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Evaluation of prostasin Levels in Serum of Patients with Ovarian Cancer as a New Potential Tumor Marker

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ABSTRACT: Prostasin has been considered as a new biomarker with high sensitivity for ovarian cancer diagnosis. This study aims at evaluating the changes in levels of serum prostasin biomarker in patients with ovarian cancer and determining the efficacy of this biomarker for diagnosis of ovarian cancer. This descriptive-analytical study was performed on women with ovarian cancer. The serum levels of prostasin and CA125 were measured using ELISA and Electrochemiluminescence techniques. The data was analyzed using SPSS Ver. 11 and the level of statistical significance was considered to be $p < 0.05$. Totally, 110 subjects participated in this study, including 20 patients with malignant ovarian tumors, 66 patients with benign tumors and 24 healthy women. A significant increase in serum prostasin and CA125 levels was observed for malignant group comparing with the control group and the people with benign tumors ($p < 0.05$). The cut-off point, sensitivity and specificity of prostasin in diagnosis of ovarian malignancies compared with ovarian benign tumors and the control group were 9.3 µg/ml, 0.89 and 0.75, respectively. These levels were reported for CA125 in diagnosis of ovarian malignancies, ovarian benign tumors and the control group as 35.17, 0.85 and 0.75 U/ml respectively. The findings of this study show that prostasin can serve as a good biomarker for ovarian cancer diagnosis with suitable sensitivity and specificity. Further studies are required to generalize these findings.

Keywords: Cancer, Ovarian tumor, Marker, Prostasin.

ORIGINAL ARTICLE

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INTRODUCTION

Ovarian tumors, especially epithelial ovarian cancer , comprise 70%-90% of ovarian tumors, are among the fatal cancers of the female reproductive system and have been ranked seventh among the cancers in females; this cancer is the third common one in terms of the incidence for genital system, however, it is the leading one in terms of mortality rate among genital cancers (Jemal et al., 2008). Despite numerous daily demands of physicians for conducting the test, tumor marker CA125 has no sufficient sensitivity and specificity for diagnosis of ovarian cancer, meanwhile it is not specific for this organ. Nevertheless, the tumor marker is not present in 22% of epithelial ovarian cancers, or its level is normal (Rosen et al., 2005). Also in premenopausal women, its level is highly fluctuating in various conditions including menstruation, in the case of liver and kidney problems, and inflammation of abdominal cavity. So, screening using this method and confidence in the results of the test and judgments based on it is controversial and requires further investigation. On the other hand, many women in the case of presence of high levels of CA125 or borderline levels, especially in childbearing age, will become candidates for surgery, oophorectomy or even abdominal hysterectomy; meanwhile, CA125 lacks sufficient sensitivity and specificity especially in this age group. Studies conducted by Saundra et al. indicate that among the laboratory tests, only CA125 is widely available as a tumor marker. The cutoff point of the test is about 35-30 U/ml and its sensitivity is 50-60% for detecting cancer in early stages. The level of specificity of CA125 in postmenopausal women is high, but its specificity drastically reduces for premenopausal women (Saundra et al., 2011). New studies suggest that screening for ovarian cancer with the help of CA125 not only cannot reduce mortality rate due to cancer, but in some cases result in the complications due to unnecessary treatment because of false-positive results. Accordingly, the most important laboratory test for ovarian cancer is not much satisfying (Health canal. 2011). The results of several studies suggest that the sensitivity of CA125 with cut-off point of approximately 35 U/ml for the diagnosis of ovarian cancer is about 65 percent (Geuts et al., 2011). Increased level of CA125 in some autoimmune diseases such as rheumatoid arthritis and lupus is a challenge for efficacy of the test in screening for ovarian cancer (Szekanecz et al., 2008).

According to the study by Chen et al. prostasin is considered to be an tissue invasion suppressor in prostate cancer (Chen et al., 2001). In 2001, Samuel et al. showed

the presence of prostasin in ovarian cancer tissue samples by IHC and microarray techniques (Mok et al., 2001). Increased level of associated mRNA was also confirmed through Real-time PCR (Costa et al., 2009), and this indicates that prostasin can serve as a new biomarker for ovarian cancer. Given that one of the main origins for prostasin secretion is the prostate in men, it seems that lack of prostate in women is a desirable feature for using it for ovarian cancer diagnosis.

Due to the lack of studies in this field in Iran on the one hand, and the need for further studies for finding alternative new biomarkers with high specificity and sensitivity on the other hand, this study evaluated the efficacy of prostasin as a biomarker for early ovarian cancer diagnosis and follow up of the patients along with other clinical and histopathology findings.

MATERIALS AND METHODS

This descriptive-analytical study was conducted in the year 2012 on women referred to Motahari Hospital in Tabriz who had benign or malignant ovarian tumors, and the control group was selected from medical students and staff of the hospital who had no history of benign and malignant ovarian tumors or irregular menstruation. The patients were selected by random sampling method. Participation in the study was voluntary and written consent forms were signed by all participants for this study. This study was approved by the ethics committee of Shahid Beheshti University. Phlebotomy was conducted in all subjects and the serum samples were stored in the freezer at -40°C. The serum prostasin and CA125 levels were measured using Electrochemiluminescence test (ECL) .

The data was analyzed using SPSS Ver. 11 and ROC curve and ANOVA test were used for data analysis; meanwhile the level of statistical significance was considered to be $p < 0.05$.

RESULTS

Totally, 110 subjects participated in this study, including 20 patients with malignant ovarian tumors, 66 patients with benign tumors and 24 healthy women. Mean prostasin level in control group was 7.21 µg/ml (6.46-7.95; CI 95%), for the group with benign tumors it was 8.36 µg/ml (7.56-9.16; CI 95%) and for patients with malignant tumors it was 12.36 µg/ml (11.27-13.45, CI 95%) respectively. A significant increase in serum prostasin levels was observed for malignant group comparing with the control and benign groups ($p < 0.05$). Serum prostasin levels also was slightly higher in the patients with benign tumors compared with the control group, which was not statistically significant, however ($p<0.01$).

To evaluate the sensitivity and specificity of prostasin in diagnosis of malignant ovarian tumors, ROC curves and the area under these curves were calculated twice, first in comparison with the benign tumors and the control group (Figure 1) and then only in comparison with the patients with benign tumors (Figure 2). The cut-off point, sensitivity and specificity of prostasin in diagnosis of ovarian malignancies compared with ovarian benign tumors and the control group was 9.3 µg/ml, 0.89 and 0.75, respectively. The cut-off point, sensitivity and specificity of this protein for diagnosis of malignant lesions from benign lesions were 8.9 µg/ml, 0.94 and 0.66 respectively.

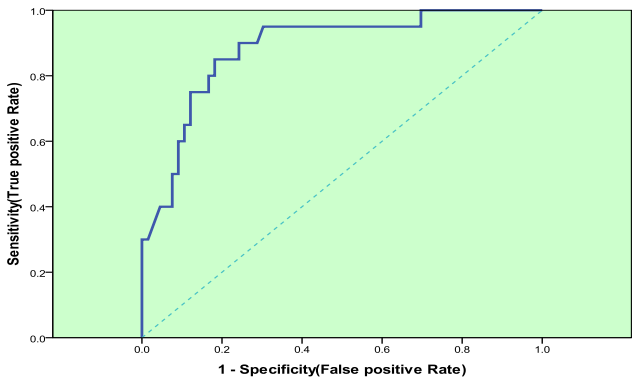

Figure 1. The ROC curve of sensitivity and specificity of prostasin for differentiating between malignant tumors, benign ones and the control subjects

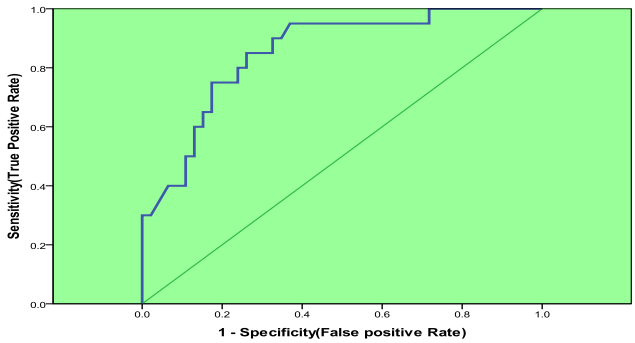

Figure 2. The ROC curve of sensitivity and specificity of prostasin for differentiating between malignant tumors and benign ones

To evaluate the sensitivity and specificity of CA125 in diagnosis of malignant ovarian tumors, ROC curves and the area under these curves were also calculated twice, first in comparison with the patients with the benign tumors and the control group (Figure 3) and then only in comparison with the subjects with the benign tumors (Figure 4). The cut-off point, sensitivity and specificity of CA125 in diagnosis of ovarian malignancies compared with ovarian benign tumors and the control group were reported as 35.17, 0.85 and 0.75, respectively. These levels for differentiating between malignant lesions and benign lesions were 35.17 U/ml, 0.84 and 0.56 respectively.

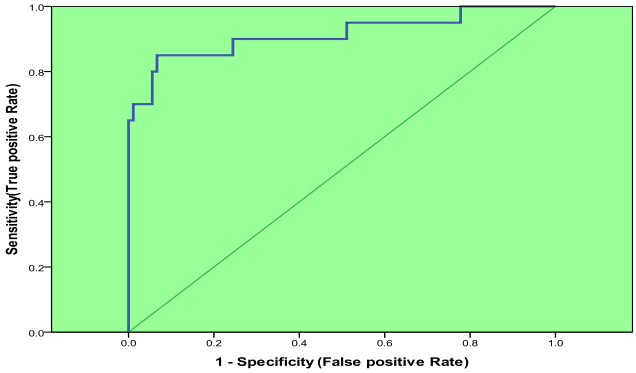

Figure 3. The ROC curve of sensitivity and specificity of CA125 for differentiating between malignant tumors, benign ones and the control subjects

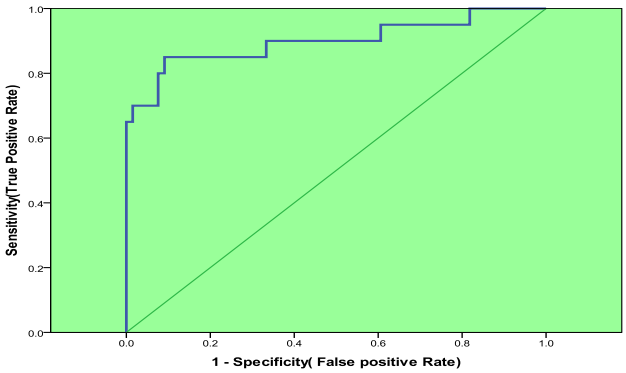

Figure 4. The ROC curve of sensitivity and specificity of CA125 for differentiating between malignant tumors and benign ones

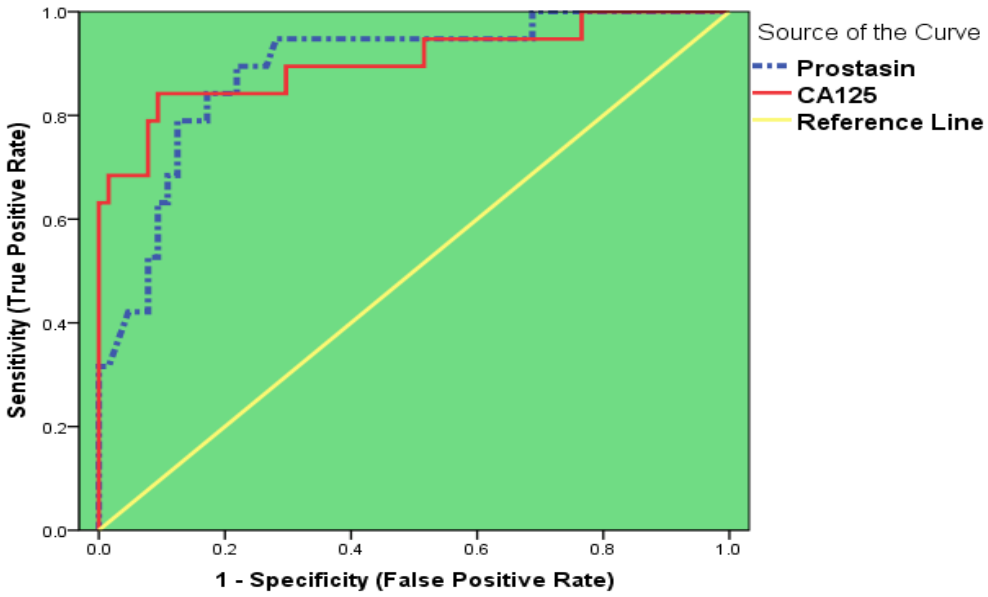

Figure 5. Comparison of ROC curves of sensitivity and specificity of CA125 and prostasin for differentiating between malignant tumors, benign ones and the control subjects

Comparison of the ROC curves and the area under them suggests that for CA125, the area under the curve is slightly greater than that for prostasin which implies that the relative diagnostic advantage of CA125 over prostasin (0.91 to 0.89) (Figure 5).

DISCUSSION

In this study, serum level of prostasin and CA125 biomarkers were studied in patients with ovarian cancer. The findings of the present study showed that prostasin can be used as a biomarker with high efficacy in ovarian cancer diagnosis. This compound is widely measured in clinics in order to determine the likelihood of malignancy before surgical excision and to monitor the disease and for the purpose of prognosis. However, despite the above-mentioned issues, serum CA125 level is affected by a wide range of physiological conditions, benign ovarian diseases and malignant non-ovarian diseases, and these reduce the sensitivity and specificity of the test in the diagnosis of ovarian cancer especially in early stages, and in the absence of adequate serum levels of this antigen. Prostasin application for diagnosis of ovarian cancer has been demonstrated in previous studies.

In the present study, the mean serum CA125 level in patients with malignant ovarian tumors was significantly higher than the same in control group and in the patients with benign ovarian diseases ($p < 0.05$). Therefore it can be used as an efficient biomarker for the

diagnosis of ovarian cancer in terms of sensitivity and specificity.

The AUC value of CA125 test in the study by Kuk et al. for differentiating between benign and malignant ovarian diseases was 0.92; while the AUC value of CA125 test for differentiating between malignant ovarian diseases and normal subjects was 0.93 (Kuk et al., 2010). The values in the present study were 0.90 and 0.91 and showed little difference with the results of the previous study.

In a research conducted by Rice et al for ovarian cancer diagnosis, the sensitivity and specificity of these markers have been compared with those of CA125 and the AUC value of CA125 was 0.934 in the comparison (Rice et al., 2010), which was consistent with the results of current study.

In a study accomplished by Diamandis regarding the diagnostic value of 6 types of tissue kallikreins and CA125, the mean serum CA125 levels were 14.5 IU/ml and 18 IU/ml in normal people and in the patients with benign ovarian tumors respectively; the AUC value of CA125 for differentiating between malignant lesions and benign and normal ones was 0.87 (Eleftherios et al., 2011), which is consistent with results of the present study, i.e. the AUC value of 0.914. The mean CA125 in normal subjects during the present study was 15.3 IU/ml, and it was very close to the results obtained by Diamandis. However, the mean CA125 in patients with benign tumors was largely different from the results observed during the study (18 vs. 44.3). This could be due to the differences in the types of benign lesions, because in the current study, the benign tumors had mostly similar views with malignant lesions.

Regarding the sensitivity and specificity of the results of this study, since the AUC value of prostasin is 0.88, it can be used for differentiating malignant diseases from benign ones the and normal subjects, so prostasin can be a useful biomarker in diagnosis of ovarian cancers. In the study by Chen, the serum prostasin level in epithelial ovarian cancers was significantly higher than the same in normal ovarian tissue. The mean prostasin levels in patients with malignant ovarian tumors was significantly higher than the same in the normal people; and a significant decrease was also observed postoperatively and after surgical resection of malignant tumors in the protein levels (Mok et., 2011). In the present study also a significant increase was observed in prostasin levels in malignant group comparing with the benign and the control groups, which is consistent with the above findings. Yet, in another study, aiming at full investigation of serum tests for finding the accurate marker of epithelial ovarian cancer diagnosis, the AUC values for CA125 and prostasin were 0.907 and 0.80 respectively; these values were lower than those AUC values obtained in this study (Yip, Chen et al. 2011). In the study by Samuel, prostasin was considered as a potential biomarker for ovarian cancer diagnosis. Mean serum prostasin levels in patients with malignant tumors and in normal people were 13.7 µg/ml and 7.5 µg/ml respectively, which are consistent with the results reported in this study (Mok et al., 2001).

Despite many advances made in the diagnosis and treatment of ovarian cancer, still a lot of people around the world suffer from the problems due to late diagnosis of the disease and are faced with huge and costly associated burdens. Therefore, further studies are needed to identify new biomarker with higher sensitivity and efficacy. The results of this study showed that prostasin can be used for early diagnosis of ovarian cancers.

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