

# CA-125 not only a Predictor of Ovarian Diseases but Challenges and Controversies in other Organ Systems – Review of Literature

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## 1. Introduction

CA-125 is a protein that is more prevalent in ovarian cancer cells than in other cells. It's possible to measure by blood test. The test is most appropriate used to follow women who already been diagnosed with ovarian cancer. In women with known ovarian cancer a rise in CA-125 usually means a progression or recurrence of the disease. A decrease in CA-125 means that the disease is responding to treatment. In fact, only about 3 out of 100 healthy women with elevated CA-125 usually does not mean ovarian cancer in present [1]. However, CA-125 is secreted by different celomic epitheliums, therefore they may be increased in malignant diseases, also such as pulmonary and extrapulmonary tuberculosis [2]. Also, it was reported that CA-125 is a sensitive marker of peritoneal dissemination of colorectal cancer in men and women [3]. Also, there was shown CA-125 significance in cirrhosis and correlation with disease severity and portal hypertension [4], hepatocellular carcinoma [5], systematic lupus erythematosus [6], tuberculosis [7] and sarcoidosis [8]. In this article we are going to shortly describe the controversies that marker CA 125 is not only associated with ovarian cancer.

## 2. Ovary Diseases

As mentioned, the value of cancer antigen -125 is predictive for malignant germ cell tumors of ovary (ovarian cancer, peritoneal cancer and sometimes uterine and cervical cancer), but it can be associated also with other ovaric diseases, such as:

- Endometriosis
- Pregnancy

- Uterine fibroids
- Ectopic pregnancy
- Ruptured cyst

The normal range for CA 125 is 0 – 35 units/ml. A CA 125 level over 35 is only a potential indicator.

CA-125 is used to monitor progress with ovarian cancer, but sometimes it is used to screen for the disease, and the blood test results have it's liminations:

- Absence of tumor markers for some cancers – some cancers do not produce any tumor markers
- False negatives – particularly in early-stage cancers, tumor markers may not be elevated
- False positives – in number of benign conditions the tumor markers can be increased

Furthermore, the test is falsely elevated in a portion of the population due to conditions unrelated to cancer, i tis unreliable in screening premenopausal women, because ovulation as well as menstruation can cause elevated levels of CA-125. Well trained gynecologic oncologists are specifically knowledgeable about how to interpret a CA 125 test result in treatment of ovarian cancer, but they should be also aware about other diseases that cause increase of this biomarker.

## 3. Other Conditions that Cause an Increase of CA 125 Levels

### 3.1. Pulmonary Tuberculosis

As mentioned, CA 125 is secreted by different celomic epitheliums

and levels may be increased in other medical conditions, such as pulmonary and extrapulmonary tuberculosis. The tumor marker CA 125 has been proposed as a useful diagnostic tool for tuberculosis. High levels of this biomarker are still reported in patients with tuberculosis, including pleural, peritoneal, pelvic, millitary, and intra-abdominal disease. Although the diagnostic value of CA 125 to help differentiate pulmonary tuberculosis from other pulmonary infections has been poorly studied, there should also be thought about this cause of elevation of this biomarker, because CA 125 levels have been determined in mesothelial cell lines by immunohistochemistry methods and in bronchial epithelial cells by immunoperoxidase stained techniques [2].

### 3.2. Colorectal Carcinoma

Peritoneal dissemination of cancer is difficult to diagnose. CA 125 is a sensitive marker of peritoneal dissemination of gastric cancer, but its accuracy in men is controversial. CA 125 concentrations have lower sensitivity but higher specificity, and diagnostic accuracy compared with biomarker CEA. Huang et al. confirmed in their study, that concentration of CA 125 did not increase significantly from stage I to IV (without peritoneal dissemination) unless peritoneal dissemination was present. CEA concentration was increased significantly only in patients with stage VI without peritoneal dissemination. CEA concentration was not significantly higher in patients with peritoneal dissemination compared with patients without metastases. In the study, CA 125 concentration correlated with the severity of peritoneal dissemination and was a better predictive marker in both men and women. In conclusion, CA 125 concentration seems to be a better tumor marker than CEA concentration for predicting peritoneal dissemination. This finding suggests that CA 125 concentration should be measured as part of the pretreatment evaluation. Early detection leads to well-prepared therapy and improves the prognosis in patients [3].

### 4. Inflammatory Bowel Diseases

The aim of Ataseven et al. was to assess the levels of CA 125 in patients with ulcerative colitis and Crohn's disease. In conclusion their data suggested that serum CA 125 levels may be increased in patients with inflammatory bowel diseases [9].

### 5. Cirrhosis and Correlation with Disease Severity and Portal Hypertension

Edula GR et al. in their retrospective study concentrated on evaluation of the prevalence and significance of elevated CA 125 levels in patients with cirrhosis being treated in a tertiary care liver center and its correlation with objective markers of disease severity. Elevated CA 125 levels were noted in 85% of the study population. Near-normal CA 125 levels were noted in patients with cirrhosis but undetectable ascites on ultrasound imaging. No differences were observed in mean values between male and female patients. Also might be an indication that elevated CA 125 levels could be related to mechanical stretch of the peritoneum rather than portal

hypertension itself. The presence or absence of esophageal varices did not correlate with the CA 125 levels [10].

### 6. Systemic Lupus Erythematosus

Bevan et al., suggested that some tumor antigens are expressed on inflammatory cells and have carbohydrate motifs involved in cell adhesion. They expressed possibility that variations in tumor marker concentrations in patients with autoimmune disease may occur according to the degree of disease activity present and the amount of autoantibody produced. In patients with systemic lupus erythematosus, CA 125 levels have been demonstrated to correlate with disease activity. Treatment of active SLE has previously been shown to return elevated CA 125 levels to the normal range. This leads to conclusion that tumor markers may be falsely elevated in rheumatic disease, particularly when disease activity is high, and tumor marker concentrations may fall with immunosuppressive therapy, therefore clinicians should interpret tumor marker results with caution in patients with rheumatic disease [6].

### 7. Tuberculosis

Tuberculosis should be kept as a possibility in patients with multisystem disease especially in developing countries. CA 125 is an epithelial marker derived from coelomic epithelium. Therefore, CA 125 is an important investigation in evaluating a pelvic mass. However, any process that disrupts the epithelial lining of the peritoneum has the potential to raise its levels. It can be elevated in many non-neoplastic conditions such as hepatitis, pancreatitis, menstruation etc. Clinicians from Oxford University illustrated a patient who presented with elevated CA 125 levels but was ultimately diagnosed as having disseminated tuberculosis. In this case pleural fluid analysis for malignant cells was negative. On examination there was left upper motor facial palsy and left hemiparesis. CT scan of abdomen showed an adnexal mass with hypodense lesions in liver and spleen with mesenteric lymphadenopathy. Contrast-enhanced MRI brain showed evidence of ill-defined, irregular, peripherally enhancing lesion of mixed intensity in right frontoparietal lobe associated with perifocal edema and an additional lesion in the right parietal lobe. There was confirmed diagnosis of disseminated tuberculosis to multiple organs [7].

### 8. Sarcoidosis

CA 125 is classically associated with ovarian carcinoma. It has also been reported to be elevated in certain granulomatous conditions. Meena K. et al. described a patient with sarcoidosis and an elevated serum CA 125 level. They came to conclusion that peritoneal sarcoidosis may „mimic“ ovarian carcinoma in that it may present with peritoneal or abdominal findings and an elevated serum CA 125 level [8].

### 9. Conclusion

CA 125 is a cell-surface glycoprotein present in normal fallopian tubes, endometrium and in ovarian surface epithelium. But serum CA 125 levels may be elevated in a variety of conditions such as

infections, menstruation, ovarian hyper stimulation, and non-gynecologic conditions like active hepatitis, acute pancreatitis and above-mentioned medical conditions. Therefore, clinicians should be careful with the diagnosis concentrated strictly on gynecological cause.

This review of literature shows only some cases in which there was possibility of misdiagnosing the patient. Biomarker CA 125 is not specific only for gynecology but includes other organ systems and that should be warning for every clinician who comes in contact with evaluating the biomarkers.