Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Expression of Estrogen Receptor (ER), Progesterone Receptor (PR), Her2/neu in Various Types of Epithelial Ovarian Tumors

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Article Info

10.30699/jogcr.9.1.7

Received: 2023/05/26;
Accepted: 2023/10/09;
Published Online: 22 Jan 2024;

Use your device to scan and read the article online

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ABSTRACT

Background & Objective: The highest mortality rate in gynecologic cancers is attributed to ovarian origin. Expression of the estrogen and progesterone receptors (ER and PR) and human epidermal growth factor receptor 2 (Her2/neu) in endometrial cancer and breast cancer was found to be associated with the response to treatment and prognosis. However, because of inconsistent results from previous studies, the data regarding ovarian cancer is still inconclusive.

Materials & Methods: The current retrospective cross-sectional study was performed on 234 tissue samples of different types of ovarian tumors (benign, borderline and malignant) from the archive of the University Kebangsaan Malaysia Medical Center (UKMMC) during 10 years. Tissue microarrays (TMAs) were constructed on representative areas of formalin-fixed paraffin-embedded tissue blocks using ER, PR and HER2 immunohistochemical staining.

Results: The prevalence of ER and PR overexpression was 36% and 35% in benign tumors, 8% and 24% in borderline tumors and 51% and 46% in malignant tumors, respectively. ERα overexpression was more common among serous malignant ovarian tumors (49%) (P<0.001). PR positivity was more prevalent in serous benign tumors (P=0.02). There was no significant relationship between the stage of the tumor and the status of ERα (P=0.12) and PR (P=0.19). Her2/neu overexpression was only seen in borderline neoplasms (8%) and malignant mucinous tumors (4%). No association was found between Her2/neu overexpression and the level of tumor differentiation, clinical stage, tumor size, or patient's age.

Conclusion: The observed ER positivity in serous carcinoma and Her2/neu overexpression in malignant mucinous tumors, could be considered as a clue for choosing therapeutic agents. The role of anti-HER2 therapy in clear cell carcinoma is still debated and needs more investigation.

Keywords: Ovary, Müllerian, Estrogen Receptor, Progestrone Receptor, HER2/neu, Immunohistochemistry

Introduction

The exact etiology of ovarian cancer is still not known; however, some risk factors have been identified for ovarian cancer, including early menarche and late menopause, having no pregnancy, obesity, receiving hormone replacement treatment at menopause, and ethnicity. The majority of these risk factors are related to changes in serum sex hormone levels in women **(1)**.

At present, clinicopathological parameters are used to determine the prognosis of ovarian cancer. These parameters include stage, histological characteristics, grade, and post-operative residual tumor. However, these indicators are still inadequate for determining the prognosis of ovarian cancer. For instance, the clinical outcomes of ovarian cancer differ between patients with similar clinicopathological characteristics. Therefore, there is a need for biological tumor markers that can reliably predict tumor aggressiveness to enable clinicians to determine prognosis and tumor response to treatment and thus identify the high-risk patients who need to be treated more aggressively or require alternative treatment and close follow-up **(2)**.

Recent developments in molecular biology and immunologic methods have led to the nomination of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2/neu) as potential biomarkers for the clinical behavior of different cancers **(3)**. Epidemiological studies provided solid evidence suggesting the

implications of steroid hormones, especially estrogen and progesterone, for ovarian carcinogenesis (4).

Estrogen and progesterone are important hormones secreted from the ovaries and act through specific hormone receptors. The proliferative and apoptotic effects of sex hormones are mediated through estrogen and progesterone receptors in ovarian cancer cells (1). There is a body of literature that shows a significant association between ER or PR overexpression and survival rate and longevity that are considered better clinical outcome indicators in relation to cancer subtypes and ethnicities. However, the underlying mechanisms are still unknown (3).

Human epidermal growth factor receptor 2 (Her2/neu) belongs to the epidermal growth factor receptor family (4). Her2/neu is important in tumor cell growth and metastasis and is involved in expansion and progression of various human cancers (4). Her2/neu has been proposed as a predictor of poor prognosis (5). Various studies evaluated Her2/neu in targeted therapy for ovarian tumors; however, the findings of the previous studies were not conclusive (5, 6). Deeper evaluation of ER and PR signaling as well as Her2/neu expression is required to improve ovarian cancer treatment. This study was designed to assess the status of ER, PR, and Her2/neu expression and their relationship with clinicopathologic characteristics in different ovarian tumors.

Methods

Study population:

The Ethics Committee of the University Kebangsaan Malaysia Medical Center (UKMMC) approved this study. A total of 243 samples were collected from the UKMMC archive of pathology over the course of 10 years. Exclusion criteria were metastatic carcinoma, inappropriate or missing tissue blocks, or clinicopathological data. The diagnosis and histopathological type of the tumors were confirmed by two pathologists after reviewing the histopathological slides.

H&E staining of formalin-fixed paraffin-embedded tissue blocks was used to select representative areas. Tissue microarray (TMA) consisted of 1.0 mm diameter core tissue extracted from marked areas by Alpheleys TMA Booster tissue core extractors (Plaiser, France), and re-embedded into recipient paraffin blocks. Normal ovarian tissues were used as control tissue in the TMA blocks. Histopathology reports were obtained from the Laboratory Information System and the medical record archives of the surgical department in order to extract information regarding the patient's age, histological type of the tumor, and stage. Patient information was kept anonymous and patients were coded accordingly. The stage of the ovarian tumor was also assessed in this study. In order to increase the number of cases in each stage, sub-categories of each stage were merged together (Ia, Ib and Ic were merged to form stage I; stage IIa, IIb and IIc were merged to form stage II and IIIa, IIIb and IIIc were merged to form stage III).

Immunohistochemistry Staining

The 1:400 dilution of monoclonal mouse anti-human Progesterone Receptor Clone PgR 636 Ready-To-Use (Code IS068, Dako, Denmark) and monoclonal rabbit anti-human Estrogen Receptor α Clone EP1 Ready-To-Use (Code IS084, Dako, Denmark) were used for immunohistochemical (IHC) staining. Breast carcinoma was chosen as the control tissue. IHC staining was performed using a 1:1500 dilution of polyclonal rabbit anti-human C-erbB-2 oncoprotein (Code A0485, Dako, Denmark). Breast carcinoma tissues with 3 different scoring levels (3+, 2+ and 1+) were chosen as the control tissue. The immunostaining was performed after deparaffinization, rehydrating the sections, and using the heat antigen retrieval technique. The manufacturer's standard protocols were used for immunostaining.

The ER and PR staining assessment was performed based on the guideline recommendation for ER and PR IHC testing in breast cancer proposed by the American Society of Clinical Oncology/College of American Pathologists (ASCO-CAP) (6). Scoring for Her2/neu, was performed based on the current breast cancer guidelines by the American Society of Clinical Oncology, ASCO)/College of American Pathologists (CAP) (7).

Two pathologists performed the scoring independently according to the mentioned protocols. Both pathologists were blinded to the clinicopathologic characteristics and outcomes of the patients.

Statistical analysis:

Data analysis was performed by the statistical package for social sciences (SPSS) version 23 (Chicago, Illinois, USA). Continuous variables were shown as the mean and standard deviation (SD). Categorical variables, including tumor stage and histological type of tumor, were shown as frequency and percentage. Association between different immunohistochemical stainings assessment in terms of study parameters including age and tumor clinical stage; and histological type were assessed using the chi-square test. A statistically significant association was considered when the observed p value was smaller than 0.05.

Results

A total of 234 ovarian tumor samples were identified over a 10-year period. The mean (SD) age of the subjects was 46 ± 16 years old. Most of the subjects were Malay (158, 67%) followed by Chinese (55, 23%), other ethnicities (13, 6%) and Indians (8, 4%).

Of the 234 ovarian tumors, 114 were benign tumors, 37 were borderline, and 83 were malignant tumors. The

mean age of subjects with benign tumors was 44 ± 15 years old, while the mean age of subjects with borderline and malignant tumors was 40 ± 18 and 51 ± 14 years old, respectively. In this study, the most frequent type of ovarian tumors were serous tumors (118, 50.4%), followed by mucinous tumors (93, 39.7%), endometrioid adenocarcinoma (13, 5.6%), and clear cell tumors (7, 3.0%), as well as sero-mucinous tumors (2, 0.9%) and cystadenofibromas not specific subtype (0.4%) (Figure 1). Among the serous tumors, 65 subjects (55%) were benign, while borderline and malignant tumors were seen in 4 (3%) and 49 (42%) subjects, respectively. Among the mucinous tumors, 48 (52%) were benign, while borderline and malignant tumors were seen in 31 (33%) and 14 (15%) subjects, respectively.

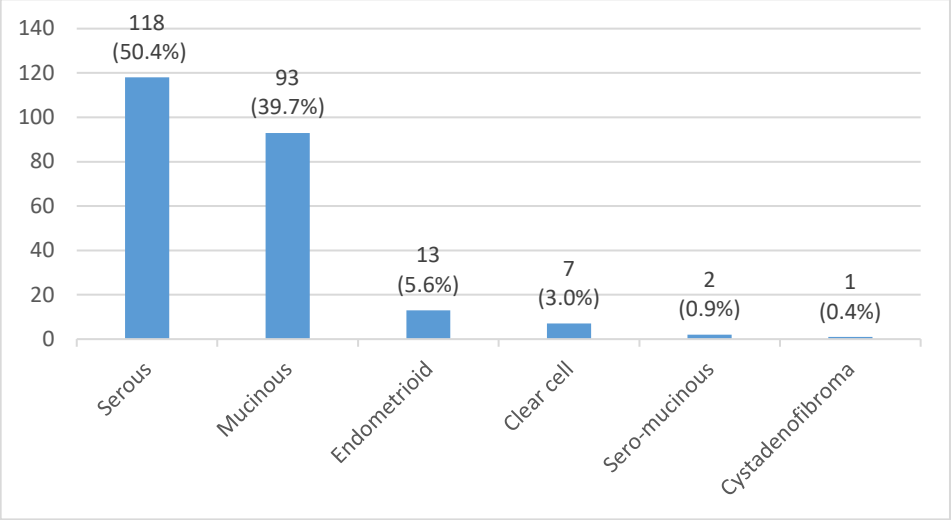

Figure 1. Distribution of tumor types amongst study subjects

This study also revealed that, although not statistically significant, benign, borderline, and malignant tumors were more frequent among Malay (66 % in benign, 69 % in borderline, and 71 % in malignant groups) compared to Chinese and Indian ethnicities.

Among the 83 subjects with malignant tumors, the mean age of ERα positive subjects was 50 ± 15 years old. No significant relationship was found between ERα status and age and ethnicity of the subjects (P=0.62 and P=0.09, respectively). Type of tumor and ERα status were significantly correlated in subjects with malignant ovarian tumors (P<0.001), which was more common among serous tumors (49%). However, no significant relationship was found between ERα status with benign and malignant ovarian tumors. No significant relationship was found between the stage of the tumor and ERα status (P=0.12).

The mean age of PR positive subjects was 49 ± 14 years old. No significant relationship was found between PR status and age and ethnicity of subjects (P=0.62 and P=0.53 respectively). No significant relationship was found between PR positivity and benign, borderline, and malignant tumors or type of malignant ovarian tumors (P=0.14 and P=0.76). However, PR positivity was significantly correlated with the type of tumor in benign ovarian tumors. In other words, PR positivity was common among serous benign tumors (P=0.02). PR status was not significantly correlated with tumor stage (P=0.19).

None of the Her2/neu positive subjects had benign tumors. Among subjects with borderline tumors, only two subjects showed Her2/neu positivity. The mean age of subjects with positive Her2/neu was 36 ± 24 years old. We found that Her2/neu positivity was only seen in borderline and malignant tumors, but not among benign tumors. Moreover, Her2 positivity prevalence was higher in borderline compared to malignant tumors.

Discussion

In 2018, ovarian cancer was ranked as the eighth most common diagnosis and etiology for cancer mortality among women **(8)**. The ovarian cancer is contributed to five percent of the total malignancies among Malaysian women. The crude incidence rate of ovarian cancer in Malaysia is 7.4 per 100,000 populations, and it is the fourth common malignancy affect Malaysian women **(9)**.

Interestingly, the ovary has the largest number of tumor types in the body, which can be divided into germ cell, epithelial, and tumors arising from sex-cord stroma, as well as metastatic neoplasms **(10)**. The most common ovarian malignancies are epithelial ovarian tumors with high grade serous carcinoma dominance **(8)**.

The reason for high mortality in ovarian carcinoma is treatment resistance. Although it was initially hypothesized that cisplatin-based chemotherapy can

improve the survival in ovarian cancer, but the recurrence percentage was still high even in patients who showed favorable chemotherapy response **(11)**. Therefore, there is a need for more effective treatment modalities and better early detection methods to reduce ovarian cancer morbidity and mortality. Therefore, "targeted" oncologic therapies were developed with the hypothesis that these therapies are more effective and less toxic compared to conventional treatments **(12)**.

Ovarian epithelial tumors are classified based on their histologic features. Therefore, ovarian epithelial cells are divided into benign, borderline, which have low malignant potential but express atypical proliferation, or malignant. This study showed that benign tumors (114/234 subjects, 48.7%) were the most prevalent ovarian tumors followed by malignant (83/234 subjects, 36%) and borderline tumors (37/234 subjects, 16%). This observation was almost similar to the findings of a previous study **(13)**.

Current study revealed that patients with malignant tumors were significantly older than those with benign tumors (44 years vs. 51 years, respectively, P<0.001) as well as borderline and malignant tumors (39 years vs. 51 years, respectively, P=0.001). This finding was similar to previous studies showing that patients with malignant ovarian tumors were older compared to those with tumors that were benign and borderline **(14-16)**. Morice P. reported that patients with borderline ovarian tumors are 10 years younger than patients with malignant tumors **(14)**.

In this study, serous tumors were the most common benign ovarian tumors (47/114, 41%) followed by mucinous tumors (27/114 subjects, 24 %). The reported prevalence of serous and mucinous malignant ovarian tumors varies between different studies. The prevalence of serous malignant ovarian tumors was reported to range from 18.9% to 70%, while the prevalence of mucinous malignant tumors was reported to vary from 3 to 12% **(17, 18)**. Although this study was not designed to identify the incidence rate of different types of ovarian tumors, the incidence rate for serous and mucinous tumors in this study were in keeping with previous studies **(17, 18)**.

ERα expression

ERα was positive (more than 1%) in 39% of all cases. 36% of benign, 8% of borderline, and 51% of malignant ovarian tumors. Similarly, a previous study reported a higher prevalence of both subtypes of ER (ERα and ERβ) in benign and malignant ovarian tumors compared to borderline tumors **(19)**. In contrast, Abu-Jawdeh et al., found that 90% of the borderline tumors of the ovary are ERα positive **(20)**. This difference might be related to the few borderline subjects found in our study.

Interestingly, ERα was only positive in serous tumors. While some previous studies found an absence of ERα expression among mucinous samples, other studies reported low to high expression of ERα in mucinous tumors **(21, 22)**. This discrepancy between studies could be explained by the utilization of different techniques or enzyme isotopes in immunohistochemistry or by histological misclassifications between mixed epithelial or subtypes of mucinous tumors, including metastatic tumors of endocervical or intestinal origin **(19, 23)**.

Ajani et al. reported that the highest PR positivity was observed in endometrioid and low grade serous carcinomas, while mucinous and clear-cell carcinomas had the lowest PR positivity. The highest ER positivity was observed in low-grade serous carcinomas, followed by high-grade serous carcinomas and the lowest ER positivity was observed in clear cell carcinomas, which were the least positive **(2)**.

Among subjects with benign and malignant tumors, a higher rate of ERα-positivity was seen among Malays compared to the Chinese. In addition, in borderline tumors, ERα was positive only in Malays. The findings of this study reflect the unique distribution of ERα expression in ovarian tumors between different ethnicities in Malaysia. Further studies are needed to assess the relationship between ethnicity and ERα expression in ovarian tumors.

PR expression

This study revealed that PR expression was seen in 35% of benign ovarian tumors, while PR expression was seen in 24% and 46% of borderline and malignant tumors, respectively. Previous studies showed different expression of PR in benign, borderline and malignant ovarian tumors **(19, 24, 25)**. Lindgren et al., showed that PR expression was higher in borderline ovarian tumors compared to benign and malignant ovarian tumors **(19)**. This difference might be due to the higher number of benign and malignant tumors and lower number of borderline tumors in the current study compared to the other studies.

In benign tumors, PR was positive in 47% of serous tumors and 14% of mucinous tumors, similar to the findings of a previous study by Sylvia, Kumar and Dasari **(26)**.

ER positivity was observed more in serous (30%) compared to mucinous (8%) carcinomas, and this association was stronger among serous compared with mucinous types. This finding was in line with the results of the study conducted in Tunisia and Mexico **(27, 28)**.

The findings of this study reflected the different distribution of PR positivity among different ethnicities (Malaysian and Chinese) but this difference did not reach statistical significance. The effect of ethnicity on PR presentation in ovarian tumors should be evaluated in further studies.

Her2/neu expression

Importantly, this study revealed that Her2 was positive only in borderline (2/26, 8%) and malignant

ovarian tumors (2/52, 4%). None of the benign tumors expressed Her2/neu.

Of borderline tumors, 2/4 cases were serous, and 2/4 cases were mucinous (Figure 2). Among malignant tumors, all were mucinous, and no immunoreactivity was seen in serous, clear cell, or endometrioid carcinoma. We also found that Her2/neu was present only in stage I tumors.

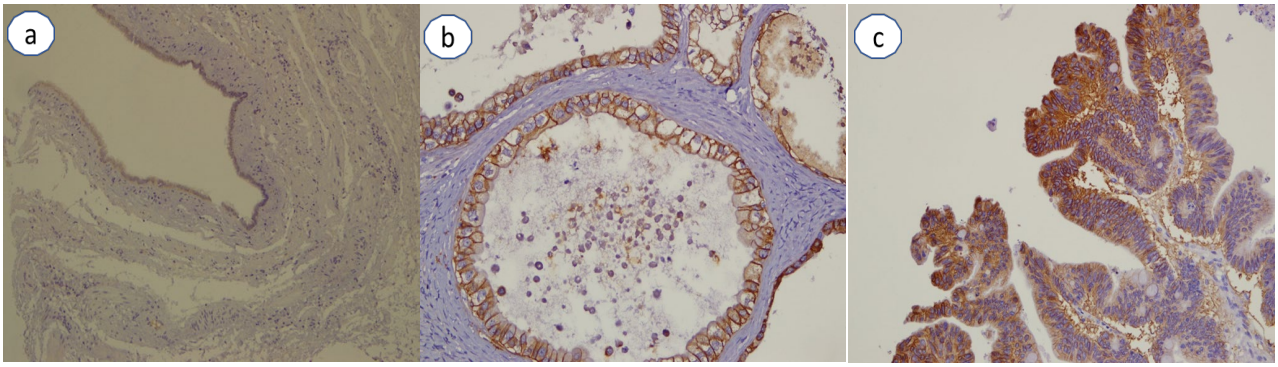

Figure 2. Her2/neu expression by IHC staining in ovarian tumors: negative expression in serous benign ovarian tumor (a); Strong and complete membranous expression in borderline serous ovarian tumor (b) and malignant ovarian mucinous tumor (c).

Although it was previously reported that Her2/neu overexpression was more common in mucinous carcinoma **(29)**, the current study failed to identify a significant difference in Her2/neu expression between histologic subtypes of ovarian carcinoma. Furthermore, the current study failed to identify a significant relationship between Her2/neu status and age, tumor size, and clinical stage.

The findings of previous studies in terms of Her2/neu expression in malignant ovarian tumors have been conflicting. The prevalence of Her2/neu overexpression ovarian tumors was reported to vary from as low as 4% to 69%. Similarly, the findings of previous studied regarding the association between HER2/neu gene or protein abnormalities and age, tumor characteristics, including tumor subtype, stage, grade, and size were inconsistent. The prevalence of Her2/neu gene amplification has been reported to range between 2% and 12.5 % **(30)**.

The reasons for these controversial results in terms of Her2/neu overexpression prevalence and association with cancer parameters could include inappropriate fixation, differences in sensitivity and specificity of the kits, difference in IHC staining method, differences in antibody clonality and interobserver variability in scoring, absence of standard interpretation guidelines in ovarian tumors, and heterogeneity of ovarian tumors **(30)**. The intratumoral heterogeneity in Her2/neu expression was reported to be as high as 20% among epithelial ovarian carcinomas. This extent of intratumoral heterogeneity can alter IHC results and may also influence Her2/neu targeted therapies **(30)**.

A recent meta-analysis showed that HER2 expression in ovarian cancer was associated with poor prognosis and could therefore be used as a prognostic biomarker in ovarian cancer **(6)**. However, this finding was not supported by our study probably due to the few Her2/neu positive subjects in our study. Therefore, this relationship needs to be investigated in further research.

Conclusion

This study revealed that ERα and PR were widely positive in different ovarian cancer types, while Her2/neu was only positive in borderline and malignant ovarian tumors. Moreover, Her2/neu positivity in borderline tumors was higher compared to malignant tumors. Therefore, a panel of these markers would help differentiate borderline and malignant ovarian tumors. This panel may also help in defining the prognosis of ovarian tumors and the development of targeted therapy.

Acknowledgments

None.

Conflict of Interest

There are no conflicts of interests.

Funding

None.

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How to Cite This Article:

Ameli, F., Entezarian, M., Masir, N., Chin, T. G. Expression of Estrogen Receptor (ER), Progesterone Receptor (PR), Her2/neu in Various Types of Epithelial Ovarian Tumors. J Obstet Gynecol Cancer Res. 2024;9(1):7-13.

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