

# Biomarkers for Early Detection of Ovarian Cancer: A Review

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## Abstract

Ovarian cancer, with its asymptomatic early stages, poses a significant challenge for early diagnosis and survival improvement. The utilization of tumor markers, including CA -125 and HE4 has become crucial in detecting these silent killers. Additionally, gene-based markers like BRCA1 and BRCA2 mutations are increasingly acknowledged for indicating ovarian cancer susceptibility. Promising emerging biomarkers, such as microRNAs and circulating tumor cells, offer new research avenues and diagnostic possibilities for the early detection of ovarian cancer. This article provides a comprehensive review of current specific markers, gene-based indicators, emerging markers, and other notable approaches in the early identification of ovarian cancer.

**Keywords:** Early detection- Biomarkers- CA125- HE4- microRNAs- mesothelin

*Asian Pac J Cancer Biol*, **9** (1), 81-85

Submission Date: 11/15/2023

Acceptance Date: 12/21/2023

## Introduction

Ovarian cancer stands as the primary cause of gynecological cancer-related deaths, claiming around 140,000 lives annually globally [1]. In its early stages, ovarian cancer often exhibits no symptoms, earning it the ominous label of a “silent killer” with only 20% of cases diagnosed at stages [2]. Computer simulations indicate that detecting pre-clinical disease sooner could enhance survival rates by 10-30% and prove cost-effective [3]. As the cancer progresses, symptoms become more noticeable, contributing to ovarian cancer’s highest mortality rate among gynecological diseases [2]. current detection method involves transvaginal ultrasonography and the use of cancer antigens [CA-125]. while CA-125 has played a significant role in diagnosis and prognosis, the lack of highly sensitive biomarkers for early detection contributes to the high fatality rate [4]. Ongoing research explores the combination of multi-biomarkers like HE4, FOLR, kallikerin, miRNA, ROMA, and CA-125, aiming for increasing sensitivity in the early diagnosis of ovarian cancer [5]. this review provides an overview of current biomarkers, gene-based approaches, emerging markers, and other notable indicators in the quest for early detection of ovarian cancer.

### 1.1. Significance of Early diagnosis in ovarian cancer

Ovarian cancer [OC] is a complex group of diseases characterized by variations in appearance and behavior at the biological level. Despite being less prevalent than breast cancer, OC has a disproportionately high impact, leading to a significant number of deaths. In the advanced stage [stage -3] OC proves fatal for the majority of patients, with recurrence in about 75% of cases after surgery and chemotherapy. Globally, OC Is recognized as the most lethal gynecological cancer and ranks fifth in cancer-related deaths among women in the Western world. such as biomarker testers, could improve the chances of early detection [6].

### 2. Current Specific Biomarkers for Ovarian Cancer

#### 2.1 .CA-125(Cancer Antigen 125)

CA -125 has served as a tumor marker for over 30 years, primarily for diagnosing ovarian cancer monitoring treatment response, and detecting recurrence [7]. This classic biomarker, with a sensitivity of 50-60% and 90%specificity in early-stage postmenopausal women, is elevated in 90% of epithelial ovarian cancer cases [8]. Although it is commonly used, CA-125 alone lacks

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the sensitivity for early-stage detection, especially in premenopausal women various benign conditions can elevate CA-125 levels, making it insufficient for widespread cancer screening. However, clinical trials, such as the Risk of Ovarian Cancer Algorithm [ROCA], aim to enhance CA-125's sensitivity by combining it with other markers, achieving an 86% sensitivity for early detection [9]. The ROCA categorizes women based on CA-125 levels and scores, guiding further procedures for low, high, and intermediate-risk groups [10]. Notably, CA-125 is the solo marker elevated in endometrioma cases, with 40% sensitivity and 91% specificity using a 35U/ml cut-off [11].

### 2.2. HE4 (Human Epididymis Protein 4)

HE4 belongs to the whey acidic four disulfide core [WFDC]protein family and was initially identified in the digital epididymis epithelium [12]. Studies have indicated that HE4 when combined with CA-125, serves as a more specific biomarker for ovarian cancer compared to either marker alone. Also as a single marker, HE4 had the highest sensitivity (72.9% at 95%), and when combined with CA125 sensitivity increased to 76.4% (at 95% specificity) [8]. The greater performance of HE4 may be due to its superior specificity compared to CA125 as it is unaffected by benign pelvic disease such as endometriosis. Recent meta-analyses have reported similar results, demonstrating that HE4 displays greater performance than CA125 in terms of differential diagnosis between benign pelvic disease and ovarian cancer [13]. Variations of HE4 levels in variable situations were also evaluated. Bolstad et al. observed altered HE4 levels based on Body Mass Index (BMI), while Ferraro et al. found no significant HE4 level differences among 103 patients grouped by BMI. This discrepancy might stem from Ferraro et al.'s inclusion of both genders, introducing potential bias. In summary, BMI doesn't seem to affect serum HE4 levels, similar to CA125 [11]. This underscores HE4's potential as a reliable biomarker for assessing treatment response and predicting outcomes in ovarian cancer.

### 2.3. Osteopontin(OPN)

Osteopontin is a secreted extracellular glycoprotein, synthesized by vascular endothelial cells and osteoblasts [10]. OPN was initially detected by a cDNA microarray study of all ovarian cell lines and human ovarian surface epithelium where it was found to be higher in ovarian cancer compared to its healthy counterparts [13]. Osteopontin may serve as a potential diagnostic biomarker for ovarian cancer and could potentially influence cancer therapy and be used in the development of novel anti-tumor treatments [14]. The levels of osteopontin in 32 out of 40 peritoneal metastatic biopsies were found to be significantly elevated compared to the levels found in primary ovarian tumor tissues among women with Stage III EOC. In addition, the elevated OPN levels were independently correlated with extremely poor prognosis among these women (n = 32), whereas 75% of the women found with no increase in OPN levels had a 36-month survival rate (n = 8). Furthermore, the high levels of

osteopontin could be measured in the urine samples of patients with high-grade ovarian cancer, so this test could potentially be used clinically as a noninvasive tool for the early diagnosis of ovarian cancer [2].

### 2.4. Kallikreins

kallikreins (KLKs) are a family of 15 serine proteases encoded by a group of genes located on chromosomes 19q13 which participate in a diverse range of cellular processes and pathways through regulating proteolytic cascades [13]. They are expressed in epithelial and endocrine tissues regulated by hormones in cancer and they are shed and detected in human body fluids [15]. A total of 12 out of 15 KLKs are upregulated in ovarian cancer, with some KLKs correlating to poor prognosis and late-stage disease (4-7, 10 and 15), as well as chemoresistance (KLK 4 and 7) to a first-line paclitaxel agent [2]. Bioinformatics studies of KLK6 and KLK7 reveal their potential as biomarkers of early-stage and low-malignant carcinomas of ovarian cancer. The sensitivity of these biomarkers is raised on their combinations [5].

### 3. Gene-Based Ovarian Cancer Biomarkers

Since sequencing the entire human genome was achieved for the first time in 2001, genome technology has led to improvement in the diagnosis of cancer and the selection of cancer treatment. Cancer is believed to result from changes in genes, environmental factors, or a mix of both. Considering the close relationship between genetic mutations and ovarian tumorigenesis, it is certain that research on the gene level would provide novel ovarian cancer biomarkers [16].

#### 3.1. Inherited gene mutations

At least 20% of all epithelial ovarian cancers (EOCs) are heredity, with germline mutations of the breast cancer ½ (BRCA1 and BRAC2) tumor suppression genes accounting for approximately 90% of cases. Most of the remaining 10% are caused by germline mutations of the DNA mismatch repair (MMR) genes, primarily hmlh1 and hmsh2, which are susceptibility genes of Lynch syndrome [17]. Generally, 1 in 280 women carries a germ-line BRCA mutation, genetic testing for the BRCA gene should be performed after genetic counseling by cancer genetics professionals. Previous studies showed that both BRCA proteins participate in multiple functions, such as DNA repair, transcriptional regulation of gene expression, and cell cycle. More than 250 mutations may occur in both BRCA genes. Main mutations are frameshift or nonsense variety, accounting for 80% of BRCA gene mutations [16]. The lifetime risk of ovarian cancer in BRCA1 carriers is 40% to 50%, and 20% to 30% in BRCA2 carriers. Mutations of MMR genes are a mechanism that corrects mutation arising during DNA replication or damage [7]. Overall the above-mentioned genes can potentially identify patients at higher risk for developing ovarian carcinoma [17]. Therefore, some suggested that comprehensive genetic testing is warranted for all women with invasive ovarian carcinoma, regardless of age or family [16].

### 3.2. Epigenetic changes

Epigenetic mechanisms such as DNA methylation and histone modifications play important roles in tumor initiation and progression as regulators of gene expression. Since aberrant DNA methylation occurs early in cancer development and can be easily detected in clinical samples, measurement of methylation status provides great potential as a biomarker to detect early-stage ovarian cancer [16]. Using sensitive methylation-specific PCR, the methylation status of six tumor suppressor gene promoters, including BRCA1, RASSF1A, APC, p14ARF, p16INK4a, and DAPK kinase were evaluated [18]. At least one or more hypermethylations were observed in tumor DNA obtained from 41 of 50 patients with ovarian or primary peritoneal tumors (82% sensitivity). In addition, hypermethylation was not found in nonneoplastic tissue or serum from 40 control women (100% specificity) [19]. Moreover, epigenetic markers can be assayed in the circulating DNA of the blood, which provides the promise of a non-invasive test [17].

### 3.3. Gene expression

Thousands of genes in a small sample of tumor tissue. With clinical value for distinguishing normal ovarian tissue from ovarian tumors, gene expression profiling can provide useful information to discover novel biomarkers [16]. Using oligonucleotide arrays, the researchers identified 275 genes predicted to encode proteins with increased/decreased expression in ovarian cancer [20]. Studying gene expression in FFPE samples from five high-grade stage 1 serous carcinoma and 5 stage 1 broad-line tumors revealed elevated levels of surviving, MCM3, E2Fs, VTCN1, and SYNE1, AKAP14, KNDC1, and DLEC1 were underexpressed in serous carcinoma [21]. In addition to its role as a biomarker for early detection, gene-expression profiling can provide various information in ovarian cancer research, including prognosis, prediction of chemotherapy response, and mechanisms of chemoresistance [16].

## 4. Emerging Biomarkers for Ovarian Cancer

The opinion of ovarian cancer is presently concentrated on confined imaging ways and the attention of certain biomarkers circulating with established situations of perceptivity and particularity. The addition of recently linked biomarkers banded below is presently arising to round the clinical practice to increase early discovery.

### 4.1. Exosomes

Exosomes are endocytic and miscellaneous membrane-deduced vesicles that are laboriously buried by colorful forms of cells, and they can be imaged by electron microscopy [2]. Exosomes include several motes similar to proteins, metabolites, RNAs, DNAs, and lipids and are used in cell communication. Exosomes can be detected and insulated with several labels, especially cell face proteins including those set up only in the primary towel. MAGE3/6 proteins have a cell face biomarker especially featured for ovarian cancer [22]. In addition, recent clinical trials set up that the situations of exosomes

were three to four times more advanced in the rotation of ovarian cancer cases compared to normal individualities [23]. While exosomes are known to be ideal biomarkers in the opinion of cancer due to their unique characteristics, there's still a long way to go in developing exosome-grounded assays.

### 4.2. MicroRNAs

The disquisition of the microRNA (miRNA) class has entered the utmost attention of all sncRNAs to date. At present, > 2800 mortal mature miRNAs have been linked and are registered at miRbase Release 22. miRNAs are involved in post-transcriptional regulation of gene expression through their list to a reciprocal target. Depending on the region they bind to, they can lead to repression or declination of the target [24]. MiRNA genes are transcribed to produce miRNA, which is adhered to form-miRNA. In the cytoplasm, pre-miRNA is farther adhered to induce a miRNA duplex. The mature miRNA regulates gene expression by targeting mRNA for fractionalization or restatement suppression grounded on miRNA-mRNA complementarity [6]. Aberrant miRNA expression in OC is associated with chemoresistance, including let-7e, miR-30c, miR-125b, miR-130a, miR-335, miR-340, miR-381, and miR-520f [25]. Altered miRNA expression in OC correlates with the complaint stage, treatment response, and overall survival. miR-21, miR-200a, and miR-200c have individual and prognostic values, while let-7f and miR-141 are associated with worse progression-free survival. miR-193a acts as an excrescence suppressor [26]. In an informational study by Yokoi et al., the demarcation of early-stage ovarian cancers from benign excrescences was achieved with an emotional perceptivity of 86 and a particularity of 83 by employing a panel of eight miRNAs. Similarly, the presence of miRNAs was detected in EVs insulated from dressed ovarian cancer cell lines [6].

### 4.3. Circulating tumor cells

Circulating Excrescence DNA ( zctDNA) allows the non-invasive discovery of ovarian cancer mutations, similar to PIK3CA and KRAS, with implicit individual and prognostic labels in liquid vivisection. separate from lymphocyte DNA, cfDNA exhibits characteristic fractured size [6]. Ct-DNA has the implicit to be abundantly present in serum owing to its small molecular size and the fact that excrescences frequently metastasize through the circulating system [13]. Swisher et al. detected excrescence-specific TP53 mutations in cfDNA using traditional PCR, with a 30 discovery rate in tube or serum samples. ctDNA analysis shows implicit as an anon-invasive system for relating cancer-specific mutations across different stages [6]. Advanced sequencing technologies, similar to tagged amplicon sequencing (TAM-Seq) and duplex sequencing, enhance ctDNA discovery with high perceptivity (as low as 2 allelic fragments) and particularity (97 for TAM-Seq). The integration of ctDNA with CA125 in a multi-cancer disquisition achieved a high perceptivity of 98 for detecting ovarian cancer, primarily in advanced-stage excrescences [22]. CtDNA provides precious

perceptivity for threat assessment and monitoring of EOC rush. Genomic profiling reveals frequent mutations in TP53, ARID1A, KRAS, and PIK3CA. The analysis also indicated that ctDNA could serve as an independent threat factor and an implicit biomarker for assessing ovarian cancer prognostic [27].

## 5. Other Prominent Biomarkers

### 5.1. Mesothelin

Mesothelin is the surface glycoprotein on mesothelial cells lining the peritoneum, pleura, and pericardium. MLN may also be biologically relevant to ovarian cancer due to its potential role in peritoneal implantation and metastasis through its interaction with CA125 [28]. Increased serum mesothelin in 60% at 98% specificity. 100% serious borderline and serous cystadenocarcinoma urine sample expresses mesothelin. Moreover, 42% of patients with early-stage ovarian cancer had elevated mesothelin in urine compared to only 12% of patients who had elevated mesothelin in serum, suggesting the potential of mesothelin as an early-detection biomarker [8]. The double determination ELISA is effective in precisely assessing serum mesothelin levels, serving as a potential tumor marker. It proves valuable for monitoring treatment response in patients with mesothelin-expressing cancers [13].

### 5.2. Apolipoprotein A1 (ApoA1)

ApoA1 is a major protein component in high-density lipoprotein with anti-atherogenic, anti-inflammatory, and antioxidant properties. Ovarian cancer patients decreased serum ApoA1 levels. In multiple assays, the combination of ApoA1, and CA125 achieved a sensitivity of up to 94% at a specificity of 98% at early-stage ovarian cancer [5]. This proposed multiplexed panel assay is also cost-effective and should be conducted to develop a clinically beneficial test kit [2].

### 5.3. B7-H4

B7-H4, a 282 amino acid surface protein found on various immune cells, acts as a suppressor of T-cell responses and may contribute to the development of malignancies. Using quantitative PCR analysis, B7-H4 was expressed in 100% of tissue from serious, endometrial, and clear cell carcinoma but in only 9% of mucinous cancers [8]. A combination of B7-H4 and CA125 detected a greater fraction of early-stage ovarian cancer (65%) than either CA125 (52%) or B7-H4 (45%) alone [9]. B7-H4 has also been investigated in the PLOCO trail specimens [29].

In conclusion, biomarkers for early detection of ovarian cancer play a crucial role in improving patient outcomes. Tumor markers, particularly CA125, are used widely in the diagnosis of ovarian cancer but have limitations in sensitivity and specificity, especially in the early stage and certain subtypes of the disease. Combining multiple markers, like CA125 and HE4, enhances diagnostic accuracy. Additional biomarkers such as microRNA, mesothelin, and circulating tumor

cells show promise in improving both accuracy and early detection. Further research is needed to refine and validate these biomarkers for better outcomes in ovarian cancer management.

## Acknowledgments

### Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute .
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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