Pre-Operative Prediction of Serum CA125 Level in Women with Ovarian Masses

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Objective: *To assess the accuracy of serum CA125 at the level of more than 35 U/mL in predicting ovarian cancer, using histopathology as a gold standard.*
Material and Method: *Blood samples were obtained from 120 women with ovarian masses scheduled for elective surgery at Siriraj Hospital between October 1, 2003 and August 31, 2004 and sent for the assay of serum CA125 levels.*
Results: *Of the 120 women enrolled, ovarian cancer was found in 59 cases (49.2%) and benign ovarian mass in 61 cases (50.8%). The sensitivity, specificity, and accuracy of serum CA125 at the cutoff level of 35 U/mL for prediction of ovarian cancer were 83.1%, 39.3%, and 60.8%, respectively; with 57.0% positive predictive value, 70.6% negative predictive value, 60.7% false positive rate, and 16.9% false negative rate.*
Conclusion: *As stand-alone modality, serum CA125 of more than 35 U/mL in predicting ovarian cancer revealed modest diagnostic accuracy. There is a need to be careful for false positive in women at reproductive age group and false negative results in early-stage disease or ovarian cancer with low level of serum CA125.*

Keywords: *Serum CA125, Ovarian mass, Ovarian cancer*

J Med Assoc Thai 2007; 90 (10): 1986-91
Full text. e-Journal: *http://www.medassocthai.org/journal*

Ovarian cancer is the sixth most common cancer in women worldwide and is the leading cause of death among gynecologic malignancies in Western Europe and North America. In Thailand, ovarian cancer is the second most common cancer of the female genital tract after cervical cancer with an annual incidence of 5.6 per 100,000 women, and a death rate of 2.6 per 100,000 women per year[1]. Due to the often asymptomatic nature of the early stage of disease, many cases of ovarian cancer present in the advanced stage for which the 5-year survival rate remains low[2]. Less than one-third of patients with ovarian cancers have been diagnosed before the tumor cells have spread[3]. It is beyond an obvious indictment of the authors' ability to detect the condition in its earliest stages. Thus, when suspicious evidence of ovarian mass has been found, the importance lies in the fact that it could be malignant. Several attempts have been made to discriminate these conditions for an appropriate operation at the time of initial exploration, eliminating the morbidity and expense of a second procedure. Clinicians have a wide range of investigations that are helpful in the diagnosis of ovarian cancer such as pelvic examination, ultrasonography, and tumor markers levels. One of the most distinguished and reliable tumor markers is Carbohydrate Antigen 125, or CA125.

The estimation of clinical value of CA125 in pre-operative diagnosis and monitoring of ovarian malignancies has been mentioned. Available data suggests that CA125 is elevated in the majority of epithelial ovarian malignancies prior to clinical presentation. Large screening trials for ovarian cancer indicated the use of serum CA125 cutoff value at higher than 35 U/mL as suggesting malignancy[4-9]. Therefore, the level of 0-35 U/mL of serum CA125 has been used as normal value in most service laboratories including the immunology laboratory, Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University.

The present study then aimed to assess the accuracy of serum CA125 level at more than 35 U/mL in

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preoperative differentiation of ovarian cancer from benign ovarian disease in women who presented with an ovarian mass.

Material and Method

From October 1, 2003 to August 31, 2004, 120 consecutive women with an ovarian mass were admitted to the Division of Gynecology, Department of Obstetric and Gynecology, Faculty of Medicine Siriraj Hospital to undergo diagnostic laparotomy. They were recruited in the present study after having been approved for the inclusion criteria.

After the protocol was accepted by Ethical Committee of Faculty of Medicine Siriraj Hospital, the patients were counseled and invited to join the present study with informed consent. Peripheral venous blood samples were drawn for CA125 study within 1 week before the operation. The blood was centrifuged right after drawing at 1,000 rpm for 10 minutes then serum was collected and stored at -20°c before assay. Serum CA125 was analyzed by electrochemiluminescence using a commercial kit, Elecsys CA125 II (Roche, Indianapolis, USA). The inter-assay and intra-assay coefficients of variation were less than 10%. The detection limit of the assay was 0-3 U/mL. Patients, who did not agree to participate, had a known case of prior malignancy or recurrent ovarian cancer, as well as pregnancy with ovarian mass, were excluded from the present study.

All women who entered into the present study then underwent the exploratory laparotomy according to the indicated procedures followed by the successful operations. Patients with invasive or borderline ovarian cancers, as well as other unexpected gynecologic malignancies, received surgical resection and complete surgical staging if localized diseases were present. The pathological analysis of all surgical specimens for the gold standard or definite diagnosis of each case was performed by the same gynecologic pathologists.

The accuracy of serum CA125 at the cutoff level of 35 U/mL in differentiating a benign ovarian mass from ovarian cancer was evaluated by descriptive statistical analysis. The sensitivity, specificity, positive and negative predictive values were analyzed at 95% confidence interval. False positive and negative rates, accuracy, and prevalence were calculated.

Results

One hundred and twenty women with ovarian mass had peripheral venous blood drawn for CA125 study and underwent surgery. The patients' age ranged from 18 to 91 with a mean of 46 $\pm$ 14 years. Half of the patients (51%) were nulliparous and more than one-third (41%) were in the postmenopausal period. Benign ovarian masses were found in 51% (61/120) of the patients, while 49% (59/120) had a malignant ovarian tumor of which, one-third (36%) were in advanced-stage disease. The distribution of types of ovarian masses and serum CA125 level including mean, standard deviation, median, and range are shown in Table 1.

With a cutoff level of 35 U/mL of serum CA125 as the discriminator between benign and malignant ovarian masses, the sensitivity and specificity were 83.1% (95%CI, 71.5-90.5) and 39.3% (95%CI, 28.1-51.9), respectively. The positive predictive value was 57.0% (95%CI, 46.4-66.9) and the negative predictive value was 70.6% (95%CI, 53.8-83.2) with a false positive and negative rate of 60.7% and 16.9%, respectively. The accuracy rate of this serum CA125 level was 60.8% (Table 2).

Table 1. Distribution of types of ovarian masses and serum CA125 level

Ovarian mass	N	%	Serum CA125 (U/mL)					
			N ($\leq$ 35)	N (> 35)	Mean	SD	Median	Range
Benign ovarian mass	61	50.8	24	37	104.3	184.7	50.9	8.7-1093.0
Benign ovarian tumor	14	11.7	9	5	105.5	284.9	23.6	9.2-1093.0
Tumor-like conditions	47	39.1	15	32	104.0	184.7	51.0	8.7-911.9
Ovarian cancer	59	49.2	10	49	879.5	1356.0	230.9	6.6-6123.0
Common epithelial tumor	51	42.5	10	41	913.3	1378.8	230.9	6.6-6123
Stromal tumor	2	1.7	0	2	250.3	46.0	230.3	197.5-262.8
Germ cell tumor	3	2.5	0	3	1389.2	2077.7	155.7	155.7-3788.0
Other tumors	3	2.5	0	3	228.6	36.7	233.7	188.4-263.8
Total	120	100.0	34	86	485.5	1031.9	92.0	6.6-6123.0

Table 2. Contingency table arranged to show the prediction of malignant ovarian tumor by serum CA125 at the cutoff level of 35 U/mL*

Serum CA125	Histopathology		Total
	Ovarian cancer	Benign ovarian mass	
> 35 U/mL	49	37	86
≤ 35 U/mL	10	24	34
Total	59	61	120

* sensitivity = 83.1% (49/59); specificity = 39.3% (24/61); positive predictive value = 57.0% (49/86); negative predictive value = 70.6% (24/34); false positive rate = 60.7% (37/61); false negative rate = 16.9% (10/59)

Serum CA125 at the cutoff level of 35 U/mL was found to be better in distinguishing ovarian cancer from a benign ovarian tumor than tumor-like conditions with increased specificity, positive predictive value, and accuracy (Table 3). The sensitivity, specificity, positive predictive value, and accuracy of serum CA125 were also improved in differentiating adnexal mass in postmenopausal women compared to the premenopausal group (Table 4).

Discussion

Ovarian tumors cause common diagnostic and management problems to the physicians. The problem of pre-operative diagnosis of benign or malignant nature of ovarian masses has not yet been completely solved. Various diagnostic procedures have been used including physical examination, gray-scale ultrasound[10-12] and tumor markers such as CA125[8,13-15]. Surgery can be optimally planned if it is known beforehand whether an ovarian neoplasm is benign or malignant. The type of operation and the experience of the surgeon are important factors for the prognosis of ovarian cancer[16].

CA125 antigen is a glycoprotein with a high molecular weight and is recognized by a monoclonal antibody (OC-125). It is expressed in the amnion and embryonic coelomic epithelium[5]. The antigen can also be in many adult tissues such as the epithelium of the fallopian tubes, endometrium, endocervix, and ovaries[17]. In addition, it is found in mesothelial cells of the pleura, pericardium, and peritoneum. Therefore,

Table 3. The prediction of ovarian cancer at the cutoff level of 35 U/mL of serum CA125 in comparison between tumor-like conditions and benign ovarian tumor

	Tumor-like conditions and Ovarian cancer (n = 106)	Benign ovarian tumor and Ovarian cancer (n = 73)
Sensitivity	83.1% (95%CI, 71.5-90.5)	83.1% (95%CI, 71.5-90.5)
Specificity	31.9% (95%CI, 20.4-46.2	64.3% (95%CI, 38.8-83.7)
Positive predictive value	60.5% (95%CI, 49.6-70.4)	90.7% (95%CI, 80.1-95.9)
Negative predictive value	60.0% (95%CI, 40.7-76.6)	47.4% (95%CI, 27.3-68.3)
False positive rate	68.1% (95%CI, 53.8-79.6)	35.7% (95%CI, 16.3-61.2)
False negative rate	16.9% (95%CI, 9.5-28.5)	16.9% (95%CI, 9.5-28.5)
Accuracy	60.4% (95%CI, 50.9-69.2)	79.5% (95%CI, 68.8-87.1)

Table 4. The prediction of ovarian cancer at the cutoff level of 35 U/mL of serum CA125 in comparison between premenopause and postmenopause

	Premenopause (n = 71)	Postmenopause (n = 49)
Sensitivity	81.5% (95%CI, 63.3-91.8)	84.4% (95%CI, 68.2-93.1)
Specificity	31.8% (95%CI, 20.2-46.6)	58.8% (95%CI, 36.0-78.4)
Positive predictive value	42.3% (95%CI, 29.9-55.8)	79.4% (95%CI, 63.2-89.7)
Negative predictive value	73.6% (95%CI, 51.2-88.2)	66.7% (95%CI, 41.7-84.8)
False positive rate	68.2% (95%CI, 53.4-80.0)	41.2% (95%CI, 21.6-64.0)
False negative rate	18.5% (95%CI, 8.2-36.7)	15.6% (95%CI, 6.9-31.8)
Accuracy	50.7% (95%CI, 39.3-62.0)	75.5% (95%CI, 61.9-85.4)

some normal body tissues can produce a certain and low level of circulatory or serum CA125. This tumor marker is found elevated during menstruation or pregnancy and in some benign conditions such as endometriosis, peritonitis, or cirrhosis, particularly with ascites[6,18]. It is also increased in vascular invasion, tissue destruction and inflammation associated with malignant disease. Serum CA125 is significantly elevated in over 90% of patients with advanced epithelial ovarian cancer and approximate 40% of overall cases with advanced intra-abdominal malignancies[19].

The diagnostic value of serum CA125 in distinguishing a benign from a malignant ovarian mass has been demonstrated in the literature with a sensitivity ranging from 56%-100% and a specificity ranging from 60%-92% according to the selected cutoff values and pre- or postmenopausal status of the patients[7,9,15,20,21]. The cutoff level of 35 U/ml as reported by several studies has been used as a screening test for ovarian cancer in asymptomatic women[6-9,18,19]. The reliability of clinical use of this level needed to be evaluated in patients with ovarian mass.

The sensitivity of 83.1% in the present study is within the range mentioned above; however, the specificity of 39.3% is somewhat lower than those previously reported. Thirty-seven women in the presented series had false positive results (a benign ovarian mass with serum CA125 > 35 U/mL) and 10 had false negative results (an ovarian cancer with serum CA125 < 35 U/mL), giving the false positive and false negative rate of 60.7% and 16.9%, respectively. Tumor-like conditions were the most common in the false positive group with 26 endometriosis, 4 pelvic inflammatory diseases, and 2 functional cysts. A recent published study has shown that elevated serum CA125 (> 35 U/mL) could be found in many benign conditions such as menstruation, pregnancy, functional cyst, pelvic infection, and endometriosis[6,7,15,20,22-24]. Since these conditions are more likely to occur in a woman in reproductive age, so determination of serum CA125 is more specific in predicting ovarian cancer when it is used in postmenopausal woman with pelvic mass[15]. The present findings are consistent with those mentioned in the literature. Among the benign ovarian tumors, five cases were interpreted as malignancy due to serum CA125 level of higher than 35 U/mL. Four out of the five cases had slightly increased serum CA125 while the other with Meigs' syndrome had markedly elevated serum CA125 level (1093 U/mL). This benign tumor, subsequently classified as fibroma with prominent ascites in the present study, had also been reported elsewhere in the literature to cause highly elevated serum CA125[25]. Ten women in the present series had their ovarian masses misinterpreted as benign (serum CA125 < 35 U/mL). Jacob et al demonstrated that elevated serum CA125 (> 35 U/mL) could be detected in approximately 50% of patients with stage I and in more than 90% of those with advanced disease[6]. Gadducci et al reported that mucinous tumors expressed CA125 less frequently than non-mucinous ones[22]. The observation that all women with false negative results in the present study had stage I ovarian cancer, half of which were mucinous type; is similar to those previously reported.

The main limit of serum CA125 is that it may be high in benign diseases, especially in the reproductive age. To increase the discriminative power of evaluating the risk of ovarian cancer in a woman with ovarian mass, many studies have stressed the usefulness of the combination of serum CA125 level with menopausal status, pelvic ultrasonography, and other surum tumor markers[11,20,26-28]. The present results demonstrated that the reliability of serum CA125 level for predicting ovarian cancer in a woman with ovarian mass increased after the authors excluded tumor-like conditions and evaluated in postmenopausal woman.

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การใช้ค่า serum CA-125 ในการทำนายมะเร็งรังไข่

มงคล เบญจาภิบาล, ชานนท์ เนื่องตัน

วัตถุประสงค์: *เพื่อประเมินความถูกต้องของค่า serum CA-125 ที่มีค่ามากกว่า 35 U/mL ในการทำนายก้อนที่รังไข่โดยเปรียบเทียบกับผลการตรวจชิ้นเนื้อทางพยาธิวิทยา*

วัสดุและวิธีการ: *สตรีจำนวน 120 รายที่ได้รับการวินิจฉัยว่าเป็นก้อนที่รังไข่และรอรับการผ่าตัดที่โรงพยาบาลศิริราช ตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2546 ถึงวันที่ 31 สิงหาคม พ.ศ. 2547 ได้รับการเจาะเลือดเพื่อตรวจหาค่า serum CA-125*

ผลการศึกษา: *จากกลุ่มตัวอย่าง 120 ราย พบเป็นก้อนที่รังไข่ชนิดไม่ร้ายแรง 61 ราย คิดเป็นร้อยละ 50.8 และพบเป็นมะเร็งรังไข่ 59 ราย คิดเป็นร้อยละ 49.2 ค่า serum CA-125 ที่มากกว่า 35 U/mL ในการทำนายมะเร็งรังไข่พบว่ามีความไวร้อยละ 83.1, ความจำเพาะร้อยละ 39.3, คุณค่าในการทำนายผลบวกร้อยละ 57.0, คุณค่าในการทำนายผลลบร้อยละ 70.6, ผลบวกลวงร้อยละ 60.7 ผลลบลวงร้อยละ 16.9 และความถูกต้องร้อยละ 60.8*

สรุป: *ค่า serum CA-125 ที่มากกว่า 35 U/mL สามารถช่วยในการทำนายมะเร็งรังไข่ได้ดีพอควร แต่ต้องระวังผลบวกลวงในกลุ่มผู้ป่วยที่ยังอยู่ในวัยที่มีระดู และผลลบลวงในกลุ่มผู้ป่วยมะเร็งรังไข่ในระยะเริ่มแรก หรือกลุ่มเนื้องอกรังไข่บางชนิดที่ค่านี้อยู่ในเกณฑ์ปกติ*