RESEARCH ARTICLE

Clinical Significance of Combined Detection of Serum Tumor Markers in Diagnosis of Patients with Ovarian Cancer

Jing Bian[1], Bo Li[2], Xian-Juan Kou[3]*, Tian-Zhou Liu[1], Liang Ming[1]*

Abstract

Objective: To explore the predictive value of tumor markers, including cancer antigen 72-4 (CA72-4), cancer antigen 15-3 (CA15-3) and cancer antigen 125 (CA125), in single or combined detection, for the diagnosis of ovarian cancer. Methods: 120 patients diagnosed with ovarian cancer from August 2011 to March 2013 and 80 patients diagnosed with benign ovarian tumors were enrolled in this test, along with 50 health examination women randomly selected from the database as controls. Serum levels of CA72-4, CA15-3 and CA125 in this study were determined by electrochemiluminescence (ECL). Results: Serum levels of CA72-4, CA15-3 and CA125 in ovarian cancer were higher than those in healthy group and benign group ($P<0.01$).The sensitivity of combined detection of those three tumor markers for diagnosis of ovarian cancer was obviously higher than with single detection with each marker ($P<0.01$). Conclusions: CA72-4, CA15-3 and CA125 could be a good combination in the diagnosis of ovarian cancer. Patients whose tumor markers continue to increase should be highly suspected of malignancy.

Keywords: Combined detection - tumor markers - ovarian cancer - CA 72-4 - CA 15-3 - CA 125

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Introduction

Ovarian cancer is the third most common malignancy, but has the highest lethallty rate in women (Foley et al., 2013). It has developed into a long-standing and serious problem for women. The majority patients are diagnosed at stage III and IV as the tumor lacks specific symptoms at an early stage (Foley et al., 2013). The 5-year survival rate in women at the advanced stage is less than 15%, whereas it will be 90% if it detected in early stage (Hall et al., 2013). Therefore, early detection could bring better outcomes in women.

The clinical diagnosis of ovarian cancer depends on the clinical findings and image examination, however, ovarian cancer can hardly be diagnosed at early stage (Foley et al., 2013; Frede et al., 2013). Nowadays we diagnosed ovarian cancer by cytological diagnosis and histopathologic biopsy, which have higher specificity but lower sensitivity. So many patients lost the best therapy time as mentioned above. So early detection and early diagnosis of ovarian cancer is critical for clinical treatment. With the deepening of research on tumor, some new detection means constantly used in clinical, including tumor markers. The experiment detected the serum level of cancer antigen 72-4 (CA72-4), Cancer antigen 15-3 (CA15-3), Cancer antigen 125 (CA125) in ovarian cancer patients, to evaluate clinical value of combined detection of the three tumor markers in ovarian cancer.

Materials and Methods

Table 1 shows the tested groups. 120 women newly diagnosed with ovarian cancer in our hospital during the period of August 2011 to March 2013, Clinical stages and histological classification based on the criteria of the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) were established in all cases. The ovarian cancer histopathology was established in all cases by tissue biopsy of tumor or after surgery treatment from tumor cancer tissues. 80 patients diagnosed with benign ovarian tumor were enrolled in the study, all had to be confirmed benign or malignant by histology or cytology, and did not receive radio-chemotherapy.The average age of cancer patients are 56, benign patients are 54. 50 case Healthy control are randomly selected from Physical examination in our hospital women staff members, whose average age are 57. Specimen collection 3ml venous blood from specimens were obtained in cancer group, benigh group and healthy control from the empty stomach. After centrifugation, serum samples were was stored at -20°C until analysis.

Serum level of CA72-4, CA15-3 and CA125 were detected by electrochemiluminescence (ECL). Reagents were provided by Roche Group. The experiment was operated according to the instruction and operation manual. Critical values of CA72-4, CA15-3 and CA125 seperated were 6.9 U/ml, 25 U/ml and 35 U/ml.

*[1]Department of Laboratory, The First Affiliated Hospital of Zhengzhou University, [2]The Stem Cells Research Center, Medical College of Zhengzhou University, Zhengzhou, Henan Province, [3]College of Health Science, Wuhan Sports University, Wuhan, Hubei Province, China *For correspondence: shallyvans@hotmail.com, shallyvans@126.com.*

Table 1. Characteristics of Ovarian Cancer Patients

Group	Number of patients
Ovarian cancer patients	120 (100%)
Median age (range)	56 (45-79)
Tumor stage	
IA-T1aN0M0	12 (10%)
IB-T1bN0M0	10 (8.3%)
IC-T1cN0M0	12 (10%)
IIA-T2aN0M0	8 (6.7%)
IIB-T2bN0M0	9 (7.5%)
IIC-T2cN0M0	9 (7.5%)
IIIA-T3aN0M0	10 (8.3%)
IIIB-T3bN0M0	9 (7.5%)
IIIC-T3cN0M0	12 (10%)
IV (metastases)	29 (24%)
Menopausal status:	
postmenopausal	120 (100%)
Benign ovarian tumor patients	80 (100%)
serous cystadenoma	30 (37.5%)
mucinous cystadenoma	25 (31.25%)
mature teratoma	25 (31.25%)
Median age (range)	54 (48-70)
Menopausal status:	
postmenopausal	80 (100%)
Healthy control	50 (100%)
Median age (range)	55 (47-65)
Menopausal status:	
postmenopausal	50 (100%)

Table 2. Serum Level of CA72-4, CA15-3 and CA125 in Healthy Control, Benigh Group and Malignancy Group (Mean±SD)

Groups	CA72-4 (u/ml)	CA15-3 (u/ml)	CA125 (u/ml)	
Malignancy group				
Stage I	12.9±6.3	40.6±14.1	45.2±10.1	**
Stage II	16.1±5.2	45.3±13.3	47.8±12.7	**
Stage III	20.3±6.6	56.7±24.6	78.5±11.6	**
Stage IV	19.6±10.6	61.8±30.0	69.3±14.1	**
Total group	12.5±7.6	50.4±20.4	87.6±34.2	**
Benigh group	4.1±3.2	21.7±11.2	33.5±19.1	
Healthy control	3.9±1.5	13.5±5.6	16.3±13.6	

**statistically significant when comparing patients with benign

Table 3. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of Tumor Markers in Ovarian Cancer (%)

Ovarian cancer	Diagnostic items (100%)	CA72-4	CA15-3	CA125
Stage I	Sensitivity	31.3	34.6	31
	Specificity	69.1	60.3	90.7
	PPV	63.1	71	69.4
	NPV	67.3	78.9	69.5
Stage II	Sensitivity	29.6	36.9	32.3
	Specificity	73.2	67.5	85.1
	PPV	66.7	71.3	79.4
	NPV	61	78.3	56.3
Stage III	Sensitivity	32.7	40	48.6
	Specificity	70.1	87.6	78.4
	PPV	67.8	89.6	84.7
	NPV	60.3	41.3	56.9
Stage IV	Sensitivity	34.2	46.3	47.9
	Specificity	71.3	88.2	81.2
	PPV	70.3	84.2	79.4
	NPV	54.6	39.6	41.7
Total group	Sensitivity	39.6	45.6	41.2
	Specificity	76.2	84.6	83.4
	PPV	75.6	80.3	82.4
	NPV	39.8	46.3	42.9

Table 4. Sensitivity and Specificity of Combined of CA72-4, CA15-3 and CA125 for Ovarian Cancer Diagnosis

Ovarian cancer	Diagnostic criteria (100%)	CA72-4 +CA15-3	CA72-4 +CA125	CA15-3 +CA125	CA72-4 +CA15-3+ CA125	
Stage I	Sensitivity	80.6	79.9	80.2	83.7	**
	Specificity	71.3	71.6	70.3	70.9	
Stage II	Sensitivity	87.6	80.6	84.6	84.5	**
	Specificity	70.4	76.3	72.5	71.8	
Stage III	Sensitivity	87.6	83.7	87.3	89.3	**
	Specificity	70.3	76.5	71.7	74.5	
Stage IV	Sensitivity	84.5	85.6	87.6	85.1	**
	Specificity	70	73.2	74.9	70.2	
Total group	Sensitivity	85.6	81.1	86.1	88.6	**
	Specificity	70.2	74.6	73.4	71.6	

**statistically significant when comparing with single detection of each marker (P<0.01)

The data were analyzed by normal distribution, non-parametric test (Non-Normal Data Distribution) , Positive Rate Among groups was compared by χ^2 test; serum level of tumor markers among groups were compared by ANOVA or Wilcoxon rank sum test. Date analysis were performed by SPSS13.0 Statistical Analysis Software. It was p<0.05 statistically significant difference.

Results

Serum levels of CA72-4, CA15-3 and CA125 in cancer group, benigh group and healthy control were showed in Table 2.The serum levels of tumor markers in cancer group were significantly higher, compared with benigh group and healthy control, a statistically significant difference (p<0.01); Compared benigh group with healthy control , however, was not statistically significant (p>0.05, Table 2).

Table 3 showed sensitivity and specificity of tumor markers in ovarian cancer, simple for ovarian cancer, CA125 has relatively higher specificity for diagnosis, up to 90.7%.

Sensitivity and specificity of combined of CA72-4, CA15-3 and CA125 for ovarian cancer diagnosis were showed in Table 4. We considered Joint Detection of those three tumor markers for ovarian cancer diagnosis , owing to the lowest sensitivity of single tumor marker. We set four combinations modes, CA72-4 plus CA15-3, CA72-4 plus CA125, CA15-3 plus CA125, any couple of the three markers, and the last mode, CA72-4, CA15-3 plus CA125. We found any couple of the tumor markers has higher sensitivity than single marker, p<0.01.

Discussion

An ideal serum tumor marker for early diagnosis of cancer should have the following characteristics.

1. Sensitive enough to detect scattered tumors the first time.

2. Specificity enough to detect a given type of cancer, and not appeared in non-cancer (healthy and benign) region, or released only in response to cancer but not inflammation or any other pathologic disease.

Nowadays, most serum tumor markers are neither sensitive nor specific enough for cancer diagnosis. Clinical laboratory echnicians found that combined tumor markers has relatively higher sensitivity in daily work. Researchers found that combined detection had great value in the diagnosis, analysis of effect, recurrence detection and prognosis of cancer (Duffy et al., 2013; Li et al., 2013; Sisik et al., 2013; Wang et al., 2013; Yu et al., 2013).

CA125 is one of the tumor marker in hybridoma family, the most widely used serum marker in the detection of ovarian tumor from surface epithelium (Radka et al., 2013). Normal ovary (Adult and fetal) epithelial cells are not expressed. Threshold concentrations of CA125 in healthy person are below 30 U/mL (Scholler et al., 2007). CA125 levels are increased in 80%-85% of women in the advanced stages of ovarian cancer. Elevated serum levels of CA125 are related with cancer patients such as ovarian cancer, gastric cancer and breast cancer, etc (Bast et al., 1981). In ovarian cancer patients, CA125 could be coming down soon after operation or effect chemotherapy, recurrence of ovarian cancer may be detected through elevated levels of CA125 in the blood—long before clinical symptoms, However, elevated serum levels of CA125 are associated with benigh diseases such as Pelvic Inflammation, Endometriosis, ovarian cyst, even tuberculosis, due to the lack of a strongly specificity (O'Brien et al., 2001; Yin et al., 2001).

CA72-4, a high molecular weight glycoprotein, which highly increases in the benigh disease as below, pancreatitis, cirrhosis, pulmonary disease, rheumatism, and so on (Mizumoto et al., 2010). It has hyper specificity in benigh disease. It has reported that CA72-4 has tremendous value in detection of residual tumors. long-term follow-up investigation found that Continuously rising level of CA72-4 could be a marker of residual tumors (Zheng et al., 2001).

Higher level of CA15-3 could be detected in women with breast cancer or ovarian cancer, it is a mucin belonging to glycoprotein family encoded by the MUC 1 gene , CA 15-3 could be associated with poor outcome. It is reported that worse prognosis in cancer patients due to high level of CA15-3, and CA15-3 is one of the early discovering prognostic factors and the widely used tumor marker in cancer (Ruibal et al., 2012).

Our research found that serum levels of tumor markers mentioned above is obviously higher in cancer patient than in benigh and healthy individuals, simple for ovarian cancer, One of the three markers, CA125, has relatively higher specificity for ovarian cancer diagnosis, almost reach 91%, though the three markers in single have relatively high specificity for cancer detection, they all have common shortcoming- low sensitivity. In order to improve the sensitivity of first visit ovarian cancer , we used combined detection, after combination, we found that there was little diffrence in specificity but significantly variation in sensitivity.

Furthermore, CA72-4, CA15-3 and CA125 may have better clinical application for first visit ovarian cancer diagnosis and differential diagnosis, and in practical work, reasonable tumor marker combinations have cost-effective alternatives for patients. The combination detection could have significance for diagnosis and histological classification of early ovarian cancer.

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