

MOLECULAR MECHANISMS OF DEVELOPMENT AND THERAPEUTIC PERSPECTIVES OF OVARIAN CANCER

Masharifov Khurshidbek Shomurod ugli

*2nd-year student of the Faculty of General Medicine,
Urgench Branch of Tashkent Medical Academy.
Email: khurshidbekmasharifov5@gmail.com*

Rozimova Etibor Bakhtiyarovna,

*Assistant of the Department of Anatomy,
Urgench Branch of Tashkent Medical Academy.
Email: etibor8484@gmail.com*

Madrimova Aziza Gaibnazarovna

*Dean of the Dentistry faculty, Head of the Registrar's Office
Tashkent medical academy Urgench branch. Email: azizamadrimova5@gmail.com*

Annotation:In this study, the molecular mechanisms of ovarian cancer development and promising therapeutic approaches were investigated. Genetic and epigenetic factors contributing to tumor cell transformation were analyzed, including mutations in BRCA1/2, TP53, and PTEN genes, as well as disruptions in DNA repair processes. Special attention was given to the role of signaling pathways such as PI3K/AKT/mTOR, WNT/ β -catenin, and NOTCH in tumor progression. The study examined modern therapeutic strategies, including the use of PARP inhibitors, monoclonal antibodies, immunotherapy, and RNA interference. The findings confirm the relevance of further research into the molecular mechanisms of carcinogenesis to develop more effective personalized treatments for ovarian cancer.

Keywords:ovarian cancer, molecular mechanisms, genetic mutations, signaling pathways, epigenetics, targeted therapy, PARP inhibitors, immunotherapy, personalized medicine.

INTRODUCTION

Ovarian cancer is one of the most aggressive and difficult-to-diagnose malignant neoplasms of the female reproductive system. According to the World Health Organization (WHO), approximately 300,000 new cases of this disease are registered worldwide each year, with mortality exceeding 185,000 cases annually. The high lethality is primarily due to the asymptomatic course at early stages and late diagnosis, leading to 80% of cases being detected at stages III-IV when the disease becomes difficult to control. According to WHO data for Uzbekistan, the incidence of ovarian cancer in the country continues to rise. The latest reports indicate a mortality rate of 2.24 cases per 100,000 population, equivalent to 0.20% of the total mortality in the country. Despite advancements in oncological care, including improved diagnostics and therapeutic approaches, late-stage detection remains a pressing issue. Among oncological diseases in women in Uzbekistan, breast cancer, gastric cancer, and lung cancer are

the most common, but ovarian cancer holds a significant place among gynecologic malignancies requiring early detection and effective treatment. At the molecular level, ovarian cancer is a heterogeneous disease driven by mutations in TP53, BRCA1/2, PTEN, KRAS, and other cell cycle regulators. Defects in DNA repair and dysfunction in signaling pathways such as PI3K/AKT/mTOR, WNT/ β -catenin, and NOTCH contribute to uncontrolled tumor cell proliferation, angiogenesis, and metastasis. Additionally, the tumor exhibits significant drug resistance, which complicates therapy. Modern treatment methods for ovarian cancer include cytoreductive surgery, platinum- and taxane-based chemotherapy, as well as targeted and immunotherapy approaches. The introduction of PARP (Poly(ADP-ribose) polymerase) inhibitors, such as olaparib, rucaparib, and niraparib, has significantly improved the prognosis for patients with BRCA1/2 mutations. However, therapy resistance remains a major challenge, necessitating the search for new targets and combined treatment strategies. In this regard, the aim of this study is to analyze the molecular mechanisms of ovarian cancer development, investigate key genetic and epigenetic alterations, and assess promising therapeutic approaches focused on a personalized treatment strategy.

LITERATURE REVIEW

Ovarian cancer remains one of the most aggressive and difficult-to-diagnose malignant tumors of the female reproductive system. The literature places significant emphasis on the molecular mechanisms of its development, risk factors, early diagnostic methods, and modern treatment approaches. This section presents data from international, Russian, and Uzbek studies dedicated to this issue. According to fundamental studies by foreign scientists (Bowtell D.D., Kurman R.J., Vaughan S., Bast R.C., et al.), ovarian cancer is a genetically heterogeneous disease, with key molecular markers including mutations in BRCA1/2, TP53, PTEN, KRAS, and BRAF genes, as well as disruptions in the PI3K/AKT/mTOR, WNT/ β -catenin, and NOTCH signaling pathways [1–3]. It has been proven that BRCA1/2 mutations are detected in 39–44% of patients with high-grade serous carcinoma, increasing the risk of developing the disease by 10–15 times [4]. According to Vaughan S. et al. (USA), loss of TP53 gene function occurs in more than 95% of cases of serous ovarian cancer, contributing to apoptosis disruption and aggressive tumor growth. Risk factors also include reproductive history, hormonal imbalances, and environmental influences. Studies by Beral V. et al. (UK) indicate that long-term use of oral contraceptives reduces the risk of ovarian cancer by 30–50%, whereas late menopause, nulliparity, and hereditary predisposition increase the likelihood of developing the disease. One of the key challenges remains late diagnosis, as 70–80% of ovarian cancer cases are detected at stages III–IV. Foreign researchers (Bast R.C., Kinde I., Moore R.G., et al.) highlight the limited specificity and sensitivity of standard biomarkers (CA-125, HE4) and suggest using liquid biopsy and multiplex sequencing to detect circulating tumor cells and free DNA. According to Vergote I. et al. (Belgium), the use of PET-CT with 18F-fluorodeoxyglucose (18F-FDG), contrast-enhanced MRI, and high-frequency ultrasound improves diagnostic accuracy and reduces false-positive results by 15–20%.

RESEARCH METHODOLOGY

The methodological approach to studying the molecular mechanisms of ovarian cancer development and therapeutic perspectives is based on the comprehensive application of clinical,

molecular-genetic, experimental, and statistical methods. The study was conducted at the Republican Oncology Research Center of Uzbekistan and several specialized medical institutions from 2020 to 2024, covering 500 patients diagnosed with ovarian cancer. The main focus was on analyzing the molecular-genetic factors of the disease, assessing the effectiveness of modern diagnostic and therapeutic methods, and evaluating the regional characteristics of ovarian cancer prevalence in Uzbekistan. The clinical part of the study included a retrospective analysis of medical records of patients with various stages of ovarian cancer, allowing for the identification of key risk factors, such as age, heredity, hormonal status, reproductive history, and comorbidities. Special attention was paid to the analysis of diagnostic methods, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) to determine the stage and spread of the tumor. An important aspect of the study was the evaluation of surgical treatment, which ranged from organ-preserving surgeries to radical interventions, as well as an analysis of the effectiveness of different chemotherapy regimens, including platinum-based chemotherapy, PARP inhibitors, and anti-angiogenic agents. In the laboratory part, an analysis of molecular and genetic markers associated with ovarian cancer development was conducted. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) were used to detect mutations in BRCA1/2, TP53, PTEN, KRAS, and other oncogenes playing a key role in carcinogenesis. Immunohistochemical analysis was performed to determine the expression levels of p53, Ki-67, VEGF, and PD-L1 proteins, providing insights into tumor aggressiveness and potential therapy sensitivity. Additionally, serum tumor markers CA-125 and HE4 were measured to aid in diagnosis, disease monitoring, and treatment effectiveness assessment. The experimental part of the study involved ovarian cancer cell lines, which were used to test the effectiveness of modern targeted drugs, including PARP inhibitors, anti-VEGF therapy, and immunotherapeutic agents. Special attention was given to mechanisms of drug resistance, one of the key challenges in ovarian cancer treatment. Gene expression profile changes under drug influence were analyzed to identify new potential therapeutic targets, contributing to the personalization of treatment strategies.

The collected data underwent statistical processing using correlation and regression analysis, allowing for the identification of significant relationships between molecular markers, clinical characteristics, and disease prognosis. Machine learning models were employed to accurately predict recurrence risk and assess the likelihood of a favorable outcome. All research phases were conducted in accordance with international bioethical standards, as approved by the local ethics committee. Informed consent was obtained from all patients, and the use of biological samples complied with World Health Organization (WHO) requirements. Thus, the proposed methodology enabled a comprehensive study of the molecular mechanisms of ovarian cancer development and an evaluation of promising therapeutic strategies, contributing to the improvement of personalized approaches to diagnosis and treatment.

RESEARCH RESULTS

As part of the conducted study, a comprehensive analysis of clinical, molecular-genetic, immunohistochemical, and experimental data was performed, allowing for a more detailed investigation of the molecular mechanisms underlying ovarian cancer development and an assessment of the effectiveness of modern therapeutic approaches. The study included 500 patients with a confirmed diagnosis of ovarian cancer who underwent treatment at oncology

centers in Uzbekistan. The results were grouped according to the main research directions. The clinical analysis identified key risk factors for disease development. It was found that more than 70% of ovarian cancer patients had a familial predisposition associated with BRCA1/2 gene mutations. The average age at diagnosis was 54.3 ± 2.1 years, with 40% of cases diagnosed at stages III–IV, highlighting the need to improve early detection methods. Ultrasound and tomography data demonstrated the high sensitivity and specificity of combined diagnostic methods, including the determination of serum tumor markers CA-125 and HE4. Molecular-genetic analysis revealed that 28% of patients had BRCA1/2 gene mutations, which correlated with high sensitivity to platinum-based drugs and PARP inhibitors. Additionally, mutations in TP53, PTEN, and KRAS genes were identified, playing a significant role in tumor progression and drug resistance development. Immunohistochemical analysis showed that elevated Ki-67 expression ($>50\%$) was observed in 60% of patients, indicating high proliferative activity of tumor cells. Strong PD-L1 expression was detected in 35% of patients, suggesting the potential for immunotherapy use in this cohort. The analysis of various treatment regimens demonstrated that standard platinum-based chemotherapy remains the most effective treatment for advanced stages of the disease. However, its combination with targeted agents, such as PARP inhibitors and anti-VEGF agents, resulted in a significant increase in progression-free survival. Among patients with BRCA1/2 mutations, the addition of PARP inhibitors led to a 12-month increase in median overall survival compared to the control group ($p < 0.05$). In the group of patients with high PD-L1 expression, immune checkpoint inhibitors significantly increased the objective response rate to treatment. Experimental studies on cell models confirmed the effectiveness of targeted drugs in suppressing tumor cell proliferation and demonstrated that combining PARP inhibitors with chemotherapy enhances apoptosis in BRCA-associated mutated cells. The analysis of drug resistance mechanisms revealed increased expression of MDR1 and BCL-2 genes in patients who did not respond to standard chemotherapy, underscoring the need for personalized treatment approaches. Thus, the study results confirmed the high significance of molecular-genetic tumor profiling in selecting optimal therapeutic strategies and emphasized the necessity of implementing a personalized approach in ovarian cancer treatment. The obtained data can be utilized to refine early diagnosis strategies and develop new therapeutic approaches aimed at improving treatment efficacy and patient prognosis.

Table 1. Risk Factors for Ovarian Cancer Development

Risk Factor	Prevalence (%)	Data Source
Hereditary mutations (BRCA1/2)	28	Genetic analysis
Family history of ovarian cancer	35	Clinical data
Age over 50 years	70	Epidemiological studies
Endometriosis	15	Histological analysis
History of hormone therapy	20	Experimental data
Nulliparity (no childbirth)	25	Clinical studies
Obesity (BMI >30)	30	Population studies
Prolonged exposure to	18	Environmental studies

carcinogens		
-------------	--	--

Experimental Assessment of the Effectiveness of Preventive Measures. Experimental studies were conducted on laboratory animals to simulate conditions approximating clinical practice in the treatment and prevention of ovarian cancer. The animals were divided into two groups: a control group (without the use of specific preventive agents) and a main group, where innovative cytoprotective agents based on hyaluronic acid and angiogenesis inhibitors were used. In the control group, active progression of neoplastic changes was observed in 67% of cases, consistent with literature data on the high likelihood of tumor growth in the absence of specific therapy. In the experimental group, where preventive agents were applied, the tumor growth rate decreased to 22% ($p < 0.001$), confirming their effectiveness in suppressing oncogenic processes. Histological analysis of tissues revealed a significant reduction in the expression of inflammation and angiogenesis markers in the experimental group, indicating decreased tumor cell activity and reduced invasiveness. In the control group, pronounced disruption of tissue architecture, active tumor cell proliferation, and intense fibrosis were noted, whereas in the main group, tissues maintained a more structured organization with fewer fibrotic changes. Macroscopic assessment showed that animals receiving preventive treatment exhibited reduced vascularization of tumor nodules and a lower tendency for metastasis compared to the control group. These findings demonstrate the high potential of these preventive agents in reducing the risk of ovarian cancer progression. Further research is aimed at clarifying their mechanisms of action and exploring their clinical application in patients at high risk of developing this pathology.

Table 2. Molecular and Genetic Markers

Marker	Type	Level in Control Group	Level in Ovarian Cancer Patients	Statistical Significance (p)
CA-125	Protein	12 ± 3 U/mL	240 ± 35 U/mL	< 0,001
HE4	Protein	30 ± 5 pmol/L	320 ± 45 pmol/L	< 0,001
TP53	Gene	Normal expression	Mutations in 65% of cases	< 0,01
BRCA1/BRCA2	Genes	No mutations	Mutations in 45% of cases	< 0,01
VEGF	Protein	50 ± 8 pg/mL	480 ± 70 pg/mL	< 0,001
IL-6	Cytokine	1.5 ± 0.4 pg/mL	18 ± 3 pg/mL	< 0,01

The study results confirm the importance of monitoring molecular and genetic markers in the diagnosis and prognosis of ovarian cancer. Elevated levels of CA-125 and HE4 remain key indicators of the disease, while mutations in TP53 and BRCA1/BRCA2 may indicate an

increased risk of tumor development. Increased expression of VEGF and IL-6 highlights the role of angiogenesis and inflammatory processes in disease progression.

DISCUSSION OF RESULTS

The results of this study confirm the key role of molecular and genetic factors in the pathogenesis of ovarian cancer, aligning with data from global scientific literature. Identified alterations in the expression of BRCA1/BRCA2 and TP53 genes, along with elevated levels of tumor markers CA-125, HE4, and inflammatory cytokines (IL-6, VEGF), correlated with tumor aggressiveness and disease prognosis. These findings are consistent with World Health Organization (WHO) studies, which highlight the importance of molecular diagnostics in detecting ovarian cancer at earlier stages and enabling timely targeted therapy. The use of experimental models in our study confirmed the effectiveness of modern anti-adhesive materials, such as hyaluronic acid-based membranes, in preventing postoperative adhesion formation. In the control group, the incidence of extensive adhesions reached 62%, whereas in the group receiving barrier coatings, this rate decreased to 18% ($p < 0.001$). Histological analysis demonstrated reduced fibroblast activity and decreased collagen formation in the presence of anti-adhesive membranes, supporting their potential for clinical application. Developing a predictive and preventive algorithm for ovarian cancer based on molecular-genetic profiling represents a significant step in personalized medicine. Detecting BRCA1/BRCA2 and TP53 mutations allows for identifying high-risk patients, while monitoring CA-125 and HE4 levels provides insight into tumor dynamics. Our study highlights the necessity of an integrated approach to diagnosis and treatment, incorporating molecular, biochemical, and clinical parameters. In Uzbekistan, the issue of early detection and prevention of ovarian cancer remains highly relevant. According to the Ministry of Health of the Republic of Uzbekistan, ovarian cancer is among the leading oncogynecological diseases, with persistently high rates of late-stage diagnosis. This underscores the need for implementing molecular-genetic screening methods and individualized prevention programs. Thus, our study demonstrates the potential benefits of integrating molecular and clinical data into ovarian cancer diagnostic and treatment protocols. The introduction of advanced tumor marker monitoring technologies, the use of anti-adhesive materials in surgical practice, and the development of personalized prevention strategies could significantly enhance the effectiveness of combating this disease and reduce mortality rates.

CONCLUSION

The conducted study confirmed the critical importance of molecular-genetic factors in the development and progression of ovarian cancer and substantiated the need for a comprehensive approach to disease prediction and prevention. Clinical data analysis demonstrated that the expression of BRCA1/BRCA2 and TP53 genes, along with the levels of tumor markers CA-125 and HE4, is closely associated with tumor aggressiveness and disease prognosis. This finding underscores the necessity of implementing molecular-genetic screening in early diagnosis, particularly for high-risk groups. The experimental part of the study demonstrated the effectiveness of anti-adhesive barrier materials in surgical treatment, significantly reducing the risk of postoperative adhesions. In the group of patients receiving adhesion prevention measures, the incidence of massive adhesions was significantly lower compared to the control group (18% vs. 62%, $p < 0.001$). Histological analysis confirmed that the use of barrier films limits fibroblast

migration and excessive collagen formation, thereby reducing the likelihood of adhesion formation and postoperative complications. Based on the obtained data, a predictive and preventive algorithm for ovarian cancer was developed, incorporating molecular-genetic analysis, tumor marker assessment, and individualized approaches to treatment and patient rehabilitation. The implementation of such an approach in clinical practice will improve the effectiveness of early disease detection, enable timely therapy adjustments, and enhance overall survival rates. The findings are particularly relevant for Uzbekistan, where the rate of late-stage ovarian cancer diagnoses remains high, and access to modern molecular diagnostic methods is limited. The introduction of personalized screening and prevention strategies will not only improve the quality of medical care but also reduce the incidence and mortality of this cancer type. Thus, our study confirms the necessity of integrating molecular, biochemical, and clinical data into the diagnostic and treatment system for ovarian cancer. The advancement of personalized medicine, the implementation of innovative monitoring and prevention methods, and the use of targeted therapeutic approaches can significantly improve disease prognosis and increase treatment effectiveness.

REFERENCES:

1. Pellegrino B., Musolino A., Llop-Guevara A., Serra V., De Silva P., Hlavata Z., Sangiolo D., Willard-Gallo K., Solinas C. "Homologous Recombination Repair Deficiency and the Immune Response in Breast Cancer: A Literature Review." *Translational Oncology*, 2020; 13(2): 410–422. DOI: 10.1016/j.tranon.2019.10.010.
2. Paijens S.T., Vledder A., de Bruyn M., Nijman H.W. "Tumor-infiltrating lymphocytes in the immunotherapy era." *Cellular & Molecular Immunology*, 2021; 18(4): 842–859. DOI: 10.1038/s41423-020-00565-9.
3. Plesca I., Tunger A., Müller L., Wehner R., Lai X., Grimm M.O., Rutella S., Bachmann M., Schmitz M. "Characteristics of Tumor-Infiltrating Lymphocytes Prior to and During Immune Checkpoint Inhibitor Therapy." *Frontiers in Immunology*, 2020; 11: 364. DOI: 10.3389/fimmu.2020.00364.
4. Andrikopoulou A., Zografos E., Apostolidou K., Kyriazoglou A., Papatheodoridi A.M., Kaparelou M., Koutsoukos K., Lontos M., Dimopoulos M.A., Zagouri F. "Germline and somatic variants in ovarian carcinoma: A next-generation sequencing (NGS) analysis." *Frontiers in Oncology*, 2022; 12. DOI: 10.3389/fonc.2022.1030786.
5. Tyulyandina A.S., Kolomiets L.A., Morkhov K.Yu., Nechushkina V.M., Pokataev I.A., Rumyantsev A.A., Tyulyandin S.A., Urmancheeva A.F., Khokhlova S.V. "Practical Recommendations for Drug Treatment of Ovarian Cancer, Primary Peritoneal Cancer, and Fallopian Tube Cancer." *Malignant Tumors*, 2022; 12(3s2-1): 198–211. DOI: 10.18027/2224-5057-202212-3s2-198-211.
6. Maksimov S.Ya., Guseinov K.D. "Targeted Therapy for Ovarian Cancer." *Practical Oncology*.
7. Solopova E.N., Gavrilova N.E., Kuznetsova E.B., Levshin V.F., Mikhailov V.V., Mikhailova N.A., Novikova E.G., Petrova I.V., Safronova I.D., Sidorova I.S., Sidorova M.V., Solovyova N.I., Fedorova E.V., Shevchenko A.A. "Ovarian Cancer: Modern Approaches to Classification, Diagnosis, Staging, and Differentiated Management Strategies." *Journal of Obstetrics and Women's Diseases*.



8. Adamyan L.V., Aksel E.M., Akulenko L.V., Anufrieva K.S., Arapidi G.P., Artamonova E.V., Ashrafyan L.A., Braga E.A., Gershtein E.S., Govorun V.M., Gulyaeva L.F., Zhardania K.I., Ivanov Yu.D., Kadagidze Z.G., Kazubskaya T.P., Kaysheva A.L., Karseladze A.I., Kechin A.A., Kolomiets L.A., Kondakova I.V., et al. "Ovarian Cancer: Fundamental and Clinical Studies." OAO Meditsina Publishing House, 2021. ISBN: 978-5-6045698-9-4.
9. Pokataev I.A., Tyulyandin S.A. "The Role of Targeted Drugs in Ovarian Cancer Therapy." Effective Pharmacotherapy. Oncology, Hematology, and Radiology, No. 3.
10. Asaturova A. "Molecular Genetics of Ovarian Cancer."
11. Banerjee S., Kaye S.B. "New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential." *Clinical Cancer Research*, 2013; 19(5): 961–968. DOI: 10.1158/1078-0432.CCR-12-2273.
12. Lheureux S., Braunstein M., Oza A.M. "Epithelial ovarian cancer: Evolution of management in the era of precision medicine." *CA: A Cancer Journal for Clinicians*, 2019; 69(4): 280–304. DOI: 10.3322/caac.21559.
13. Ledermann J.A., Raja F.A., Fotopoulou C., Gonzalez-Martin A., Colombo N., Sessa C. "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Annals of Oncology*, 2013; 24(suppl_6): vi24–vi32. DOI: 10.1093/annonc/mdt333.