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High Cytoplasmic and Membranous Epidermal Growth Factor Receptor (EGFR) Expression as a Risk Factor for High-Grade Ovarian Carcinoma (HGOC)

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High-grade ovarian carcinoma (HGOC) is one of the most aggressive grades of ovarian cancer and causes high mortality. The molecular mechanisms underlying the development and progression of high-grade ovarian carcinoma related to high EGFR expression are still not fully understood. This study aimed to evaluate the cytoplasmic and membranous EGFR expression as a risk factor for high-grade ovarian carcinoma. This study employed a case-control design with consecutive sampling among ovarian cancer patients at BaliMed Denpasar Hospital and the Anatomical Pathology Laboratory, Faculty of Medicine and Health Sciences, Warmadewa University. EGFR expression was analyzed immunohistochemically and assessed by H-score. Data were analyzed using the chi-square test and binary logistic regression. P-value = 0.05 was considered significant. This study involved 40 ovarian cancer samples, with the majority (86.7%) aged =50 years. The most common histopathological type was endometrioid (45%). As many as 80% of high-grade ovarian cancer (HGOC) cases showed high EGFR expression (>50%), in contrast to low-grade ovarian cancer (LGOC) (40%). High EGFR expression increased the risk of HGOC by 10.5 times (p = 0.001). Multivariate analysis revealed that high EGFR expression was an independent risk factor for HGOC, with an aOR of 41.5 (p-value = 0.008; 95% CI: 2.65–649.14). High EGFR expression was significantly associated with an increased risk of HGOC. Patients with high EGFR expression had a greater risk of HGOC than patients with low to moderate EGFR expression.

Keywords: EGFR; Expression; High-grade; Ovarian carcinoma; Risk factor.

Ovarian carcinoma is one type of gynecological cancer with a high morbidity and mortality rate worldwide. According to a 2020 World Health Organization (WHO) study, ovarian cancer was the tenth most frequent disease among women worldwide.[1] Despite having a lower incidence than breast cancer, ovarian cancer has a threefold higher death rate, and by 2040, the death rate from this illness is predicted to rise sharply.[2] Despite advances in therapeutic strategies, survival rates remain dismal, with a five-year survival rate of less than 30% in advanced stages. High-grade ovarian carcinoma *(*HGOC) is the most aggressive subtype and is responsible for the majority of ovarian cancer mortality.[3] HGOC can originate from various types of ovarian carcinoma. All types of ovarian carcinoma experience various additional mutations, but it is challenging to predict

histopathologically the possibility of becoming HGOC, thereby requiring molecular examination to predict its possibility.[4]

Nowadays, therapeutic strategies have been devised to curtail or mitigate the aggressive nature of ovarian carcinoma. One such approach relies on determining the presence or absence of epidermal growth factor receptor (EGFR) expression.[5] EGFR, a tyrosine kinase receptor part of the ErbB receptor family, is involved in various essential biological processes, including cellular migration, differentiation, and division.[6] The unchecked proliferation of cells and their resistance to programmed cell death are often triggered by EGFR activation via its ligands, initiating an intracellular signaling cascade. Many malignancies, including colorectal, head and neck, and lung cancers, have been associated with EGFR overexpression or mutations. In ovarian cancer, EGFR overexpression has been identified in a substantial proportion of cases, particularly in high-grade subtypes.[7]

Numerous studies have documented that elevated EGFR expression is observed in various cases of ovarian carcinoma and is associated with unfavorable outcomes. Research findings indicate that between 50% and 70% of high-grade serous ovarian carcinoma cases exhibit overexpression of EGFR.[8] Sophisticated diagnostic tools, such as immunohistochemistry and quantitative PCR, have been employed to detect this biomarker. While higher levels of EGFR are frequently noted in high-grade tumors compared to their low-grade counterparts, the precise molecular pathways driving the initiation and progression of high-grade ovarian carcinoma remain inadequately understood. Consequently, this research sought to investigate the relationship between cytoplasmic and membranous EGFR expression and the risk of developing high-grade ovarian carcinoma.

MATERIALS AND METHODS

Study design

This research utilized a case-control methodology to explore the relationship between cytoplasmic and membranous EGFR expression and the likelihood of developing high-grade ovarian carcinoma. The study was carried out between July and December 2024 at the Anatomy Pathology Laboratory, Faculty of Medicine and Health Sciences, Warmadewa University, in collaboration with BaliMed Denpasar Hospital.

Patient recruitment and sample collection

The research samples in this study were collected using the consecutive sampling method, based on specific eligibility criteria. This study will involve female patients who have been histopathologically diagnosed with ovarian carcinoma, are e”18 years old, have adequate tumor tissue specimens for immunohistochemical examination of EGFR expression, and have complete clinical and pathological data. Patients who have undergone chemotherapy or radiation therapy before tissue specimen collection will be excluded. Furthermore, this study will not include individuals with inadequate data, a history of ovarian cancer, or other gynecologic malignancies. All of the tissue samples from ovarian cancer patients who were registered at BaliMed Denpasar Hospital were kept and examined at Warmadewa University’s Faculty of Medicine and Health Sciences’ Anatomy Pathology Laboratory. The study allocated samples into two distinct groups in a 1:1 proportion: one group consisted of individuals diagnosed with low-grade ovarian cancer, while the other group comprised patients with high-grade ovarian cancer (HGOC), designated as the case group.

Immunohistochemistry for EGFR expression

The IHK procedure involves cutting paraffin-embedded tissue into thin slices, followed by deparaffinization, rehydration, and antigen retrieval. The tissue is then incubated with anti-EGFR primary antibodies, followed by enzyme-conjugated secondary antibodies. Visualization is performed using chromogenic substrates. The degree and location of EGFR expression on the tumor cell membrane and cytoplasm are used to evaluate the staining results. The H-score, which combines staining intensity (0–3) with the proportion of positive cells (cytoplasmic and membranous staining), defines EGFR expression. A score of at least 200 is frequently regarded as high expressiveness, while the highest score is 300. The level of staining is classified as follows: 0 indicates no staining, 1+ indicates weak or faint staining, 2+ indicates moderate staining that is clearly visible but not strong, and 3+ indicates strong and definite staining. Low expression

(<10%), moderate expression (10–50%), and high expression (>50%) were also used to determine the proportion of positive tumor cells.[9]

Statistical analysis

Data were analyzed using SPSS ver.24 software. Descriptive analysis was performed to determine the proportion of characteristics in the study sample. Chi-square analysis was conducted to evaluate the relationship between cytoplasmic and membrane EGFR expression and HGOC, with risk interpretation displayed as an Odds Ratio (OR). Multivariate analysis was performed using binary logistic regression, controlling for confounding variables, to determine the independent relationship between cytoplasmic and membrane EGFR expression and HGOC. Data were considered significant if the p-value was d"0.05.

RESULTS

A total of 40 samples of patients with ovarian carcinoma were analyzed in this study. The majority of patients were aged 50 years or older, comprising 35 people (86.7%), while only 5 patients (13.3%) were under 50 years old. Based on histopathological type, the endometrioid type was the most common, occurring in 18 patients (45.0%), followed by the clear cell type in 12 patients (30.0%), and the serous type in 10 patients (25.0%). In terms of the degree of malignancy, the samples were evenly divided between the high-grade and low-grade groups, with each group comprising approximately 20 patients (50%) (Table 1).

Table 1. Sample characteristics

Characteristics	n = 40 (%)
Age (year)	
<50	5 (13.3%)
≥50	35 (86.7%)
Histopathologic type	
Endometrioid	18 (45,0%)
Serous	10 (25,0%)
Clear Cell	12 (30,0%)
Grade group	
High Grade	20 (50%)
Low Grade	20 (50%)

The results of the analysis of the relationship between EGFR expression and the grade of ovarian carcinoma showed that high EGFR expression (>50%) was found in 80% of patients with high-grade ovarian carcinoma (HGOC), compared to 40% in patients with low-grade ovarian carcinoma (LGOC). In contrast, low to moderate EGFR expression (d"50%) was more common in the LGOC group (60%) than in the HGOC group (20%). Chi-square analysis showed a statistically significant relationship between EGFR expression levels and the grade of ovarian carcinoma malignancy (p = 0.001), with an odds ratio (OR) of 10.542 (95% CI: 2.271–48.757), indicating that patients with high EGFR expression had more than a 10-fold increased risk of developing HGOC compared to those with low to moderate EGFR expression (Table 2).

Based on multivariate analysis using binary logistic regression, high EGFR expression (>50%) still showed a significant association with the incidence of high-grade ovarian carcinoma (HGOC), with a p value of 0.008. Patients with high EGFR expression had an adjusted odds ratio (OR) of 41.503 (95% CI: 2.653–649.143), indicating that they were more than 41-fold at risk of developing HGOC compared to patients with low to moderate EGFR expression, after controlling for age and histological type variables. Meanwhile, age e"50 years (OR: 10.529; p = 0.156) and serous histological type (OR: 1.833; p = 0.556) did not

Table 2. Relationship between EGFR expression and ovarian carcinoma grade

Variable	Ovarian Carcinoma Grade		OR	95%CI	p-value
	HGOC n=20	LGOC n=20			
EGFR Expression					
High (>50%)	16(80.0%)	8(40.0%)	10,542	2,271-48,757	0.001*
Low-Moderate (≤50%)	4(10.0%)	12(60.0%)			

*Analysis was carried out using a chi-square test. The result was considered significant if the p-value was ≤0.05.

show a statistically significant association with the degree of malignancy (Table 3).

Figure 1 illustrates EGFR expression in ovarian carcinoma tissues with varying degrees of malignancy. Panel A shows high EGFR expression in high-grade ovarian carcinoma, characterized by intense brown staining that extends to the membrane and cytoplasm of tumor cells. In contrast, panel B shows low EGFR expression in low-grade ovarian carcinoma, with fainter and more limited staining.

DISCUSSION

This study involved 40 samples of ovarian cancer, with 80% of the study subjects being women aged e"50 years. These findings are in line with findings reported in several studies conducted in Europe and the United States, where most patients with ovarian cancer were diagnosed in the age range of 60-64 years.[10] According to a study done at Prof. Dr. I.G.N.G. Ngoerah General Hospital between 2013 and 2014, the highest incidence of ovarian cancer occurred in people aged 41 to 50, with an average age of 44.52. This data is quite different from that.[11] The majority of cancer cases are linked to aging and are discovered after the age of fifty. Carcinogenesis may result from the accumulation of genetic and epigenetic alterations caused by aging, as well as cumulative damage to DNA repair systems.[12,13] The accumulation of mutations is likely related to the type of ovarian cancer, where ovarian cancer can be classified into type I and type II ovarian cancer which type II ovarian cancer typically characterized with high p53 mutation and impaired function of the homologous recombination repair pathway so that it is possible that aging is related to a higher risk of HGOC.[14,15]

Based on Table 1, it was found that the most common histopathological type of ovarian carcinoma cases was the endometrioid type, with a percentage of 45% of all cases studied. Meanwhile, the serous type and clear cell type showed a relatively balanced distribution, at 25% and 30%, respectively. This finding indicates a shift in the pattern compared to previous data from Prof. Dr. I.G.N.G. Ngoerah Hospital in

Table 3. Multivariate analysis for EGFR expression and ovarian carcinoma grade

Variable	B	S.E.	Adjusted OR	95%CI	p-value
EGFR expression (high; >50%)	3.726	1.403	41.503	2.653-649.143	0.008*
Age (≥50 years old)	2.354	1.233	10.529	0.939-118.036	0.156
Histologic type (serous)	0.606	1.030	1.833	0.243-13.793	0.556

*Analysis was carried out using a binary logistic regression test. The result was considered significant if the p-value was ≤0.05.

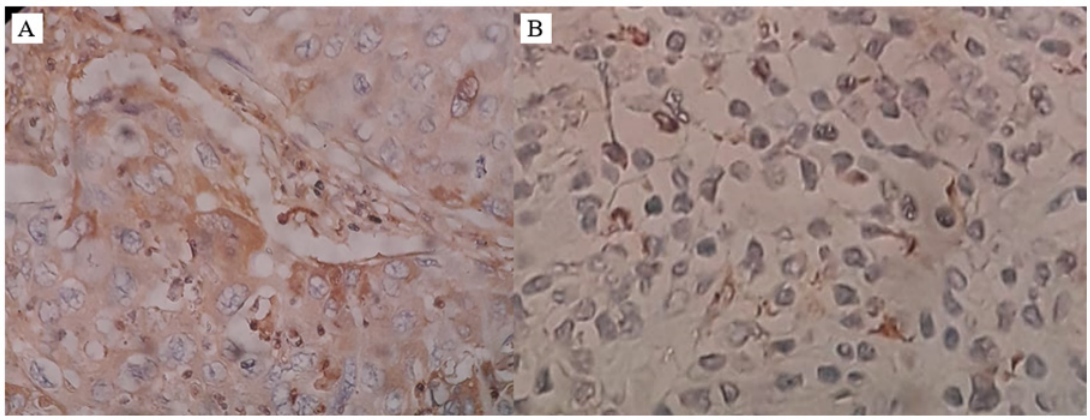

Fig. 1. A) High EGFR expression in high-grade ovarian carcinoma, B) Low EGFR expression in low-grade ovarian carcinoma

2013–2014, where the serous type was reported as the most common type of ovarian carcinoma. This difference may be influenced by various factors, including population and diagnostic methods.[11] In this study, the majority of cases were endometrioid-type ovarian carcinomas, which is likely related to the background of endometriosis in several cases, suggesting that histogenesis originates from the endometriosis mechanism in ovarian tissue.

This study showed a significant association between epidermal growth factor receptor (EGFR) expression and the incidence of high-grade ovarian carcinoma (HGOC) in patients with ovarian cancer. Through bivariate analysis using the chi-square test, it was found that patients with high EGFR expression levels had a 10.542 times greater risk (95% confidence interval [CI] = 2.271–48.757; p-value = 0.001) of developing high-grade ovarian cancer (HGOC) compared with patients with low EGFR expression (Table 2). These results indicate that high EGFR expression has a statistically strong association with an increased risk of HGOC-type ovarian cancer. Furthermore, multivariate analysis was performed by controlling for role variables such as age and histopathology type. The results showed that high EGFR expression remained an independent risk factor for HGOC, with a customized odds ratio (aOR) of 41.503 (95% CI = 2.653–649.143; p-value = 0.008) (Table 3). This supports the hypothesis that EGFR expression plays a crucial role in the pathogenesis of HGOC, regardless of other factors that may influence it. However, the extensive confidence intervals indicate an overestimation, which is likely due to the limited sample size in this study. Therefore, further studies with stronger designs, stricter variable controls, and larger sample sizes are needed to verify these findings and clarify the role of EGFR in the development of HGOC more accurately.

Research on the direct relationship between epidermal growth factor receptor (EGFR) expression and the risk of high-grade ovarian cancer (HGOC) in ovarian cancer patients is still relatively limited. Most previous studies have focused more on the relationship between EGFR characteristic expression and the clinicopathological features and prognosis of ovarian cancer patients in general. However, several findings support the critical role of EGFR in the development of ovarian cancer, exceptionally high-grade serous types. One study by Lin et al. showed that patients with high-grade serous ovarian carcinoma showed significantly increased EGFR expression. This increase was associated with more aggressive tumor growth and poor response to standard therapy, which ultimately affected the patient's long-term prognosis. EGFR expression is known to trigger the activation of cellular signaling pathways that play a role in tumor cell proliferation, invasion, and resistance to apoptosis. Therefore, although further studies are needed to specifically elucidate the causal relationship between EGFR expression and HGOC incidence, current evidence suggests that EGFR has the potential to be an essential biomarker in early detection, tumor classification, and determining more effective therapeutic strategies for ovarian cancer patients.[8] However, these findings did not focus on evaluating the relationship between EGFR expression and the incidence of HGOC.

A high proliferation index in ovarian cancer cells has been associated with increased EGFR expression. EGFR expression's prognostic significance in ovarian malignancies is still debatable, nevertheless. Higher blood EGFR levels were linked to a worse progression-free survival (PFS) in patients with epithelial ovarian cancer, according to research by Tas et al., suggesting prognostic importance.[16] In contrast, Mehner et al. found no significant association between EGFR expression in ovarian tumors and clinicopathological factors such as tumor stage or grade.[17] This difference in results may be due to differences in measurement methods. Tas et al. measured serum EGFR levels, which reflect systemic conditions,16 while Mehner et al. analyzed EGFR expression at the cellular level of the tumor, which is more influenced by local factors.[17] Tas et al.'s study focused more on direct clinical aspects.[16] At the same time, Mehner et al. used a broader and review analysis, which may not be sensitive enough to detect a direct relationship between biomarkers and clinical prognosis.[17] In addition to methodological variations in scoring the EGFR tissue staining, variations in antibodies, tissue processing, staining methods, and patient demographics could impact those studies. This study determined that EGFR expression was characterized by cytoplasmic and membranous EGFR staining.

High EGFR expression in ovarian cancer, particularly in high-grade ovarian carcinoma (HGOC), can be identified through immunohistochemical staining, which reveals strong staining intensity in the membrane and cytoplasm of tumor cells (Figure 1A). This is in contrast to low-grade ovarian carcinoma, which shows weaker EGFR staining in the membrane and cytoplasm of cells (Figure 1B). Previous studies have shown that EGFR expression on the cell membrane can increase receptor activation through interaction with growth ligands, such as EGF, which then triggers the activation of downstream signaling pathways, including RAS/RAF/MEK/ERK and PI3K/AKT. Activation of these pathways plays an important role in cancer cell proliferation, survival, and invasion. In addition, the presence of EGFR in the cytoplasm also indicates a similar potential for tumor aggressiveness, as seen in various other types of cancer. In ovarian cancer, increased EGFR expression is associated with higher tumor grades and a greater cancer cell proliferation index, reflecting the ability of tumors to grow and spread rapidly. High EGFR expression can also indicate poor differentiation of cancer cells, which is generally associated with more malignant tumor behavior and worse prognosis. Thus, detection of EGFR expression is not only useful as a diagnostic biomarker, but can also help in determining more aggressive and targeted therapeutic strategies in patients with HGOC.[17–19]

Although this study cannot yet elucidate the exact mechanism by which ovarian EGFR expression causes HGOC, it provides preliminary evidence to support the hypothesis based on existing theories regarding the role of EGFR in tumor progression. The PI3K/AKT/mTOR pathway, which regulates biological functions such as tumor cell growth, proliferation, and survival, is believed to be involved with EGFR. The mechanistic target of rapamycin (mTOR) pathway is triggered when phosphatidylinositol 3-kinase (PI3K) phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which subsequently attracts and activates AKT.[20,21] The unregulated PI3K/AKT/mTOR pathway also leads to the loss and mutation of phosphatase and tensin homolog (PTEN), which in turn results in excessive cellular proliferation and survival signals.[22] The PI3K/AKT/mTOR pathway's activation also encourages metabolic reprogramming in cancer cells, which improves the environment for tumor development and stress-tolerant survival. Persistent activation of the PI3K/AKT/mTOR pathway frequently results in alterations of the p53 gene, among other contributing causes.[23] Another signaling mechanism influenced by EGFR is abnormal DNA transcription and replication (ADTR), which is a consequence of genomic instability. This, in turn, fosters further mutations, accelerating the tumorigenic process.[24] Thus, high cytoplasmic and membranous EGFR expression hypothetically serves as a key initiator of downstream signaling pathways, which promote the development of ovarian carcinoma into HGOC.

However, there is one crucial point that needs to be emphasized in this study, which is the main limitation: no separate analysis was carried out between cytoplasmic and membrane EGFR expression, despite both having different mechanisms, although they share the same primary function. EGFR is a transmembrane tyrosine kinase receptor that, when activated by ligands such as EGF, undergoes dimerization and autophosphorylation, thereby activating signaling pathways including RAS/RAF/MEK/ERK and PI3K/AKT, which support cell proliferation and survival. Membrane expression of EGFR indicates canonical signaling activity. At the same time, its presence in the cytoplasm reflects receptor internalization, degradation, or non-canonical roles such as regulation of gene transcription or interaction with cellular organelles. High cytoplasmic expression is often associated with malignancy and resistance to therapy. These differences in location suggest complex molecular functions of EGFR and may have implications for cancer prognosis.[25–28]

The primary strength of this study lies in the case-control design employed, which enabled the researchers to systematically investigate the association between epidermal growth factor receptor (EGFR) expression and the risk of developing high-grade ovarian carcinoma (HGOC). Using immunohistochemistry, this study specifically assessed the location of EGFR expression, both in the membrane and cytoplasm of tumor cells, providing more insight into the potential biological role of EGFR in the

pathogenesis of HGOC. The internal validity of this study was enhanced by the use of strict inclusion and exclusion criteria, as well as consecutive sampling, which helped reduce selection bias. However, this study also has several limitations that need to be taken into consideration. The relatively small sample size is a significant weakness, as it resulted in extensive confidence intervals in the multivariate analysis. This reduces the precision of the estimates and may compromise the reported risk assessment; therefore, interpretation of the results should be done with caution. In addition, interpretation of EGFR expression involving cytoplasmic and membrane staining also has the potential for bias, primarily if not performed by experienced observers or without consistent assessment standards. This variability in interpretation may impact the final results, making it challenging to generalize the findings to a broader population. Therefore, further studies with larger sample sizes and more objective immunohistochemical assessments are needed to confirm these findings and improve the external validity of the study.

CONCLUSION

An elevated risk of HGOC was substantially linked to high EGFR expression. The idea that EGFR is essential for the development and aggressiveness of ovarian tumors was supported by the fact that patients with high EGFR expression were more likely to develop HGOC than those with low to moderate EGFR expression. It is recommended that additional research with a larger sample size and stricter control of confounding variables be conducted to validate the independent association between EGFR expression and HGOC, given the study's notable limitations, including its small sample size and wide confidence intervals.

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability

This statement does not apply to this article.

Ethics Statement

This research has received a research permit from the Research Ethics Committee of Udayana University/Prof. I.G.N.G. Ngoerah Hospital, Bali, with number 2979/UN14.2.2.VII.14/ LT / 2022.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not Applicable.

Author Contribution

Ni Wayan Armerinayanti: Conceptualization, Methodology, Writing – Original Draft, Visualization, Supervision, Project Administration, Funding Acquisition, Resources; Desak Putu Oki Lestari: Data Collection, Analysis, Writing – Review & Editing; I Gede Wikania Wira Wiguna: Analysis, Writing – Review & Editing

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