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# Immunohistochemical expression of estrogen receptors, progesterone receptors, and human epidermal growth-factor receptor 2/neu in epithelial ovarian tumors

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# Immunohistochemical expression of estrogen receptors, progesterone receptors, and human epidermal growth-factor receptor 2/neu in epithelial ovarian tumors

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## Abstract

**Background and objectives**

Epithelial ovarian cancer (OC) is a clinically, morphologically, and molecularly heterogeneous disease. Estrogen receptor (ER) β is highly represented in normal ovarian epithelial cells and benign tumors, but ERα is the main form expressed in OC. ERα-positive OC had a favorable outcome. Progesterone receptor (PR) expression in ovarian tumors is a good prognostic marker associated with longer progression-free survival. Human epidermal growth-factor receptor (HER) 2 expression is associated with a worse prognosis. The aim of the study was to evaluate immunohistochemical (IHC) expression of ER, PR, and HER2/neu in ovarian epithelial tumors and to correlate their expression with different demographic, clinical, and pathological parameters.

**Patients and methods**

Sixty cases of primary ovarian epithelial tumors were studied according to their expression to ER, PR, and HER2/neu.

**Results**

There was a statistically significant relation between ER IHC and histopathological type of borderline tumor cases and also between PR IHC and histopathological types of both borderline and malignant tumor cases. A statistically significant relation was found between PR IHC and tumor grade and FIGO stage. Triple-negative tumors are significantly associated with mucinous carcinoma and with FIGO stage IV.

**Interpretation and conclusion**

Larger studies on a wider scale of patients, especially those with triple-negative ovarian tumor cases, are needed in order to elucidate the exact role of ER, PR, and HER2/neu as a possible prognostic marker in epithelial OC. Other markers are recommended to be used in association with ER, PR, and HER2/neu in order to improve test sensitivity.

**Keywords:** Borderline tumors, estrogen receptors, human epidermal growth-factor receptor 2/neu, ovarian cancer, ovarian epithelial tumors, progesterone receptors

## Introduction

Ovarian cancer (OC) is the most fatal gynecologic cancer, with 152 000 deaths worldwide annually [1]. It is the second most common gynecologic malignancy and the fifth leading cause of cancer death in females in developed countries [2].

In Egypt, primary malignant ovarian neoplasms represented 1.82% of all primary malignant neoplasms at National Cancer Institute (NCI) and 32.58% of malignant neoplasms of the female genital system. Primary malignant ovarian neoplasms represented 42.76% of all ovarian tumor cases. The epithelial carcinoma represented 81.61% of all primary ovarian malignant neoplasms. The most common types were papillary

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serous cystadenocarcinoma (46.36%) followed by mucinous cystadenocarcinoma (18.31%) and then endometrioid adenocarcinoma (7.64%) [3].

Epithelial ovarian cancer (EOC) is a clinically, morphologically, and molecularly heterogeneous disease [4]. It comprises four major histologic types (serous, endometrioid, mucinous, and clear cell), which are classified as low grade (well differentiated) or high grade (poorly differentiated) based on cytological atypia [5].

Recent advances in tumor molecular characterization have revealed that EOC can be divided into two distinct groups termed type-I and type-II carcinomas. Type-I tumors are uncommon and include low-grade serous, endometrioid, clear-cell, mucinous carcinomas, and Brenner tumors. They are genetically stable, clinically indolent, and are typically detected early; although, when diagnosed at advanced stages, type-I tumors tend to have a poor prognosis. Type-II tumors are more prevalent and include high-grade EOC (primarily high-grade serous OC), undifferentiated, and malignant–mixed mesodermal tumors. They typically present at advanced clinical stage and show high chromosomal instability with more than 80% displaying TP53 mutations and changes of the homologous-recombination DNA-repair pathway [6].

The ovaries are the primary source of estrogens, they are critical regulators of growth and differentiation in normal ovaries [7]. Through their mitogenic action, estrogens play a role in ovarian carcinogenesis [8]. Estrogens' biological actions are mediated by the estrogen receptors (ER), ERα and ERβ, which function as nuclear hormone-inducible transcription factors that bind to the estrogen-responsive elements present in the promoter regions of target genes and provide signaling systems for cell division and differentiation [9]. Although 67% of OCs are associated with ER expression, anti-estrogen therapy achieved limited success and the advantage of hormonal therapy has not been systematically studied [10]. Many studies have revealed that ERβ is highly represented in normal ovarian epithelial cells and benign tumors, but ERα is the main form expressed in OC [8]. ERα-positive OC had a favorable outcome [11].

ERβ expression is decreased in many tumors, including OC [12]. Loss of ERβ expression increases the risk for metastasis [13] and correlates with shorter overall survival and the poor clinical response to chemotherapy in OC [14].

Progesterone is a steroid hormone produced by the corpus luteum in the ovaries. It works together with estrogen to promote follicle maturation, ovulation, and corpus luteum formation [9]. The effects of progesterone are mediated by progesterone receptor (PRs) [15].

PR expression, especially PR-B in ovarian tumors, is a favorable prognostic marker associated with longer progression-free survival [11,16].

PR activation leads to apoptosis in OC cells, which could explain the improved survival associated with PR-positive tumors [17].

The human epidermal growth-factor receptor (HER) family of receptors is implicated in the etiology of a variety of human malignancies. They participate in cellular proliferation and differentiation by regulating cell growth, survival, and differentiation via numerous signal-transduction pathways [18].

HER2 amplification and overexpression play a key role in the pathogenesis of different cancer types: breast, ovarian, gastric, and esophageal carcinomas [19].

The mechanism of carcinogenesis is the unlimited formation of homodimers and heterodimers of HER2/neu that increases the proliferation and migration of cells, inhibition of apoptosis, neoangiogenesis, and in the end leads to tumor formation and metastasis [20].

HER2 expression in EOC is more commonly detected in the serous subtype, in older patients, advanced stage, and high-grade differentiation. Its overexpression or amplification in OC ranges from 2 to 66% [21]. Some studies have shown that HER2 expression is associated with a poor prognosis, while others have not found any relation between HER2 and survival [22].

## PATIENTS AND METHODS

The pathology files at the Pathology Departments of Kasr Al-Aini, Al-Galaa Teaching and Ahmed Maher Teaching Hospitals were revised to retrieve 60 cases of primary epithelial ovarian tumors, borderline and malignant subtypes covering different age groups from January 2017 to December 2019. These specimens were collected through surgical procedures, including total hysterectomy with oophorectomy and ovarian cystectomy.

Demographic and clinicopathological data were obtained from the patients' medical files and pathological reports, including age, type, grade, and stage.

Sections from the paraffin-embedded tumor blocks of the selected cases were cut at 4-μm thick and then stained by hematoxylin and eosin for routine histopathological examination.

Three extra sections were cut from each paraffin block to be stained with ERα, PR, and HER2/neu using streptavidin–biotin–peroxidase technique.

The antibodies used were monoclonal rabbit anti-human ERα (Dako Omnis, Santa Clara, CA, USA, clone EP1, 1: 50) and monoclonal mouse anti-human PR (Dako USA, clone PgR636, 1: 50), which identify the ERα and PR nuclear protein antigens.

The primary antibody used for HER2/neu antigen was polyclonal rabbit anti-human C-erbB-2 (MBO/TEG, Dako USA, 1: 800).

ER and PR nuclear staining were considered as positive in ER and PR [23]. According to the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) issued guidelines, the tumors with

more than or equal to 1% positively staining cells should be considered ER/PR positive [24].

HER2/neu was scored visually according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines: (a value of 0 represents no immunostaining; 1+: weak incomplete membranous staining of <10% of tumor cells; 2+: complete membranous staining, either uniform or weak of ≥10% of tumor cells; and 3+: uniform intense membranous staining of ≥30% of tumor cells). Scores of 0 and 1+ were considered as negative for HER2/neu expression, 3+ as immune-positive, while 2+ was weakly or borderline positive [25].

The immunohistochemical (IHC) staining results were analyzed and correlated with the demographic, clinical, and histopathological parameters of the cases using Statistical Package for Social Sciences (SPSS, Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.), version 21 using $\chi^2$ test. The significance of the results was assessed by determining the P value. A P value of less than 0.05 was considered statistically significant.

## RESULTS

This retrospective cohort study was conducted on a total number of 60 EOTs, 40 malignant and 20 borderline tumors. Patient's ages ranged between 19 and 72 years with a mean age 44.12 years and median age 42.5 years. In malignant cases, ages ranged between 22 and 72 years with a mean age of 48.90 years and median age is 48.00 years. In borderline cases, ages ranged between 19 and 60 years with a mean age of 34.55 years and median age is 34.00 years.

Among the 40 malignant cases of OCs, 20 (33.3%) cases were serous carcinoma, 11 (18.3%) were endometrioid, four (6.7%) were clear-cell carcinoma, three (5%) were mucinous, only one (1.7%) case was malignant Brenner, and only one (1.7%) case was undifferentiated carcinoma. While among the 20 borderline cases, 20 (21.7%) cases were serous borderline tumor, six (10%) were mucinous borderline tumor, and only one (1.7%) case was Brenner tumor.

Among the 40 malignant cases, 19 (47.5%) cases were grade 3, 17 (42.5%) were grade-2 tumors, and only four (10%) cases were grade 1.

Out of 29 hysterectomy specimens, 15 (51.7%) cases were FIGO stage I. Ten (34.5%) were stage II, two (6.9%) were stage III, and also two (6.9%) cases were stage IV.

ER expression was low in borderline tumors (9/20 cases, 45%) compared with malignant tumors (27/40 cases, 67.5%). PR expression was higher in malignant cases (30/40 cases, 75.5%) compared with borderline tumors (13/20 cases, 65%). About 56.6% of cases showed combined ER and PR IHC expression.

All of the ovarian tumor cases showed loss of IHC expression of HER2/neu (100%).

There was a statistically significant relation between ER IHC and histopathological type of borderline tumor cases (P = 0.023), among 20 cases of BOTs, nine cases were ER positive, out of them, eight (88.9%) cases were borderline serous tumor (Fig. 1) and one (11.1%) case was borderline Brenner tumor. Eleven cases were ER negative, six (54.5%) of them were borderline mucinous tumor and five (45.5%) cases were borderline serous tumor.

There were no statistically significant correlations between ER IHC expression and types of ovarian tumor cases (malignant and borderline), histopathological type of malignant cases, tumor grade, or tumor FIGO stage (P = 0.094, 0.089, 0.226, and 0.175, respectively).

There was a statistically significant relation between PR IHC and histopathological types of both borderline and malignant tumor cases (P = 0.001 and 0.006, respectively). Among 20 cases of BOTs, 13 cases were PR positive, out of them, 12 (92.3%) cases were borderline serous tumor (Fig. 1) and one (7.7%) case was borderline Brenner tumor. Seven cases were PR negative, six (85.7%) cases were borderline mucinous tumor, and one (14.3%) case was borderline serous tumor. Among 40 malignant cases, 30 cases were PR positive, out of them, 18 (60%) cases were SC (Fig. 2), nine (30%) were endometrioid (Fig. 3), two (6.7%) were clear cell, and one (3.3%) case was undifferentiated carcinoma.

Also, there was a statistically significant relation between PR IHC and tumor grade (P = 0.053). Among 30 PR-positive malignant cases, 15 cases were grade 2 (50%) (Fig. 3), 11 (36.7%) were grade 3, and four (13.3%) cases in grade 1. While among 10 PR-negative cases, eight (80%) cases were grade 3.
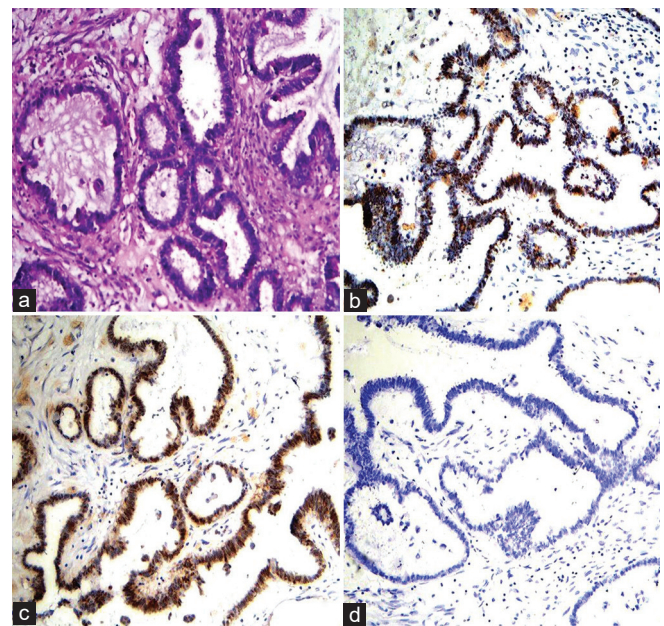


**Figure 1:** Borderline serous tumor (a), (b) ER, negative (×200), (c) PR, negative (×200), (d) HER2/neu, negative (×200).

A statistically significant relation is found between PR IHC and tumor FIGO stage (*P* = 0.034). Among 23 PR-positive malignant cases in hysterectomy specimens, 13 (56.5%) cases were FIGO stage I, eight (34.8%) were FIGO stage II, and two (8.7%) cases were FIGO stage III.

There were no statistically significant correlations between PR IHC expression and types of ovarian tumor cases (malignant and borderline).

Accordingly, seven cases were triple negative, including three cases of MC (42.9%) (Fig. 4) and one case for each CCC (Fig. 5), EC, MBT, and SC (14.3%) with a statistically significant relation (*P* = 0.001). Moreover, five (71.4%) cases

were grade 3 and two (28.6%) cases were grade 2, with no statistically significant correlation (*P* = 0.323).

There was a statistically significant relationship between the triple-negative IHC expression and the tumor FIGO stages (*P* = 0.004). About 50% of cases were FIGO stage IV and 25% of cases were at FIGO stages I and II, respectively.

## Discussion

EOTs are the most common type of ovarian tumors, representing 60 and 85% of malignant ovarian tumors [26]. EOTs include a heterogeneous group of several histopathological structures [27].
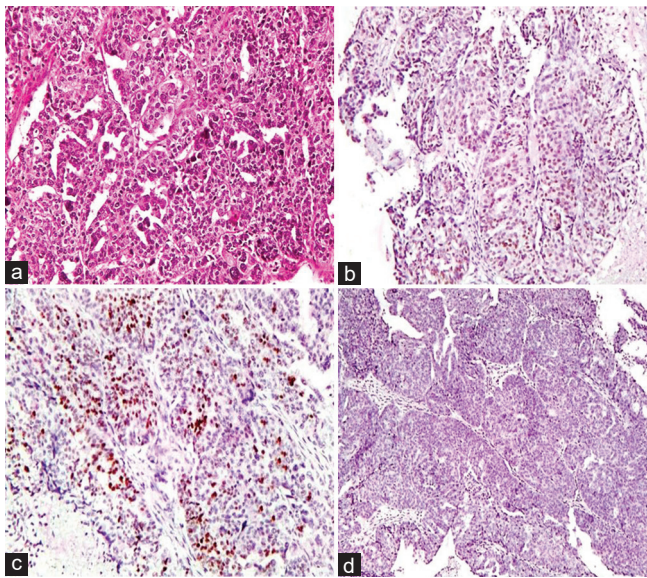


**Figure 2:** High-grade serous carcinoma (a), (b) ER, positive (×200), (c) PR, positive (×200), (d) HER2/neu, negative (×200).



epithelial tumor) (X200).                    negative: triple negative

**Figure 3:** Endometrioid adenocarcinoma, grade 2 (a), (b): ER, positive (×200), (c) PR, positive (×200), (d) HER2/neu, negative (×200).



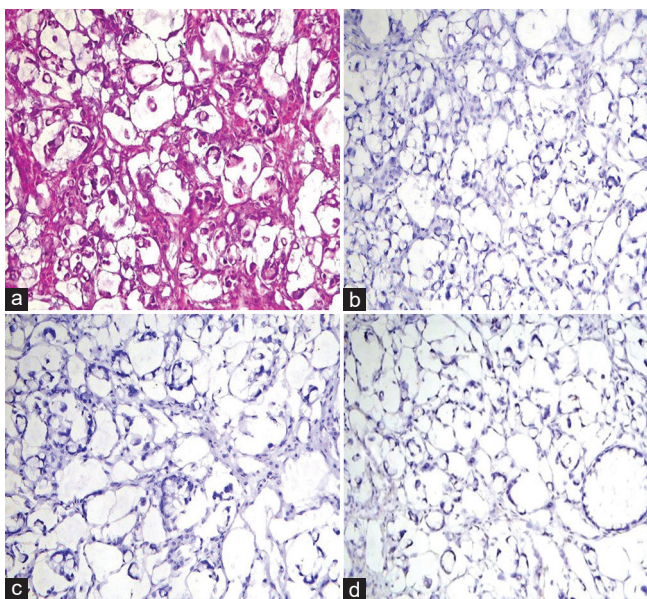**Figure 4:** Mucinous adenocarcinoma, grade 2 (a), (b, c, and d) ER, PR, and HER2/neu, negative: triple-negative epithelial tumor (×200).
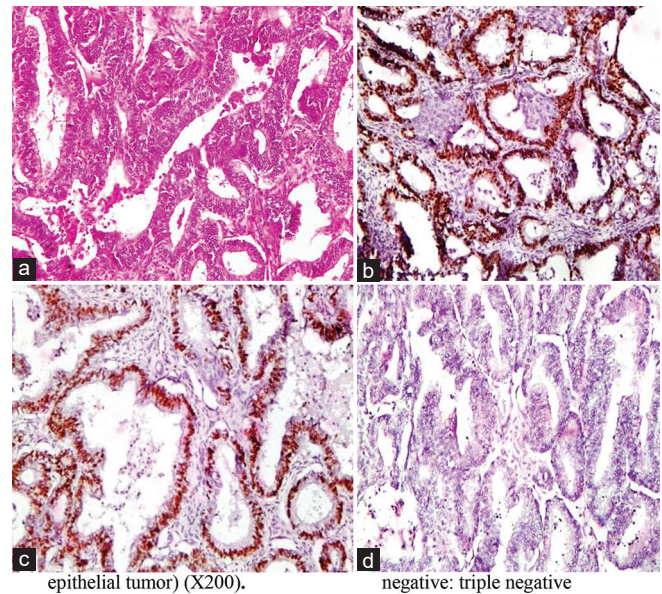


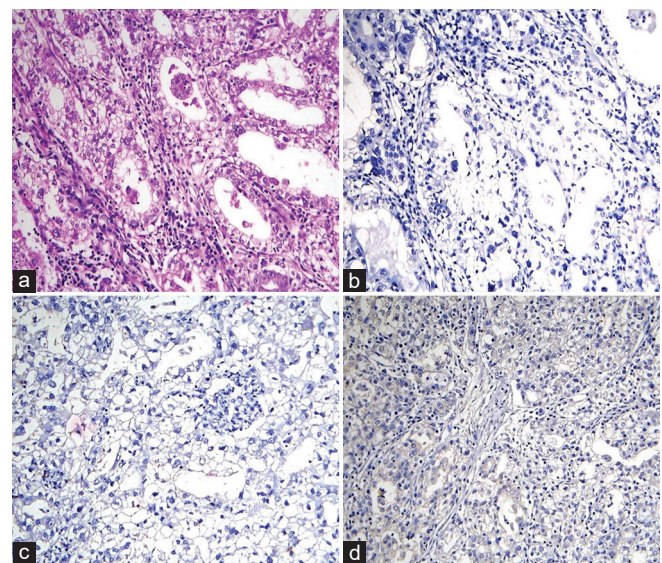**Figure 5:** Clear-cell carcinoma, grade 3 (a), (b, c and d) ER, PR, and HER2/neu, negative: triple-negative epithelial tumor (×200).

Concerning the IHC expression of ER and PR among EOT cases, our study revealed more frequent expression of PR (71.7%) than ER (60%). Expression of ER/PR was more frequently expressed in malignant cases (67.5 and 75%, respectively) compared with borderline tumors (45 and 65%, respectively).

These results were in agreement with the results obtained by Farooq *et al*. [28], Atla *et al*. [29], and Dhatwalia *et al*. [30], who revealed that more cases showed expression of PR than ER expression in EOT and OC cases. Naik *et al*. [31] and Verma *et al*. [23] reported that the number of ER-positive cases was higher in malignant than borderline tumors. Sylvia *et al*. [32] revealed that the number of cases with PR expression was higher in malignant compared with borderline tumor type and the frequency of ER expression was lower in malignant cases than in borderline tumors. Both malignant and borderline tumors showed positivity for HER2/neu. Sallum *et al*. [33] reported that most BOTs and carcinomas were ER and/or PR negative. Naik *et al*. [31] and Verma *et al*. [23] showed that the IHC expression of PR was frequently higher in borderline tumors as compared with that in malignant tumors. Shen *et al*. [34] reported that the frequency of ER expression was more in malignant cases than PR and the frequency of PR positivity in the borderline tumors was higher than that in OC. Garg *et al*. [35] reported lower PR expression in their study than ER expression in OC cases.

Among the borderline tumor cases, our study revealed that IHC expression of ER/PR was more frequent in serous borderline tumor cases (88.9 and 92.3%, respectively). These findings are in agreement with the study done by Shen *et al*. [34].

According to OC cases, our study showed that the frequency of ER/PR positivity is more in SC cases (55.6 and 60%, respectively), followed by EC (29.6 and 30%, respectively).

Studies done by Høgdall *et al*. [36], Sieh *et al*. [37], and Anwar *et al*. [38] were in agreement with our results as they revealed that ER expression was more frequent in SC followed by EC than MC and CCC.

We found no significant difference in ER/PR expression between BOT and OC cases. In BOTs, the frequency of ER and PR expression was significantly higher in serous than in BBTs ($P = 0.023$ and $P < 0.001$, respectively). In carcinomas, no difference was detected in ER expression between different histopathological subtypes of OCs, while PR expression was significantly higher in the frequency of SC versus EC, CCC, and UC ($P = 0.006$).

Our findings were in agreement with the results done by Lindgren *et al*. [39], Høgdall *et al*. [36], Arias-Pulido *et al*. [40], Tangjitgamol *et al*. [41], and Sallum *et al*. [33] who found that there was no statistical difference in ER/PR expression between BOT and OC. Similarly, Sylvia *et al*. [32], Farooq *et al*. [28], Atla *et al*. [29], and Dhatwalia *et al*. [30] revealed that the frequency of PR expression was significantly higher in serous tumors as compared with other histopathological types.

In contrast to our results, Verma *et al*. [23] revealed that the difference in ER expression among different histopathological categories was found to be statistically significant, while the difference in PR expression was not statistically significant. Shen *et al*. [34] revealed that there was no difference in the frequency of ER or PR expression in BOTs.

Our HER2/neu findings showed loss of IHC expression among all the included cases (100%). Wu *et al*. [42] reported that HER2/neu expression was limited in OC cases by 6.7% and it was not encountered in ovarian borderline tumors that are nearly approximated to our results. While Goel *et al*. [43] reported that all borderline tumor cases showed loss of IHC expression of HER2/neu, which is in agreement with our study.

In contrast with our study, Hadisubroto and Suwiyoga [44] revealed that the number of malignant cases with HER2/neu expression was higher than borderline tumors, and Ajani *et al*. [45] reported that HER2/neu expression between OC cases was 37%.

According to the tumor grade and its correlation with IHC, our study found a higher ER expression in grade-3 tumors (51.9%) compared with grade-2 (37%) and grade-1 tumor (11.1%), and it was not statistically significant. While PR expression was more frequent in grade-2 tumors (50%), followed by grade-3 (36.7%) and grade-1 tumor (13.3%), and it was statistically significant ($P = 0.053$).

Partly in agreement with our study, Naik *et al*. [31] and Verma *et al*. [23] reported that there was no correlation between expression of ER/PR and grade of malignant tumor. Dhatwalia *et al*. [30] revealed that ER/PR expression was higher in high-grade tumors with no statistical correlation between ER/PR expression and tumor grade. Also, Farooq *et al*. [28] showed that PRs were expressed in low-grade tumors and ERs were mostly expressed in high-grade tumors.

On the other hand, Tanvanich *et al*. [46] revealed that positive ER expression was significantly lower in well-differentiated than moderately and poorly differentiated carcinomas, whereas there was no significant association between PR and grade of tumor. Buchynska *et al*. [47] demonstrated that higher-grade tumors had low ER positivity. In addition, Sylvia *et al*. [32] and Atla *et al*. [29] reported that correlation between ER-positive tumors with grade was statistically significant.

There was no significant correlation between ER expression and tumor FIGO stages, but there was a significant correlation between PR expression and tumor FIGO stages with more expression in FIGO stage I (56.5%) ($P = 0.034$).

Similar to this study, Anwar *et al*. [38] revealed that a higher percentage of stage-I tumors exhibited ER/PR. In addition, Garg *et al*. [35] revealed a significant association between PR expression and early FIGO stages. Ajani *et al*. [45] and Dhatwalia *et al*. [30] showed no statistical correlation between ER and tumor FIGO stages.

In contrast to our results, Burges *et al*. [48], Sylvia *et al*. [32], Farooq *et al*. [28], Atla *et al*. [29], Kaur *et al*. [49], and Verma

*et al.* [23] showed that ER/PR expression increases with increasing FIGO-stage tumor.

We found that seven (17.5%) cases were triple-negative tumors, including three (42.9%) cases of mucinous and one case of each serous, endometrioid, clear-cell, and malignant Brenner tumor (14.3%). The most frequent tumor grade was grade 3 (71.4%).

Sylvia *et al.* [32] were partly in agreement with our study. They reported that 24.24% were triple-negative tumors. But there was no high-grade or advanced-stage tumors.

On the other hand, de Toledo *et al.* [50] and Ajani *et al.* [45] reported that among TNEOC cases, most of them were in the early FIGO stage.

We reported that there was a statistically significant relationship between the triple-negative IHC expression and the histopathological tumor types and the tumor FIGO stages ($P = 0.001$ and $0.004$, respectively). But there was no statistically significant correlation between triple-negative IHC expression and tumor grades. These results were in concordance with the study done by Ajani *et al.* [45], who reported that a significant percentage of MC was negative for ER, PR, and HER2/neu, and this was statistically significant. No significant association was also found between the TNEOC and histological grade.

In contrast with our results, Liu *et al.* [51], Demir *et al.* [52], de Toledo *et al.* [50], and Ajani *et al.* [45] reported that there was no significant association between the TNEOC and the histopathological subtypes and between TNEOC and FIGO stages.

In conclusion, larger studies on a wider scale of patients, especially those with triple-negative ovarian tumor cases, are needed in order to elucidate the exact role of ER, PR, and HER2/neu as a possible prognostic marker in EOC. Other markers are recommended to be used in association with ER, PR, and HER2/neu in order to improve test sensitivity.

### Ethical Clearance

The study was approved by the institutional Ethics Committee of Ahmed Maher Teaching Hospital No. AMH-00033.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Conflicts of interest

There are no conflicts of interest.

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