Original Article

Comparison of the Serum Level of Cancer Antigen 125 and Human Epididymis Protein 4 in Ovarian Cancer Patients and Healthy Groups in Isfahan City

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Abstract

Background: Ovarian cancer is the most common fatal malignancy of the gynecology tract. The purpose of this study was to compare serum levels of tumor markers cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) in both healthy groups and patients with ovarian cancer. **Materials and Methods:** this case–control study was performed on Seyed Al-Shohada Hospital in Isfahan. Research on the treatment of 44 patients with ovarian cancer and 44 healthy controls was performed. CA125 and HE4 were measured in serum by sandwich ELISA method. **Results:** Average CA125 in ovarian cancer patients (83.30 ± 43.99 μ/ml) was significantly higher than in healthy controls (12.39 ± 5.50 μ/ml) ($P < 0.001$). Average HE4 in ovarian cancer patients (295.41 ± 133.33 PM) was significantly higher than in healthy controls (114.64 ± 17.31 PM) ($P < 0.001$). **Conclusions:** HE4 test is complementary of CA125 test in women with epithelial ovarian cancer. It is also used to study the disease process.

Keywords: *Cancer antigen 125, human epididymis protein 4, ovarian cancer, tumor marker*

Introduction

Tumor markers have a major role in the screening, diagnosis, and monitoring of most of the gynecologic cancers. Epithelial ovarian cancer (EOC) is the most common fatal gynecologic malignancy. The disease is often asymptomatic in the early stage of the most cases; therefore, they will be diagnosed at an advanced stage. Cancer antigen 125 (CA125) is one of the most reliable serum markers for EOC; CA125 elevates in half of the early stages of EOC.[1] CA125 as mucin 16 or muc16 is a protein that in humans encoded by the muc16 gene.[2,3] Muc16 is composed of three different domains: N-terminal domain, C-terminal domain, and tandem-repeat domain. The N-terminal and tandem-repeat domains are both entirely extracellular and highly O-glycosylated.[4,5] However, recently, a new biomarker (human epididymis protein 4 [HE4]) for early detection of EOC was introduced by the United States Food and Drug Administration.[6] In addition, serum levels of HE4 are elevated in at least one-third of the patients with EOC who do not have tumors that overexpress CA125.[7,8] CA125 serum level increases in about 90% of women with advanced EOC, but it was lesser in early stage.[2,9] Therefore, in this study, the CA125 tumor marker for monitoring treatment or diagnosis of cancer recurrence is used.[8] Because WFDC2contains two WAP domains and a four-disulfide bond core made up of eight cysteine residues.[10] HE4 glycoprotein, molecular weight and 25 KD are encoded by genes WFDC2.[11,12] The gene on the ong arm of chromosomes 20, 12, and 13 is located.[13] The HE4 gene product is an N-glycosylated protein which is secreted into the extracellular environment and can be detected in the blood of patients with ovarian cancer.[14] However, with limited tumor markers studied in Iran, most of the results are studied abroad. Given the prevalence and mortality of ovarian cancer in women in our study, we investigated the potential of this type of cancer markers in populations of women engage in Isfahan.

Materials and Methods

The case–control study was conducted on referrers to Seyed Al-Shohada Hospital in Isfahan. Patients with ovarian cancer who

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had previously undergone ovarian surgery but had residue, patients with abdominal mass who had biopsy with diagnosis of ovarian cancer, and/or relapsed patients at the time of the study who were undergoing chemotherapy were studied. Sampling began in February 2012 and continued until the end of May 2013. Consumers' tobacco and patients with other diseases that elevated HE4 (other conditions that increase HE4 include breast cancer, endometrial cancer, lung cancer, gastrointestinal cancer, pregnancy, benign gynecologic disorders, hypertension, and congestive heart failure) were not entered into the study. The healthy controls were selected from between volunteers in studies conducted for age, smoking history, history of ovarian cancer in first-degree relatives, who were matched with the patient group. After obtaining consent from the participants, blood was collected from both the groups. Samples were centrifuged at 1200 g for 10 min. The serum was then collected and stored at −70°C until analyzed. Serum CA125 levels were determined by the CA125 EIA kit (Fujirebio) and serum HE4 levels were determined by the HE4 EIA kit (XEMA). For describing the rate of CA125 and HE4 in patients and control groups for any of the variables, frequency, mean, and standard deviation were used. Kolmogorov–Smirnov test was used to determine the distribution of the data. The normal distribution of data, the analysis of the test results for one-way repeated-measures analysis of variance, and *t*-test for comparison between groups (independent samples *t*-test) were used. All the data were analyzed with SPSS statistical software (version 22) for Windows (SPSS Inc, Chicago, II., USA).

Results

The mean age of patients with ovarian cancer was (23–87 years) equivalent to 53.15 ± 30.53 years of healthy control aged 86–23 years of 54.15 ± 32.43 years. The mean concentrations of CA125 in patients and healthy groups were 83.30 ± 43.99 μ/ml and 12.39 ± 5.50 μ/ml, respectively. The serum CA125 is a significant difference between the two groups and the using independent *t*-test showed that the mean concentrations of CA125 in patients with ovarian cancer are significantly higher than in healthy groups ($P < 0.001$) [Figure 1]. The mean concentrations of HE4 in patients and healthy groups were 295.41 ± 133.33 PM and 114.64 ± 17.31 PM, respectively. The concentration of HE4 is a significant difference between the two groups; using independent *t*-test, it was shown that the mean concentration of HE4 in ovarian cancer patients is significantly higher than in healthy groups ($P < 0.001$) [Figure 2]. There was a significant correlation between age and level of HE4. The correlation of 0.67 is indicative of strong correlation. In other words, with increasing age, HE4 concentration increased in patients [Figure 3].

The evaluation of HE4 and CA125 indicates that the sensitivity of HE4 is more than CA125 and by less error (and more accuracy) [Figure 4 and Table 1].

Discussion

To date, the best marker for ovarian cancer is CA125. The serum markers are widely used to monitor treatment, diagnosis, or relapse.[8] One of the most promising new serum biomarkers is HE4. HE4 is a glycoprotein that is highly expressed by EOC.[14,15]

A study done in 2006 showed that the serum levels of tumor marker CA125 are the most important determinants of prognosis in ovarian cancer.[16]

Serum CA125 levels were measured in 430 patients with ovarian surgery, and ultrasound and measurement of

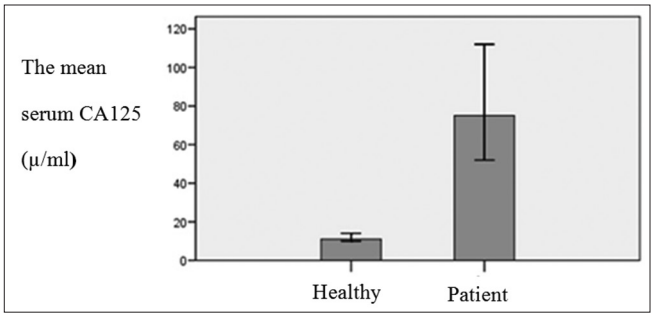

Figure 1: Comparison of serum cancer antigen 125 in both healthy groups and patients with ovarian cancer

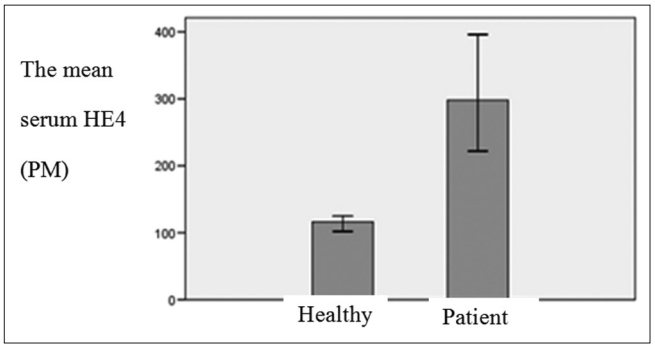

Figure 2: Comparison of serum human epididymis protein 4 in healthy groups and patients with ovarian

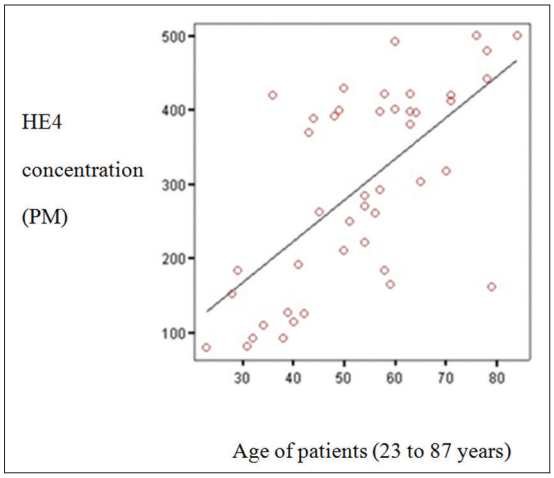

Figure 3: Distribution of human epididymis protein 4

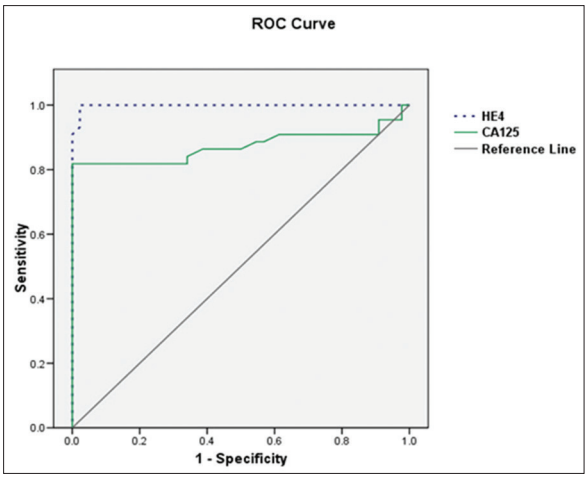

Figure 4: Evaluation of cancer antigen 125 and human epididymis protein 4 sensitivity

Table 1: CA125 and HE4 sensitivity

Factor	Area under the ROC curve (%)
HE4	97
CA125	87

HE4: Human epididymis protein 4, ROC: Receiver operating characteristic, CA125: Cancer antigen 125

CA125 can help in predicting the malignancy of ovarian masses and help increase diagnostic accuracy.[17]

A study was done on 73 women with ovarian cancer after measuring CA125 and HE4 concluded that the markers could be used to predict ovarian cancer.[15]

A study was done in 2012 showed that serum HE4 levels alone and in combination with CA125 as a diagnostic marker for patients with ovarian tumors.[8]

Studies on women with ovarian cancer showed that using CA125 and HE4 may help predict pelvic masses benign or malignant.[18]

Tumor marker CA125 and HE4 in 73 healthy women and 90 women with benign ovarian disease were measured and concluded that HE4 and CA125 are more accurate to use these markers in addition to imaging criteria to differentiate malignant mass from benign.[11]

Studies on serum levels of HE4 showed that HE4 serum concentrations vary significantly on the basis of age.[19]

CA125 and HE4 efficacy in patients with ovarian cancer were examined. This study showed that HE4 can predict ovarian cancer recurrence more than CA125.[14]

Studies on HE4 showed that preoperative plasma levels of HE4 are a marker of ovarian cancer aggressiveness and predictor of death. HE4 levels increased significantly with age.[20]

Conclusions

Our study on 44 patients with ovarian cancer who were taken chemotherapy and 44 patients were in the control group, showed that the mean serum CA125 in patients with ovarian cancer is significantly higher than healthy groups. The results of the survey showed that HE4 increases in ovarian cancer patients. There is a significant correlation between CA125 and HE4 (correlation of 0.72, which indicates a strong correlation between the two factors). The results of this study are in agreement with the results of other researchers in this field.

This study also showed HE4 is more sensitive than CA125 for detection and follow-up of patients with ovarian cancer.

The researchers suggest, based on the existing research facilities, to promote broader study for tumor markers of ovarian cancer in Iran.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kobayashi E, Ueda Y, Matsuzaki S, Yokoyama T, Kimura T, Yoshino K, *et al.* Biomarkers for screening, diagnosis, and monitoring of ovarian cancer. Cancer Epidemiol Biomarkers Prev 2012;21:1902-12.
2. Yin BW, Lloyd KO. Molecular cloning of the CA125 ovarian cancer antigen: Identification as a new mucin, MUC16. J Biol Chem 2001;276:27371-5.
3. Yin BW, Dnistrian A, Lloyd KO. Ovarian cancer antigen CA125 is encoded by the MUC16 mucin gene. Int J Cancer 2002;98:737-40.
4. Santillan A, Garg R, Zahurak ML, Gardner GJ, Giuntoli RL, Armstrong DK, *et al.* Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. J Clin Oncol 2005;23:9338-43.
5. Kabawat SE, Bast RC Jr., Bhan AK, Welch WR, Knapp RC, Colvin RB. Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. Int J Gynecol Pathol 1983;2:275-85.
6. Li J, Dowdy S, Tipton T, Podratz K, Lu WG, Xie X, *et al.* HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev Mol Diagn 2009;9:555-66.
7. Rosen DG, Wang L, Atkinson JN, Yu Y, Lu KH, Diamandis EP, *et al.* Potential markers that complement expression of CA125 in epithelial ovarian cancer. Gynecol Oncol 2005;99:267-77.
8. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, *et al.* The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol 2008;108:402-8.
9. Mutz-Dehbalaie I, Egle D, Fessler S, Hubalek M, Fiegl H, Marth C, *et al.* HE4 is an independent prognostic marker in endometrial cancer patients. Gynecol Oncol 2012;126:186-91.

10. Ruggeri G, Bandiera E, Zanotti L, Belloli S, Ravaggi A, Romani C, *et al.* HE4 and epithelial ovarian cancer: Comparison and clinical evaluation of two immunoassays and a combination algorithm. Clin Chim Acta 2011;412:1447-53.
11. Kirchhoff C, Habben I, Ivell R, and Krull N. A major human epididymis-specific cDNA encodes a protein with sequence homology to extracellular proteinase inhibitors. Biol Reprod. 1991; 45:350-7.
12. John R, Martha H, Jeffrey A, Ledbetter M, Schummer M, Charles D, *et al*. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. Cancer Res 2003;63:3695-700.
13. Iwabuchi H, Sakamoto M, Sakunaga H, Ma YY, Carcangiu ML, Pinkel D, *et al.* Genetic analysis of benign, low-grade, and high-grade ovarian tumors. Cancer Res 1995;55:6172-80.
14. Schummer M, Ng WV, Bumgarner RE, Nelson PS, Schummer B, Bednarski DW, *et al.* Comparative hybridization of an array of 21,500 ovarian cDNAs for the discovery of genes overexpressed in ovarian carcinomas. Gene 1999;238:375-85.
15. Andersen MR, Goff BA, Lowe KA, Scholler N, Bergan L, Drescher CW, *et al.* Use of a symptom index, CA125, and HE4 to predict ovarian cancer. Gynecol Oncol 2010;116:378-83.
16. Yousefi Z, Homaei F. Risk factors and prognostic factors in ovarian cancer. Iran J Med Counc Islam Repub 2004;24:279-88.
17. Arab M, Maktabi M, Jam H, Kemeaei P, Dolo S. Addition of serum CA125 measurements to increase the accuracy of ultrasound in the diagnosis of malignancy before surgery in patients with ovarian mass. Hamedan Univ Med Sci Health Serv 2011;18:42.
18. Chan KK, Chen CA, Nam JH, Ochiai K, Wilailak S, Choon AT, *et al.* The use of HE4 in the prediction of ovarian cancer in Asian women with a pelvic mass. Gynecol Oncol 2013;128:239-44.
19. Moore R, Miller M, Eklund E, Karen H, Bast B, Messerlian G. Serum level of the ovarian cancer bio marker HE4 are decreased in pregnancy and in increase with age. Oncology 2012; 206:349.
20. Trudel D, Têtu B, Grégoire J, Plante M, Renaud MC, Bachvarov D, *et al.* Human epididymis protein 4 (HE4) and ovarian cancer prognosis. Gynecol Oncol 2012;127:511-5.