International Journal of Medical Sciences And Clinical Research

VOLUME Vol.05 Issue06 2025
PAGE NO. 34-36
DOI 10.37547/ijmscr/Volume05Issue06-07

The Significance of Angiogenesis Processes and Their Target Biomarkers in Ovarian Cancer: Clinical and Prognostic Analysis

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Received: 14 April 2025; **Accepted:** 10 May 2025; **Published:** 19 June 2025

Abstract: This article analyzes the expression of immunohistochemical markers (p53, Ki-67, VEGF, and CD34) in various histological types of ovarian cancer, along with their clinical-morphological features and prognostic significance. Marker expression levels were evaluated in relation to tumor progression, treatment effectiveness, and recurrence risk. The obtained results provide a scientific foundation for formulating individualized therapeutic strategies.

Keywords: Ovarian cancer, immunohistochemistry, p53, Ki-67, VEGF, CD34, histotype, prognosis.

Introduction: Ovarian cancer ranks third among malignant neoplasms of the female reproductive organs. Approximately 85% of patients have epithelial forms of ovarian cancer, with well-differentiated tumors accounting for about 80%, while poorly differentiated tumors make up around 20–30% [1].

Currently, ovarian cancer remains one of the most widespread oncological diseases worldwide. Each year, an estimated 314,000 new cases are diagnosed, and approximately 207,000 deaths occur due to this disease. It ranks seventh in incidence and eighth in mortality among cancers in women globally.

Regional incidence per 100,000 population shows the highest rates in Europe (11.4), followed by North America (10.7), with lower rates in Asia (5.0) and Africa (4.2).

Age distribution indicates that ovarian cancer is most commonly observed in women over 50, particularly between ages 55 and 65. However, about 15% of cases occur in women under 40. Overall, ovarian cancer accounts for 3–4% of all female cancers and remains a serious medical and social issue [1].

In Uzbekistan, ovarian cancer ranks 6th–7th among all female malignancies. Each year, 700–800 new cases are diagnosed. The national incidence is approximately 4.5–5.0 per 100,000 women—an average rate for Central Asia. The five-year survival rate is about 30–35%, primarily due to late-stage diagnoses.

Around 60–70% of ovarian cancer cases in Uzbekistan are detected at advanced stages (III–IV), which results in poor prognosis and low survival rates. Ovarian cancer accounts for 4–6% of all malignant tumors in women. Among women aged 70 and older, this figure rises to 7–8%, and in women aged 40–54, it is about 6.5–7.5%.

Annually, an average of 400–500 women die from ovarian cancer in Uzbekistan, representing 5–6% of all cancer-related deaths. In women under 30, ovarian cancer is responsible for 40–60% of deaths from genital tumors. The lifetime risk for a girl born in Uzbekistan of developing ovarian cancer is estimated at 0.8–1.0%, while the risk of dying from it is about 0.5–0.6%.

For a 30-year-old woman, the mortality risk from

ovarian cancer is approximately 15–17 times higher than from other causes. This gap decreases with age: at ages 50–54 the risk is 7–8 times higher, and at 60–64 about 3–4 times. Among women over 75, the likelihood of dying from other causes exceeds that of ovarian cancer.

The survival rate for ovarian cancer remains very low. Within the first year after diagnosis, one in three patients dies. Based on summarized data from European cancer registries, the overall survival rates for ovarian cancer are:

- 1-year: 63%
- 3-year: 41%
- 5-year: 35% [1]

The key factors contributing to poor prognosis and recurrence are:

- Absence of early symptoms
- Lack of reliable diagnostic tools
- Ineffective treatment [2]

Ovarian cancer is a heterogeneous disease in terms of etiology and clinical presentation. Tumor development is primarily due to genetic damage (mutations) of cells, which increases their sensitivity to endogenous and exogenous carcinogens. Contributing factors may include mumps virus, asbestos exposure, hormonal imbalances, immune deficiency, and others [3–5].

This tumorigenesis is consistent with the "two-hit hypothesis" proposed by A. Knudson in 1971, which suggests that both a germline and a somatic mutation must occur for tumor development. In hereditary forms, the germline mutation is inherited from one parent. However, this alone is insufficient for malignancy—an additional somatic mutation in the homologous chromosome is required. In sporadic cases, both mutations occur in a single somatic cell [6].

The genetic nature of cancer is now well established. It is proven that malignant tumors may originate from a single (monoclonal) tumor cell due to accumulated mutations in specific DNA regions, leading to the synthesis of defective proteins [7].

Discovery of proto-oncogenes and tumor suppressor genes confirms the mutational origin of cancer. Mutations, such as point mutations, can change the structure and expression of these genes, resulting in malignant transformation. Proto-oncogenes were first discovered through retroviruses that carried oncogenic sequences. Molecular biological studies have shown that normal DNA of various eukaryotic cells contains sequences homologous to viral oncogenes, now known as proto-oncogenes. Mutations or overexpression of these genes lead to increased protein production and potential malignancy. These genes are highly conserved and play essential roles in normal cellular functions [8].

LITERATURE REVIEW

Recent studies have significantly expanded our understanding of the etiopathogenesis, histogenesis, and biomarker expression in ovarian cancer. Prat J. (2012) identified five main histological types of ovarian cancer, each with distinct clinical-biological features. Bell et al. (2011) highlighted TP53 mutations as predominant in serous carcinomas and PTEN and ARID1A mutations in endometrioid tumors. McCluggage (2011) described distinct morphological and immunohistochemical characteristics for each subtype.

Ki-67 is a proliferation marker whose high expression correlates with tumor aggressiveness and biological activity. VEGF plays a central role in angiogenesis, indicating rapid tumor growth and metastatic potential. CD34 serves as a marker of microvessel density, allowing assessment of tumor vascularization and tissue nutrition.

These findings underscore the critical prognostic and therapeutic relevance of immunohistochemical analysis in ovarian cancer. The article's next sections analyze how each marker is expressed across histotypes and how they influence clinical and oncological outcomes.

MATERIALS AND METHODS

This study included 130 female patients diagnosed with ovarian cancer and treated at the Republic Specialized Oncology Center from 2020 to 2024. All patients underwent clinical, instrumental, and laboratory evaluation. Tumors were classified histologically as serous, mucinous, endometrioid, or clear cell types.

Tumor tissue samples for immunohistochemical (IHC) analysis were fixed in formalin and embedded in paraffin blocks. Sections were stained with hematoxylin and eosin. IHC staining was performed using monoclonal antibodies against p53, Ki-67, VEGF, and CD34. All analyses were conducted according to Leica Microsystems standards.

Marker expression was evaluated using scoring systems: nuclear staining for p53 and Ki-67; cytoplasmic and vascular density for VEGF and CD34.

Statistical analysis was performed using SPSS 26.0. Associations between marker expression and histotypes were analyzed using the χ^2 test and ANOVA. Differences with $P<0.05$ were considered statistically significant.

RESULTS

In serous adenocarcinomas, high p53 expression was observed in 75% of cases, suggesting high mutation frequency. In mucinous tumors, p53 expression was low, with only 20% showing high expression. In endometrioid carcinomas, moderate p53 expression was observed in 55% of cases.

Analysis of Ki-67 proliferation index showed values ranging from 60–90% in high-grade serous carcinomas, indicating high biological activity. In endometrioid tumors, Ki-67 ranged from 35–60%, and in mucinous tumors, 15–40%. In clear cell tumors, expression was 45–75%.

VEGF expression was highest in serous and clear cell types—80% and 72% respectively—highlighting the central role of angiogenesis in tumor progression. In endometrioid and mucinous subtypes, VEGF expression was moderate to low.

Microvessel density assessed by CD34 was highest in serous tumors (34.2±2.1 units/100 fields), followed by clear cell (31.1±2.0), endometrioid (28.5±1.7), and mucinous (23.4±1.5).

DISCUSSION

The study demonstrates that immunohistochemical marker expression differs by histological type and can guide prognosis and treatment. High p53 expression was associated with aggressive tumor growth and higher recurrence risk, warranting more intensive therapy.

Patients with high Ki-67 index should be considered high-risk, and chemotherapy regimens must be tailored accordingly. Elevated VEGF levels support the use of anti-angiogenic therapies (e.g., bevacizumab). CD34 expression reflects vascular supply, which can inform radical surgical or vascular-targeting strategies.

CONCLUSION

1. The histological type of ovarian cancer directly influences immunohistochemical marker expression.

2. Expression levels of p53, Ki-67, VEGF, and CD34 serve as significant indicators for prognosis, recurrence risk, and treatment response.

3. Analysis of these markers provides a scientifically grounded basis for personalized therapeutic approaches.

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