CAN WE DETERMINE AN OPTIMUM CUT-OFF VALUE FOR CA-125 IN DIFFERENTIATION OF ADNEXIAL TUMORS?

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ABSTRACT

• ***Objective:*** *CA-125 is a mouse immunoglobulin 1 monoclonal antibody against the ovarian cancer cells and was first demonstrated by Bast. This is also a mucine like glycoprotein bigger than 200 000 Dalton. CA-125 is a tumor marker that helps clinicians in gynecology about the diagnosis and prognosis of the adnexial tumors. Increase in CA-125 is seen in endometriomas, ovarian inflamatory disease, and benign ovarian tumors like serous cystadenomas, as well as in non-gynecologic cancers like pancreas, colon, stomach, breast and pulmonaries.*

In patients with epithelial ovarian cancer, increased or decreased CA-125 levels have correlation with the activity of the disease in more than 90% of the patients. For differential diagnosis between benign and malign ovarian tumors and also for determination of the prognosis of the adnexial tumors, defining an ideal cut-off value is the objective of this research.

• ***Material and Method:*** *We examined the sensitivity, specificity, positive predictive and negative predictive value of CA-125 in patients with benign and malign ovarian tumors. In this retrospective study we took 168 patients whose CA-125 levels are known. Histopathologically malign lesions were detected in 30 patients, and benign lesions in 138 patients. CA-125 < 35 U/ml is accepted as normal level. Using numeric logistic system, we tried to find an ideal cut-off value for CA-125 to differentiate between benign and malign lesions.*

• ***Results:*** *In malign ovarian cancers the average value of CA-125 was 183.344 (minimum 7.76, maximum value is 1032). The sensitivity of CA-125 in malign ovarian tumors, was 78.94%, specifity was 86.92%, positive predictive value was 63.82% and negative predictive value was 93.38%.*

• ***Conclusion:*** *For differentiation of adnexial mass as benign or malign, CA-125 is found to be significant. But the sensitivity and specificity changed according to the estimated cut-off value of CA-125. When the cut-off value taken as 35 U/ml, then only 30 out of 38 cases could be labeled as malign. If the cut-off value is 65 U/ml, 25 of 38 malign cases are determined. The increase in specificity determines 124 benign cases instead of 113. If the cut-off is 35 U/ml, CA-125 gives one negative result for every 6 positive results.*

• ***Key Words:*** *CA-125, ovarian mass, tumor markers, adnexial tumors.* ***Nobel Med 2010; 6(2): 75-78***

ÖZET

ADNEKSİYAL KİTLELERİN AYIRIMINDA CA-125 İÇİN OPTİMUM BİR EŞİK DEĞER BELİRLEYEBİLİR MİYİZ?

• **Amaç:** CA-125, ilk olarak Bast tarafından gösterilmiş olup, over kanseri hücrelerine karşı gelişen bir fare immunoglobulin 1 monoklonal antikorudur. Musin benzeri bir glikoprotein olup, moleküler ağırlığı 200000 Dalton' dan fazladır. CA-125, jinekolojide adneksiyal kitlelerin tanı ve prognozunu belirlemede klinisyene yardım eden bir tümör belirtecidir. CA-125' deki artış, seröz kistadenoma gibi benign ovarian tümörlerde, endometriomalarda ve ovarian inflamatuar hastalıkta görülmektedir. Ayrıca, pankreas, kolon, mide, meme ve akciğer kanseri gibi jinekolojik olmayan kanserlerde de yükseldiği gözlenmiştir. Epitelyal ovarian kanseri olan hastaların %90'nından fazlasında CA-125 seviyesindeki artma veya azalma, hastalığın aktivitesi ile ilişkili bulunmuştur. Bu ilişki açısından ve benign, malign kitle ayırımında CA-125 için ideal bir eşik değer belirlemek bu araştırmanın amacıdır.

• **Materyal ve Metod:** Bu çalışmada benign ve malign ovarian kitleleri olan hastalarda CA-125' in sensitivite, spesifite, pozitif ve negatif prediktif değerini inceledik. Bu retrospektif çalışmada, CA-125 seviyelerini bildiğimiz 168 hasta seçtik. Histopatolojik olarak hastaların 30 tanesinde kitle malign, 138 tanesinde benign olarak belirlendi. CA-125 < 35 U/ml, normal seviye olarak kabul edildi. Numerik lojistik sistem kullanılarak benign ve malign lezyonların ayırımında CA-125 için ideal bir eşik değer belirlemeye çalıştık.

• **Bulgular:** Malign ovarian kanserlerde CA-125 in ortalama değeri 183,344 (minimum 7,76, maximum 1032) olarak bulunmuştur. Malign ovarian tümörlerde CA-125 in sensitivitesi %78,94, spesifitesi %86,92, pozitif prediktif değeri %63,82 ve negatif prediktif değeri %93,38 bulunmuştur.

• **Sonuç:** Adneksiyal kitlenin benign veya malign olarak ayırıcı tanısında CA-125 anlamlı bulunmuştur. Fakat, sensitivite ve spesifitesi CA-125' in seçilen eşik değerine göre değişmektedir. Eşik değeri 35 U/ml olarak alındığında 38 malign vakadan 30'u belirlenebilmektedir. Eşik değeri 65 U/ml olarak alındığında ise 38 malign vakadan 25'i belirlenebilmektedir. Spesifitedeki artış, 113 yerine 124 benign vakayı belirlemektedir. Eşik değeri 35 U/ml iken CA-125, her 6 pozitif sonuca karşılık bir negatif sonuç vermektedir.

• **Anahtar Kelimeler:** CA-125, ovarian kitle, tümör belirteçleri, adneksiyal tümörler **Nobel Med 2010; 6(2): 75-78**

INTRODUCTION

CA-125 is a mouse immunoglobulin 1 monoclonal antibody against the ovarian cancer cells and was first demonstrated by Bast. Multiple CA-125 indicators are mucine like glycoproteins bigger than 200000 Dalton. The expression of this antigen in adults is seen in tissues derived from coelomic epithelium. These tissues are pleura, pericard and peritoneal mesothelial epitel, fallopian tubes, endometrium and endocervical epitelium.

CA-125 is not present in ovaries in adults and fetus. But markers are expressed in 80% of epithelial ovarian cancers. In 80% of advanced ovarian cancer, the level of the marker is high (>35 U/ml), but in clinically determined stage 1 ovarian cancer, the marker is elevated in 25% and 50% of the patients.

Studies showed that the increasing trend of CA-125 is more significant than just one high value for the predictivity of ovarian cancer. As a screening method, the value of CA-125 is limited because it can not determine the early stage ovarian cancer.[1] The increase of CA-125 is seen in endometriomas, ovarian inflammatory disease and benign ovarian tumors like serous cystadenomas.[2] Also seen in non-gynecologic cancers like pancreas, colon, stomach, breast and pulmonaries.[3] In patients with epithelial ovarian cancer, increasing or decreasing CA-125 levels have correlation with the activity of the disease in more than 90% of the patients.[4]

Niloff and colleagues showed in one study that if CA-125 levels are decreased to 35 U/ml and lower, the results of second look laparotomy is negative in 14 of 36 patients and also none of them have mass bigger than 1 cm.[5] In consecutive measurement, high level of CA-125 shows the persistent disease.[6] Before the recurrence of disease, in 85% of the patients, an increase of CA-125 is seen.[7] It has been told in literature that increasing of CA-125 levels begins approximately 5 months (1-14 months) before the recurrence diagnosis.[8]

Makar and colleagues,[9] in a study with 687 invasive epithelial ovarian cancer patients, concluded that preoperative CA-125 level is not an independent prognostic factor but postoperative CA-125 (cut-off > 65 U/ml) level is an independent prognostic factor.[10] Geisler and colleagues[11] stated that high preoperative→

CA-125 levels decreases the survival period. Nagele and colleagues,[12] estimated that preoperative CA-125 level higher than 65 U/ml increases the risk of death because ovarian cancer 6.37 fold according to the CA-125 level lower than 65 U/ml. However, in patients with the preoperative CA-125 levels < 500 U/ml, optimal cytoreduction is 73%, in patients with the preoperative CA-125 levels > 500 U/ml optimal cytoreduction is 22%.[13, 14]

In chemotherapy, the half-life period of CA-125 is a prognostic factor alone. During the chemotherapy, decreasing rate is related closely with response to chemotherapy and survival.[15]

MATERIAL and METHOD

In this retrospective study, between 2001-2006, among the patients with adnexial masses operated in Taksim Education and Research Hospital's Gynecology and Obstetrics Clinic, 168 patients are taken into the study. Histopathologically 30 patients had malign and 138 patient had benign lesions. Mean age for malign ovarian tumor was 60.7, mean age for benign adnexial mass was 38.08. CA-125<35 U/ml value is taken as normal. Data are shown as ± SD (Standard Deviation). Numeric averages between malign and benign groups are compared with Mann-Whitney U test. $P < 0.05$ is taken as significant. By using numeric logistic method, in differentiation of malign and benign tumors we tried to determine an ideal cut-off value for CA-125. Also the sensitivity, specificity, positive predictive value, negative predictive value, correct diagnosis and odds ratio were calculated.

RESULTS

The mean value of CA-125 in malign ovarian cancers is 183.344 (Min. 7.76, Max. 1032). The mean value in benign cases is 20.874 (Min. 2.63, max. 143.2). For CA-125; TP (True positive): 30, FN (False negative): 8, TN (True negative): 113, FP (False positive): 17. For CA-125, sensitivity is 78.94%, specificity is 86.92%. PPV (positive predictive value) is 63.82%, NPV (Negative predictive value) is 93.38%. If the cut-off value of CA-125 is taken 65 and higher; TP: 25, FN: 13, TN: 124, FP: 6, Sensitivity is 65.78%, specificity is 95.38%, PPV is 80.64%, NPV is 90.51.

DISCUSSION

CA-125 is the most reliable marker in ovarian carcinoma but as a screening test, it's value is controversial.[16, 17] CA-125 may be helpful in certain conditions such as malign and benign ovarian lesions, particularly in the postmenopausal period, response to chemotherapy, and

Table 1: CA-125 Cut-off is 35 U/ml

	Low	High	Total
Malign	8	30	38
Benign	113	17	130
Total	121	47	168

Table 2: CA-125 Cut-off is 65 U/ml

	Low	High	Total
Malign	13	25	38
Benign	124	6	130
Total	137	31	168

tumor recurrence.[18-20] Increased levels of CA-125 are detected 30% in stage 1 disease, 90% in advanced stage disease.[16, 21] IF PPV (Positive predictive value) of a screening test is 10%, that means, to determine a cancer it takes 10 surgery operation, so this is an acceptable ratio.[22] Considering that ovarian cancer prevalence after 50 years of age is 40/100000. 10% PPV with 67% sensitivity, the specificity of CA-125 must be higher than 99.7%.[23]

In postmenopausal period, specificity for CA-125 is much lower than 99.7%, so this shows us that this marker is not effective in screening.[24, 25] In differential diagnosis of adnexial masses, chosen cut-off values for ovarian carcinoma, sensitivity of CA-125 changes between 56-100% and specificity changes between 60-92%.[26, 27] Numerous studies show that in postmenopausal period, when the adnexial mass is evaluated by ultrasonography, CA-125 is quite reliable.

A multicenter study in Italy, when the cut-off is taken as 60 U/ml, diagnostic accuracy is found higher than ultrasonography (83% against 81%). When the ultrasonography and CA-125 is combined diagnostic accuracy is 94%.[28] In a study from Netherland questioning the differentiation of malign and benign adnexial masses, pelvic examination has an accuracy of 76%, transvaginal ultrasonography has 74%, CA-125 (cut-off = 35 U/ml) has 77% and in patients who have negative results in all of these.[29, 30]

We examined the value of CA-125 in differentiation of benign and malign lesions in 30 patients who have malign and 138 patients who have benign adnexial masses. When the cut-off value is taken as 35 U/ml, sensitivity, specificity, PPV, NPV is 78.94%, 86.92%, 63.82%, 93.38% respectively. When the cut-off value is taken as 65 U/ml, sensitivity decreases to 65.78%,→

specificity increases to 95.38%. Also PPV increases to 80.64%. If cut-off value is 35 U/ml, 30 of 38 malign cases are determined. If cut-off value is 65 U/ml, 25 of 38 malign cases are determined. The increase in specificity determines 124 benign cases instead 113. If the cut-off is 35 U/ml, CA-125 gives 1 negative result for every 6 positive results.

CONCLUSION

Results of this study proposes ideal cut-off limit for CA-125 to be 28 U/ml. Higher and lower values, sensitivity and specificity decreases optimum cut-off value for CA-125, can be determined with multicentric trials comprimising more cases.

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