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Geeta Bilonia
Ph.D. Scholar, department of Biochemistry, SMS, Medical College, Jaipur, Rajasthan, India

Dr. Rati Mathur
Senior Professor, department of Biochemistry, SMS, Medical College, Jaipur, Rajasthan, India

Dr. Suresh Singh
Professor, department of Surgical Oncology, SMS, Medical College, Jaipur, Rajasthan, India

Corresponding Author:
Dr. Rati Mathur
Senior Professor, department of Biochemistry, SMS, Medical College, Jaipur, Rajasthan, India

Comparative study of significance of serum human epididymis protein 4 (HE4) and carbohydrate antigen 125 (CA125) as an early tumour marker in female patients with ovarian cancer

Geeta Bilonia, Dr. Rati Mathur and Dr. Suresh Singh

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Abstract
Aim: To determine the usefulness of serum human epididymis protein4 (HE4) along with Carbohydrate Antigen 125 (CA125) as an early tumour marker in female patients with ovarian cancer.
Method: The ovarian cancer patients were recruited from OPD/IPD of Surgery and Oncology department of SMS Hospital, and evaluated serum HE4 and CA125. Total 262 subjects were included in this study.131 ovarian cancer Patients were divided according to different stages and 131 control subjects also included.
Results: Serum HE4 and CA125 level raised significantly in ovarian cancer patients. Further increases with the advanced stage of the ovarian cancer.
Conclusion: Both HE4 and CA125 can be useful diagnostic tumour marker in ovarian cancer.

Keywords: HE4, CA125, ovarian cancer

Introduction
Ovarian cancer (OC) is the leading cause of death in all gynecological malignancies [1].The annual incidence of ovarian cancer is 204,000, with 125,000 deaths. In developed countries, ovarian cancer remains the most lethal of all gynecologic malignancies. One of the reasons for the high fatality rate is that more than 70% of women with ovarian cancer are diagnosed with advanced disease. There is a close correlation between stage at presentation and survival; therefore, early detection of ovarian cancer represents the best hope for mortality reduction and longterm disease control. There is preliminary evidence that screening can improve survival but the impact of screening on mortality from ovarian cancer is still unclear [2]. Epithelial ovarian cancer set by the World Health Organization (WHO) recognizes eight histological tumor subtypes: serous, mucinous, endometrioid, clear cell, transitional cell, squamous cell, mixed epithelial and undifferentiated. Within each subtype, tumors are further described as benign, malignant, or borderline, and depending upon tumor subtype; classified as low or high-grade. Borderline tumors are considered to have low malignant potential and indolent behavior [3].
(CA125) is the most widely used tumor marker in ovarian cancer; however, its predictive power is far from ideal. It is elevated in about 80% of women with epithelial ovarian cancer (EOC) but only in 50% of women with early stage disease [4]. The specificity of CA125 is limited, since it can be elevated in a range of common benign gynecologic or non-gynecologic conditions [14]. Furthermore, the sensitivity and specificity of CA125 are not high enough for population screening for the detection of early stage ovarian cancer [6].
(HE4), also known as WAP type four disulphide core 2 (WFDC2), is one of the most promising markers for improving the sensitivity and specificity. HE4 is primarily expressed in the reproductive and respiratory tracts [7] and is over expressed in ovarian cancer cells, especially in histologic subtypes of serous or endometriod carcinoma [8] and it has been suggested to be a serological marker of ovarian cancer [13].

Material & Method

The present case-control comparative study was conducted in the Department of Biochemistry, in association with the Department of Surgery and Oncology SMS Medical College and Attached group of Hospitals, Jaipur. Total 262 subjects here included in this study and divided into two groups as follows: Group 1 comprised of 131 Healthy Control & Group 2 comprised of 131 ovarian cancer patients. Patients were also divided according to different stages.

Inclusion Criteria

Willingness to participate has included in this study and those who have given written consent. Female patients (age >23years) diagnosed with ovarian cancer.

Exclusion Criteria

Patients having other cancer, collagenopathy and all other diseases that affect the level of HE4 and CA125, previously diagnosed cases of ovarian cancer who is taking chemotherapy or radiotherapy, history of OCP & pregnancy, patients with benign ovarian diseases.

Venous blood sample was withdrawn for investigations taking all aseptic precautions. Serum was separated and investigated for HE4 by ELISA and CA125 Chemiluminescence method [11].

Ethical approval and Informed consent The Protocol was approved by institutional Ethics committee. Informed written consent was obtained from all study subjects.

Statistical Analysis The data was analyzed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations were calculated. The statistical tests applied for the analysis were one- way ANOVA with Post-hoc Bonferroni test. The confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

Results

Table 1: shows Serum HE4 and CA125 concentrations in ovarian cancer patients (case) and healthy controls groups. Both Serum HE4 and CA125 concentration were higher in ovarian cancer subjects as compared to controls.

Table 2: demonstrates serum HE4 and CA125 concentration in different stages of ovarian cancer. Both HE4 and CA125 concentration were higher in advanced stage of ovarian cancer. The results were highly significant. ($p<0.001$)

Table 3 and 4: presents descriptive multiple (Intra groups) comparisons of serum HE4 and CA125 in different stages (I, II, III, IV) of Ovarian cancer respectively. Both HE4 and CA125 concentration is significantly higher in advanced stage in ovarian cancer and the level increases further with metastasis

Table 1: Serum HE4 (Pmol/l) and CA125(U/ml) levels in ovarian cancer v/s healthy controls

Marker	Case(N=131)	Control(N=131)	p-value
	Mean± SD	Mean± SD	
HE4 (Pmol/l)	313.83± 173.59	57.26± 34.39	<0.001 (Sig.)
CA125 (U/ml)	216.77±285.68	12.38±8.85	<0.001 (Sig.)

Test applied: Independent sample t-test

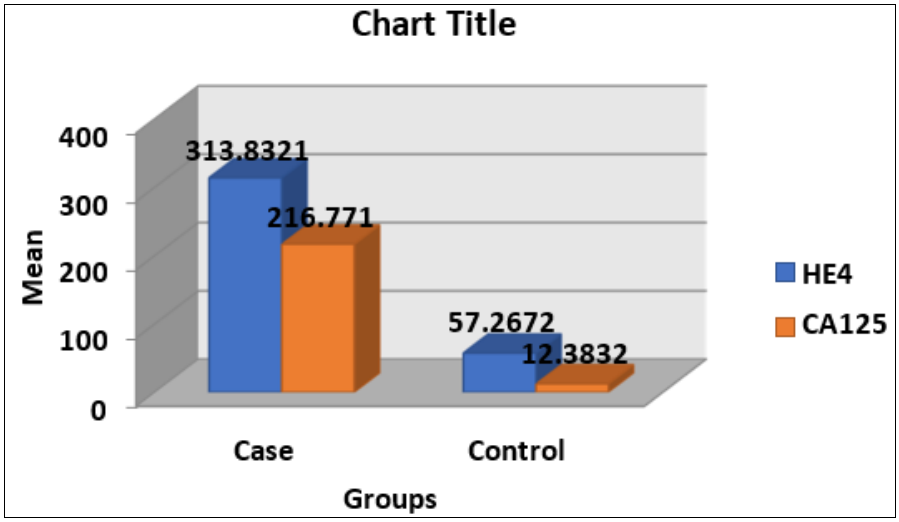

Fig 1: Serum HE4 (Pmol/l) and CA125 (U/ml) levels in ovarian cancer v/s healthy controls

Table 2: Serum HE4 and CA125 levels in different stages of ovarian cancer

Stage	N (131)	HE4 (Pmol/l) Mean±SD	CA125 (U/ml) Mean±SD
1	30	212.30±109.63	39.80±14.82
II	30	215.66±104.35	56.16±19.94
III	40	331.17±164.93	193.77±101.01
IV	31	484.70±150.21	573.12±388.29
F-value		26.70	48.60
P-value		0.001	

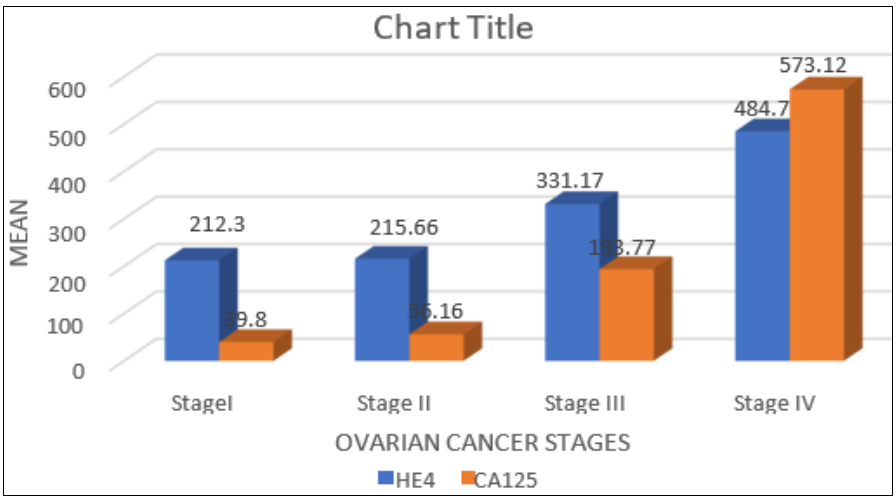

Fig 2: Serum HE4 and CA125 in different stages of Ovarian cancer

Table 3: Multiple (Intra stages) Comparison of serum HE4 by Post Hoc- Bonferroni test

Marker	Stages	N	Mean	Std. Deviation	**p-value					
					I vs II	II vs III	III vs IV	I vs III	I vs IV	II vs IV
HE-4	I	30	212.3000	109.63298	0.925 (NS)	0.004 (Sig.)	0.001 (Sig.)	0.003 (Sig.)	0.001 (Sig.)	0.001 (Sig.)
	II	30	215.6667	104.35825						
	III	40	331.1750	164.93151						
	IV	31	484.7097	150.21189						
	Total	131	313.8321	173.59888						
p-value	0.001 (sig.)									
F-value	26.708									

Test applied: One-way ANOVA. **Post-Hoc Bonferroni test for paired comparison

Table 4: Multiple (Intra stages) Comparison of serum CA125 by Post Hoc- Bonferroni test

Marker	Stages	N	Mean	Std. Deviation	p-value**					
					I vs II	II vs III	III vs IV	I vs III	I vs IV	II vs IV
CA125	I	30	39.8000	14.82635	0.988 (NS)	0.023 (Sig.)	0.001 (Sig.)	0.008 (Sig.)	0.001 (Sig.)	0.001 (Sig.)
	II	30	56.1667	19.94835						
	III	40	193.7750	101.01091						
	IV	31	573.1290	388.29754						
	Total	131	216.7710	285.68863						
p-value	0.001 (Sig.)									
F-value	48.609									

Test applied: One-way ANOVA. **Post-Hoc Bonferroni test for paired comparison

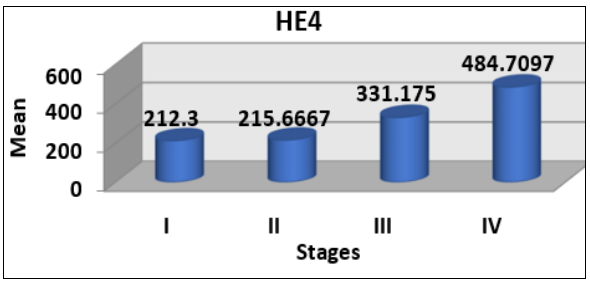

Fig 3: Serum HE4 levels in different stages of ovarian cancer

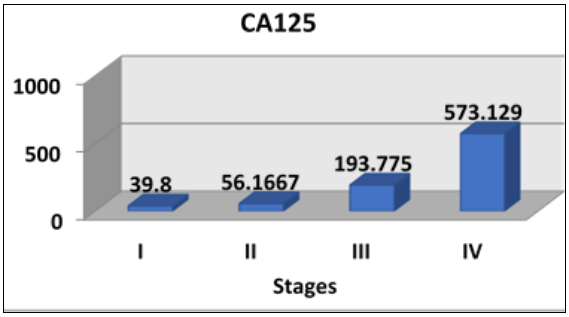

Fig 4: Serum CA125 levels in different stages of ovarian cancer

Discussion

Our study results depict that HE4 concentration was higher in ovarian cancer patients as compared with healthy control subjects and the level rose significantly in ovarian cancer patients with advanced stages. Our results are consistent with observation made in 2007, Moore *et al*, HE4 (human epididymis protein 4) is a noval marker which is a secreted glycoprotein and over expressed by serous and endometrioid EOC. Numerous studies have defined the utility of HE4 in the diagnosis of ovarian cancer. HE4 is part of a family of protease inhibitors that functions in protective immunity which is over expressed in ovarian cancers, especially in serous and endometrioid histotype. It is secreted by the cell and then detectable in the bloodstream of patients with ovarian carcinoma via an enzyme immunoassay. Human Epididymis secretory protein 4 was first identified in the epithelium of the distal epididymis using Northan blot analysis and in situ transcript hybridization, which was referred to as WFDC2 because it contained two whey acidic protein (WAP) domains and a four-disulphide core comprising eight cysteine residues. HE4 was found to be over expressed in ovarian cancer, whereas its expression in normal tissue was low. It has been used for the early

screening and differential diagnosis of ovarian cancer, as well as for monitoring disease recurrence and progression. The biological functions of CA125 were complex but seem to enhance the malignant potential of ovarian cancer cells. CA125 played an important role in cellular adhesion, invasion, and intraperitoneal metastasis. Many studies had shown that CA125 exists in the serum of patients with epithelial ovarian cancer [6]. Although CA125 was the most widely used biomarkers in ovarian cancer, [7] the sensitivity and specificity of CA125 were far from ideal as is its levels were elevated in approximately, 80% of ovarian cancer. CA125 is the most frequently used biomarkers for ovarian cancer detection.

Conclusion

Ovarian cancer is one of the most common and leading causes of cancer death among women worldwide. Early diagnosis of ovarian cancer can provide patients a wider range of therapeutic options as well as a higher success rate of therapy that lowers mortality. Quantitative analysis of tumour markers is the most convenient method to screen ovarian cancer. Our study results suggested that serum HE4 and CA125 can be useful serum tumour marker in patients with ovarian cancer. Serial determination of these markers may be beneficial for early detection of metastasis.

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