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EMERGING PROTIEN AND GENETIC BIOMARKERS FOR EARLY STAGE OF OVARIAN CANCER

Penumudi Sruthi*, SURYAKALYANAM RISHIKA, BUDAGALA GAYATHRI, CHANDU BABU RAO

Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur-522017, Andhra Pradesh, India.

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Abstract: Ovarian cancer remains one of the leading causes of cancer-related mortality among women worldwide, largely due to its asymptomatic nature during early stages and late clinical detection. Standard treatment approaches, including surgical tumor debulking followed by systemic chemotherapy, often face limitations because a significant proportion of patients eventually develop chemoresistance, resulting in poor therapeutic outcomes and reduced survival rates. Consequently, there is an urgent need to identify reliable biomarkers that can improve early detection, predict disease progression, and guide therapeutic strategies. This review focuses on both established and emerging predictive biomarkers associated with ovarian cancer. It highlights commonly used diagnostic and prognostic biomarkers such as CA125, HE4, osteopontin, and vascular endothelial growth factor, while also discussing novel candidates including tumor mutation burden markers, DNA repair pathway components, and cell cycle regulatory genes. Furthermore, the review outlines advanced molecular and genomic technologies utilized in biomarker discovery, including transcription profiling, microRNA analysis, and whole genome approaches. These technologies contribute to a better understanding of ovarian cancer heterogeneity and molecular signaling pathways. Identifying and validating predictive biomarkers can enhance early diagnosis, facilitate personalized treatment, and improve patient prognosis, thereby offering promising prospects for more effective ovarian cancer management.

Keywords: Early detection of recurrence, novel biomarkers, ovarian carcinoma, screening.

***Corresponding Author**
Penumudi Sruthi

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INTRODUCTION

Ovarian cancer is a highly heterogeneous disease that remains a major cause of cancer-related mortality among women worldwide. The disease consists of multiple subtypes, with high-grade serous ovarian cancer being the most aggressive and responsible for most ovarian cancer deaths. Genetic mutations, including TP53 mutation and homologous recombination deficiency, are frequently observed in aggressive forms of ovarian cancer and contribute to tumor progression and therapeutic resistance. Early diagnosis plays a crucial role in improving patient survival, yet ovarian cancer is often diagnosed at advanced stages due to the absence of specific symptoms [1]. Tumor heterogeneity also complicates biomarker discovery and the development of effective therapeutic strategies. Molecular targeted therapies, including poly ADP ribose polymerase (PARP) inhibitors, have improved survival in patients with BRCA mutations, highlighting the importance of molecular biomarker identification [2].

.Ovarian cancer development involves multiple genetic and molecular signaling pathways. Understanding these pathways may help identify new diagnostic and prognostic biomarkers and improve personalized treatment approaches. The review focuses on recently discovered biomarkers, currently available clinical biomarkers, and modern laboratory techniques for identifying novel ovarian cancer markers. .Ovarian cancer is the leading cause of death from gynecological malignancies and remains a major global health burden. In the United States, ovarian cancer ranks among the top causes of cancer mortality among women, with thousands of new cases diagnosed annually. Despite advances in treatment, survival rates remain low due to late-stage diagnosis..Epithelial ovarian cancer is characterized by significant biological heterogeneity, which affects disease progression and treatment outcomes. Biomarkers play an important role in

ovarian cancer management by monitoring therapeutic response, detecting recurrence, and differentiating benign from malignant pelvic masses. CA125 is widely used in clinical practice; however, it has limitations in early-stage detection [3]. The integration of multiple biomarkers, including HE4 and multivariate index assays such as RMI and ROMA, has improved diagnostic accuracy. Emerging biomarkers and imaging technologies are currently being investigated to enhance early detection and improve patient survival outcomes..Early detection of ovarian cancer remains a major clinical challenge. Evidence suggests that advanced-stage ovarian cancer may originate from earlier stages, emphasizing the importance of detecting the disease during its initial development. Gene expression studies demonstrate similar genetic patterns between early-stage and advanced-stage ovarian cancers, supporting this progression model [4]. .Screening for ovarian cancer is essential because early-stage disease has significantly higher survival rates than advanced-stage cancer. Stage I ovarian cancer can be cured in most patients, whereas survival decreases drastically once the disease spreads beyond the ovaries. However, only a small percentage of cases are diagnosed during early stages due to lack of effective screening tools. .Ovarian cancer remains one of the most lethal gynecological malignancies due to late diagnosis and lack of reliable early detection markers. Biomarkers such as CA125 and HE4 are widely used for diagnosis and disease monitoring; however, their diagnostic accuracy remains limited Several multivariate index assays, including RMI, ROMA, and OVA1, have been developed to improve diagnostic performance. In addition, emerging biomarkers such as circulating tumor DNA, microRNA, methylation markers, and autoantibodies show potential for early disease detection and prognosis prediction [5].

OVARIAN CARCINOMA

Ovarian carcinoma is a malignant tumor that originates in the ovaries and represents one of the most lethal gynecological cancers worldwide. It is often referred to as a "silent disease" because early stages usually present with minimal or nonspecific symptoms, which leads to delayed diagnosis. Most patients are diagnosed when the cancer has already progressed to advanced stages, resulting in poor survival outcomes. Ovarian cancer is a heterogeneous disease composed of several histological and molecular subtypes, with epithelial ovarian cancer being the most common and aggressive form. Biomarkers such as CA125 and HE4 are widely used for diagnosis and disease monitoring, although they have limitations in sensitivity and specificity. Recent research focuses on identifying novel molecular and genetic biomarkers to enhance early detection, improve prognosis prediction, and develop personalized therapeutic strategies [6].

1. **Monitoring Ovarian Cancer during Treatment and For Recurrence**

Management of ovarian cancer has improved over the last three decades, with an increase in 5-year survival from 38 to 46%, related to the more consistent use of cytoreductive surgery and combination chemotherapy with platinum compounds and taxanes.

1.1 CA125

CA125 is a high molecular weight (5 million Dalton) heavily glycosylated transmembrane mucin (MUC16) which is overexpressed in 80% of epithelial ovarian cancers. CA125 is cleaved just outside the cell membrane and is then shed into body fluids where it can be detected with double determinant immunoassays, providing the first clinically useful
Biomarker for monitoring the response to treatment of ovarian cancer.

1.2 HE4

Human epididymis protein 4 (HE4) is a 20–25 kDa protein that is secreted by epithelial cells and belongs to the family of whey acidic four-disulfide core (WFDC) proteins. Compared with its expression in normal tissues including ovary, the WFDC2 (HE4) gene is increased in the majority of ovarian cancers [7].

SCREENIG OF WOMEN AT AVERAGE RISK

Large clinical trials have evaluated screening strategies using serum CA125 testing and transvaginal ultrasound (TVS) either individually or in combination. These studies showed that although screening can detect ovarian cancer at earlier stages in some cases, it often results in a high rate of false-positive findings. False-positive results can lead to unnecessary surgical procedures, which may expose women to additional health risks without clear survival benefits. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial evaluated simultaneous cancer mortality among women at average risk. Similarly, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) assessed multimodal screening approaches that used serial CA125 measurements interpreted through risk algorithms along with ultrasound imaging [8].

CHLORIDE INTRACELLULAR ION CHANNELS AS BIOMARKERS FOR OVARIAN CANCER

The CLIC family in vertebrates consists of six evolutionarily conserved protein members. These proteins are unusual, existing in cells as both soluble and membrane bound proteins, where they demonstrate "moonlighting" activity, exhibiting two independent functions. In the membrane bound form, CLIC proteins act as ion channels. While in the soluble form, they act as oxidoreductase enzymes, which are most likely involved in cell protective functions like detoxification and/or anti-oxidative roles. Several studies have also shown CLIC proteins to have important extracellular activities with CLIC1, CLIC3 and CLIC4 found on endometrium/placenta cell exosom. In a recent bioinformatics study of patient survival as a function of the relative mRNA levels,

across several human cancers, the data clearly indicates low or high CLIC expression levels, influence patient survival .For example, high CLIC1 and CLIC3 mRNA expression were associated with advanced stages of liver cancer. However, to better understand the therapeutic potential of these proteins, it is important to further deduce details regarding their tissue expression and release into blood [9-10].

DIAGNOSTIC APPROACHES FOR THE ANALYSIS OF EXOSOME ASSOCIATED CLICS AS BIOMARKERS FOR EARLY DETECTION OF OVARIAN CANCER

EXs have been successfully isolated from blood, urine, ascites, cerebrospinal fluid, amniotic fluid, semen, saliva, and bile thus providing an array of possibilities for their detection using several different techniques, with some examples as highlighted in Figure 1. Some of the currently available techniques that analyse EX proteins from different human body fluids, with or without EX isolation, include flow cytometry, protein microarray (EX Array), diagnostic magnetic resonance, nanoplasmonic sensing technology and microfluidics.

Recently, a number of studies have proposed exosomal proteins as diagnostic biomarkers of breast cancer where one such study showed EXs isolated using anti-CD24 and anti-EpCAM-coupled magnetic beads as potential breast cancer-specific markers [11].

ATTEMPTS TO EARLY STAGE OF OVARIAN CANCER DETECTION

Early-stage detection of ovarian cancer, also known as ovarian carcinoma or malignant ovarian neoplasm, has remained a significant clinical challenge due to the absence of clear symptoms during the initial stages of disease development. However, CA125 lacks sufficient sensitivity and specificity for early diagnosis of ovarian carcinoma or ovarian malignancy, as elevated levels may also occur in benign gynecological conditions and inflammatory disorders. To improve diagnostic accuracy, researchers have explored the use of additional biomarkers including mesothelin, kallikrein-related peptidases, and human epididymis protein 4 (HE4). Combining multiple tumor markers into biomarker panels has shown improved sensitivity and specificity for detecting early ovarian tumors and epithelial ovarian cancer. Imaging techniques such as transvaginal ultrasonography have also been investigated as screening tools for early identification of ovarian neoplasms [12].

BIOLOGICAL REQIREMENTS FOR EARLY DETECTION

The early detection of ovarian cancer, also referred to as ovarian carcinoma or ovarian malignancy, requires specific biological characteristics that enable identification of the disease before clinical symptoms appear. An effective early detection biomarker or biological indicator must be produced by early-stage ovarian tumors or malignant ovarian neoplasms and released into easily accessible body fluids such as blood or serum. A suitable biomarker should demonstrate high sensitivity, meaning it can accurately detect small or early ovarian tumors without missing cases.

1. Biological requirements for early detection

The ultimate success of any screening strategy for malignant disease depends upon the clinical biology of a cancer. The expectation that screening for ovarian cancer will impact favorably on survival depends upon several assumptions regarding the biology of the disease. For effective screening:

1) Most tumors must arise from single clones of cells within the ovary rather than from multiple foci throughout the abdominal cavity

2) Most metastatic disease should develop by progression from clinically detectable stage I lesions

3) The length of time that ovarian cancers remain localized to the ovary (Stage I) must be sufficiently long to permit cost-effective screening at practical intervals .

2. Epidemiologic requirements for early detection

Ovarian cancer is neither a common nor a rare disease. Prevalence of epithelial ovarian cancer in the post-menopausal population of the United States or Europe is approximately 1 in 2500. Therefore, an effective screening strategy must have sensitivity greater than 75% and specificity greater than 99.6% to attain a positive predictive value (PPV) of 10%. Although the limit of 10% for the PPV is arbitrary, most advocates and gynecologic oncologists feel that no more than 10

laparotomies per case of ovarian cancer detected would be acceptable.

3. Strategies for Early Detection

3.1. Ultrasonography

Initial investigations employed transabdominal ultrasonography (TAU) as a screening tool for identifying ovarian malignancies. With advancements in imaging technology, transvaginal sonography (TVS) was later introduced, offering enhanced visualization and greater anatomical detail of the ovaries compared to the transabdominal approach.

3.2. Serum markers

Use of serum markers for early detection has largely focused on CA125, a heavily glycosylated high molecular-weight mucin (MUC 16). Serum CA125 levels are elevated in 50–60% of patients with early stage ovarian cancer and in 90% of patients diagnosed with late stage ovarian cancer.

3.3. Concurrent combination of CA 125 and transvaginal sonography

The Prostate, Lung, Colon and Ovary (PLCO) Screening Trial has studied postmenopausal women between 55 and 74 years, randomizing 37,000 to the screening arm of the trial and another 37,000 to participate as non-screened controls. For ovarian cancer screening, CA125 levels have been obtained upon entry into the trial and then annually for 5 years.

3.4. Proteomic markers

Biomarkers have been sought by proteomic analysis of sera from ovarian cancer patients and from healthy

individuals. Mass spectrometry (MS) uses mass to charge ratios to identify patterns of both known and unknown proteins. Two different approaches have been used. The first attempts to identify differences in patterns that consistently differentiate healthy individuals from cancer patients [13].

AN OVERVIEW OF OVARIAN CANCER BIOMARKERS AND CELL SIGNALLING PATHWAYS

Ovarian cancer, also known as ovarian carcinoma, ovarian malignancy, or malignant ovarian neoplasm, involves complex molecular alterations that influence tumor development, progression, and therapeutic resistance. Biomarkers play an essential role in the diagnosis, prognosis, and monitoring of ovarian tumors and epithelial ovarian cancer. These biological indicators include proteins, genes, and molecular compounds released by ovarian tumors or produced in response to tumor growth. Several well-established biomarkers such as carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4) are widely used in clinical practice for detecting ovarian adenocarcinoma and monitoring disease progression. These pathways regulate essential cellular functions such as cell proliferation, apoptosis, angiogenesis, and metastasis [14].

6. POTENTIAL BIOMARKERS FOR OVARIAN CANCER DETECTION

1. Potential Protein Biomarkers for Ovarian Cancer Detection

Protein biomarkers have been widely studied during the past 3 decades and more than 100 potential biomarkers have been evaluated. Folate receptor alpha (FOLR1) is a membrane protein regulating the binding and cellular uptake of folic acid into cells ovarian cancer.

2. Potential Multivariate Index Assays for Ovarian Cancer Detection

Karlsen et al. established the Copenhagen Index (CPH-I) in 2015 based on age along with the serum levels of HE4 and CA125. This model has been tested to have sensitivity of 69% and a specificity of 85% for the differentiation of malignant and borderline tumors a multivariable model based on five proteins (CA125, OPN, HE4, leptin, and prolactin.

3. Potential Role of Autoantibodies (AABs) in the Early Detection of Ovarian Cancer

The genetic alteration of cancer cells leads to an aberrant expression of tumor-associated antigens (TAA) that can be recognized by the immune system, resulting in the generation of corresponding AABs the presence of anti-TP53 AABs could be detected in only ~20% of patients when diagnosed, with this percentage slightly rising 40

4. Potential Role of Circulating Tumor DNA (ctDNA) in the Early Detection of Ovarian Cancer

ctDNAs are DNA fragments that are released from cancer tissues into circulating bodily fluids such as blood, urine, and ascites through apoptosis, necrosis, lysis, and active secretion Moreover, the half-life of ctDNA is short at around 1 h, which confers the ability to monitor the real-time tumor progression [15].

5. Potential Role of Methylation in the Early Detection of Ovarian Cancer

During cancer development and progression, the hypermethylation of CpG islands in the gene promoter is a frequent event that leads to the repression of transcription, the silencing of tumor suppressor genes, and the activation of oncogenes, ultimately promoting the cancer transformation Singh et al. used a quantitative TaqMan-based qPCR assay (MethyLight) and a clonal bisulfite sequencing method to analyze the DNA methylation status of ovarian cancer in the frequently methylated tumor suppressor genes HOXA9 and HIC1

7. PREDICTION OF RESPONSE TO TREATMENT

There is not a reliable biomarker or signature that predicts response or lack of response to paclitaxel. This is an important unmet need Some 70% of patients responded to cisplatin alone or to a combination cisplatin with paclitaxel, but only 42% responded to paclitaxel alone. In subsequent large, randomized trials, a combination of platinum and taxanes produced longer overall survival than did platinum alone. A fraction of cancers from patients with wild-type BRCA1/2 will also respond to PARP-inhibitors, presumably related to some other defect in HRR [16].

8. FUTURE DIRECTIONS

Currently, investigators from the NCI-funded Ovarian SPOREs are collaborating with each other and with the Early Detection Research Network and the PLCO to evaluate most of the markers in Within the next 5 years, results of the UKCTOCS trial in the United Kingdom should be available to test whether survival can be improved through use of sequential analysis of CA125 followed by TVS [17]. If this trial is positive, there will still be a need to improve sensitivity of the initial phase through the use of multiple biomarkers In the long run, further exploration of urine biomarkers may be desirable, considering the potential convenience of urinary assays in screening populations.

9. CONCLUSION

Ovarian cancer is a high-mortality gynaecological condition affecting women all over the world. While substantial improvement has been made in the detection and overall five year survival rate of ovarian cancer patients, both rates remain very low If the UKCTOCS shows a mortality advantage when an additional five years of follow-up is analyzed, the similarly designed NROSS trial has demonstrated that screening with CA125 followed by TVS is feasible in the United States Finding preclinical disease at an earlier stage could reduce long-term ovarian cancer mortality by 10%–30%. Multivariate panels using other

biomarkers to complement CA125 have been shown to have an improved diagnostic performance compared with CA125 alone and a multivariate index panel with the RMI, OVA1, and ROMA has been approved by the FDA for use in clinics.

10. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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None

12. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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