grade while 15.8% were low grade.

Immunohistochemistry:

In total, ER expression was seen in 22 (44%) and PR expression was seen in 19 (38%) cases. Out of 50 cases, 26 (52%) were ER, PR negative, 17 (34%) were ER, PR positive, 10% were ER positive, PR negative and 4% were PR positive, ER negative. There was a statistically significant ER expression in malignant tumors (p value <0.05) in comparison to benign and borderline tumors. ER expression was higher in postmenopausal women, and PR expression was higher in premenopausal women, while both ER, PR expression was higher in malignant, serous and high grade tumors. Among histological type, ER, PR expression was significantly higher in serous tumors (<0.05). Statistical analysis showed no correlation between ER, PR expression and age, menopausal status, grade and FIGO stage (p value >0.05).

Table 2: - Correlation of ER, PR Expression with clinical parameters (n = 50)

Variable	ER expression (%)	P value	PR expression (%)	p value
Menopausal status (n=50)				
1.Pre & peri menopausal	14 (41.8)	0.778	13 (38.2)	1.000
2.Post menopausal	8 (50.0)		6 (37.5)	
Tumour Type (n=50)				
1.Benign & Borderline	10 (32.3)	0.043	11 (35.5)	0.866
2.Malignant	12 (63.2)		8 (42.1)	
Figo stage (n=19)				
1 1. I & II	6 (66.7)	1.000	6 (66.7)	0.111
2. III & IV	6 (60.0)		2 (20.0)	
Histological type				
1.Serous tumors	19 (76)	0.000	17 (68)	0.000
2.Non serous tumors	3 (12)		2 (8)	
Grade (n=19)				
1.Low	1 (33.3)	0.523	1 (33.3)	1.000
2.High	11 (68.7)		7 (43.7)	

DISCUSSION

Ovarian cancer is the fourth most common cause of cancer-related death in women, with 30-40% overall survival at 5 years. [7] Majority of patients with ovarian cancer present with advanced disease, so the treatment options at presentation are confined to a combination of debulking surgery and platinum-based chemotherapy, which are only partially effective. [8] Increasing age, early menarche, late menopause, nulliparity and delayed child bearing are associated with increased risk of ovarian cancer. [9]

In the present study, patient's age varied from 18-90 years with mean 50.5±16.3 years. Maximum numbers of patients were in 18-39 years of age group (38%). These observations are concordant with that of Manker et al [10] and Rao NK et al. [11] Benign tumors were more common (54%) followed by malignant tumors (38%) as is also evident from various published studies. [12,13] Higher ER expression (42.1%) than PR (35.5%) in patients >40 years of age is similar to Kaur J et al. [14] The expression of ER and PR was higher in malignant tumors (63.2%) with p value <0.05 and 42.1% with p value >0.05 respectively, which was also observed by Verma R et al [15] and Verma N et al. [16] Similarly the expression of ER, PR was significantly higher in serous tumors than non-serous tumors (p value<0.05) and in high grade tumors than low grade tumors similar to Verma R et al. [15]

CONCLUSION

ER expression was higher in postmenopausal women, malignant tumors, serous tumor, higher grade tumors and FIGO stage I/II, while increased PR expression is seen more in premenopausal women, serous, malignant and high grade tumors. So, assessing the expression of ER, PR in surface epithelial ovarian tumors can help in understanding the biological behaviour of the tumor and modifying treatment modalities. Our study is limited by small sample size and follow up, hence large sample sized studies with follow up are recommended.

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