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Expression of Estrogen and Progesterone Receptors in Primary Epithelial Ovarian Malignancies Seen at the Jos University Teaching Hospital

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ABSTRACT

Introduction: Ovarian cancer is the 8th most common cancer in women globally, and is responsible for majority of gynaecological cancer deaths. Epidemiological evidence suggests that steroid hormones are implicated in ovarian carcinogenesis, therefore a role for targeted hormonal therapies. **Objectives:** This study is aimed at determining the histopathological pattern of ovarian epithelial cancers and steroid hormone receptor expression at the Jos University Teaching Hospital between the 1st January 2004 and 31st December, 2013. **Methods:** This was a hospital based retrospective study of ovarian surface epithelial cancers. Patients' biodata were obtained from the hospital records and cancer registry. Tissue slides and blocks were retrieved from the archives. Specimens confirmed as epithelial ovarian cancers by Haematoxylin and Eosin were subjected to immunohistochemistry to demonstrate estrogen receptor and progesterone receptor positivity. **Results:** A total of 75 ovarian cancers were seen, 46 (61.3%) of which were epithelial ovarian cancers, out of which forty 40 (53.3% of ovarian cancers and 87% of epithelial ovarian cancers) cases met the inclusion criteria. The age range, mean age, median age and peak age at diagnosis were: 20 to 75 years; 45.43±14.46 years; 46 years and fifth decade of life respectively. Serous carcinoma was the most common histological subtype accounting for 25(62.5%) cases. The high grades (grades 2 and 3) were commoner in all the histological subtypes. Estrogen positivity was seen in 17 (42.5%) and progesterone positivity in 29 (72.5%) of the cancers. **Conclusion:** Serous adenocarcinoma, the commonest histological variants of ovarian cancers in this study, exhibits higher expression of estrogen receptor and showed significant correlation between ER expression and the serous histological morphology.

Keywords: Ovary, Cancer, Estrogen, Progesterone, Receptor.

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INTRODUCTION

Ovarian cancer is the 8th commonest cancer in women globally, accounting for 3.6% of all cancers in 2020.[1] It is responsible for most death among all gynaecological cancers.[2] It has been projected that by 2040, the number of women around the world diagnosed with ovarian cancer will rise almost 37%.[3] A woman's lifetime risk of developing ovarian cancer is 1 in 75, and her chance of dying of the disease is 1 in 100.[4]

Ovarian cancer presents with vague nonspecific symptoms usually in advanced stages of the disease.[5] The disease is often diagnosed at advanced stages, because early premalignant lesions are not easily detected. This may be responsible for the late presentation, making ovarian epithelial cancers (OEC) as the most lethal gynecological malignancy.[6] Approximately 70% of women with OEC have advanced disease at presentation and 65% of women die within 5 years of diagnosis.[6]

Recent advances in pathology and genetics have shown that different histologic subtypes of OEC have distinct risk factors. The genetic instability, pathogenesis of these epithelial cells is responsible for the biological behavior of these cancers and response to chemotherapy.[7]

The assessment and management of patients with ovarian cancer is changing because epidemiological evidence suggests that steroid hormones are implicated in ovarian carcinogenesis.[8] As estrogen favors neoplastic transformation and progesterone offers protection against ovarian cancer development, this has therapeutic implication.[8,9,10] This called therefore a role for targeted hormonal therapies: antiestrogens, aromatase inhibitors and progestins either alone or in combination with chemotherapeutic drugs in the treatment of ovarian cancer.[8,9,10]

This study aimed to determine the histopathological pattern of ovarian epithelial cancers and steroid hormone receptors expression at the Jos University Teaching Hospital between 1st January 2004 and 31st December 2013.

MATERIALS AND METHODS

This was a hospital - based retrospective study of ovarian surface epithelial cancers at the histopathology Department of the Jos University Teaching Hospital between 1st January 2004 and 31st December, 2013. Ethical clearance was obtained from the Jos University Teaching Hospital Ethical Clearance Committee. All ovarian epithelial cancers diagnosed histologically during the study period with traceable archival slides or tissue blocks were included in the study. Specimens with insufficient tissue for immunoperoxidase staining for PR and ER as well as needle aspiration cytologies and missing blocks were excluded from the study.

The histological diagnosis and biodata were obtained from the records and cancer registry of the hospital. Tissue slidesand blocks were retrieved from the archives. Where slides are faded or missing, fresh sections of 5µm thickness were cut from the paraffin-embedded formalin fixed tissue blocks and stained with Haematoxylin and Eosin for histological analysis.

The slides were interpreted by using an Olympus microscope Leica DM 500 with a field diameter of 10mm. Characterization was based on WHO 2014 classification.[11] The microscopic grading of Shimizu and Silverberg which assesses architectural pattern, nuclear pleomorphism and mitotic activity was used to grade and assign the tumors into different histological grades.[12]

Specimens confirmed as epithelial ovarian cancers by Haematoxylin and Eosin were subjected to immunohistochemistry to demonstrate estrogen receptor and progesterone receptor positivity. This process employed staining with immunoperoxidase (from Slovakia and as described by DB-Biotec Slovakia) for estrogen and progesterone receptors (in a dilution of 1:100). The primary antibodies used were monoclonal rabbit antihuman PR (DB-Biotec Slovakia) and monoclonal rabbit antihuman ER (DB-Biotec Slovakia). The secondary antibody used was UltraVision Quanto Detection System (primary antibody amplifier quanto) by Fischer which identified the PR and ER protein antigen. The positive control used was that of breast staining for ER and PR. Interpretation

of the nuclear ER and PR immunostaining was performed using the Quick scoring system according to the American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) which was obtained by the addition of the intensity of immunostaining with the proportion of positively nuclear stained cells.

Data collected was analyzed using EPI Info® statistical software (version7). The information obtained was reported using frequencies, percentages, tables and charts where applicable to display data. Statistical analysis was used to evaluate statistical associations between expression of ER and PR and clinicopathological parameters (age, grade and histological subtypes). Statistical level of significance was defined as $p < 0.05$.

As a hospital-based study, it may not reflect the exact distribution of sample for the entire community because not all cases in the community will present at the hospital.

RESULTS

A total of 643 ovarian biopsy samples were received at the Jos University Teaching Hospital during the period of study. Seventy five (11.7% of total ovarian biopsies) were diagnosed as ovarian cancer. Of these cancers, forty six 46 (7.1% ovarian biopsies and 61.3% of ovarian cancers) were epithelial ovarian cancers, out of which forty 40 (53.3% of ovarian cancers and 87% of epithelial ovarian cancers) cases met the inclusion criteria.

The age range was 20 to 75 years, mean age at diagnosis of 45.43±14.46years, and the median age was 46 years. The peak age of occurrence was in the fifth decade of life. Table,1.

Serous carcinomas were the most common histological subtypes accounting for 25(62.5%) cases, followed by mucinous carcinomas which accounted for 9(22.5%) cases. Table, 2.

The high grade cancers (grade 2 and 3) were commoner than the low grade malignancy in all the histological subtypes. Fig.1. For the serous carcinomas, 15(37.5%) cases were high grade and 10(12.5%) low grade.

Estrogen positivity was seen in 17(42.5%) and progesterone positivity in 29(72.5%) of the cancers. Table, 2. The relationship between ER and PR reactivity with histological morphologic types are presented in Table, 2. The relationship between ER and PR reactivity with histological morphologic types and histological grade are presented in Table, 3. The correlation between histological type, age and tumor grade with ER/PR status respectively is presented in Table 4.

Table, 1. Age distribution of Ovarian Epithelial Cancers

Age Range	Frequency	Percentage (%)
11-20	1	2.5
21-30	7	17.5
31-40	6	15
41-50	15	37.5
51-60	4	10
61-70	6	15
71-80	1	2.5
Total	**40**	**100**

Table, 2.Distribution of Ovarian Epithelial Cancers according to hormone receptor expression.

Histological Subtype	Number of cases (%)	Immunomarker staining			
		ER–VE (%)	ER +VE (%)	PR -VE (%)	PR +VE (%)
Serous Carcinoma	25(62.5)	11	14	7	18
Mucinous Adenocarcinoma	9(22.5)	8	1	3	6
Endometrioid Carcinoma	4(10.0)	2	2		4
Clear Cell Carcinoma	2(5.0)	2		1	1
Total	**40(100.0)**	**23(57.5)**	**17(42.5)**	**11(27.5)**	**29(72.5)**

Table 3. Distribution of Ovarian Epithelial Cancer hormone receptor status according to Histological grade.

Hormone Receptor Status Of Histological Types	Histological Grade					
	Grade I		Grade II		Grade III	
Serous Carcinoma	+VE	-VE	+VE	-VE	+VE	-VE
ER	8	2	5	6	1	3
PR	7	3	7	4	4	0
Mucinous Carcinoma	+VE	-VE	+VE	-VE	+VE	-VE
ER	1	3	0	3	0	2
PR	2	2	3	0	1	1
Endometrioid Carcinoma	+VE	-VE	+VE	-VE	+VE	-VE
ER	0	1	2	0	0	1
PR	1	0	2	0	1	0
Clear Cell	+VE	-VE	+VE	-VE	+VE	-VE
ER	0	1	0	1	0	0
PR	1	0	1	0	0	0

Table, 4. Correlation between ER and PR Expression and Demographic Parameters.

a. ER/PR Status and Age

Parameters	ERn=17(42.5%)		chi-square	p-value	PR n= 29 (72.5%)		chi-square	p-value
Age (years	ER+	ER-			PR+	PR-		
<45	8	12	0.102	0.749	15	5	0.122	0.723
>45	9	11			14	6		

b. ER/PR Status and Grade

Grade	ER+value	ER-	Chi-square p-	PR+	PR-	chi-square p-value
1	9	7	0.1973*	10	6	0.5247
2	7	10		13	4	
3	1	6		6	1	

c. ER/PR Status and histological subtype

Histological subtype	ER+	ER-	chi-square	p-value	PR+	PR-	chi-square	p-value
Serous	**14**	**11**	**4.848**	**0.028**	**18**	**7**	**0.008**	**0.927**
Non serous	**3**	**12**			**11**	**4**		
***=fishers exact**								

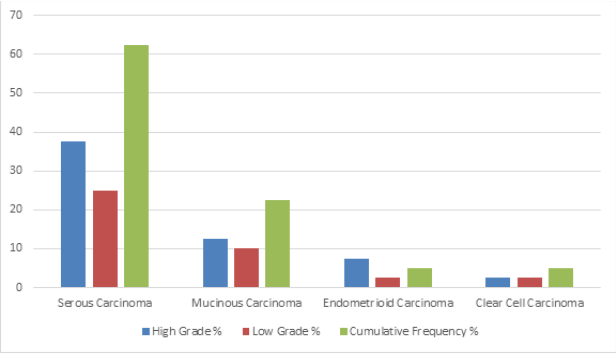

Figure 1.Histological distribution of Epithelial Ovarian Cancers according to Histological Grade.

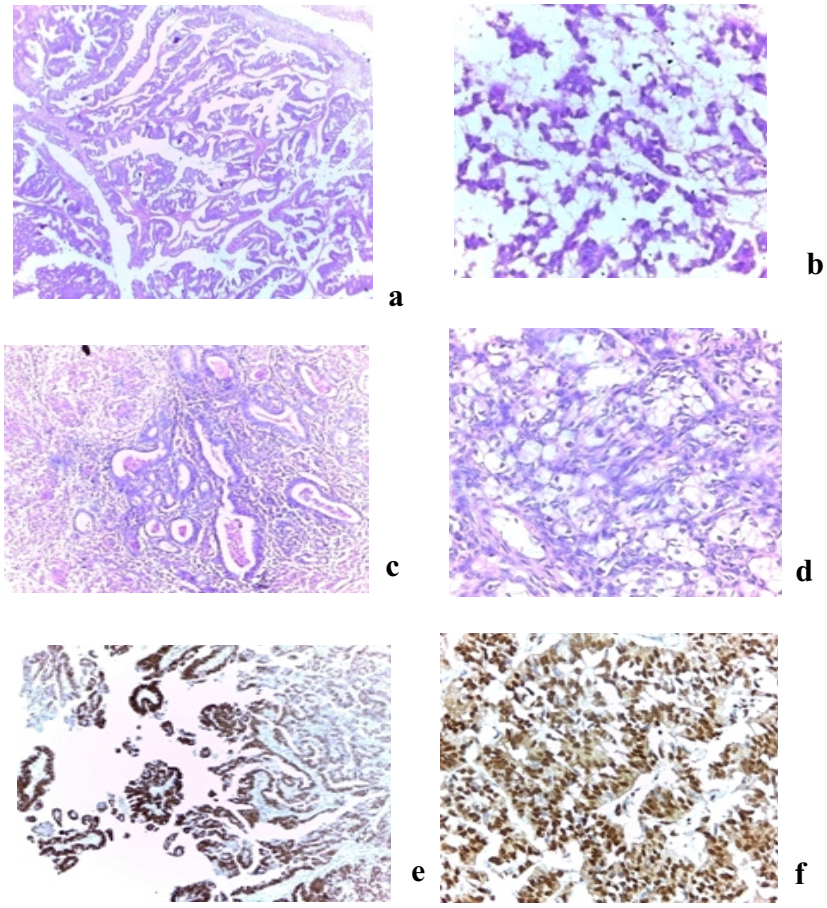

Figure 2. Photomicrograph showing
a. Papillary Serous Adenocarcinoma with papillary projections and stroma invasion of tumor cells. (H&E) stain x40
b. Mucinous Adenocarcinoma with intracellular and extracellular mucin bathing tumor cells. H&E stain x40
c. Endometrioid Carcinoma with endometrial-like glands lined by neoplastic cells, luminal secretion, stroma invasion and adjacent inflammation. H&E stain x40.
d. Clear Cell Carcinoma with malignant cells having clear vacuolated cytoplasm and stroma invasion). H&E stain x40.
e. Strong nuclear immunostaining for ER with intense brown staining of the nuclei of tumor cells. ER stain x40.
f. Strong nuclear immunostaining for PR with intense brown staining of the nuclei of tumor cells. PR stain x40.

DISCUSSION

Worldwide, epithelial ovarian cancer is the leading cause of death from gynecological malignancies.[13] Malignant ovarian tumors are mostly detected at an advanced stage.[5,6]In addition to cytotoxic chemotherapy used conventionally for the treatment of advanced cases of EOC, favorable results have been reported following endocrine treatment.[14]Since steroid hormone receptors have prognostic significance in hormone treatment of the different types of ovarian cancer, it is important to identify those tumor groups that contain steroid receptors, so that patients who may benefit from hormonal therapy may be identified.[14]Estrogen and progesterone receptors are important hormones secreted mainly by the ovaries.[8,9,10]They act through their specific receptors and have been implicated in the pathogenesis of gynecologic malignancies including breast, endometrial and ovarian cancers.[8,9,10]

In this study, the mean age at the diagnosis of epithelial ovarian cancers was 45.43±14.46years. This is consistent with other African reports. Ajani et al found a

mean age of 52.2±12.6years in a study with 90 epithelial ovarian carcinomas.[15]Similar values of 48.6years and 45.7years were reported by Udoye et al and Faretigun et al in Port Harcourt and Lagos respectively.[16,17] Akakpo in Ghana reported a mean age of 49years.[18]However, a higher figure was reported in the United State of America and United Kingdom: 63years and 62years respectively.[19] The relatively lower mean age in Africa might be as a result of a decrease life expectancy than in Caucasians. As such more of the cancers are seen at a relatively younger age in Africa than in Western climes where the reverse is true with increasing number of aged people.[21,22,23]

The commonest histological variant of ovarian cancers in this study was that of epithelial origin. Among these, the commonest is the serous adenocarcinoma. This is consistent with earlier studies. Udoye et al in Port Harcourt found serous ovarian carcinomas to constitute 51.9% of epithelial ovarian cancers.[16]This was corroborated by Ajani et al and Nnadi et al in Ibadan and Sokoto where serous adenocarcinomas constituted 70% and 65.7% respectively of ovarian cancers.[15,23]Mucinous adenocarcinoma is the second commonest carcinomas seen in this study accounting for 22.5% of cases. This is consistent with reports by Nnadi et al, Ajani et al, and Iyoke et al in Sokoto, Ibadan and Enugu who recorded mucinous adenocarcinomas to constitute 21.1%, 26.7%, and 24% respectively.[15,23,24]
The maximum number of epithelial ovarian cancer occurred between 41-50years in this study. Summyia Farooq reported that the maximum number of EOC occurred in 31-40years 50(34.73%).[25]

In this study, Estrogen receptor positivity was seen in 17(42.5%) cases, while Progesterone receptor positivity was seen in 29(72.5%) cases. This is similar to what was reported by Sylvia et al from India where ER and PR were expressed in 33% and 63.6% of EOC respectively.[26]It however contrast with reports by Ayadi et al in Tunisia where ER and PR expressivity were 35.1% and 33.1%;.[27]A wide range of steroid hormone receptor expression in EOC have been reported: 32-77% for ER and 15-69% for PR.[27]The high variability in the percentages of receptor positivity may be related to the different assay methods employed in the different studies. Higher figures were obtained in earlier studies using biochemical techniques or flow-cytometry as compared with recent studies using immunohistochemistry.

There was a significant association between ER and histological subtypes (p = 0.028). A higher proportion of serous (56%) than mucinous (11.1%) were observed to be ER positive. There was a stronger association with serous subtype compared with the mucinous (non-serous) type. This is similar with what was reported by Ayadi et al from Tunisia and pulido et al from Mexico.[27,28]There was significant ER negative expression in mucinous carcinoma (88.9%) in this study which agrees with what has been reported in the literature.[27,28,29,]

In this study 56.3% of ER positive EOC were well differentiated (grade 1) and 14.3% were poorly differentiated (grade 3) which contrast with what was reported by Ajani et al where 59.1% ER were grade 3 and 18.2% were grade 1.[15]This findings however corroborates what was found in other studies where ER was more expressed in grade 1 tumours than grade 3 tumours.[27] There was no significant association found between ER and grade. There was a greater proportion of both serous and endometrioid carcinomas, 72.0% and 100.0% respectively than mucinous carcinomas (66.7%) that were PR positive. Similar findings were observed by Ajani et al where PR expression was greater in serous (41.3%) and endometrioid (50.0%) than in mucinous carcinomas (22.5%), and Arias-Pulido et al from Mexico where PR expression was also greater in serous (54.9%) and endometrioid (71.4%) than in mucinous carcinomas (20.0%). However no significant correlation was observed between PR expression and histological subtypes (p=0.927).

In this study, no significant positive correlation was found between grade and PR expression with 85.0% of PR positive epithelial ovarian cancers being grade 3(poorly differentiated) tumours and 62.0% being grade

1(well differentiated) tumours. It however contrasts with other studies where PR was found to be more expressed in grade 1 tumours than grade 3 tumours.[27] There was no significant association between PR and age.

This study showed that serous cancers are more common than other histological subtypes. Estrogen and progesterone showed higher expression in serous and endometrioid carcinomas than in other subtypes. The study also showed significant correlation between ER expression and serous histological subtypes as compared to non-serous subtypes. Therefore the expression of estrogen and progesterone receptors may help to select patients with epithelial ovarian cancers for hormonal therapy. We recommend that more local studies be encouraged to contribute to the existing body of knowledge concerning the subject in view. All histologically diagnosed ovarian (epithelial) cancers, irrespective of epidemiological and histological determinants, should be subjected to basic immunohistochemical analysis (ER, PR) which may aid selection of appropriate targeted hormonal treatment regimen. Also future studies employing larger sample size to predict response to endocrine therapy should be done.

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