

ASSOCIATION OF STEROID RECEPTOR EXPRESSION WITH THE CLINICAL AND HISTOLOGICAL FINDINGS IN PATIENTS WITH ENDOMETRIAL CANCER

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ABSTRACT

Objective: To determine the association of estrogen and progesterone receptor expression with the clinical and histological findings of endometrial cancer.

Study Design: Prospective observational study.

Place and Duration of Study: Jinnah Postgraduate Medical Centre, Karachi between Sep 2017 to Oct 2019.

Methodology: A total of 130 patients were diagnosed with endometrial carcinoma. Data from patient files were collected regarding tumour histology, grade, stage, tumour receptor expression, and the clinical characteristics: parity, menopausal status. The receptor expression profile was documented for each patient. Data were analyzed using SPSS version 25. The association between ER/PR expression categories and clinical/histological features were explored using the chi-square test.

Results: The estrogen and progesterone receptor expressions were significantly associated with low-grade (Grade I and II) tumours and with Stage I and Stage II endometrial carcinoma with $p < 0.001$. About 34 (34.7%) cases of endometrioid histology were negative for both estrogen and progesterone receptors. The ER and PR negativity was strongly associated with Grade III endometrial cancer ($p = 0.003$). The majority of the stage IV cancers were negative for both the ER and PR receptors with a $p < 0.001$.

Conclusion: Estrogen and progesterone positivity was associated with endometrioid adenocarcinoma, well-differentiated, and less advanced stage of endometrial cancer at the time of diagnosis.

Keywords: Endometrial carcinoma, Endometrioid cancer, Estrogen, ER expression, Progesterone, PR expression.

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INTRODUCTION

Endometrial cancer is a tumour arising in the inner lining of the uterus. More than 90% of uterine cancers occur in the endometrium. It is the sixth most frequent malignancy worldwide, preceded by cancers such as that of the breast, colon, rectum, and lung¹. In developed countries, like the United States, it is a leading cause of death. A much lower incidence is found in developing countries in Asia, Africa, and South America². In the United States, an estimated 61,880 women were diagnosed with endometrial cancer this year.

The frequency of cases of endometrial carcinoma among women is on the rise due to increasing obesity, which is a well-known modifiable risk factor for this cancer. Certain other factors are known to increase the risk of developing endometrial carcinoma including, anovulation, early menarche, late menopause, diabetes mellitus, unopposed estrogen, hormonal replacement therapy, lack of physical exercise, and heavy smoking³.

The most common manifestation of the cancer is postmenopausal vaginal bleeding. Endometrial cancer

is rare in patients younger than 35 years of age⁴. The majority of patients with endometrial carcinoma are in their fifth or sixth decade at the time of the diagnosis. The mean age of endometrial carcinoma is about 60 years.

There are two main types of endometrial cancer. One of these types is estrogen-dependent, which occurs in younger women. Endometrioid histological subtypes constitute the majority of these tumours. These cancers are often low-grade and associated with a favourable prognosis while the other group consists of more aggressive variants of this disease (serous and clear cell type) with a worse prognosis⁵. The former develops under the influence of endometrial hyperplasia while the latter is associated with endometrial atrophy.

Women with existing breast cancer are more at risk of developing concomitant endometrial cancer. Reproductive and hormonal disturbances such as postmenopausal estrogen levels or BMI are strongly associated with breast and endometrial cancers and weakly with ovarian cancers. This may explain the co-existence of these cancers. Due to diversity in histopathological features of endometrial carcinoma, the clinical course and outcome may greatly vary accordingly⁶.

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A cancer is called estrogen-receptor-positive (or ER+) if it has receptors for estrogen. This suggests that the cancer cells, like normal breast cells, may receive signals from estrogen that could promote their growth. The cancer is progesterone-receptor-positive (PR+) if it has progesterone receptors. Both estrogen and progesterone hormone receptors have significant positive associations with prognosis, clinical outcome, and survival rates^{7,8}. In the present study, the association of ER and PR positivity of endometrial cancer with the clinical and histological characteristics have been explored.

METHODOLOGY

This was a prospective, observational study conducted at the Oncology Ward, Jinnah Postgraduate Medical Center, the largest public sector tertiary care hospital in Karachi, Sindh, from Sep 2017 to Oct 2019. Ethical approval from the Institutional Review Board (#F2-81-IRB/2017-GENL/161/JPMC) was taken from JPMC Research Department. A non-randomized consecutive sampling technique was employed to recruit participants into the study.

Inclusion Criteria: The study included clinically diagnosed endometrial cancer cases with estrogen and progesterone receptor status.

Exclusion Criteria: All the patients with incomplete receptor expression profile, clinical or histological data were excluded from the study. Patients with undiagnosed or suspicious lesions were also not included in the study.

The incidence of endometrial carcinoma was reported to be 2% in recent study by Abid *et al*, which was kept as the reference for calculating the sample size for the study⁹. By keeping the confidence level of 95%, a margin of error as 2.41, and a population of 100,000, a sample size of 130 was obtained. All surgical specimens were immunohistochemically analyzed to determine the estrogen and progesterone receptors status. Age, ethnicity, any known comorbidity, reproductive history, histology, grade, stage, and ER/PR status of the cancer was recorded. All data was recorded in a predefined proforma.

The data was analyzed using the SPSS-25. The chi-square test was performed to observe statistical significance among variables. The hormone receptor status was categorized into 2 main groups i.e., ER positive PR positive and ER negative PR negative. The *p*-value of ≤ 0.05 was considered as significant. Data was presented as graphs and in tabular form.

RESULTS

A total of 130 women were diagnosed with endometrial carcinoma during the study period. The mean age of patients was 53.07 ± 11.04 years. The majority of them were Urdu speaking with a frequency of 70

Table-I: Demographic and clinical profile of study participants (n=130).

Characteristics	n (%)
Age in years (Mean \pm SD)	53.07 \pm 11.04
Ethnicity	
Urdu Speaking	70 (53.8%)
Punjabi	28 (21.5%)
Sindhi	14 (10.8%)
Pushtoon	10 (7.7%)
Other	8 (6.2%)
Menopausal Status	
Premenopausal	26 (20%)
Postmenopausal	104 (80%)
Parity	
Nulliparous	16 (12.3%)
1 child only	38 (29.2%)
2-3 children only	36 (27.7%)
4 or more children	40 (30.8%)
Comorbidity	
Hypertension (HTN)	28 (21.5%)
Diabetes Mellitus (DM)	8 (6.2%)
Concomitant HTN & DM	18 (13.8%)
No Known Comorbidity (NKCM)	76 (58.5%)
Family History of Cancer	
Positive	45 (34.6%)
Negative	85 (65.4%)
Histological Variant of Endometrial Cancer	
Endometrioid adenocarcinoma	98 (75.4%)
Serous	14 (10.8%)
Clear cell	8 (6.2%)
Other	10 (7.7%)
Stage of Endometrial Cancer	
Stage I	30 (23.1%)
Stage II	18 (13.8%)
Stage III	28 (21.5%)
Stage IV	54 (41.5%)
Grade of Cancer	
Grade I or Well-differentiated	24 (18.5%)
Grade II or Moderately differentiated	56 (43.1%)
Grade III or Poorly differentiated	50 (38.5%)
Hormonal Receptor Status	
ER positive, PR positive	66 (50.8%)
ER negative, PR negative	54 (41.5%)
Only ER positive	6 (4.6%)
Only PR negative	4 (3.1%)

(53.8%), followed by Punjabi, 28 (21.5%) other ethnicities. Twenty-six (20%) women were premenopausal at the time of diagnosis while, the majority of them i.e., 104 (80%) of the patients were postmenopausal (Table-I).

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Hypertension was reported to be the most frequently presented comorbidity with a frequency of

status were not statistically associated with ER and PR expression in the present study (Table-II & III).

Table-II: Association of estrogen and progesterone receptor positivity with clinical and histological characteristics of endometrial carcinoma.

ER & PR Positive							
Parameters	Yes	No	p-value	Parameters	Yes	No	p-value
Histological Variant				Histological Variant			
Endometrioid	60 (61.22%)	38 (38.78%)	<0.001	Endometrioid	34 (34.7%)	64 (65.3%)	0.005
Serous	-	14 (100%)		Serous	10 (71.4%)	4 (28.6%)	
Clear cell	-	8 (100%)		Clear cell	6 (75%)	2 (25%)	
Parity				Parity			
Nulliparous	8 (50%)	8 (50%)	0.947	Nulliparous	6 (37.5%)	10 (62.5%)	0.726
Parous	58 (50.88%)	56 (49.12%)		Parous	48 (42.1%)	66 (57.9%)	
Menopausal Status				Menopausal Status			
Premenopausal	14 (53.85%)	12 (46.15%)	0.725	Premenopausal	14 (53.8%)	12 (46.2%)	0.215
Postmenopausal	52 (50%)	52 (50%)		Postmenopausal	42 (40.4%)	62 (59.6%)	
Grade				Grade			
Grade I	18 (75%)	6 (25%)	<0.001	Grade I	6 (25.0%)	18 (75%)	0.003
Grade II	34 (60.71%)	22 (39.29%)		Grade II	18 (32.1%)	38 (67.9%)	
Grade III	14 (28%)	36 (72%)		Grade III	30 (60%)	20 (40%)	
Staging				Staging			
Stage I	28 (93.33%)	2 (6.67%)	<0.001	Stage I	2 (6.7%)	28 (93.3%)	<0.001
Stage II	16 (88.89%)	2 (11.11%)		Stage II	2 (11.1%)	16 (88.9%)	
Stage III	12 (42.86%)	16 (57.14%)		Stage III	14 (50%)	14 (50%)	
Stage IV	10 (18.52%)	44 (81.48%)		Stage IV	36 (66.7%)	18 (33.3%)	

28 (21.5%) patients. Seventy-six (58.5%) reported no known comorbidities. Forty-five (34.6%) women had a positive family history of cancer. In the present study, endometrioid adenocarcinoma 98 (75.4%) was the most commonly reported histology variant of endometrial cancer, followed by Serous 14 (10.8%), and clear cell 8 (6.2%). Over one-half of the women were positive for both ER and PR, while 54 (41.5%) were negative for both ER and PR. Only, 6 (4.6%) patients were positive for ER only while 4 (3.1%) patients were positive for PR only (Table-I).

The current study found a statistically significant association of the estrogen and progesterone receptor with low grade (Grade I and II) tumours and with stage I and stage II endometrial carcinoma with $p < 0.001$ (Table-II).

In the present study, about 34 (34.7%) cases were negative for both estrogen and progesterone receptors in patients with an endometrioid type of cancer. Over 3/4th of both serous and clear cell type histology of endometrial carcinoma were negative for both ER and PR expression ($p=0.005$). The estrogen and progesterone receptor negativity was strongly associated with poorly differentiated or Grade III endometrial cancer with a statistically significant p -value of 0.003. Most of the stage IV cancers were negative for both the ER and PR receptors with a $p < 0.001$. Parity and menopausal

Table-III: Association of estrogen and progesterone receptor positivity with clinical and histological characteristics of endometrial carcinoma.

ER & PR Negative			
Variable	Yes	No	p-value
Histological Variant			
Endometrioid	34 (34.7%)	64 (65.3%)	0.005
Serous	10 (71.4%)	4 (28.6%)	
Clear cell	6 (75%)	2 (25%)	
Parity			
Nulliparous	6 (37.5%)	10 (62.5%)	0.726
Parous	48 (42.1%)	66 (57.9%)	
Menopausal Status			
Premenopausal	14 (53.8%)	12 (46.2%)	0.215
Postmenopausal	42 (40.4%)	62 (59.6%)	
Grade			
Grade I	6 (25%)	18 (75%)	0.003
Grade II	18 (32.1%)	38 (67.9%)	

When staging was distributed according to the histology variants, it was observed that all Stage I & Stage II cancers belonged to the endometrioid histology. In Stage III cancers, 14 (50%) were of endometrioid adenocarcinoma subtype while only 4 (14.3%) were serious types. In Stage IV, 36 (66.7%) belonged to the endometrioid type of endometrial cancer, with 8 and 9 cases of clear cell and serous type respectively (Figure).

DISCUSSION

Traditionally, endometrial carcinoma is divided into two main subtypes i.e. type 1, which is estrogen-

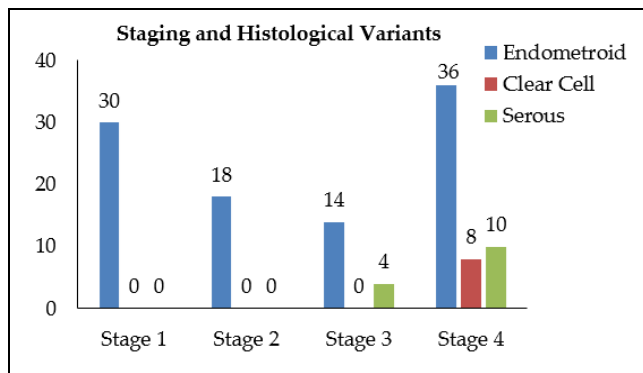


Figure: Staging and histological variants among our study participants.

dependent and Type 2 which is estrogen-independent. Type 1 has been associated with less aggressive histology and a better prognosis. On the other hand, type 2 has been shown to be more aggressive in nature with ER/PR negativity¹⁰. Endometrioid adenocarcinoma histology is usually estrogen and progesterone receptor expression positive while serous and clear cell carcinoma is ER/PR negative tumors¹¹. The other classification is dependent upon the metabolic, endocrine, and clinical characteristics of the disease. Type I cancers are known to be estrogen-driven tumours, more commonly associated with obesity, hormone receptor positivity, and endometrial hyperplasia. These cancers have a better prognosis with a lower grade disease at the time of diagnosis. Type-II cancers are non-estrogenic, more common in lean patients with hormone receptor-negative status. These types of cancers carry a poorer prognosis¹².

The present study reported significant findings with respect to endometrial carcinoma in a tertiary care centre in Karachi. We observed the frequency of ER, PR positivity in 33 (50.80%) patients and ER, PR negativity in 27 (41.5%) patients. It was found that more than half the patients were positive for both estrogen and progesterone receptors. We also observed a strong correlation of endometrioid histology with estrogen and progesterone receptor positivity ($p < 0.05$). In a recent systematic review and meta-analysis of over 98 studies, estrogen and progesterone receptor expression were linked with favourable prognosis and clinical outcome. The determination of hormone receptor status holds immense significance in prognostic evaluation among patients¹³. In the present study, more aggressive subtypes i.e. serous and clear cell histology were significantly correlated with the absence of both ER and PR expression. This finding is in accordance with another study where aggressive malignancies of

endometrial carcinoma have been associated with HER2 over-expression and absence of ER and PR expression. Both serous and clear cell histology is associated with poor prognosis and lower survival rates¹⁴. Unfortunately, in our setting evaluation of hormone receptor expression is not routinely done. Management and treatment plans are largely based on histological variants, the grade, the stage of cancer and other associated clinical factors.

Endometrioid adenocarcinoma histology was the most frequently reported endometrial cancer in our setting. Other reported subtypes were clear cell and serous. Out of 80% of patients were postmenopausal at the time of the diagnosis. Our findings are in agreement with the studies conducted by Fanning, Ambros, and Hernandez *et al*¹⁵⁻¹⁷. In a Norwegian study, it was reported that about 79% of their patients with diagnosed endometrial cancer belonged to the endometrioid histological subtype¹⁸. The majority of them were moderately differentiated, carried a better prognosis and increased survival rate. In contrast to some studies¹⁹, our study reported that the majority of the patients had moderately to poorly differentiated disease at the time of diagnosis. High-grade endometrial cancers were historically associated with hormone replacement therapy or in breast cancer patients who were treated with Tamoxifen²⁰.

Endometrial cancer is often diagnosed at an early stage while, in the present study, the majority of the patients were diagnosed at an advanced stage or presented with a high-grade carcinoma. The contradictory findings can be explained by the fact that in poor-income countries like Pakistan, the health care of women and children are greatly compromised. The women in Pakistan often do not inform their spouses or family members of any symptoms they experience out of shame. One of the most common manifestations of endometrial carcinoma is postmenopausal bleeding²¹. The risk of endometrial carcinoma in women with postmenopausal bleeding increases with age from 1% at the age of 50 years to approximately 25% at the age of 80 years²²⁻²³. However, due to a lack of health education and awareness, many women do not get a consultation from their primary physicians and present very late in the course of the disease when the symptoms become unmanageable.

As stated earlier, 80% of the patients in the present study were postmenopausal at the time of diagnosis. This finding may coincide with the studies from European countries where a rise in postmenopausal

women with diagnosed endometrial cancer has been observed, more specifically in Northern and Western countries. One recent Chinese study has reported menopausal status to be of significant importance with the majority of the patients presenting after menopause²³. However, a contrast in trend has been observed in Denmark, France, and Switzerland²⁴. This high frequency of endometrial cancer in postmenopausal women can be explained by the changes in reproductive behaviour and prevalence of overweight and obesity among women, and also an increase in the use of hormone replacement therapy. The recent rise in the use of combined oral contraceptives (COCP) among our population may explain a decline in endometrial cancer in younger women.

The present study also evaluated the association of certain known risk factors with ER and PR expression. Nulliparity and Menopausal status did not have any significant association, while Grade and Stage of tumour were significantly associated with ER and PR expression ($p < 0.005$). This finding is in line with other studies where steroid expression is associated with low-grade disease and a better survival rate²⁵.

LIMITATION OF STUDY

One of the limitations of this present study is the limited sample size. Another limitation could be the lack of certain variables including HER2 receptor expression, Body Mass Index (BMI) of patients, and a more detailed reproductive history of patients. Future researches can be focused on evaluating targeted therapy for endometrial cancer concerning the risk factors and prognostic factors.

CONCLUSION

The present study reported a high frequency of ER and PR positive expression. The most common histology observed was endometrioid adenocarcinoma histology. Our study also highlighted the strong association of ER and PR expression with grade, histology and stage of the tumour. ER and PR receptor positivity may have prognostic value and can be exploited to develop more targeted therapy.

Conflict of Interest: None.

Authors' Contribution

AS: Conception, data collection, GH: Supervision of data, critical review, PM: Data review, data acquisition, SB: Manuscript writing, MS: Statistical analysis, KA: Manuscript writing.

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