The value of mesothelin in the diagnosis and follow-up of surgically treated ovarian cancer

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Summary

Objective: To assess the value of serum mesothelin concentration for diagnosis of ovarian cancer and for monitoring the therapeutic effect of surgical treatment. *Materials and Methods:* The study consisted of 42 patients with ovarian cancer undergoing surgery, 48 with benign ovarian tumors, and 49 healthy controls. Blood was drawn pre-operatively and one month post-operatively to test serum mesothelin levels. *Results:* Mesothelin values were higher in the ovarian cancer group compared to controls and higher pre-operatively vs post-operatively in the ovarian cancer group. For the diagnosis of ovarian cancer, the positive predictive value of serum mesothelin was 80.5%, the negative predictive value was 81.6%, sensitivity was 78.6%, and specificity was 83.3%. *Conclusion:* Serum mesothelin is increased in ovarian cancer, has high-specificity, and can be used in the pre-operative diagnostic evaluation for ovarian cancer.

Key words: Mesothelin; Ovarian cancer.

Introduction

Ovarian cancer is a severe disease that threatens the health and lives of many women; in the United States, for example, the incidence and mortality rates of ovarian cancer are ranked fifth and fourth among cancers, respectively [1]. The five-year survival rate after a diagnosis of ovarian cancer is about 30%, but 85% or more of those who survive > five years are diagnosed with Stage I ovarian cancer [2]. To increase the survival rate and quality of life of women with ovarian cancer, it is necessary to improve the rate at which early-stage ovarian cancer is diagnosed.

In recent decades, some serum biomarkers such as CA 125, HE4, CA72-4, CA15-3, glycodelin, MMP7, SLP1, Plau-R, and Muc-1 have been studied in the diagnosis of ovarian cancer. Of these, CA 125 is the most extensively-examined predictive marker [3-5], but it is elevated only in about 50%-60% of patients with early-stage ovarian cancer. Furthermore, it has a low specificity [6], and its positive predictive value is < 10% as a single marker; the addition of ultrasound screening to measurements of CA 125 improves the positive predictive value to approximately 20% [7]. HE4 is effective for ovarian cancer detection [8, 9] and has received approval from the US Food and Drug Administration (FDA) as a recurrence-monitoring marker. Limited information suggests that rising HE4 could detect a recurrence earlier than CA 125 [9, 10].

Because of the limited sensitivities and specificities constraining the use of CA 125, HE4, and other biomarkers, new technologies for the detection of early-stage ovarian cancer are needed. One possible candidate is mesothelin, a plasma membrane differentiation antigen that is strongly-expressed in mesothelial cells and has been suggested as a marker for ovarian cancer diagnosis [11, 12] or remission monitoring [9]. The goal of this study was to evaluate if mesothelin is independently effective in monitoring disease diagnosis and remission.

Materials and Methods

Subjects

The Ethics Committee of the Shandong University Qilu Hospital approved the research protocol. Informed consent was obtained from each of the patients and control participants.

A total of 126 women were hospitalized for an "ovarian tumor" from January 2011 to March 2012 who intended to undergo surgical intervention were randomly selected as study subjects. Of these, 49 women were diagnosed with ovarian cancer, 64 were diagnosed with a benign ovarian tumor, and 13 women were diagnosed with other diseases.

Women with ovarian cancer and benign ovarian tumors were excluded if they had received hormone therapy or chemotherapy or their condition occurred in combination with other malignancies. After screening, the ovarian cancer group included 42 patients: eight (19%) FIGO Stage I cases, 12 (29%) FIGO Stage II cases, 15 (36%) FIGO Stage III cases, and seven (17%) FIGO Stage IV cases. All participants were Asian Chinese. The cancers had different histological types, as follows: serous papillary carcinoma (n = 29), endometrioid carcinoma (n = 2), mucinous carcinoma (n = 4), clear cell carcinoma (n = 6), and mixed cystadenocarcinoma (n = 1). Another 48 women with benign ovarian tumors were recruited for the benign ovarian tumor group. These patients also had different histological types, as follows: serous cystadenocarcinoma (n = 18), mucinous cystadenocarcinoma (n = 9), mixed cystadenocarcinoma (n = 2), and simple ovarian cyst

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Table 1. — *Demographics and clinical characteristics of the study population*.

Characteristics	Ovarian cancer Stage I/II (n = 20)	Ovarian cancer Stage III (n = 15)	Ovarian cancer Stage IV (n = 7)	Normal (n = 49)	Ovarian benign tumor (n = 48)
Age (years)					
Mean (SD)	55.1 (2.8)	57.7 (2.4)	58.9 (1.4)	53.2 (2.6)	51.9 (3.1)
Range	47-59	52-61	55-62	46-58	44-60
Age distribution					
< 55	11 (55%)	5 (33%)	1 (14%)	30 (61%)	40 (83%)
> 55	9 (45%)	10 (67%)	6 (86%)	19 (39%)	8 (17%)
Histology					
Serous	15 (35.7%)	10 (23.8%)	4 (9.5%)		
Mucinous	3 (7.1%)	1 (2.4%)	0		
Clear cell	0	4 (9.5%)	2 (4.8%)		
Endometrioid	2 (4.8%)				
Mixed cystadeno-carcinoma		1 (2.4%)			

(n = 19). Finally, 49 healthy, age-matched individuals who had undergone medical examinations in this hospital were recruited for the healthy control group. Table 1 gives the demographics and clinical characteristics of the study population. Diagnoses of ovarian cancer and ovarian benign tumors were made by pathologists after surgery.

Serum samples

Blood samples from patients were collected before surgical intervention and at one month after surgery. Blood was collected in a clotting tube, and within four hours of collection, clotted blood was centrifuged at 2,000 ×*g* for ten minutes, then serum was aliquoted and stored at −80°C until assayed.

Determination of mesothelin

Soluble mesothelin concentrations were determined in duplicate following the manufacturer's instructions using a double determinant ELISA assay. Mesothelin concentrations were determined from a standard curve performed on each plate and expressed as nM. Dilution of samples was carried out if necessary using the diluent supplied by the manufacturer. All assays were performed on coded samples by technical staff unaware of each patient's diagnosis. A serum mesothelin value greater than or equal to 2.5 nM was considered to be positive [13, 14].

Statistical analysis

Laboratory measurements of mesothelin were analyzed and are presented as means ± standard deviation. Comparisons between groups were performed using one-way ANOVA. Comparisons between the ovarian cancer pre-operative values and ovarian cancer post-operative values were made using paired t-tests. Homogeneity of sample variances was assessed using the homogeneity test of variances. All statistical analyses were performed using GraphPad Prism 3.0. A p value of < 0.05 was considered statistically significant.

Results

Comparison of serum mesothelin among different groups

Serum mesothelin was significantly elevated in malignant cases (3.91 ± 1.08 nM) compared to healthy controls (0.43 ± 0.35 nM), and in malignant compared to benign cases (0.99 ± 0.52 nM) ($p < 0.05$). In addition, post-operative mesothelin values (2.82 ± 0.64 nM) were significantly lower than pre-operative values (3.91 ± 1.08 nM) in the ovarian cancer group ($p < 0.05$).

Analysis of the diagnosis value of serum mesothelin

The positive-negative cutoff for serum mesothelin was 2.5 nM; any value greater than or equal to 2.5 nM was considered positive. In the benign tumor group, eight of 48 patients were mesothelin-positive; in the ovarian cancer group, however, 33 of 42 met or exceeded the cutoff value. The positive predictive value of serum mesothelin was 80.5%, the negative predictive value was 81.6%, sensitivity was 78.6%, and specificity was 83.3%.

Discussion

Here the authors investigated whether a newly-discovered cell-surface glycoprotein, mesothelin, can be independently effective in monitoring disease diagnosis and remission in ovarian cancer. Pre-operative serum mesothelin values for the ovarian cancer group were significantly higher than in healthy controls while post-operative serum mesothelin was significantly higher in the ovarian cancer group than in healthy controls. Values for the benign tumor group did not differ from those of healthy controls. For the diagnosis of ovarian cancer, the positive predictive value of serum mesothelin was 80.5%, the negative predictive value 81.6%, the sensitivity 78.6%, and the specificity 83.3%. The results indicate that serum mesothelin is increased in ovarian cancer and can be used in diagnostic evaluation.

In the re-examination at one month post-operatively for ovarian cancer patients, serum mesothelin was significantly lower than pre-operative values in the cancer patient group. The result indicates that serum mesothelin has a significant value in the surveillance of surgical therapeutic effect. Because of the limited number of cases and short follow-up, further study is ongoing regarding the use of this marker as an early warning in relapsed patients.

In summary, serum mesothelin measurement has a significant value in diagnostic distinction of epithelial ovarian benign and malignant tumors, and dynamic surveillance of serum values is a convenient way to monitor the surgical effect.

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