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Invited critical review

Human epididymis protein 4 (HE4) in laboratory medicine and an algorithm in renal disorders

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ABSTRACT

Over the past three decades, cancer antigen (CA) 125 has been utilized for monitoring women who were treated for ovarian cancer. However, this tumor marker showed several limitations such as false elevation in benign pelvic diseases and, in turn, no alterations in ovarian tumors at early stages with a relatively high ratio. For more than ten years, the human epididymis protein 4 (HE4) has become available for the routine laboratory repertoire, showing a higher sensitivity and specificity compared to that of CA125 in ovarian malignancies, but also in other types of tumors based on recently accumulated clinical data. Despite its remarkable diagnostic characteristics, in certain cases, the evaluation of HE4 results may be problematic when patients suffer from additional conditions that may alter HE4 level. Besides the direct effects of age and smoking, menopause status and decreased renal function also show a substantial impact on HE4 values, which should be considered in each patient. For this purpose, we attempted to create a new formula and an algorithm that may be helpful to predict the probability of the presence of ovarian tumor by using the concentrations of HE4 and CA125.

Contents

Abbreviations: HE4, Human epididymis protein 4; CA125, Cancer antigen 125; TVU, Transvaginal ultrasound; EOC, Epithelial ovarian cancer; CMIA, Chemiluminescent microparticle immunoassay; RMI, Risk of malignancy index; ROMA, Risk of ovarian malignancy; SMRP, Soluble mesothelin-related peptide; SI, Symptom index; CEA, Carcinoembryonic antigen; NSE, Neuron-specific enolase; BMI, Body mass index; CKD, Chronic kidney disease; eGFR, Estimated glomerular filtration rate; AUC, Area under the curve; ROC, Receiver operating characteristics.

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1. Introduction

Ovarian cancer has a major impact on health care, being the second most common malignancy in women, but is still the leading cause of death in females who have gynecological tumors in the Western world [1]. Although this tumor type may develop at young ages, the median patient age is 65 years; hence, the majority of the cases are postmenopausal women [2]. It is potentially curable at an early stage with 80%–90% survival rate by primary surgery and chemotherapy, but patients with high-grade disease still have poor prognosis and a high mortality rate [3]. The major cause of the high mortality is the delayed diagnosis when therapeutic interventions are already hardly effective. Because of these facts, novel—especially soluble—biomarkers are strongly needed for the early identification of the disease.

In contrast to breast, bowel, and cervical cancer screening, which provide convincing results, screening in ovarian malignancies with the measurement of serum cancer antigen (CA)125 and transvaginal ultrasound (TVU) examination did not show benefits in mortality as yet, and only one-third of the patients are diagnosed in stages I/II as reviewed in Ref. [4]. There are additional laboratory approaches especially in familiar tumors via the investigation of BRCA1 and BRCA2 mutations, since there is evidence that certain BRCA mutation carriers are at increased risk for both breast and ovarian cancers [5]. However, recent data on the efficacy of screening were not encouraging in reducing the mortality of hereditary cases [6]. Therefore, early detection of these pelvic malignancies is still an unsolved issue.

In the past decade, a soluble tumor marker, the human epididymis protein 4 (HE4) has gained widespread use as an effective biomarker in the diagnosis and follow-up of patients with ovarian cancer [7]. Numerous—mostly clinical studies [8–11]—showed a considerable elevation of HE4 values in gynecological oncology patients resulting in the firm conclusion that this tumor marker is more specific for ovarian cancer compared to the previously widely used CA125, which was basically the only tumor marker for this malignancy in the past decade [12]. Moreover, HE4 was found to perform better than TVU as a second-line screening approach [13]. Despite these facts, HE4 is still not approved for screening in ovarian tumors [4].

In this review, we attempt to summarize the use of HE4 in different malignant disorders predominantly in ovarian cancer, and we also suggest an algorithm for the appropriate evaluation of elevated HE4 values in patients with impaired renal function.

2. Serum HE4 acts as a reliable ovarian cancer marker

In early reports, Schummer et al. [14] and Wang et al. [15] applied "high-density" cDNA array hybridization to identify transcripts that showed increased expression levels in ovarian cancer compared to normal ovarian tissues. Out of the several thousands of ovarian cDNAs studied, the gene of HE4—earlier cloned as WFDC2 [16]—was significantly overexpressed in a variety of ovarian tumors compared to normal tissues, and demonstrated a clear tumor-restricted expression pattern [14,15]. Based on these early findings, HE4 soon emerged as a potential candidate biomarker [17]. This protein was classified as a member of the whey acidic protein (WAP) showing a large homology with other serine proteinase inhibitors such as elafin and secretory leukocyte protease inhibitor (SLPI) [18,19]. They have a major role in the defense of the lung and skin against proteolytic enzymes secreted by inflammatory cells [20]. The WFDC2 gene encodes a 13-kDa protein that becomes glycosylated and also undergoes alternative splicing reaching its mature size of 25 kDa [15,17]. Based on the first comprehensive analysis of the expression of HE4, it was described that HE4 was produced not only by malignant but also by healthy tissues (trachea, salivary glands, lungs, thyroid, and prostate) at a baseline level [20]. Besides serous ovarian tumors, pulmonary, gastrointestinal, endometrial, and breast carcinomas also displayed considerable immunoreactivity for HE4 [11,20]. However, the highest expression was consistently found in epithelial ovarian cancer (EOC) [11,20,21]. Finally, the immunological quantitation of serum HE4 levels was established, and it was rapidly introduced as a novel laboratory marker in EOC [7]. HE4 alone had a significantly higher sensitivity in stage I ovarian cancer than did CA125 alone [8]. Furthermore, HE4 was less frequently abnormal than CA125 in benign ovarian diseases [8]. Hence, the utilization of HE4 with CA125 successfully classified patients into low-risk and high-risk groups for the effective triage of women with EOC to surgery [22]. Based on the menopausal status, the sensitivity of HE4 was 76% in premenopause and 92% in postmenopause at a specificity of 75% [22]. HE4 showed a substantial discrimination power in subjects with adnexal masses, e.g. ovarian cyst or endometriosis [23–25]. Furthermore, this tumor marker not only demonstrated a higher sensitivity at the diagnosis of EOC than CA125 (96.9% vs. 85.7%) but also indicated the recurrence of the disease with earlier increased levels during a 20-month follow-up [26]. Finally, serum HE4 level may be a suitable predictor for the survival of patients. Patients with elevated HE4 levels had a shorter surveillance than that of patients with normal HE4 (20.1 vs. 24.2 months) in advanced EOC [21]. Taken together, as it was concluded by a recent systematic literature search, HE4 is a promising and reliable EOC marker [27].

The measurements of HE4 were initially performed on conventional immunoassays; nowadays, fully automated analyzers (e.g. chemiluminescent microparticle immunoassay; CMIA) are readily available [27,28]. HE4 concentrations were found to be comparably measured on both assays, and showed similar clinical values but with a greater precision for CMIA [29].

There was an increasing interest and several attempts have been put forward to appropriately implement HE4 along with CA125 into the routine diagnostic repertoire. One such approach that became widely accepted was to use mathematical algorithms to combine the two markers with radiological examination for a better evaluation of patients suspected of having gynecological malignancies. The first such approach has long been suggested by Jacobs and coworkers [30] by combining the values of CA125 with ultrasound and menopausal status, resulting in the creation of the risk of malignancy index (RMI). This strategy was further developed when HE4, in combination with CA125 plus ultrasonographic features and menopausal status, demonstrated high accuracy in ovarian tumor differentiation [31]. Similarly to RMI, another multiple marker bioassay, the risk of ovarian malignancy (ROMA) was described utilizing the HE4 and CA125 values for the prediction of epithelial ovarian pelvic masses [22,32]. Although ROMA score was found to be better than RMI score in the diagnosis of EOC [32], another study failed to demonstrate its superiority over HE4 alone [33]. Another decision-rule was employed called symptom index (SI) based on the patient complaints about pelvic and abdominal symptoms, and the combination of HE4, CA125, and SI was proposed to predict ovarian cancer [34]. Finally, Van Gorp et al. described that subjective assessment by ultrasound was superior to both RMI and ROMA scores in discriminating benign from malignant adnexal masses [35]. They emphasize that ultrasound examiners take demographic, clinical, and ultrasound information into account when they evaluate an adnexal mass and they apply their experience from previous examinations during subsequent evaluations of the adnexal masses that resulted in a superior performance compared to sheer laboratory results or their mathematical combination [35]. Regardless of its beneficial characteristics, it should be pointed out that—similarly to classic tumor markers [36]—even HE4 has some limitations in the detection of tumors, while its level may be elevated in benign diseases without evidence of malignancy [9,11,25], thus detailed anamnesis in addition to radiological and laboratory examinations are still required for the complex diagnostic work-up.