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Molecular Genetic Markers of Ovarian Cancer

Bon LI*, Maksimovich NYE, Dremza IK, Varabyou HY, Kharyk AA, Misik VA and Kipen KM

Department of Pathophysiology, Grodno State Medical University, 80 Gorky St, 230009, Grodno, Belarus

***Corresponding author:** Bon LI, Department of Pathophysiology, Grodno State Medical University, 80 Gorky St, 230009, Grodno, Belarus

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ABSTRACT

Ovarian cancer (OC) is a collective term for a group of diseases that differ in their morphological and molecular characteristics and represent one of the leading causes of death among patients with gynecological malignancies. The insufficient accuracy of standard diagnostic methods necessitates the search for new, more convenient, and precise techniques. This article reviews recently discovered ovarian cancer biomarkers, the theoretical foundations for their application, and their clinical significance. The need for further research into novel markers and the integration of existing ones into clinical practice is highlighted.

Keywords: Ovarian Cancer; Biomarker; Diagnostics

Abbreviations: HRD: Homologous Recombination Deficiency; OC: Ovarian Cancer; miRNAs: MicroRNAs; Log-2FC: log2 Fold Change; TPM: Transcripts Per Million; IHC: Immunohistochemical; ELISA: Enzyme Linked Immunosorbent Assay; PFS: Progression Free Survival; OS: Overall Survival; DSB: Double-Strand Break; ssDNA: Single-Stranded DNA; RPA: Replication Protein A; MMR: Mismatch Repair

Introduction

To date, ovarian cancer remains one of the primary causes of mortality among patients with cancers of the reproductive system [52]. It is currently well-established that OC is an umbrella term for several diseases characterized by distinct morphological and molecular profiles [53]. According to the classification of ovarian tumors by origin, they are divided into epithelial, mesenchymal, sex cord-stromal, germ cell tumors, tumor-like lesions, and other tumors not categorized elsewhere. The predominant type is epithelial ovarian cancer, which accounts for approximately 90% of cases [52]. Epithelial cancer, in turn, is subdivided into several morphological categories: serous carcinomas, mucinous carcinomas, endometrioid carcinomas, clear cell carcinomas, transitional cell Brenner tumors, as well as mixed and undifferentiated types [54]. Due to differences in morphology, etiology, molecular biology, the requirement for targeted chemotherapy, and, consequently, treatment prognosis and survival rates, it is essential to differentiate between all cancer types. A number of biomolecules have been identified as criteria for differential diagnosis, such as FOXL2 for adult-type granulosa cell tumors [55], DICER1 for Sertoli–Leydig cell tumors [56], CTNNB1 for microcystic stromal tumors [57], and SMARCA4 for small cell carcinoma of the ovary, hypercalcemic type [58]. However, this information remains insufficient for the comprehensive diagnosis of all cancer types, creating a clear need for further development in this field.

MicroRNAs

MicroRNAs (miRNAs) are short RNA molecules that regulate gene expression and participate in various biological processes. Their biogenesis involves the transcription of pri-miRNA and its subsequent cleavage into pre-miRNA. The mature form is produced in the cytoplasm following the cleavage of pre-miRNA and functions through complementary binding to mRNA, leading to its degradation or translational inhibition. Dysregulation of miRNAs is associated with the development of various human diseases, including ovarian cancer [1]. Aberrant miRNA expression in this malignancy possesses significant diagnostic and prognostic potential [2]. Currently, over 2,500 miRNAs have been identified that are capable of influencing gene expression within signaling pathways [3-5].

The let-7 and miR-200 families exhibit alterations in ovarian cancer, with the let-7 family potentially being significant for chemotherapy selection [5,6]. A decrease in the expression of miRNA processing enzymes correlates with tumor stage progression and adverse outcomes. Both the let-7 and miR-200 families frequently demonstrate changes in ovarian cancer [6]. Chemoresistance in ovarian cancer is

linked to the aberrant expression of several miRNAs, including let-7e, miR-30c, miR-125b, miR-130a, miR-335, miR-340, miR-381, and miR-520f, among others [7]. Circulating miRNAs in blood and urine are promising diagnostic markers, as they correlate with histotypes, treatment resistance, and prognosis [8]. Specifically, miR-21, miR-200a, and miR-200c hold diagnostic and prognostic value, while let-7f and miR-141 are associated with shorter progression-free survival. Furthermore, miR-193a acts as a tumor suppressor [9]. In a study by Yokoi et al., an eight-miRNA panel was able to distinguish early-stage ovarian cancer from benign tumors with a sensitivity of 86% and a specificity of 83% [10].

BRCA1 and BRCA2

These genes belong to the category of genes encoding enzymes involved in DNA repair systems. Although alternative pathways for repairing double-strand breaks exist, clinically significant mutations in the BRCA1 and BRCA2 genes lead to genomic instability. This instability arises from the accumulation of genetic damage, which facilitates the malignant transformation of cells [11-13]. The probability of mutations in the BRCA1 gene is four times higher than in the BRCA2 gene [14]. Hereditary forms of ovarian cancer account for 10% to 15% of the total number of cases [15]. The lifetime risk of developing ovarian cancer in the presence of pathogenic BRCA1 mutations is estimated to be between 20% and 50%, whereas for BRCA2 mutations, this figure is approximately 10% to 20%. According to research findings, the mean age at diagnosis for ovarian carcinoma is lower in BRCA1 mutation carriers compared to BRCA2 mutation carriers [16-17]. In terms of histological characteristics, high-grade serous ovarian carcinoma is the predominant subtype among carriers of both BRCA1 and BRCA2 mutations [18]. In a cohort screening conducted by Stavropoulou et al. involving 592 patients with sporadic ovarian cancer, 27 individuals (4.6% of the total sample) were identified as carriers of the most common BRCA1 mutations [16]. A study by De Leeneer et al. involving 193 cases of sporadic breast and ovarian cancer showed that among seven women with concurrent breast and ovarian cancer, three (42.9%) were carriers of BRCA1/2 mutations [17]. In Poland, an evaluation of 148 consecutive ovarian cancer patients identified BRCA1/2 mutations in 21 women, representing 13.9% of the total cases [20]. In the Russian Federation, the prevalence of BRCA1/2 mutations among 74 patients was higher, with the carrier frequency reaching 19% [21]. In a study conducted by Pohlreich [see note below], among patients with a burdened family history of ovarian cancer, 13 out of 40 subjects (33%) were BRCA1/2 mutation carriers. In the group of patients without a burdened family history, mutations were identified in 23 out of 283 individuals (8%) [22].

B7-H4 (VTCN1)

The B7-H4 protein, encoded by the VTCN1 gene (V-set domain containing T-cell activation inhibitor 1), is a transmembrane protein localized on the cell surface. Differential expression analysis of the VTCN1 gene conducted by Lysanne D. A. N. de Muynck et al. revealed high log2 fold change (Log2FC) values. For primary tumors, this value was 8.56, while for metastases, it was 6.53. In healthy tissues, including the ovaries, omentum, peritoneum, and lymph nodes, VTCN1 RNA expression was virtually absent, with transcripts per million (TPM) levels below 0.5. Immunohistochemical (IHC) analysis confirmed B7-H4 protein overexpression in 86% of the examined tumor samples (74 out of 86). Furthermore, an analysis of expression stability demonstrated that high B7-H4 levels were maintained in both primary tumors and their corresponding omental, peritoneal, and lymph node metastases, indicating the stability of this marker during disease progression ($p > 0.05$). Notably, expression remained high in specimens obtained both after primary cytoreductive surgery and following neoadjuvant chemotherapy, suggesting that the marker is resistant to the effects of the administered treatment [23].

HE4

The HE4 protein, encoded by the WFDC2 gene, is a glycoprotein belonging to the class of serine protease inhibitors. This protein serves as a potential biomarker for ovarian cancer and can be detected in blood and urine samples using enzyme-linked immunosorbent assay (ELISA). HE4 overexpression is characteristic of specific histological subtypes of ovarian tumors, with an occurrence frequency of 100% in endometrioid carcinomas and 93% in serous carcinomas. In combination with other prognostic factors, HE4 can serve as an additional predictor of mortality in ovarian cancer, particularly in the serous histotype [24]. According to the results of a meta-analysis conducted by Nalini et al., which included 38 studies involving a total of 14,745 participants, serum HE4 demonstrated significant diagnostic value as an ovarian cancer biomarker. The marker's performance indicators were characterized by acceptable sensitivity (0.79) and clinically significant specificity (0.92) [25]. In a study by Barr et al. involving 1,229 symptomatic women, the combination of CA125 and HE4, along with the ROMA (Risk of Ovarian Malignancy Algorithm) algorithm, were evaluated for ovarian cancer diagnosis. The ROMA algorithm showed the best performance (AUC = 0.96). In women under 50 years of age, the combination of CA125 and HE4 demonstrated higher sensitivity and specificity, whereas the ROMA algorithm was more effective in the older age group. Individually, HE4 possessed higher sensitivity but lower specificity compared to CA125 [26]. A study by Chudecka-Głaz et al. evaluated the prognostic significance of HE4 during first-line chemotherapy in ovarian cancer patients. It was established that HE4 levels predict platinum sensitivity and are associated with progression-free survival (PFS), overall survival (OS), and surgical outcomes. HE4 demonstrated potential as a valuable biomarker for assessing treatment efficacy and prognosis [27]. In another study by Chudecka-Głaz et al. involving 188 ovarian cancer patients, elevated HE4 levels at diagnosis, after cytoreduction, and during first-line chemotherapy were associated with a high risk of recurrence. Increased HE4 levels were also observed in cases of large residual tumors following primary surgery and in platinum-resistant patients. At the time of the second recurrence, significantly higher HE4 levels were detected in patients with residual lesions exceeding 10 mm [28].

CA-125

CA125 is a glycoprotein encoded by the *MUC16* gene located on chromosome 19 [29]. In a study by Ahmad et al., the highest CA125 levels were observed in the serous ovarian cancer subtype and stage II, followed by stages III, I, and IV [30]. Cooper et al. confirmed that elevated preoperative CA125 values are associated with serous histology, advanced stages (III–IV), high-grade malignancy, and the presence of ascites [31]. Measuring CA125 is most informative in postmenopausal women, where it demonstrates higher sensitivity, specificity, and predictive value [32]. However, Antovska et al. concluded that CA125 has limited efficacy as a standalone test [33]. Yang et al. found that while CA125 alone identifies more than half of early-stage ovarian cancer cases, its combination with HE4 Ag-AAb complexes increased the detection rate to 81% [34]. Consequently, Kim et al. recommended using CA125 in combination with HE4 and the ROMA algorithm to improve diagnostic accuracy [35]. Furthermore, Sorensen and Mosgaard established that the serum CA125/CEA ratio can be utilized for the preoperative differential diagnosis of ovarian masses.

Their results showed that with a CA125/CEA index above 25, the probability of a malignant ovarian tumor reaches 82% [36]. Andersen et al. revealed that the combination of CA125 and a symptom index identified cancer in 89.3% of women, including 80.6% of those with early-stage disease and 95.1% of those with advanced forms [37]. CA125 is widely used for monitoring ovarian cancer and assessing treatment response [38-40]. Potenza et al. showed that the normalization of CA125 by the fourth cycle of chemotherapy indicates a positive response to treatment [41]. Akhavan et al. also demonstrated the prognostic value of CA125 decline dynamics following neoadjuvant chemotherapy [42]. An analysis by Rodriguez et al., involving 103 patients with stage III–IV disease, established that a preoperative level of ≤1000 U/mL is associated with a high probability of complete cytoreduction [43]. In a study by Piatek et al., it was found that a 5 U/mL increase in CA125 levels at 3 and 6 months post-treatment is associated with a significant reduction in 5-year survival. Additionally, a preoperative CA125 level exceeding 535 U/mL indicates the presence of lymph node metastases [44]. Chiang et al. found that patients with low CA125 levels (<35 U/mL) have a higher likelihood of successful interval debulking surgery and longer progression-free survival compared to patients with levels >100 U/mL [45]. Chan et al. demonstrated that elevated CA125 levels before the initiation of chemotherapy are independently associated with lower recurrence-free survival (HR = 2.13, 95% CI: 1.23–3.69; p = 0.007) and overall survival (HR = 1.99, 95% CI: 1.10–3.59; p = 0.022) [46]. Baseline CA125 levels prior to maintenance chemotherapy correlate with the risk of recurrence, and its rise serves as an early marker of clinical relapse [44,47-49]. Paik et al., in a study of 99 patients with recurrent epithelial ovarian cancer, established that rising CA125 levels are associated with an increased probability of extrapelvic and multiple recurrences [50]. Finally, Wilder et al. showed that a gradual increase in CA125 levels within the normal range over a period of 1–3 months is associated with an elevated risk of ovarian cancer recurrence [51].

RAD51

RAD51 is one of the key proteins involved in DNA repair via the double-strand break (DSB) pathway. It catalyzes the resynthesis of the damaged genomic region. Numerous studies have reported RAD51 overexpression in various types of cancer [59]. This may indicate a compensatory repair mechanism for damaged DNA in tumor cells, suggesting that dysregulation of this protein's expression could lead to an increased mutational burden [52]. For RAD51 to function correctly, two additional protein complexes are required: BCDX2 (comprising RAD51B, RAD51C, RAD51D, and XRCC2) and CX3 (comprising RAD51C and XRCC3). These two complexes act at different stages of DNA repair: BCDX2 is responsible for the recruitment and stabilization of RAD51 at damage sites, whereas the CX3 complex acts following RAD51 recruitment [60]. The BRCA1–PALB2–BRCA2 complex exhibits mediator activity, loading the RAD51 protein onto single-stranded DNA (ssDNA) regions coated with replication protein A (RPA), thereby recruiting RAD51 to the repair site [61,62]. Research into RAD51C gene mutations has shown that variants associated with a partial or complete loss of RAD51C functionality are linked to an increased risk of ovarian cancer (OC) [52]. According to meta-analytical data, mutations such as c.706-2A>G, c.577C>T (p.Arg193Ter), c.224dupA (p. Tyr75Terfs), and c.955C>T (p.Arg319Ter) are associated with OC [63].

In another study, the variant c.790G>A (p.Gly264Ser) was interpreted as a moderate-penetrance risk allele [64]. Investigations within the Finnish population have revealed that the c.93delG and c.837+1G>A mutations (in BRCA1/BRCA2-negative cases) confer a higher risk for familial or sporadic OC, a lower risk for familial breast cancer (BC) combined with OC, and no association with BC-only populations. In the same study, the c.790G>A (p.Gly264Ser) mutation did not reach statistical significance, although a trend toward an increased risk of OC was observed [65]. Similarly to RAD51C, mutations in its paralog RAD51D are also associated with ovarian cancer. The majority of these mutations (approximately 80%) consist of nonsense mutations or frameshifts, with the most frequent being c.694C>T (p.Arg232Ter), c.270_271dupTA (p.Lys91Ilefs), c.556C>T (p.Arg186Ter), and c.748delC (p.His250Thrfs). Statistically, these mutations are associated with a high risk of developing OC, with the exception of p.Lys91Ilefs, which is considered a moderate-risk variant in Caucasian populations [66].

The MMR System

The DNA Mismatch Repair (MMR) system is a complex consisting of seven core proteins—MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, and PMS2—essential for the detection and correction of DNA replication errors. The MMR complex functions through the interaction of several heterodimers: MSH2–MSH6 (MutSα), MSH2–MSH3 (MutSβ),

MLH1–PMS2 (MutLα), MLH1–PMS1 (MutLβ), and MLH1–MLH3 (MutLγ) [67-70]. Alterations or epigenetic inactivation of MMR genes are associated with microsatellite instability (MSI). MSI is considered both a risk factor for the development of malignancies and a predictor of a positive response to immunotherapy, due to the high burden of aberrant antigens that render the tumor immunogenic [71,72]. Some studies have established that MMR deficiency (dMMR) occurs more frequently in non-serous ovarian cancer (OC), specifically in endometrioid and clear cell carcinomas [73]. Mutations in the MLH1 and MSH2 genes are most commonly observed in patients diagnosed with early-onset non-serous OC [74]. Furthermore, in vitro studies have linked MMR deficiency to resistance to platinum-based chemotherapy [67]. The expression of MLH1 and MSH2 proteins, assessed by staining intensity, varied depending on the histopathological subtype and disease stage; these proteins exhibited more intense staining in serous OC compared to non-serous subtypes [19,75].

Conclusion

In this study, key molecular and genetic markers determining the biological behavior of ovarian cancer were analyzed. It has been established that conventional diagnostic methods possess insufficient specificity during the early stages of the disease. The analysis of current data confirms that the implementation of molecular profiling—specifically the determination of BRCA1 and BRCA2 mutation status—has radically transformed patient management strategies. The identification of germline and somatic mutations in these genes, as well as the assessment of Homologous Recombination Deficiency (HRD), are now mandatory diagnostic steps that allow for the prediction of response to PARP inhibitors and platinum-based agents. Thus, a shift from histological classification to the molecular-genetic stratification of ovarian tumors is a prerequisite for improving patient survival rates. Integrating genetic panels into routine clinical practice will not only optimize therapeutic approaches but also enable the identification of risk groups among healthy women for timely preventive interventions.

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