The Use of HE-4 in Gynecological Cancers

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Abstract
Diagnosing cancer at an early stage and also distinguishing malignancy from benign disease are important areas of medical research. Using tumor biomarkers is a noninvasive procedure for this purpose. HE-4 is a novel biomarker that can be used in gynecologic oncology for early diagnosis, determination of prognosis and follow up. The use of HE-4 in ovarian and endometrial cancers is summarized in this review.

Keywords: HE-4; Ovarian carcinoma; Endometrial carcinoma

Introduction
Human epididymis protein 4 (HE-4) is a whey acidic protein which consists of four disulfide bonds and the gene is located on the short arm of the 20th chromosome [1-3]. It was first discovered on the surface of the epididymal epithelium and has been shown in many other tissues including female reproductive tract [2,4]. In 2006, it was shown that the serum levels of HE-4 was elevated in ovarian, endometrial, lung and breast adenocarcinomas [2]. HE4 is also approved as a biomarker by Food and Drug Administration (FDA) for monitoring ovarian cancer (OC) [1,3]. The recommended upper limit for HE4 is 150pmol/L for premenopausal and postmenopausal women [1]. The main limitation of this cut-off value is that the level of serum HE-4 can differ with increasing age and also HE-4 is cleared through glomerular filtration so the reduced renal function may alter the results [1,5,6]. Also menstrual cycle fluctuations have been shown with HE-4, in follicular phase the values are reported to be lower [7]. In this review we aimed to briefly summarize the use of biomarker HE-4 in gynecological cancers.

HE-4 and Ovarian Cancer
OC is the leading death from gynecological cancers in developed countries and more than 200,000 new cases are diagnosed world wide annually [3,8]. Since most of the patients are diagnosed at an advanced stage, OC remains the most lethal gynecologic malignancy. Because of the poor rate of survival, new techniques are needed to detect and screen OC. Novel biomarkers are studied for this purpose. Cancer antigen 125 (CA-125) has been used for screening and for the follow up of patients diagnosed with OC [1,9]. It is the most widely used biomarker in gynecology. However, CA-125 has some limitations in clinical use. The marker can be elevated in some benign gynecological conditions and non gynecological conditions, such as endometriosis, infections, pelvic inflammatory disease, pregnancy, other malignancies and conditions with peritoneal, pleural and pericardial inflammation [1,6,9]. Because of these limitations and the low specificity, new biomarkers have been used for detecting early stages of OC. HE-4 was found to increase the sensitivity and specificity for the detection of OC [10-12]. Also HE-4 was found to be overexpressed in clear cell, endometrioid and serous epithelial ovarian carcinomas [1,13].

As HE-4 is not found to be elevated in other medical conditions like CA-125, it can be used as a marker in the diagnosis of OC. In 2009, Moore et al. used an algorithm combining CA-125, HE-4 and the menopausal status of the patients, which is called the Risk of Malignancy Algorithm (ROMA). With this algorithm 94% of the patients diagnosed with epithelial ovarian cancer were classified as high risk [14]. There have been many articles published since then with HE-4 in detecting OC. In meta-analysis researchers concluded that the sensitivity and specificity of preoperative HE-4 concentration was greater than CA-125, in detecting OC [11,15].

HE-4 has also been studied in OC for its prognostic value. High levels of HE-4 was correlated with poor prognosis in OC with poor progression free survival [3,15]. In a recent meta-analysis, high levels of HE-4 was associated with advanced stage and serous subtypes. HE-4 was not significantly elevated in lymph node metastasis and high grades [15].
High levels of HE-4 was also associated with frequent recurrence in OC [16]. HE4 is a new target for chemotherapy response in OC and has role in optimal cytoreduction. If HE-4 levels are measured before first-line chemotherapy in epithelial ovarian carcinoma patients, it can predict the therapy response [17,18]. It is also suggested that cut off values for optimal cytoreduction should be calculated, then HE-4 can be used as a surgical outcome predictor [19]. However, the cut off values for HE-4 in the diagnosis and prognosis of OC is still conflicting. More studies are needed for modification of cut off values for premenopausal and postmenopausal women to increase the sensitivity and specificity.

**HE-4 in Endometrial Cancer**

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries, its incidence is 14.7 and its mortality rate is 2.3 per 100,000 population [20]. Most of the patients are recognised in an early stage and the cure rate is almost 95% in early stage cancers [21]. It is important to diagnose cancers at an early stage for improving prognosis. Tumor markers have been used for this purpose. CA-125 has also been used in EC to stratify the risk groups and to individualize therapy. However, there are conflicts in this area of research. Although high levels of CA-125 was found to be an independent risk factor for poor prognosis, some researches observed no correlation between CA-125 levels and the stage of the disease [22]. Also the sensitivity and the specificity of CA-125 is lower for EC than OC [21]. Several studies have shown that HE4 is a novel sensitive and specific biomarker for EC [23-25].

HE-4 is found to be indicator of poor prognostic factors including deep myometrial invasion and tumor size in EC [25-27]. Deep myometrial invasion has been accepted as a risk factor for lymph node metastasis [28]. Such high risk patients are staged surgically with hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy. EC is mostly seen in postmenopausal patients with an average age of 60, however 8% of EC is seen in patients with younger than age 45 [29]. The main problem of young age in gynecological cancers is the desire for future fertility. As HE-4 is found to be an indicator for myometrial invasion which shows poor prognosis, it can be used to evaluate patients who desire to retain their fertility. On the other hand, HE-4 can be used to avoid over treatment in patients with early stage diseases [27,30].

HE-4 has also been used for determining prognosis and recurrence in EC. Elevated HE-4 level is an independent factor for poor prognosis and overall survival. Besides it is shown that HE-4 can detect recurrence during follow up [31,32]. HE4 levels before treatment for detecting EC is found to be in the range of 50-70pmol/L (78.8% sensitivity and 100% specificity) in a meta analysis [33].

**Conclusion**

HE-4 is a novel biomarker which can be used both in OC and EC for early diagnosis, determination of prognosis and follow up. Its sensitivity and specificity is promising in these gynecological cancers, hence there is still lack in defining the cut off values, more research is needed in this area.

**References**


