Original Research Article

Expression of estrogen receptor, progesterone receptor and KI 67 in epithelial ovarian tumors and their histopathological correlation

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Abstract

Introduction: Expression of ER, PR and Ki 67 in epithelial ovarian tumors and their histopathological correlation analyzed by immunohistochemistry. **Methods:** This study was conducted on 60 ovarian specimens received in Department of Pathology, Gandhi Medical College, Bhopal for ovarian tumors from 1st January 2012 -31st august 2016. **Results:** The expression of ER was more in malignant tumor 21/26 than borderline 5/9 and benign tumors 5/25. The PR expression was more in benign tumors 14/25 than malignant 13/26 and borderline 2/9 tumors. The Ki67 expression was more in malignant tumors 22/26 than borderline 7/9 and benign 1/25 tumors. **Conclusion:** In our study ER and Ki-67 positivity was maximally seen in malignant cases. This shows that ER was enhanced in ovarian carcinoma and Ki67 was proliferative marker. PR expression was maximally seen in benign tumors. This showed protective role of PR marker in ovarian carcinoma.

Key words: Estrogen receptor, Progesterone receptor, Ovarian tumors, Ki67.

Introduction

One major health problem in women is ovarian tumors. It is the most common tumors in women and is third most common cancer of female genital tract [1]. 22000 women are diagnosed every year with epithelial ovarian tumors out of which 15000 die [2]. The etiology and pathogenesis are still poorly understood. Current treatment methods results in poor overall prognosis. There is need to develop effective target therapy to improve survival as there is absence of definite etiological factors and effective tools for screening. Estrogen and progesterone are important hormones secreted by ovary acting through specific receptors [3]. Both the hormones and their receptors are thought to be involved in the process of tumor genesis in ovarian cancers [4]. Immuno-histochemical ER and PR assays have added the advantage that the distribution in tumor tissues as well as normal surrounding can be evaluated [5]. Hormone receptor determination in malignant ovarian neoplasms can aid in selection of patients for endocrine therapy in a manner similar to that already established for certain hormone dependent cancers [6]. Ki-67 is a proliferation marker helpful in predicting disease outcome in many types of malignancies including ovarian neoplasms [7]. This study is undertaken to analyze the IHC profile of ER, PR and Ki-67 in various ovarian epithelial tumors and attempt correlation with clinic-pathological and histopathological findings.

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Material and method

The present study was conducted to study immunohistochemical expression correlation with estrogen receptor, progesterone receptor and Ki-67 in epithelial ovarian tumors. The study was conducted in Department Of Pathology, Gandhi Medical College, Bhopal, Madhya Pradesh.

Study design- retrospective and prospective study
Setting- Histology section of Department of pathology, Gandhi Medical College, Bhopal, Madhya Pradesh during a period of 1st January 2012-31st august 2016.

Inclusion criteria- All the cases of epithelial ovarian tumors were included.

Exclusion criteria- Specimens other than epithelial ovarian tumors and Biopsies with tissue insufficient for histopathological evaluation (eg. tissue inadequate for comment, autolysed samples) were excluded.

Participants- All the cases dignosed as epithelial ovarian tumors.
Variables- staining of slides.
Data source- Gandhi medical college Bhopal
Bias-Random selection

Study size- 195 cases of epithelial ovarian tumors were included in study. This study conducted IHC in randomly selected 60 ovarian tissue samples and each sample was tested for ER, PR and Ki 67.

Statistical methods – Data was entered in Microsoft office excel work sheets. Then data was analyzed using appropriate statistical tests using software epi-info and SSPS and sofa stats. P value is considered significant if $p<0.05$.

Criteria For Reporting- ER and PR expression: >10% showing positive nuclear staining of any intensity was defined as positive [8,9].

Ki-67 interpretation**:** >50% showing positive nuclear staining of any intensity was defined as positive, which could discriminate patients into groups with different prognosis. [10]

Results

In present study, total number of cases were 195, out of which 13 (6.66%) were bilateral and 182(93.33%) were unilateral. In the unilateral cases 78(42.84%) were left and 104 (57.14%) were right.

Maximum numbers of benign serous tumor and malignant serous tumor were found in 31-40 year of age group followed by 41-50 year of age group and maximum numbers of mucinous tumor were found in 21-30 year of age group and malignant mucinous tumor were equally distributed in 21-70 year of age group. One case of Endometrioid tumor was found in 28 year of age and endometrioid carcinoma was found in 45 year of age.

Benign tumors size were maximum in the range of 5-10cm, malignant tumors were in the range of 11-15cm and borderline tumors in the range of > 16cm.

There were maximum cases of serous tumors 158 (82.05%) followed by mucinous 35 (17.94%) and endometrioid tumors 2 (1.02%). The chi-square statistic is 25.48. The p-value is significant.

In our study, maximum numbers of benign, borderline and malignant tumors were found after parity increases more than three (55.89%). The chi-square statistic is 9.657. The *p*-value is .139859. The result is *not* significant at $p < .05$.

Our study we found that significant association between tubal ligation and ovarian cancer. Tubal ligation was found in benign tumors. In benign tumors only 27 (20.6%) cases were done tubal ligation. Borderline and malignant cases not had done tubal ligation. The chi-square statistic is 6.85. The *p*-value is .03. The result is significant at $p < .05$.

Maximum cases of benign (92/160) and borderline (7/9) tumors were in pre-menopausal stages and malignant tumors (15/26) were maximally found in post-menopausal stages. The chi-square statistic is 4.039. The *p*-value is .132719. The result is *not* significant at $p < .05$. ER expression-In our study ER α positivity with IHC was maximum for malignant cases 80.76%, 55.5% followed by borderline tumors and 20.83% least in benign tumors. Serous tumors are most common type in all groups. Endometrioid tumor are negative for ER α. ER positivity was maximum for endometrioid carcinoma followed by serous carcinoma, borderline mucinous and borderline serous tumors.

PR expression-In our study, PR positivity with IHC was maximum for benign cases 58.33%, 22.22% for borderline and 50% for malignant tumors. PR positivity was maximum for endometrioid carcinoma (100%), endometrioid tumor (100%) followed by benign serous tumors (58.33%) serous carcinoma (55.00%), benign mucinous tumors (50%), borderline serous (50%), mucinous carcinoma (20%) and borderline mucinous tumors.

Ki-67 expression- Ki-67 expression was highest in malignant cases 84.61% followed by borderline 77.77% and benign tumors 4.61%. Ki 67 positivity was maximum for endometrioid carcinoma (100%) and borderline serous tumors (100%) followed by serous carcinoma (95%), borderline mucinous tumors (85.71%), mucinous carcinoma (40%) and benign serous tumors (8.33%) (table no.1)

Table-1: Expression of ER, PR and Ki67 markers in histological subtypes of epithelial ovarian tumors.

Histological subtype	ER	PR	Ki 67
Benign Serous Tumors (12)	3	7	1
Benign mucinous tumor (12)	2	6	Negative
Borderline serous tumors(2)	1	1	2
Borderline mucinous tumors(7)	4	1	6
Serous carcinoma(20)	17	11	19
Mucinous carcinoma(5)	3	1	2
Endometrioid tumor(01)	Negative	1	Negative
Endometrioid carcinoma(1)	1	1	1

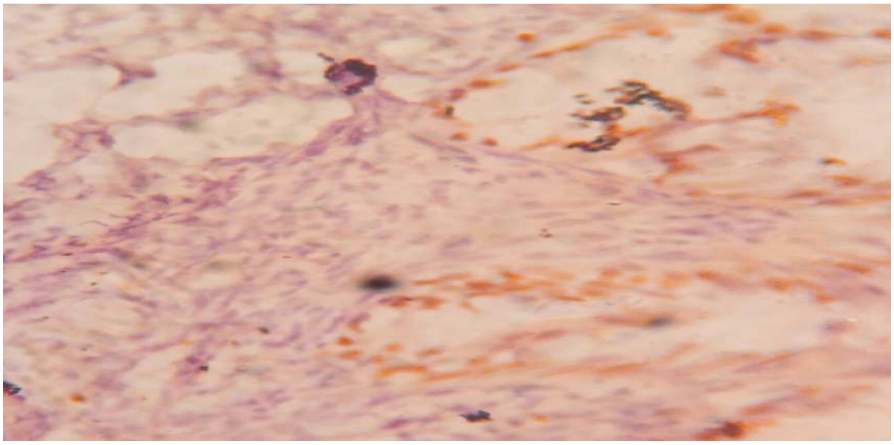

Figure-2: High power view-strong ER positivity in serous carcinoma

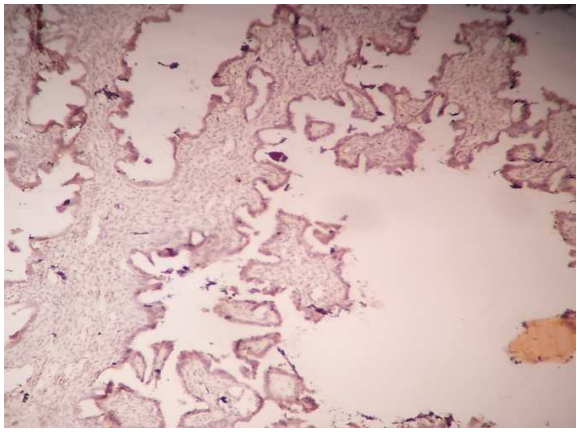

Figure-3: Low power view-Strong PR positivity in serous cystadenoma

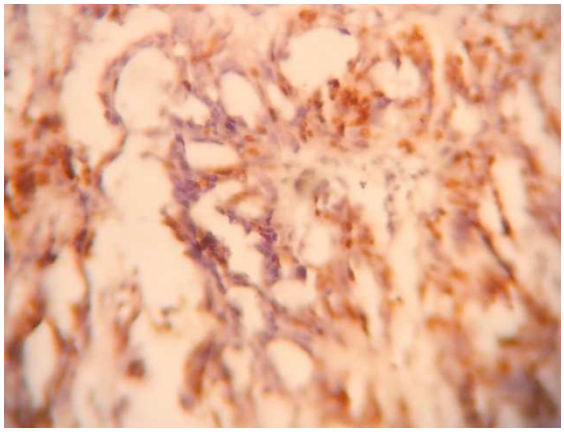

Figure-4: High power view-strong Ki67 positivity in Endometrioid carcinoma

Discussion

In present study of 195 cases of epithelial ovarian tumors over a period of 44 months from January 2012 to August 2016 in tertiary care center, Department of Pathology, Gandhi Medical College, Bhopal.

Sreeja T.T et al,[11] Pooja S. Naik et al,[12] Mary T. Sylvia et al[13] and Jha et al[14] reported maximum incidence of ovarian tumor in the age group of 30-50 year, while Ranjana Banyopadhyay [15] reported maximum number of cases in the age group of 35 year. In present study, we also found the similar results with maximum cases in the age group of 31-40 year followed by 41-50 year age group.

Sreeja T.T. et al,[11] Pooja S.Naik et al[12] and Jha R. et al[14] reported that majority of cases (64.46%,74.54% and 83.90% respectively) were benign in their studies although number of cases varies in morphological spectrum of the epithelial ovarian tumors. Mary T. Sylvia et al[13] reported minimum 28.33% of benign cases in there study. In present study, 160(82.05%) cases are benign, 9(4.61%) cases were borderline and 26(13.33%) cases were malignant which were similar to Jha R. et al[14] study. Benign serous cyst adenoma 136(85.00%) was most common histopathological diagnosis followed mucinous cystadenoma 23(14.37%) and endometrioid tumor 1(0.625%). In our study, among the malignant cases; maximum cases 20(76.92%) were of serous cystadenocarcinoma; which is similar to Mary T. Sylvia.et al[13]. This is due to ovarian tumors display histological heterogeneity.

J prat et al [16], Ruchika Garg et al[17] and Santosh kumar mondal [15] (95%, 72.7% and 41.15% respectively) reported that unilateral involvement of ovary is more common than bilateral involvement. In our study, we also found the similar result with unilateral involvement of ovary in 182 cases (93.33%) than bilateral involvement in 13 cases (6.66%).

Size of tumor- In our study, maximum numbers of benign cases 80(50%) were found in the size range of 5-10cm, and maximum numbers of malignant cases 14(53.84%) were in the size range of 15-20 cm. maximum numbers of borderline cases 5(55.55) were in the size range of more than 15cm. This finding was similar to Okugawa K et al [18].

Nulliparity is considered to be a risk factor for the development of ovarian carcinoma. Valerie McGuire et al[19], Berit Jul Mosgaar et al[20] and H-O Adami et al[21] also reported nulliparous women have high incidence of ovarian cancers. In our study risk of occurrence of ovarian tumors was found to be increased as the parity increased. This was in contrast to the above studies but similar to the study done by CA Lyoke et al[22] and Fatima Zahra et al[23]. A satisfactory explanation for this difference in the occurrence of ovarian tumors and parity has not yet been elucidated but in developmental countries nulliparity may not be a strong factor in the etiology of epithelial ovarian cancer.

Susanne K Kjaer et al [24], Cibula D et al[25], Sieh W et al[26] and Hankinson SE et al[27] reported risk decreases after tubal ligation. In our study we found similar result and also found a significant association between the tubal ligation and the ovarian carcinoma was noted with p value is significant.

A suggested explanation for association between tubal ligation and incidence of ovarian carcinoma was that following sterilization, the ovarian circulation may be impaired causing suppressed ovarian hormone production followed by some degree of anovulation, and thereby maybe a reduction in the risk of ovarian cancer. Furthermore, the levels of circulating hormones may be changed, also affecting the ovarian cancer risk. In addition, it has been hypothesized that because of a reduction in the utero-ovarian circulation, caused by the tubal sterilization, reduced concentrations of uterine growth factors reach the ovaries resulting in decreased ovarian cancer risk.

In our study we found that in both pre-menopausal and post-menopausal women maximum cases were benign 92(83.63%) and 65(79.26%) respectively. Although malignant cases were least in both pre-menopausal and post-menopausal women but the ratio of cases was reversed as compared to benign.

Table No-2: Estrogen receptor, progesterone receptor and Ki 67 expression in benign tumors.

Study by	ER	PR	Ki-67
pooja s. naik et al[12](2015)	24.39%	62.19%	4.88%
Summyia Farooq et al[28] (2013)	20.00%	30.00%	-
Luminita Giurgea et al[29](2012)	-	-	9.09%
Mary T Sylvia et al[13] (2012)	29.00%	41.20%	Index-2.17
Present study	**20.83%**	**58.33%**	**4.16%**

Table No.-3: Estrogen receptor, progesterone receptor and Ki-67 expression in borderline Tumors.

Study by	ER	PR	Ki-67
pooja s. naik et al[12] (2015)	75.00%	66.67%	83.33%
Summyia Farooq et al[28] (2013)	50.00%	50.00%	-
Luminita Giurgea et al[29] (2012)	-	-	13.30%
Mary T Sylvia et al[13] (2012)	40.00%	60.00%	Index-23.2
Sevgiye Kacar Ozkara et al[30] (2011)	-	-	Index-17.2
Emile Darai et al[31] (1998)	-	-	40%
Present study	**55.55%**	**22.22%**	**77.77%**

Table No.-4: Estrogen receptor, progesterone receptor and Ki-67 expression in ovarian cancers

Study by	ER	PR	Ki67
Zheng feng et al[32] (2005-2013)	64.4%	12.6%	-
M. Kruchten et al[33] (2015)	31%	19%	-
pooja s. naik et al[12] (2015)	81.25%	56.25%	93.75%
Marco Battista et al[34] (2014)	19.00%,	14.30%	73.80%
Summyia Farooq et al[28] (2013)	61.53%	84.60%.	-
Giurgea et al[29](2012)	-	-	61.53%
Liu, Ping et al[35] (2012)	-	-	77.70%
Mary T Sylvia et al[13] (2012)	33.00%	63.6%	Ki index- 48.6
Sevgiye Kacar Ozkara et al[30] (2011)	-	-	Ki index-41.3
L.G. Buchynska et al[36] (2009)	67%	68%	-
Hugo. Arias-Pulido et al[37] (2009),	79%	83%	-
Kyueng Whan Min et Al[38](2007),	-	-	>50%
Emile Darai et al[31] (1998)	-	-	70%
Present study	**80.76%**	**50%**	**84.61%**

This result is in favor of the carcinogenic role of estrogen in surface epithelial ovarian cancers and protective effect of progesterone in the development of ovarian cancers. Most of the researcher attributed this significant difference of hormones in carcinogenesis to different responses of various female tissues to estrogen and progesterone or their combined effects. This variable difference in hormone response again in turn is speculated to the different levels of ER and PR subtypes at tissue level, although molecular basis of this not fully understood.

The expression of Ki67 more in malignant tumor could be explained by the fact that it is a monoclonal antibody expressed by proliferating cells and is indicative of high proliferation rate and aggressiveness of malignant tumor cell as compared to borderline and benign tumors.

Mary T Sylvia [13] reported ER and PR significant higher expression after >50year of age, However Ki67 expression is decreased after >50 year of age in his study.

In our study all the three marker ER, PR and Ki 67 expression is increased after > 50 year of age.

Conclusion

In our study ER and Ki-67 positivity was maximally seen in malignant cases 80.76%, 84.61% respectively. This showed ER was enhanced in ovarian carcinoma and Ki67 was proliferative marker. PR expression was maximally seen in benign tumors 58.33%. This shows PR marker had protective role in ovarian carcinoma.ER, PR and Ki67 showed higher expression in serous tumors, older age group and in advance stage of tumor. So estimation of Estrogen, Progesterone and Ki67 may help to select the women with ovarian malignancy for hormonal therapy, which is more likely to improve the response rate as well as prognosis.

Abbreviation

ER- Estrogen receptor
PR- progesterone receptor
IHC- immunohistochemistry

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