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Invited critical review

# Detection and monitoring of ovarian cancer

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ABSTRACT

Ovarian cancer is the fifth leading cause of death among women in the United States and remains the most common cause of death from a gynecologic malignancy. Most ovarian cancers are diagnosed at an advanced stage in which 5-year survival rate is approximately 30%. Given that the 5-year survival rate is greater than 90% for women diagnosed at an early stage, early detection in women presenting with vague symptoms is crucial to improve outcome. Diagnosis of ovarian cancer is largely based on symptoms, imaging, and laboratory biomarkers. Overall, more than 200 potential biomarkers differentially expressed in ovarian cancer have been identified (Lokshin, 2012 [1]). However, no single marker has been found useful for the diagnosis of ovarian cancer. Increased sensitivity and specificity for the diagnosis of ovarian cancer are observed when multiple markers are used in combination. The Food and Drug Administration (FDA) recently cleared two algorithms to evaluate the risk of ovarian cancer for women who present with pelvic mass. In this review, we will summarize the most recent serum biomarkers and clinical applications of biomarkers for the early detection and treatment monitoring of ovarian cancers. We will also discuss the algorithms for predicting the risk of ovarian cancers.



**Contents**



## 1. Introduction

It is estimated that 22,280 new ovarian cancer cases will be diagnosed in 2012 in the United States. While this number ranks ovarian cancer as the 9th most common cancer in women, it is the fifth leading cause of death in women from cancer, with over 15,000 deaths per year in the US [2]. The 5-year survival rate for early stage ovarian cancer is approximately 92%, but it is difficult to detect ovarian cancer in an early stage due to vague clinical symptoms. Unfortunately, most patients will be diagnosed with advanced stage disease, in which the 5-year survival rate is only 30% [3]. Thus, early diagnosis of ovarian cancer will significantly improve the patients' outcome.

Most ovarian cancers are developed from three categories of cells: epithelial cells, sex cord stromal cells, and germ cells. Among them, epithelial cancers account for about 90% of ovarian cancers. The epithelial ovarian cancers are divided into five subtypes: 1) serous: ~50%; 2) mucinous: 5–10%; 3) endometrioid: 10–25%; 4) clear cell: 4–5%; and 5) transitional cells: rare [4]. Since ovarian cancer cells with various histological types may express tumor markers differently, it is important to use multiple tumor markers to detect all ovarian cancers.

The modalities for the detection of ovarian cancer include bimanual exam, transvaginal ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomographic

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scanning (PET), laboratory tumor markers, and histological examination. All these methods have variable clinical sensitivity and specificity. This review summarizes the current progress in the early diagnosis and monitoring of disease progression of ovarian cancer using serum biomarkers.

## 2. Ovarian cancer markers

In the last two decades, intensive efforts have been made to find new serum markers for the early diagnosis of ovarian cancer [1]. With advanced technology, especially the use of mass spectrometry, a large number of serum biomarkers have been found to be associated with ovarian cancer (Table 1). However, an evaluation of 49 serum markers in ovarian cancer patients indicates that CA 125, a marker discovered 30 years ago, is still the top marker for ovarian cancers [5]. A new ovarian cancer marker, human epididymis protein 4 (HE4), is also offered in some clinical laboratories.

### 2.1. Clinical application of CA 125

CA 125 was discovered in 1981 by Bast et al. with a mouse monoclonal antibody (OC 125) produced by immunizing a mouse with a serous ovarian cancer cell line [6]. CA 125 is a high molecular weight (>200 kDa) glycoprotein with a reference cutoff value of 35 U/mL. Subsequent studies showed that CA 125 was increased in 80% serous, 69% mucinous, 75% endometrioid, 78% clear cell, and 88% undifferentiated ovarian cancers. Elevated CA 125 was also observed in about 0.2–5.9% healthy women and 2.2–27.8% patients with benign ovarian disease [7]. CA 125 is elevated in 50% of stage I, 90% of stage II, >90% of stages III and IV ovarian cancer patients. However, CA 125 is also increased in other cancers such as endometrial, pancreatic, lung, breast, colorectal, and other gastrointestinal tumors [8].

CA 125 alone is not a useful routine diagnostic test for ovarian cancer screening due to its limited specificity, but it is useful for monitoring response to treatment and detecting disease recurrence [9]. Currently, measuring CA 125 is considered standard of care by many for ovarian cancer patient surveillance. The Gynecologic Cancer Intergroup (GCIG) has recommended that CA 125 alone can be used to evaluate the effectiveness of treatment. The CA 125 response criterion is defined as a 50% decrease in CA 125 as compared to the pretreated sample. Patients whose CA 125 concentrations fall within the reference range after treatment are considered complete responders [10].

According to GCIG definition, progression or recurrence is considered if the CA 125 level is greater than or equal to 2 times of the upper limit of the reference on two occasions at least 1 week apart for patients with elevated CA 125 pretreatment and normalization post treatment; or for patients whose elevated CA 125 never normalizes following treatment, CA 125 level must be greater than or equal to 2 times the nadir value on two occasions at least 1 week apart [10]. CA 125 provides a relatively sensitive and cost-effective way to monitor the relapse of ovarian cancer. However, other methods such as physical examination, CT scan, and ultrasound also play important roles in the early detection of recurrence. Gadducci et al. reported that 80% of 412 asymptomatic ovarian cancer patients were found to have recurrence during follow-up using physical examination, imaging and/or CA 125 levels, while only 23% of them were detected by CA 125 alone [11]. Similar results were observed by Von Georgi et al. [12]. These studies suggest that CA 125 recurrence criteria from GCIG might be too stringent for those patients with elevated CA 125 level but still less than 2 times the upper limit of the reference range or nadir value. Liu et al. investigated ovarian cancer progression with another criterion: progression is predicted if CA 125 ≥20 U/mL for patients with CA 125 nadir ≤10 U/mL, or if CA 125 ≥2 times the nadir for patients with CA 125 nadir >10 U/mL [13]. This criterion obtained a positive predictive value of 93%. Prat et al. evaluated the prognostic role of the CA 125 nadir in the normal range (<35 U/mL) following primary treatment and found that an absolute increase of the CA 125 level ≥5 U/mL compared with its nadir value was a strong predictor of recurrence. This new CA 125 progression criterion obtained 90% sensitivity, with a 96.4% positive predictive value and a 5.6% false-positive rate [14]. Although the application of these new recurrence criteria needs additional clinical investigation, these studies demonstrate that the appropriate use of CA125 may help oncologists detect ovarian cancer relapse earlier.

CA 125 level after primary therapy is also considered an independent prognostic marker for ovarian cancer patients. Prat et al. analyzed 96 ovarian cancer patients with elevated CA 125 levels at the time of

**Table 1**
New serum markers associated with ovarian cancers.

| Markers | Notes | Sensitivity | Specificity | Concentration[a] | References |
|---|---|---|---|---|---|
| Activin | Produced in many organs including gonads to enhance FSH biosynthesis | 23.9% | 95% | Up | [5,34] |
| Apo A1 | Apolipoprotein A1 | 7% | 95% | Down | [42, 43] |
| B2M | Beta-2-microglobulin | 5% | 95% | Up | [39, 43] |
| B7-H4 | B-7 family member expressed in activated T-cells | 40% | 95% | Up | [44] |
| CA 72-4 | Glycoprotein found on the surface of many cells | 35% | 95% | Up | [34] |
| CTAP-III | Connective tissue activating protein III | 19% | 95% | Down | [39, 43] |
| DcR3 | Tumor necrosis factor receptor | 36% | 95% | Up | [44] |
| EGF | Epidermal growth factor | 84.1% | 76.7% | Down | [39] |
| Eotaxin | Small cytokine belong to CC chemokine family | 15% | 95% | Down | [5, 45] |
| Hepcidin | Peptide hormone produced by liver | 21% | 95% | Up | [39, 43] |
| IL-6 | Interleukin-6 | 84.1% | 86% | Up | [39] |
| IL-8 | Interleukin-8 | 88.6% | 69.8% | Up | [39, 46] |
| Inhibin | Inhibits FSH production | 8.3% | 90% | Up | [34], |
| ITIH4 | Inter-alpha-trypsin inhibitor heavy chain H4 | 9% | 95% | Up | [5, 42] |
| MCP-1 | Monocyte chemoattractant protein-1 | 84.1% | 72.1% | Down | [39] |
| M-CSF | Macrophage colony-stimulating factor | 66.2% | 76% | Up | [47] |
| Mesothelin | Present on mesothelial cells, marker for remission | 35% | 95% | Up | [5, 48] |
| MMP7 | Matrix metalloproteinase-7/matrilysin, marker for remission | 35% | 95% | Up | [48–50] |
| Osteopontin | Glycoprotein firstly found in osteoblasts | 7.6% | 95% | up | [34, 50] |
| Prolactin | Peptide hormone | 34% | 95% | Up | [5] |
| Spondin 2 | F-spondin superfamily | 28% | 95% | Up | [44] |
| Transferrin | Ion-binding glycoprotein | 23% | 95% | Down | [39, 43] |
| Transthyretin | Thyroxine binding protein | 47% | 95% | Down | [5, 42] |
| VCAM | Vascular cell adhesion molecule | 34% | 95% | Up | [49] |
| VEGF | Vascular endothelial growth factor | 79.5% | 67.4% | Up | [39, 51, 52] |

[a] Up: up-regulated; down: down-regulated.