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

Prevalence and Correlation of Age, Menopausal Status, Parity, FIGO Stage, and CA-125 Level with Estrogen and Progesterone Receptor Expression in High-Grade Serous Ovarian Cancer at Dr. Soetomo General Hospital

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Article Info

10.24200/jogcr.10.10.741

Received: 2025/05/08
Accepted: 2025/06/23
Published Online: 01 Sep. 2025

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ABSTRACT

Background & Objective: Ovarian cancer ranks seventh among the most common malignant tumors and is the eighth leading cause of cancer-related death in women worldwide. One of the most aggressive histopathological subtypes is High-Grade Serous Epithelial Ovarian Cancer (HGSOC), often diagnosed at an advanced stage. In recent decades, the expression of hormone receptors such as Estrogen Receptor (ER) and Progesterone Receptor (PR) has been widely studied for its potential as both a prognostic factor and therapeutic target.

Materials & Methods: This was an analytical observational study with a cross-sectional design using secondary data from medical records. Total sampling was employed for patients meeting the inclusion criteria. ER and PR expression were analyzed using immunohistochemistry, while clinical data included age, menopausal status, parity, CA-125 levels, and history of malignancy. Associations between variables were assessed using chi-squared and Mann-Whitney U tests with a significant threshold of $P<0.05$.

Results: Of the 40 HGSOC cases, 85% were ER-positive and 50% were PR-positive. However, no significant associations were found between hormone receptor expression and age, parity, menopausal status, CA-125 level, staging, or family history of malignancy ($P>0.05$).

Conclusion: Understanding ER and PR expression with clinical characteristics was not statistically significant. The studied samples were more ER positive and 50% PR positive in HGSOC cases. Further studies with larger sample sizes and more in-depth molecular approaches are needed to clarify the role of hormone receptors in the pathogenesis and management of HGSC.

Keywords: Ovarian cancer, Estrogen receptor, Progesterone receptor, Prevalence

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1. Introduction

Ovarian cancer is among the gynecological cancers with the highest global mortality. It ranks ninth in incidence and eighth in cancer-related deaths among women, causing an estimated 184,000 deaths annually, particularly in Northern Europe and the United State **(1)**. Genetic factors such as family history-especially of breast or colorectal cancer-increase ovarian cancer risk via BRCA1 and BRCA2 mutations, which impair tumor suppressor protein function and DNA repair mechanism **(2)**.

In 2018, ovarian cancer accounted for 4.4% of all cancer-related deaths among women. Its incidence continues to rise with population growth and shifting reproductive patterns, while mortality disparities reflect unequal access to early diagnosis and treatment. **(3)** Approximately 90% of ovarian cancers originate from epithelial tissue, with High-Grade Serous Ovarian Carcinoma (HGSOC) being the most aggressive subtype and the leading cause of ovarian cancer deaths **(4)**. Due to delayed diagnosis and rapid tumor progression, five-year survival rates remain low despite therapeutic advances **(3,5)**.

Molecular biomarkers such as Estrogen Receptor (ER) and Progesterone Receptor (PR) have gained increasing attention for their potential roles in targeted therapy. Estrogen stimulates cancer cell proliferation via ER, while anti-estrogen agents can counteract this effect **(6)**. PR is involved in regulating genes linked to

proliferation and DNA repair, influencing prognosis. BRCA1 mutations generally suppress ERα expression, contributing to a triple-negative phenotype, whereas BRCA2 mutations are often associated with ER positivity and better response to hormonal therapy **(7,8)**. Moreover, progesterone may exacerbate genomic instability in BRCA-mutated tissue through PR-B **(9)**.

The interaction between BRCA mutations and hormone receptor expression highlights the potential for more personalized hormonal therapy approaches. This study aims to determine the prevalence of Estrogen Receptor (ER) and Progesterone Receptor (PR) expression in patients with high-grade serous ovarian cancer and to assess its association with clinical characteristics such as age, menopausal status, parity, FIGO stage, CA-125 levels, and family history of malignancy. This research tests the hypothesis that there is a correlation between ER/PR expression and these clinical characteristics.

2. Materials and Methods

This study aimed to analyze ER and PR expression and their relationship with clinicopathological characteristics in patients with High-Grade Serous Epithelial Ovarian Cancer (HGSC). An analytical observational study with a cross-sectional design was conducted using secondary data from HGSC patients who underwent surgery and histopathological examination at Dr. Soetomo General Hospital, Surabaya, between January 2019 and December 2022. A total of 40 cases were obtained based on all patients who met the inclusion criteria during the study period. No formal statistical sample size calculation, such as a power analysis, was performed due to the retrospective design and the limited number of available cases.

Clinical characteristics analyzed included age, menopausal status, parity, clinical stage, CA-125 levels, family history of malignancy, and history of malignancy. Patients with a history of other primary malignancies, such as breast, colorectal, endometrial, or hematologic cancers, were excluded to avoid confounding hormonal receptor expression influenced by prior treatments or overlapping etiologies. Tumor tissue was fixed in 10% neutral-buffered formalin within 30 minutes post-surgery and processed into paraffin blocks according to standard protocols. Formalin-Fixed Paraffin-Embedded (FFPE) tumor tissues were sectioned at 4 µm and mounted on poly-L-lysine-coated slides. Slides were incubated with monoclonal primary antibodies against estrogen receptor (ER, clone SP1) and progesterone receptor (PR, clone 1E2); prediluted with Tris-HCl with carrier protein and 0.1% ProClin 300 (Ventana Medical Systems, Tucson, AZ, USA). Monoclonal primary antibodies for ER (SP1) and PR (1E2) were incubated for 16 minutes at 36°C on the Ventana BenchMark ULTRA platform after standard CC1 antigen retrieval, followed by hematoxylin II counterstaining and a 4-minute bluing step, in accordance with the manufacturer's instructions. Positive controls consisted of previously confirmed ER/PR-positive high-grade serous ovarian carcinoma tissues, while negative controls were processed by omitting the primary antibody. Immunoreactivity was assessed semi-quantitatively using the H-score method, with a threshold score ≥10 considered positive. ER/PR-positive high-grade serous ovarian carcinoma tissues previously confirmed by pathology were used as positive controls. Negative controls were run by omitting the primary antibody. Imunoreactivity for ER and PR was evaluated semi-quantitatively using the H-score method by two independent pathologists blinded to clinical data. The H-score was calculated using the following formula:

$$\begin{aligned} \text{H} - \text{score} = [&1 \text{ x } (\% \text{ weak staining}) \\ &+ 2 \text{ x } (\% \text{ moderate staining}) \\ &+ 3 \text{ x } (\% \text{ strong staining})] \end{aligned}$$

Tumor samples with an H-score≥10% were considered positive, consistent with previous studies on hormone receptor expression in HGSOC.

Statistical analysis was conducted using SPSS version 26.0, employing the chi-squared or Fisher's exact test for categorical data. The chi-squared test was used for assessing associations between categorical variables when the expected frequency in each cell was ≥5. When the expected frequency was <5 in more than 20% of cells, Fisher's Exact Test was applied instead to ensure the accuracy of the P-values. The independent t-test or Mann-Whitney U test for continuous data. A P-value<0.05 was considered statistically significant. In this study, no formal correction for multiple comparisons weas applied due to the limited sample size, which could reduce statistical power and increase the risk of Type II error. As a result, the reported p-values should be interpreted with caution and considered descriptive rather than definitive.

Ethical approval for this study was obtained from the Ethics Committee of Dr. Soetomo General Hospital, with reference number 3081/104/4/VIII/2024.

3. Results

In this study, most patients with High-Grade Serous Ovarian Cancer (HGSOC) were over the age of 40, with a median age of 50 years (range: 25–69 years), and 60% were older than 40. These findings are consistent with previous studies indicating that epithelial ovarian cancer, particularly the HGSOC subtype, predominantly affects older women. Feng (2016) and Shen (2017) reported a median age of 56 years and a mean age of 53 years, respectively, among HGSOC patients **(10,11)**. Advancing age, especially postmenopause, is associated with hormonal changes and a decline in DNA repair capacity, both of which contribute to ovarian carcinogenesis.

Among 40 patients with complete menopausal data, 72% were postmenopausal at the time of diagnosis. This proportion aligns with existing literature suggesting that most HGSOC cases occur after menopause, particularly between the ages of 60 and 64 **(11)**. Feng (2016) similarly reported that 69% of patients were postmenopausal. The decline in ovarian hormonal activity after menopause, particularly in progesterone-which has a protective effect on the ovarian epithelium-may increase the risk of malignant transformation due to hormonal imbalance **(10)**.

In this study, 65% of patients were multiparous. High parity is recognized as a protective factor against ovarian cancer, with a 26% reduction in risk, especially following the first childbirth. This protection is attributed to a reduced lifetime number of ovulations, which decreases repetitive damage and repair cycles in the ovarian epithelium that can lead to mutations. Conversely, nulliparous women face a higher risk due to recurrent ovulation and chronic epithelial repair.

Immunohistochemical analysis revealed that 85% of HGSOC samples were positive for Estrogen Receptor (ER) expression (>10%), while 50% showed Progesterone Receptor (PR) positivity. These findings are consistent with those of Voutsadakis (2016), who reported ER expression in 81% and PR expression in 31% of HGSOC cases **(10)**. ER activity is known to promote tumor cell proliferation, whereas PR, which has antiproliferative properties, is less frequently expressed and is dependent on the presence of active ER. The Mann-Whitney U test showed no significant difference in age distribution between ER-positive and ER-negative groups (P=0.134), and between PR-positive and PR-negative groups (P=0.645). Tan (2021) reported no significant association between age and expression of either ER (P=0.2591) or PR (P=0.2105) **(13)**. Despite systemic estrogen levels decreasing with age, cancer cells may exploit alternative pathways to sustain proliferation via ER. The reduced PR expression observed in older patients may be related to diminished ER-mediated PR induction and disrupted hormonal regulation within the tumor microenvironment. There is no significant association that was observed between menopausal status and PR expression (P=0.068), and with ER expression (P=1.00), based on Chi-squared analysis. This suggests that PR expression tends to be higher in premenopausal patients. This finding is consistent with the understanding that PR is induced by ER, and postmenopausal hormonal decline may reduce PR expression. Shen (2017) previously reported no significant association between menopausal status and either ER or PR expression. However, data from this study may suggest a potential role for hormonal status in maintaining PR expression (Table 1) **(11)**.

Table 1. Descriptive characteristics of patients with high-grade serous epithelial ovarian cancer who underwent surgery at Dr. Soetomo General Hospital in 2019-2021

Clinical Characteristics	Total (%) n=40	Estrogen Receptor (ER)			Progesterone Receptor (PR)		
		ER Positive (n=34)	ER Negative (n=6)	P-Value	PR Positive (n=20)	PR Negative (n=20)	P-Value
Age (years)							
< 50	14(35%)	13(38.2%)	1(16.7%)	0.134	8(40%)	6(30%)	0.645
≥50	26(65%)	21(61.7%)	5(83.3%)		12(60%)	14(70%)	
Menopausal Status							
Postmenopausal	30(75%)	25(73.5%)	5(83.3%)	1.00	12(60%)	18(90%)	0.068
Premenopausal	10(25%)	9(26.5%)	1(16.7%)		8(40%)	2(10%)	
Parity							
Nulliparous	14(35%)	12(35.3%)	2(33.3%)	1.00	7(35%)	7(35%)	1.00
Multiparous	26(65%)	22(64.7%)	4(66.7%)		13(65%)	13(65%)	
Tumor Marker CA-125							
Normal	2(5%)	2(5.9%)	0	1.00	2(10%)	0	0.487
Elevated	38(95%)	32(94.1%)	6(100%)		18(90%)	20(100%)	
FIGO Stage							
I	6(15%)	5(14.7%)	1(20%)		3(15%)	3(15%)	
II	1(2.5%)	0	1(20%)		0	1(5%)	0.336
III	27(67.5%)	23(67.6%)	4(60%)	0.837	15(75%)	12(60%)	
IV	6(15%)	6(17.7%)	0		2(10%)	4(20%)	
Family History of Malignancy							
Present	3(7.5%)	3(8.8%)	0	1.00	17(85%)	20(100%)	0.231
Absent	37(92.5%)	31(91.2%)	6(100%)		3(15%)	0	
Patient Outcome							
Alive	17(42.5%)	14(41.2%)	3(50%)	1.00	11(55%)	6(30%)	0.201
Deceased	23(57.5%)	20(58.8%)	3(50%)		9(45%)	14(70%)	

Surgical History	
Biopsy	5(12.5%)
Simple TAH-BSO	20(50%)
Surgical Staging	15(37.5%)
Chemotherapy History	
Received Chemotherapy	22(55%)
No Chemotherapy	18(45%)

PR expression deregulation in HGSOC may be influenced by multiple factors beyond BRCA, including the regulation by DNA damage response proteins such as ATM and RAD51, and the inherently aggressive nature of HGSOC, which often lacks PR expression. Overall, this study confirms that high ER and low PR expression are a common pattern in HGSOC. PR expression appears more sensitive to hormonal changes, especially menopause, whereas ER expression is more stable and potentially regulated by alternative oncogenic pathways. Further research with larger sample sizes and in-depth molecular approaches is needed to elucidate the hormonal regulation mechanisms in ovarian cancer.

4. Discussion

This study aimed to evaluate the expression of Estrogen Receptor (ER) and Progesterone Receptor (PR), and their association with clinical characteristics in patients with High-Grade Serous Ovarian Carcinoma (HGSOC). HGSOC is the most common and aggressive subtype of ovarian cancer, predominantly affecting older women and typically diagnosed at advanced stages. Understanding biological factors such as hormone receptor expression and genetic status may enhance individualized therapeutic strategies and improve clinical outcome prediction.

Most patients in this study were aged above 50 years (65%), consistent with the epidemiology of HGSOC, which is commonly diagnosed in postmenopausal women. (Feng, 2016; F. Shen, 2017) However, no significant associations were found between age and ER expression (P=0.134) or PR expression (P=0.645). These findings suggest that steroid receptor expression in tumor tissues is not directly governed by a patient's biological age but is more likely influenced by epigenetic and molecular factors within the tumor microenvironment.

Most patients were postmenopausal (75%). While there was a tendency toward higher ER expression in postmenopausal patients, the difference was not statistically significant (P=1.00). Progesterone receptor expression was relatively lower in postmenopausal patients compared to premenopausal patients, with a p-value approaching statistical significance (P=0.068). This study finds that postmenopausal women tend to develop (PR-) ovarian cancer. After menopause, there is a significant decline in progesterone levels. This hormonal shift may lead to the loss of PR expression in ovarian epithelial cells, as progesterone is essential for maintaining PR activation. Additionally, dysregulation of estrogen receptor alpha (ERα) in the postmenopausal environment might impair PR expression, contributing to the development of PR(-) tumors. Studies also show that PR(-) tumors are more common in older women and are associated with higher tumor grade, suggesting that PR loss may be an indicator of tumor progression in aging tissues. These findings imply that the hormonal environment after menopause plays a critical role in shaping the molecular characteristics of ovarian cancer **(11)**. PR is known to be a marker of better cell differentiation and lower proliferative activity **(12)**.

Parity also showed no significant association with ER (P=1.00) or PR (P=1.00) expression, whether among nulliparous (35%) or multiparous (65%) women. High parity is recognized as a protective factor against ovarian cancer, with a reported risk reduction of approximately 26% among multiparous women. (King, 2004) This protection is thought to stem from a decreased lifetime number of ovulations, thereby reducing the frequency of epithelial damage and regeneration. However, in the context of tumor hormone receptor expression, our findings suggest that parity is not a major determinant, implying its protective effect may act through mechanisms beyond the ER/PR axis.

Elevated CA-125 levels, indicative of high tumor burden, were observed in 95% of patients. Nonetheless, this elevation did not correlate with ER (P=1.00) or PR (P=0.487) expression. Similarly, advanced-stage disease, dominated by stage III (67.5%), showed no significant association with ER (P=0.837) or PR (P=0.336) expression. These results indicate that ER/PR expression is not a reliable indicator of disease severity **(12)**.

A family history of cancer was reported in only 7.5% of cases and showed no significant correlation with ER (P=1.00) or PR (P=0.231) expression. Nevertheless, family history remains important as a potential indicator of genetic predisposition, particularly for BRCA1 and BRCA2 mutations.

Outcome analysis revealed a higher proportion of surviving patients in the PR-positive group (55%) compared to the PR-negative group (30%), though this

difference did not reach statistical significance (P=0.201). Although the difference in survival between PR-positive and PR-negative groups was not statistically significant, the trend observed in this study is in line with previous literature that suggests PR expression may be associated with improved prognosis due to its correlation with less aggressive tumor behavior and lower proliferation rates.

In terms of interventions, most patients underwent simple total abdominal hysterectomy with bilateral salpingo-oophorectomy (simple TAH-BSO) (50%), complete surgical staging (37.5%), or biopsy only (12.5%). Around 55% received chemotherapy. Although the Progesterone Receptor (PR) is not yet a well-established therapeutic target in HGSOC, preliminary evidence suggests potential utility; for instance, mifepristone, a PR antagonist, demonstrated a 26.5% response rate in cisplatin- and paclitaxel-resistant ovarian cancer. On the other hand, anti-estrogen therapy targeting ER-positive HGSOC has shown promise and could be considered in both primary and relapsed disease settings. In particular, endocrine maintenance therapy using aromatase inhibitors may offer a less toxic, targeted approach for selected patients. However, its clinical benefit remains to be confirmed, and future randomized controlled trials are needed to establish efficacy, optimal timing, and patient selection criteria **(13)**.

The findings of this study indicate that ER and PR expression are not significantly correlated with demographic characteristics, hormonal status, parity, or clinical indicators such as stage and CA-125. However, the observed trend toward improved survival in PR-positive patients highlights the potential prognostic value of PR in HGSOC. The lack of association between BRCA mutation and ER/PR expression supports the hypothesis that hormonal regulation in ovarian cancer is complex and not solely dependent on genetic status. An integrative approach combining molecular biomarkers and hormone receptor expression is warranted to support personalized therapy in HGSOC patients.

5. Conclusion

Based on the findings of this study, most patients with High-Grade Serous Ovarian Carcinoma (HGSOC) were older and postmenopausal, which aligns with the typical clinical characteristics of this cancer type. Estrogen Receptor (ER) expression was generally high, while Progesterone Receptor (PR) expression was comparatively lower. Although patient age was not significantly associated with ER expression, a trend toward higher PR negativity in postmenopausal women was observed (P=0.068), though this did not reach statistical significance. These observations highlight potential hormonal influences on receptor expression, warranting further investigation. Given the limited statistical power and sample size, ER/PR expression alone may not be sufficient as a standalone biomarker for clinical stratification in HGSOC. Future studies with larger cohorts and integrative molecular approaches are needed to clarify the prognostic and therapeutic relevance of ER and PR expression and to explore how these receptors may guide targeted treatment strategies.

6. Declarations

Acknowledgments

The authors would like to express their deepest gratitude to the Department of Obstetrics and Gynecology and the Department of Anatomical Pathology and the Faculty of Medicine, Universitas Airlangga- Dr. Soetomo General Hospital, for providing the facilities and opportunity to conduct this study. Special thanks are extended to all laboratory staff who assisted in the collection and analysis of samples. The authors greatly appreciate the contributions of all parties involved, both directly and indirectly, in the completion of this research. Without their support and collaboration, this study would not have been possible.

Ethical Considerations

This research has received ethical approval from the Medical and Health Research Ethics Committee Soetomo General Academic Hospital with number: 1193/KEPK/XII/2024

Authors' Contributions

Ni Nyoman Ayu Ratih Pradnyani contributed to patient care, the conception of the case report, the acquisition and interpretation of data, the literature review, and the drafting of the manuscript. Brahmana Askandar Tjokroprawiro contributed to the conception of the study, performed the literature review, and the drafting of the manuscript. Primandono Perbowo contributed to the conception of the study, performed the literature review, and the drafting of the manuscript. Grace Ariani contributed to the conception of the study, performed the literature review, and the drafting of the manuscript.

Conflict of Interest

The authors declare no conflict of interest regarding the publication of this study.

Fund or Financial Support

This study did not receive any specific grant or funding.

References

1. Gaona-Luviano P, Medina-Gaona LA, Magaña-Pérez K. Epidemiology of ovarian cancer. Chin Clin Oncol. 2020;9(4):47. [DOI:10.21037/cco-20-34]
2. Reinbolt RE, Hays JL. The Role of PARP Inhibitors in the Treatment of Gynecologic Malignancies. Front Oncol. 2013;3:237. [DOI:10.3389/fonc.2013.00237]
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49. [DOI:10.3322/caac.21660]
4. Stefanou DT, Souliotis VL, Zakopoulou R, Liontos M, Bamias A. DNA Damage Repair: Predictor of Platinum Efficacy in Ovarian Cancer? Biomedicines. 2021;10(1):82. [DOI:10.3390/biomedicines10010082]
5. Langdon SP, Herrington CS, Hollis RL, Gourley C. Estrogen Signaling and Its Potential as a Target for Therapy in Ovarian Cancer. Cancers (Basel). 2020;12(6):1647. [DOI:10.3390/cancers12061647]
6. Shen Z, Luo H, Li S, Sheng B, Zhao M, Zhu H, et al. Correlation between estrogen receptor expression and prognosis in epithelial ovarian cancer: a meta-analysis. Oncotarget. 2017;8(37):62400–13. [DOI:/10.18632/oncotarget.18253]
7. Ratanaphan A. A DNA Repair BRCA1 Estrogen Receptor and Targeted Therapy in Breast Cancer. Int J Mol Sci. 2012;13(11):14898–916. [DOI:10.3390/ijms131114898]
8. Mungenast F, Thalhammer T. Estrogen Biosynthesis and Action in Ovarian Cancer. Front Endocrinol (Lausanne). 2014;5:192. [DOI:10.3389/fendo.2014.00192]
9. Mauro LJ, Spartz A, Austin JR, Lange CA. Reevaluating the Role of Progesterone in Ovarian Cancer: Is Progesterone Always Protective? Endocr Rev. 2023;44(6):1029–46. [DOI:10.1210/endrev/bnad018]
10. Voutsadakis IA. Hormone receptors in serous ovarian carcinoma: Prognosis, pathogenesis, and treatment considerations. Clin Med Insights Oncol. 2016;10:17–25. [DOI:10.4137/cmo.s32813]
11. Shafrir AL, Rice MS, Gupta M, Terry KL, Rosner BA, Tamimi RM, et al. The association between reproductive and hormonal factors and ovarian cancer by estrogen-α and progesterone receptor status. Gynecol Oncol. 2016;143(3):628–35. [DOI:10.1016/j.ygyno.2016.09.024]
12. Tan J, Song C, Wang D, Hu Y, Liu D, Ma D, et al. Expression of hormone receptors predicts survival and platinum sensitivity of high-grade serous ovarian cancer. Biosci Rep. 2021 May 1;41(5): BSR20210478. [DOI:10.1042/bsr20210478]
13. Vetter M, Stadlmann S, Bischof E, Georgescu Margarint EL, Schötzau A, Singer G, et al. Hormone Receptor Expression in Primary and Recurrent High-Grade Serous Ovarian Cancer and Its Implications in Early Maintenance Treatment. Int J Mol Sci. 2022;23(22):14242. [DOI:10.3390/ijms232214242]

How to Cite This Article:

Pradnyani, N.N.A.R., Askandar. B., Perbowo, P., Ariani, G. Induction of Fresh Chocolate Cyst Pulp into Endometriosis Mice Model. J Obstet Gynecol Cancer Res. 2025;10(10):741-6.

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