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# SERUM TUMOR MARKERS IN ENDOMETRIAL CANCER

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## ABSTRACT

Endometrial cancer is one of the most frequent cancers in female patients throughout the world. Incidence of endometrial cancer increases with age and the most common clinical finding is perimenopausal bleeding. Early diagnose and treatment are associated with an overall high survival rate and a good prognosis. The only method to determine endometrial cancer is through invasive techniques which evaluate the endometrium. In order to provide a better risk stratification and prognosis, tumor markers are being used in multiple malignancies. Although there are no ideal markers to help diagnose endometrial cancer, studies have shown that some serum markers have a high specificity that can lead to early diagnosis and improve the patients overall outcome.

**Keywords:** Endometrial cancer, tumor marker, HE 4

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## INTRODUCTION

Endometrial cancer is one of the most frequent gynecologic cancers in developed countries. In 2012 it caused 76000 deaths out of 320000 diagnosed women, which situated this type of cancer on the third place in most common causes of death caused by cancer in women. (1)

The most frequent clinical finding in endometrial cancer is perimenopausal bleeding which leads to fast diagnosis with the use of uterine curettage. Almost 70% of endometrial cancer cases are diagnosed in an early stage. Unfortunately, the remaining 30% patients are diagnosed in an advanced stage. Treatment consists in radical surgery with radio and chemotherapy that has a very good outcome in early stages of the disease with prolonging the survival rate at 5 years in 95% of the cases, whereas in late stages, the survival rate drops to nearly 15%. Early diagnosis is directly associated with a better prognosis and is the key in improving the overall survival rate through proper treatment in an early stage.

## HUMAN EPIDIDIMIS PROTEIN 4

Human epididymis Protein 4 (HE4) also known as whey acidic four-disulfide core (WFDC) is a protein with inhibitory properties over trypsin. The gene is located on chromosome 20q12-13 and codifies a protein of 13kD. HE4 has first been isolated in epithelial cells of the distal epididymal channels being associated with fertility and sperm maturation. Later on it was shown

to be expressed in different tissues: reproductive tract, pancreas and respiratory epithelium. HE4 is currently used as a tumoral marker in the diagnosis of ovarian cancer along with CA125 marker. Since its discovery and approval of FDA in the diagnosis of ovarian cancer, great attention has been granted to this glycoprotein. In 2005 Hecht et al performed a study in ovarian cancer in which they demonstrated that HE4 was overexpressed in endometrioid and serous ovarian carcinomas. The study concluded that in 100% of cases of endometrioid histologic subtype had HE4 overexpression. Based on the embryological development of the uterus and ovaries, having in common the paramesonephric duct, it is likely that HE4 has a higher specificity. Recent findings showed that HE4 serum levels are elevated in all stages of endometrial cancer and is proven to be more sensitive than CA125 in early stage cancer. In 2011 Yang et al documented serum levels of HE4 in two groups of patients, one with malignant endometrial tissue and the other group with normal endometrium. The findings show a gradual expression increase from normal to precancerous and eventually malignant tissues. Moore et al proposed to test whether serum levels of HE4 can be correlated with myometrial and lymph node invasion. The study performed showed that HE4 was overexpressed in advanced cancer stages and suggested to use this marker in order to assess the need of lymphadenectomy preoperatively. The cut off value for HE 4 varies between 60 and 100 pmol/L but most studies have concluded that 70 pmol/L has the highest sensitivity and specificity in predicting endometrial cancer diagnosis and also recurrence.

## CA 125

Cancer antigen 125 is a glycoprotein that was first described in 1983 by Bast et al in 82% patients with ovarian cancer. CA-125 is known to have elevated serum values in benign pathologies such as endometriosis, pregnancy and inflammation but also in malignant conditions. Current papers have shown that a serum level over 35 U/ml is associated with malignant conditions, such as ovarian cancer and is correlated with tumor invasion, lymph node status, disease stage. The use of this marker has shown great interest in endometrial cancer. One study performed in 2018 compared CA-125 values in patients with abnormal uterine bleeding and concluded that patients with endometrial cancer had an elevated serum level – 19.85 U/ml in comparison with non-malignant patients with similar clinical findings – 10.95 U/ml, proving that it can differentiate benign from malignant conditions. Specificity for endometrial cancer is however low, only 20% of patients with malignant endometrial condition having an elevated serum level. High levels preoperative have shown to have a poor prognosis over disease treatment. Reports have shown that elevated HE4 and CA-125 levels have a greater predictive value over the diagnosis of endometrial cancer.

## CA 15-3

CA 15-3 is a mucin-like antigen that is frequently associated with breast malignancies. The use for diagnosing endometrial cancer is relatively low, but studies have shown elevated serum levels in patients with endometrial cancer in comparison with endometrial hyperplasia. Although only in 20% of patients high levels of CA 15-3 were found, this marker is usually associated with poor prognosis, stage of disease, tumor invasion and its aggressiveness.

## VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

Vascular endothelial growth factor (VEGF) is a protein involved in growth of blood vessels from pre-existing vasculature (angiogenesis) and de novo formation of blood vessels (vasculogenesis). Malignant tissue development in the primary tumor or metastases involve angiogenesis and is associated with elevated VEGF serum levels in many cancer types such as colon, breast, lung and also endometrial. Several studies have been developed and showed VEGF expression in all cases of endometrial cancer specimens through in situ hybridization and no expression of the marker in normal endometrial tissue. However, in tissues with atypical hyperplasia, VEGF was found in 20% of the cases. Findings also show that high serum levels of VEGF are correlated with an advanced stage of endometrial cancer. VEGF levels were more elevated in patients with

myometrial invasion, lymphovascular invasion, lymph node metastasis. These findings show that VEGF is associated with poor prognosis, since the serum levels do not elevate during earlier stages. Several therapeutic strategies have been developed in order to diminish the blood supply of malignant tissues. Since the approval for bevacizumab, an anti-VEGF antibody by the FDA as a treatment for metastatic colorectal cancer, further studies highlighting the importance of this pathway in endometrial cancer development have been done with promising results.

## LIPOCALIN-2

Lipocalin-2 is a glycoprotein involved in malignant tissue processes influencing cell proliferation, apoptosis and inflammation. Besides having an important role in chronic inflammation, lipocalin-2 also plays a role in developing insulin resistance and glucose intolerance. The role of lipocalin-2 in the mechanism of malignant cell spreading is still unclear, but several studies have shown that it determines increased production of cytokines, especially IL-8, which eventually leads to improving cell survival through stimulation of cell migration and inhibiting cell apoptosis. This leads to the conclusion that elevated serum levels of lipocalin-2 is associated with poor prognosis. Using immunohistochemistry it was found that lipocalin-2 was highly expressed in endometrial cancer tissues in contrast with normal endometrial cells. Obesity is known to be a risk factor in endometrial cancer. Elevated serum levels of lipocalin-2 have been associated with high concentrations of estrogens and glucocorticoids. Based on the fact that the adipose tissue plays an important role in estrogen secretion, patients with high BMI index, which is a risk factor for endometrial cancer, are associated with higher serum levels of lipocalin-2 and thus having a poor prognosis in clinical staging of endometrial cancer. In a study performed by Cymbaluk-Ptoska et al. it was reported that the serum cutoff of lipocalin-2 between benign endometrial lesions and malignant endometrial lesions is 160 ng/ml. The results of the study also suggested that in premenopausal patients, the specificity of lipocalin-2 (80%) was lower than HE4 (90%), but in postmenopausal patients, it would be greater (87% vs 85%). It was also concluded that the sensitivity was also greater than HE4 and CA125 (84% vs 66, respectively 52%).

## YKL-40

YKL-40, also known as human cartilage-glycoprotein 39 is considered to play a role in exhibiting growth factors for remodeling tissues processes. The exact mechanism in malignant conditions is still unknown but is considered to have a role in protecting cancerous cells from apoptosis and stimulates angiogenesis.

YKL-40 is present in multiple tumors, such as prostate, breast, colon, lungs, kidneys and also in nonmalignant human cells. In 2014, Cheng. Et al performed a meta-analysis based on 7 studies and covered 234 patients with endometrial cancer. They concluded that YKL-40 should be considered a tumor marker for endometrial cancer having a high sensitivity for diagnosis. Another study showed that YKL-40 has a greater sensitivity over CA-125 in diagnosing early stages of endometrial cancer.

## PERSPECTIVE

Evidence show that endometrial cancer develops when profound metabolic dysfunction is present, making metabolomic biomarkers a new alternative to classic serum biomarkers in diagnosing malignancies. Multiple lipid, hormonal and amino acid metabolites have been reported as possible endometrial cancer biomarkers. Future research is needed, but the results are encouraging in identifying and elucidating the role of metabolites in endometrial cancer tumorigenesis.

## CONCLUSIONS

Multiple serum markers have been studied in ordered to find an ideal tumoral marker for early diagnosis of endometrial cancer. Early treatment can lead to a very high survival rate in patients and fast diagnosis is essential. To date, there is no specific marker for endometrial cancer, but HE4 combined with CA -125 seem to have the highest sensitivity and specificity rate for early stage diagnosis.

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