

## Original Article

# Significance of serum CA-125 combined with CEA and HE-4 in diagnosis of epithelial ovarian cancer

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**Abstract:** Objective: Our aim was to investigate the significance of preoperative peripheral blood serum levels of carbohydrate antigen 125 (CA-125), carcino-embryonic antigen (CEA), and human epididymis protein 4 (HE-4) in early diagnosis and prognosis evaluation of epithelial ovarian cancer. Methods: From January 2010 to January 2014, 100 patients with newly diagnosed epithelial ovarian cancer, in the Department of Gynecology of the First Affiliated Hospital of Xinjiang Medical University, were selected for the study group. Follow up was six months and patients were divided into recurrence group and non-recurrence group, according to results of the return visit. In the same period, 100 patients with benign ovarian tumors and 100 healthy females were selected as benign control group and healthy control group. Clinical data of each group were retrospectively collected. Values of preoperative CA-125, CEA, and HE-4 in the 3 groups were measured and recorded to investigate the value of CEA and HE-4 combined with CA-125 in diagnosis of epithelial ovarian cancer. Differences of the three indicators were compared between recurrent and non-recurrent groups at the different stages. Results: Levels of serum CA-125, CEA, and HE-4 in our study group were higher than those in healthy control group and benign control group (all  $P < 0.05$ ). Serum levels of CA-125, CEA, and HE-4 in patients with middle and late ovarian cancer and recurrence group were higher than mean value of all ovarian cancer patients (all  $P < 0.05$ ). Sensitivity of the three combined indicators in predictive diagnosis of epithelial ovarian cancer was 89.4%. Conclusion: CA-125 combined with CEA and HE-4 is helpful in diagnosis of epithelial ovarian cancer.

**Keywords:** Ovarian cancer, carbohydrate antigen 125, carcino-embryonic antigen, human epididymis protein 4, early diagnosis

## Introduction

Ovarian cancer is one of the common tumors of the female reproductive system. Although its incidence is not first among female genital tract tumors, its mortality ranks first [1-3]. The main reason is that the anatomical position of the ovary is located in the pelvic cavity and early clinical manifestation of ovarian cancer is not specific, resulting in failure to detect in time [4]. Research studies have shown that more than 70% of patients with ovarian cancer are in the advanced stage and treatment rate is less than 30% [5]. Early screening is of great significance for these patients for improving the survival rate and long-term quality of life [6]. Currently,

serological detection of cancer markers including carbohydrate antigen 125 (CA-125), carcino-embryonic antigen (CEA), and human epididymis protein 4 (HE-4) is the main method for early diagnosis of ovarian cancer [1, 7]. Unfortunately, none of these three indicators can accurately and unitarily complete early diagnosis of ovarian cancer. For example, CA-125 is the first ancillary diagnostic indicator of ovarian cancer but also the primary method of evaluating effectiveness of treatment and monitoring recurrence of tumors. CA-125 is also highly expressed in benign gynecologic tumors which may weaken its accuracy to a certain extent. The same problems are found in CEA and HE-4 [8]. To this end, the purpose of this research

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**Table 1.** Basic information of ovarian cancer patients

Items	Case (n, %)
Clinical stage	
I	14 (14.0)
II	19 (19.0)
III	42 (42.0)
IV	25 (25.0)
Recurrence	
Recurred	55 (55.0)
No recurred	45 (45.0)

was to investigate the diagnostic value of combined detection of CA-125, CEA, and HE-4 in early stage of ovarian cancer.

### Materials and methods

#### General information

All of the cases and controls in this research were from the Department of Obstetrics and Gynecology of The First Affiliated Hospital of Xinjiang Medical University, from January 2010 to January 2014.

Our study group included 100 patients with newly diagnosed ovarian cancer confirmed by postoperative pathology in The First Affiliated Hospital of Xinjiang Medical University. Ages ranged from 26 to 78 years old (average age  $56.65 \pm 7.13$ ). Postoperative pathological classification included 51 cases of serous cystadenocarcinoma, 30 cases of mucinous cystadenocarcinoma, and 19 cases of endometrioid carcinoma.

The control group included 100 patients diagnosed with benign ovarian tumors, during the same period, and confirmed by postoperative pathology in The First Affiliated Hospital of Xinjiang Medical University. Postoperative pathological diagnosis included serous cystadenoma, mucinous cystadenoma, and teratoma. Ages were 22-77 years old, with an average age of  $56.10 \pm 6.72$ . Laparoscopic benign ovarian tumor removal was the surgical method.

The healthy control group was selected from 100 healthy females that underwent sterilization, anastomosis, installation or removal of contraceptive ring, and physical examination in The First Affiliated Hospital of Xinjiang Medical

University, during the same period. Healthy controls were aged 22-77 years old, with an average age of  $55.90 \pm 6.87$ .

Inclusion criteria: All patients had no history of coronary heart disease, diabetes, hypertension, or history of other diseases. Liver and kidney function was normal and clinical data were completed. Serum levels of CA-125, HE-4, and CEA were detected. Exclusion criteria: Patients with history of tumors in other organs were excluded and patients that could not complete follow up due to various reasons. Informed consent was signed by all patients in the three groups.

#### Data collection

Clinical information such as age, blood test result, surgery completion status, postoperative histological classification, and treatment plan of the above three groups of research subjects was collected, retrospectively, and necessary information such as recurrence condition was supplemented with follow up.

#### Detection of serum CA-125, HE-4, and CEA diagnostic criteria

A total of 3 mL of venous blood was taken from all selected patients after 12 hours of fasting. Quantitative detection of serum CA-125 and CEA was performed by electrochemical method and HE-4 level was detected by enzyme-linked immunosorbent assay. Diagnostic criteria were as follows: serum CA-125 reference range  $< 35$  U/mL, HE-4 reference range  $< 121$   $\mu$ g/mL, and CEA reference range  $< 5$  ng/mL. Positive predictive value in the combined test higher than any one of the three single tests indicated that the test result was positive [1, 7].

#### Observation indicator

The main observation indicators of this research were sensitivity and specificity of the combination of serum CA-125, HE-4, and CEA in diagnosis of ovarian cancer. Secondary observation indicators included differences in serum level of CA-125, HE-4, and CEA between different groups (patients of ovarian cancer, normal control, and benign ovarian tumor) as well as their difference among different stages of ovarian cancer patients.

**Table 2.** Comparison of serum levels of CA-125, HE-4, and CEA in the three groups of patients

Group	Case	CA-125 (U/mL)	HE-4 (µg/mL)	CEA (ng/mL)
Study group	100	411.13±28.44* <sup>▲</sup>	568.22±218.11* <sup>▲</sup>	15.78±1.29* <sup>▲</sup>
Benign control group	100	24.37±2.16*	92.17±54.34	2.57±1.12
Healthy control group	100	13.94±1.14	82.17±35.67	1.51±0.53

Note: Compared with healthy control group, \*P<0.05; compared with the benign control group, <sup>▲</sup>P<0.05; CA-125, carbohydrate antigen 125; CEA, carcino-embryonic antigen; HE-4, human epididymis protein 4.

was no statistical significance in differences of age between the three groups of patients (P=0.522). See **Table 1**.

*Comparison of levels of CA-125, HE-4, and CEA between different groups*

**Table 3.** Indicators of CA-125, HE-4, CEA applied in clinical test results of three groups of patients (n, %)

Diagnostic indices	CA-125 (n=100)	HE-4 (n=100)	CEA (n=100)
Study group	87 (87.0)	68 (68.0)	81 (81.0)
Healthy control group	15 (15.0)	19 (19.0)	20 (20.0)
Benign control group	24 (24.0)	22 (22.0)	23 (23.0)
χ <sup>2</sup>	47.097	28.012	36.818
P	<0.001	<0.001	<0.001

Note: CA-125, carbohydrate antigen 125; CEA, carcino-embryonic antigen; HE-4, human epididymis protein 4.

Statistical analysis found that mean levels of CA-125, HE-4, and CEA in study group were higher than those in benign control group (all P<0.05) and healthy control group (all P<0.05, **Table 2**).

*Positive rate expression of CA-125, HE-4, and CEA in each group*

As shown in **Table 3**, positive rates of CA-125, HE-4, and CEA in the study group were higher than those in healthy control group and benign control group (all P<0.05).

*Diagnostic value of separate and combined detection of CA-125, HE-4, CEA in ovarian cancer*

Results showed that sensitivity of CA125 + HE-4 + CEA combined detection of ovarian cancer was higher than any of the three individual detections (P<0.05). See **Table 4**.

*Comparison of serum levels of CA-125, HE-4, and CEA between patients in each stage of ovarian cancer, benign tumor, and recurrence group*

Levels of CA-125, HE-4, and CEA in advanced stage tumor group were higher than those in early stage tumor group but there was no statistical difference with recurrent group. The three indicators in recurrent group were higher than those of healthy control group. See **Table 5**.

## Discussion

Epithelial ovarian cancer is the highest mortality cancer in obstetrics and gynecology. It is also the fifth leading cause of female deaths. The latest statistics show that, in 2016, there were 22,280 new cases worldwide with 14,240 deaths [9]. Similar to other tumors, early diag-

## Statistical methods

Statistical software SPSS22.0 was used to process the data. Measurement data are expressed as mean ± standard deviation ( $\bar{x} \pm sd$ ). Student's t-test of independent samples was used to compare the two groups. Multiple samples mean value was compared using one-way analysis of variance with post Bonferroni test. Chi-square test was used to compare the rate and Chi-square split test (test level  $\alpha=0.05/3=0.017$ ) was used to compare pairwise between each group. A difference of P<0.05 was considered statistically significant.

## Results

### *Basic information of the three groups of research subjects*

The average age of the study group was 56.60±7.13. There were 14 cases of stage I, 19 cases of stage II, 42 cases of stage III, and 25 cases of stage IV. All cases successfully completed the surgery. After six months of follow up, there were 55 cases of recurrence and 45 cases of non-recurrence. The average age was 56.10±6.72 in benign control group and 55.90±6.87 in healthy control group. There

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**Table 4.** Comparison of diagnostic significance of separate and combined detection of serum CA125, HE-4, CEA for ovarian cancer (%)

Marker	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
CA125	84.5	86.7	86.0	87.0	85.0
HE-4	78.2	81.0	74.5	68.0	81.0
CEA	80.2	80.8	80.5	68.0	80.0
CA125 + HE-4 + CEA	89.4*	85.6	87.5	85.0	90.0

Note: combined detection of the three indicators was more sensitive than any individual detection, \*P<0.05. CA-125, carbohydrate antigen 125; CEA, carcino-embryonic antigen; HE-4, human epididymis protein 4.

**Table 5.** Comparison of serum levels of CA-125, HE-4, and CEA between patients in each stage

Group	Case	CA-125 (U/mL)	HE-4 (µg/mL)	CEA (ng/mL)
Healthy control group	100	13.40±1.14	82.17±35.67	1.51±0.53
Benign control group	100	24.79±2.16	92.17±54.34	2.57±1.12
Early cancer group	40	245.71±45.46	318.49±129.11	10.10±1.47
Middle and late cancer groups	60	465.39±34.17*	543.22±199.56*	16.80±1.51*
Cancer recurrence group	55	442.55±42.49 <sup>▲</sup>	501.19±177.12 <sup>▲</sup>	15.70±2.11 <sup>▲</sup>

Note: Compared with early stage cancer group, \*P<0.05; compared with the healthy control group, <sup>▲</sup>P<0.05. CA-125, carbohydrate antigen 125; CEA, carcino-embryonic antigen; HE-4, human epididymis protein 4.

nosis of ovarian cancer is related with patient prognosis and long-term quality of life. Currently, tumor serological indicators used in this category mainly include: CA-125, CEA, and HE-4 [10-13].

CA-125 was the first serological indicator applied for early screening of ovarian cancer but some benign gynecologic diseases (e.g., endometriosis, pelvic inflammatory disease) have also resulted in elevated serological CA-125 values, leading to false positive results [14, 15]. Our research also confirmed that there is a statistically significant difference between CA-125 content in the benign control group and the healthy control group (P<0.05).

In view of the high false positive rate of CA-125, researchers began to search for more accurate serological indicators, with HE-4 gradually entering the field of vision. HE-4, known as WAP four-disulfide core domain protein 2, is a whey acidic protein extracted from distal epithelia of epididymis. Its physiological role remains unclear but it may be involved in immune regulation and promoting germ cell maturation [16, 17]. HE-4 remains unexpressed or lower expressed in normal ovarian tissue and para-cancerous tissue but is highly expressed in ovarian tumor tissue [18]. Some studies have confirmed that HE-4 is positively correlated with clinical stage of the tumor as expression of

HE-4 in advanced stage ovarian cancer tissue is significantly higher than in early stage tumor tissue and normal ovarian tissue [19]. Our data also supports the above view. HE-4 can be used as an indicator for ovarian cancer diagnosis and monitoring of recurrence. Consistent with foreign studies, however, we also found that sensitivity of HE-4 diagnosis was relatively inadequate [20].

CEA is a carcinogen antigen of embryo, most widely used in the detection of gastrointestinal tumors. Although its characteristics are not very strong, its sensitivity to epithelial ovarian cancer is quite high. The statistical results of our study confirm this. Therefore, CEA is an important serological indicator for joint diagnosis of cancer [7].

Our results show that the curve area of combined CA-125, CEA, and HE-4 diagnosis is significantly higher than single detection and its sensitivity is also significantly higher than any one of the three indicators detection. This demonstrates that three indicators combined for detection could further improve the level of pre-operative diagnosis of ovarian cancer and provide more accurate diagnostic information for clinical diagnosis. In addition, the three indicators CA-125, CEA, and HE-4 are easy to obtain and simple to operate, with less cost. They can be applied as a clinical screening method for

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early stage ovarian cancer. They are worthy of promotion and practice for frontline clinical use.

In conclusion, diagnostic significance of the combination detection of CA-125, CEA, and HE-4 in ovarian cancer diagnosis is higher than any single indicator detection. Specificity of the three-combination detection, however, is slightly decreased. Therefore, clinical practice should be alerted concerning false positives. In addition, clinical practical applications are still lacking large samples of clinical research. Samples for repeated verification studies should be expanded to compensate for this shortcoming.

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### Disclosure of conflict of interest

None.

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