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# Diagnostic value of serum tumor markers for adnexal masses

**Research Article**

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**Abstract:** Objective: The study aim was to investigate the diagnostic value of measuring preoperative serum tumor markers in patients with adnexal masses. Methods: The study included all (358) consecutive patients treated for adnexal tumors at the Clinic of Obstetrics and Gynecology, Clinical Center of Serbia during 12 months. Tumor-marker levels (Ca 125, CEA, HE 4, Ca 19.9 and Ca 15.3) obtained from all women on admission were compared with histopathological findings in cases in which tumors were removed. Results: Women with malignant tumors had the highest levels of Ca 125, CEA and HE 4 ($p<0.01$). Mucinous adenocarcinoma produced the highest amounts of Ca 19.9 and CEA. Ca 15.3 was the highest in women with endometrioid carcinoma. There were no significant differences in the levels of all serum tumor markers between women with benign and borderline tumors ($p>0.05$). Malignant forms of tumors were well indicated by Ca 125, HE 4 and Ca 15.3 levels. The combination of Ca 125 and HE 4 resulted in the highest sensitivity, specificity, and positive or negative predictive value (91.04%, 87.6%, 67.9%, 77.2%, respectively). Conclusions: Blood levels of tumor markers can be effective? predictors of the nature of adnexal masses. For the most precise evaluation, a combination of serum tumor markers should be used.

**Keywords:** *Tumor markers • Preoperative evaluation • Adnexal masses*

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## 1. Introduction

Ovarian cancer remains the leading cause of gynecologic-cancer mortality. As there is still no effective screening test available, ovarian cancer is frequently diagnosed in advanced stages [1,2]. Preoperative discrimination between benign and malignant ovarian tumors results in appropriate referral for? evaluation? of? different therapeutic approaches [3,4]. Biomarkers have a wide range of applications in the evaluation and management of numerous tumors, including adnexal masses. Up to now, serum markers have been the most extensively used biomarkers in routine practice. However, few markers are elevated in preclinical or premalignant disease, and some of them are elevated even in various physiological benign conditions, limiting their importance for estimating the risk or their use in screening patients with adnexal tumors [5]. The aim of this study was to investigate the diagnostic value of serum tumor markers in the preoperative evaluation of patients with adnexal masses.

## 2. Method

This prospective study included all (358) consecutive patients that were treated for adnexal tumors at the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia during the period of 12 months (from May 1, 2011 - April

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30, 2012). All patients in the investigation signed an informed consent. On admission, in addition to detailed anamnesis, expert clinical examinations and ultrasound scans of the pelvic organs, tumor marker levels (Ca 125, CEA, HE 4, Ca 19-9 and Ca 15.3) were obtained from all women. Referral levels used in this study were: 0-35 IU/L for Ca 125; 0-33 IU/L for Ca 19.9; 0-38 IU/L for Ca 15.3; 0-150 pmol/ml for human epididimal protein 4 (HE 4) and 0.21-4.8 IU/L for carcinoembryonic antigen (CEA). After the extraction of all masses, the histopathological findings (HP) were analyzed. First, we compared HP findings (benign, borderline and malignant) to the tumor markers. In the next step we assessed which tumor marker most appropriately differentiated benign, borderline and malignant tumors. Furthermore, we analyzed relationships of specific HP diagnoses and serum tumor marker levels. We also investigated the relationships among? all parameters and the nature (benign/malignant) of the tumor. Finally, sensitivity, specificity, and positive or negative predictive values were calculated for the serum tumor markers with the standard formulas. For statistical analysis of the data, we applied methods of descriptive and analytical statistics (Kolmogorov-Smirnov Z test, Friedman's parametric ANOVA, Spearman's correlation, discriminant analysis and multivariate binary logistic regression). The level of significance was $p<0.05$. The data were analyzed with the SPSS 15.0 software.

## 3. Results

There were 358 women involved in the study. Out of all the cases, adnexal masses were malignant in 52, benign in 294, and borderline in 12.

Analyzing HP findings, we categorized? the malignant-tumor diagnoses into 7 groups (serous adenocarcinoma, mucinous adenocarcinoma, endometrioid carcinoma, granulosa-cell tumor, papillary adenocarcinoma, Krukenberg tumor, and "other malignant diagnoses". The "other" category included clear-cell tumor and mixed mullerian tumor that were present in just one case each?, and therefore, we evaluated those together. (Is your meaning of the preceding sentence stated correctly?) Seven different benign diagnoses (simple ovarian cyst, endometriotic cyst, hemorrhagic cyst, teratoma, benign ovarian cystadenoma, ovarian fibrothecoma and corpus luteum) were present in just one case each?, and therefore, we evaluated those together.

HP findings were significantly and positively correlated with Ca 125 ($\rho=0.272$; $p=0.000$), HE 4 ($\rho=0.296$; $p=0.000$) and Ca 15.3 ($\rho=0.468$; $p=0.000$). Higher levels of tumor markers were associated with malignant tumors.

The mean level of Ca 125 was 641.058 +/- 2543.96 (min 2.51, max 20435.00, median 27.50). There were high significant differences between tumor types regarding the level of Ca 125 ($p=0.000$). Women with malignant tumors had the highest levels of Ca 125. However, there were no significant differences between women with benign tumors and those with borderline tumors. There were significant differences between specific tumor diagnoses regarding the blood level of Ca 125 ($p=0.000$). Ca 125 was highest in serous adenocarcinoma and papillary adenocarcinoma, as well as in the group of ''other malignant tumors''. However, there were no significant differences within the group of malignant tumors regarding the levels of Ca 125 ($p=0.511$) (Table 1). Ca 125 explains (Clarify how the marker explained the case? Did it show that it was benign or malignant?) 81.3% of cases

**Table 1.** Mean levels of serum tumor markers in histopathological findings of adnexal masses.

| Diagnosis | | Number | Ca 125 | Ca 19.9 | CEA | Ca 15.3 | HE 4 |
|---|---|---|---|---|---|---|---|
| Benign | Simple ovarian cyst | 93 | 63.32 | 21.59 | 1.96 | 19.40 | 36.40 |
| | Endometriotic cyst | 76 | 79.96 | 28.01 | 1.72 | 19.56 | 87.03 |
| | Hemorrhagic cyst | 28 | 41.97 | 17.54 | 1.50 | 15.08 | 54.12 |
| | Teratoma | 38 | 37.64 | 27.57 | 2.24 | 21.19 | 62.38 |
| | Benign ovarian cystadenoma | 33 | 53.47 | 18.56 | 1.33 | 23.25 | 43.89 |
| | Ovarian fibrothecoma | 19 | 36.95 | 30.63 | 1.64 | 16.33 | 92.10 |
| | Other diagnoses | 7 | 62.40 | 7.11 | 1.47 | 0.00 | 79.70 |
| Borderline | | 12 | 281.06 | 25.11 | 2.28 | 11.83 | 112.32 |
| Malignant | Serous adenocarcinoma | 15 | 1255.53 | 10.66 | 1.38 | 156.12 | 189.72 |
| | Mucinous adenocarcinoma | 6 | 55.85 | 376.67 | 13.27 | 15.63 | 234.51 |
| | Granulosa-cell tumor | 5 | 145.70 | 3.00 | 0.20 | 12.00 | 187.45 |
| | Endometrioid carcinoma | 7 | 487.73 | 24.01 | 3.54 | 548.42 | 221.67 |
| | Papillary adenocarcinoma | 9 | 1234.93 | 15.60 | 2.16 | 55.30 | 183.00 |
| | Krukenberg tumor | 5 | 185.43 | 36.46 | 8.34 | 114.87 | 289.50 |
| | Other malignant diagnoses | 5 | 2103.47 | 21.50 | 10.53 | 93.25 | 156.90 |

(Figure 1). The cut-off at the laboratory-recommended level of Ca 125 at 35 IU/l had a sensitivity of 83.5% and specificity of 53.6%. Overall, the sensitivity of Ca 125 was 85.58%, specificity 56.09%, PPV 31.79% and NPV 94.21%.

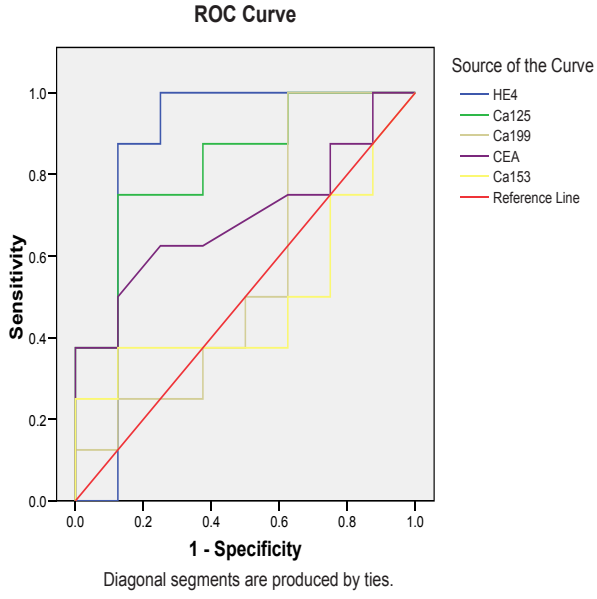


**Figure 1.** Roc curves of tumor marker.

The mean level of HE 4 was 119 +/- 123.23 (min 4.00, max 567.21, median 57.00). There were high significant differences between tumor types regarding the level of HE 4 (p=0.000). Women with malignant tumors had the highest levels of HE 4. However, there were no significant differences between women who had benign and those with borderline tumors. When specific diagnoses were evaluated, no significant differences were found (p=0.111). Moreover, there were no significant differences within the malignant tumors (Or, do you mean "group of other malignant tumors"?) regarding the levels of HE 4 (p=0.622) (Table 1). HE 4 explains (Again, clarify what "explains" means here, as noted above.) 85.9% of cases (Figure 1). The cut-off at the laboratory-recommended level of HE 4 at 150 pmol/ml had a sensitivity of 44.4% and specificity of 86.1%. Overall, the sensitivity of HE 4 was 70.18%, specificity 88.91%, PPV 59.44% and NPV 65.62%.

When Ca 125 and HE 4 were assessed together, we achieved a sensitivity of 91.04%, specificity 87.6%, PPV 67.9% and NPV 77.2%.

The mean level of Ca 19.9 was 52.85 +/- 224.66 (min 0.60, max 1880.00, median 10.00). There were no significant differences between tumor types (benign, borderline, malignant) regarding the level of Ca 19.9 (p=0.162). When all specific diagnoses were compared, Ca 19.9 was significantly higher in mucinous adenocarcinoma and the lower in granulosa-cell tumor (p=0.000). However, there were no significant differences within only the malignant tumors regarding the levels of Ca 19.9 (p=0.081) (Table 1). Ca 19.9 explains (Clarify as noted above.) 54.4% of cases (Figure 1). The cut-off at the laboratory-recommended level of Ca 19.9 on 33 IU/l had a sensitivity of 20.8% and specificity of 82.9%. The general sensitivity of Ca 19.9 was 20.00%, specificity 65.17%, PPV 29.55% and NPV 52.73%.

The mean level of Ca 15.3 was 75.83 +/- 289.41 (min 0.00, max 2412.00, median 20.40). There were no significant differences between tumor types regarding the level of Ca 15.3 (p=0.062). Ca 15.3 was the highest in women with endometrioid carcinoma. But, when all diagnoses were compared, no significant differences were found (p=0.115). Moreover, there were no significant differences within the malignant tumors regarding the levels of Ca 15.3 (p=0.622) (Table 1). Ca 15.3 explains (Clarify as noted above.) 49.2% of cases (Figure 1). The cut-off at the laboratory-recommended level of Ca 15.3 at 38 IU/l had a sensitivity of 37.5% and specificity of 87.5%. The total sensitivity of Ca 15.3 was 53.13%, specificity 96.08%, PPV 89.47% and NPV 76.56%.

The mean level of CEA was 2.83 +/- 5.97 (min 0.00 max 47.10 median 1.62). There were high significant differences between tumor types regarding the level of CEA (p=0.000). Women with malignant tumors had the highest levels of CEA, but there were no significant differences between women who had benign and those with borderline tumors. There were high significant differences between tumor diagnoses regarding the blood levels of CEA (p=0.000). The significantly highest levels of CEA were in women with mucinous adenocarcinoma and the "other malignant tumors". However, there were no significant differences within the malignant tumors regarding the levels of CEA (p=0.160) (Table 1). CEA explains (Clarify as noted above.) 69.5% of cases (Figure 1). The cut-off at the laboratory-recommended level of CEA at 4.8 IU/l had a sensitivity of 37.5% and specificity of 87.5%. The total sensitivity of CEA was 18.03%, specificity 95.09%, PPV 57.89% and NPV 75.61%.

When the findings for tumor markers were assessed all together, a significant model was achieved by the Enter method ($\chi^2$=48.868; p=0.000). The model's total classification success was 85.9% and R2 Nagelkerke 0.671.

*MALIGNANCY = 3.168 – 0.259 x CEA + 0.473 x HE 4*

Levels of tumor markers were effective? in discriminating among malignant, benign and borderline tumors. We obtained one statistically significant function (eigenvalue=0.569; % of variance=99.3; canonical correlation=0.602; Wilks λ=0.635; $\chi^2$=29.759; p=0,003). From

the largest group of? centroids for significant function, it can be concluded that Ca 125, HE 4 and Ca 15.3 had the highest scores in women with malignant tumors, and therefore, these markers well discriminate malignant tumors from other tumor types (Table 2).

**Table 2.** Correlation coefficients between discriminating variables and standardized canonical discriminant function and group centroids of discriminant function.

| Parameters | | Function 1 | Function 2 |
|---|---|---|---|
| Tumor markers | Ca 125 | 0,419(*) | 0,143 |
| | Ca 15.3 | 0,350(*) | -0,133 |
| | HE 4 | 0.268(*) | 0.121 |
| | CEA | 0,362 | 0,666(*) |
| | Ca 19.9 | 0,158 | 0,446(*) |
| Functions at Group Centroids | Malignant | 0,942 | -0,001 |
| | Benign | -0,582 | -0,016 |
| | Borderline | -0,499 | 0,361 |

*Function 1 – significant; Function 2 – not significant;*
*(*) – Largest absolute correlation between each variable and any discriminant function.*

## 4. Discussion

Mostly due to the late diagnosis of ovarian cancer, the prognosis is doubtful, because the outcome is very poor in advanced stages. Current therapies efficiently treat most patients with gynecologic malignancies detected at an early stage. Prevention of the disease could improve prognosis, but there is still no adequate screening test for ovarian cancer, even though several screening trials are ongoing [6]. Thus, the identification of oncology biomarkers for screening and the monitoring of occult tumors has been highly prioritized.

According to the literature, papillary serous cystic adenocarcinoma is the most common type of ovarian cancer, followed by mucinous, endometrioid, yolk sac, dysgerminoma and adult granulosa-cell tumors [7]. Most patients in all available studies had serous histologic features, similar to the distribution of malignant tumors in our study.

Assessment for early detection of ovarian cancer can be achieved with tumor markers such as CEA, Ca 19-9, and Ca 15-3 combined with Ca 125 levels [8-10]. Other tumor markers such as Ca 72-4, OVX1, inhibin, beta-hCG, AFP, M-CSF and most recently HE 4 should be respected (Do you mean “studied”?) for early detection of ovarian cancer as well [11,12]. In this study, we examined and compared the competence of all currently used tumor markers, even though some of them measure different (Some markers measure different what?) and some of them (Ca 19-9 and Ca 15-3 measure mucin) the same markers. (Here you’re saying markers measure markers, which needs to be clarified.)

Ca 125 is the most widely used and the most accurate tumor marker for ovarian cancer. Screening with a Ca-125 measurement and trans-vaginal ultrasonography every 6 months has been recommended for high-risk women [4,13]. However, serum Ca 125 has been investigated for ovarian-cancer screening with conflicting results [14]. Ca 125 determination is useful for the detection of the persistence and recurrence and monitoring of the therapeutic effects in the patients with epithelial ovarian carcinomas. Ca 125 is the most reliable serum marker for serial measurements to calculate the risk of cancer, which appears to have greater utility than evaluation of a single value [15]. Levels of Ca 125 may indicate the disease extent and therefore, the likelihood of successful cyto-reductive surgery [15]. Still, elevated levels of Ca 125 can also be detected in many non-malignant gynecological diseases, especially in endometriosis, and even some physiological conditions. (You should give an example of one of these conditions to complete your thought.) Numerous researchers have confirmed that Ca 125 has limitations when used to distinguish between benign and malignant ovarian masses, but have concluded that clinicians will be able to better interpret preoperative serum Ca 125 results in patients with adnexal masses by using likelihood reference tables [16-18]. The diagnostic efficiency of Ca 125 in the literature usually ranges between 70 and 90% [11,12].

Human epididymis protein 4 is a novel serum marker that is more sensitive in the prediction of risk of ovarian malignancy in patients with a pelvic mass than Ca 125 alone [19]. Researchers found elevated levels of Ca 125 in 77 % and HE4 in 85 % of cases of ovarian cancer [20]. The median Ca 125 and HE4 levels have proved to be significantly higher in the patients with ovarian carcinoma than in those with benign disease. Moreover, serum HE4 testing is a more powerful tool than Ca 125 assay to discriminate ovarian cancer from ovarian endometriosis and pelvic inflammatory disease, to detect recurrence, and to monitor the response to therapy [21]. HE4 adds valuable information, especially for premenopausal patients [22].

According to our study, Ca 125 and HE 4 are important factors for preoperative differentiation and prediction of malignancy with very high sensitivity, specificity and predictive values. HE 4 has proved to be even more sensitive than Ca 125. Still, neither helps in the differentiation between benign and borderline tumors, and neither can positively imply the exact histopathological diagnoses of adnexal masses.

The positive rate of Ca 125, Ca 19-9, Ca 15-3, and CEA in serous tumors can be 57.9, 7.9, 7.9 and 15.8%, respectively. These figures for mucinous tumors are 31.8, 40.9, 27.3 and 40.9%. The positive rate of Ca 125

in the serous group was found to be statistically significantly higher than that in the mucinous group, whereas the positive rates for Ca 19-9 and CEA in mucinous histology were significantly higher than those in serous tumors. Therefore, it can be concluded that the elevation of serum Ca 125 may suggest serous ovarian tumors, whereas the high level of serum Ca 19-9 and CEA may indicate mucinous tumors [23]. Ca 19-9 is probably the most accurate tumor marker for mature cystic teratomas, as it is the only tumor marker with a mean serum level above the cut-off value. As the tumor becomes larger, this relationship becomes more distinct [24].

We found no significant differences between tumor types regarding the level of Ca 19.9 and Ca 15.3. There were also no significant differences within the group of malignant tumors regarding these two markers. Ca 19.9 was the highest in mucinous adenocarcinoma and the lowest in granulosa-cell tumors. Ca 15.3 was the highest in women with endometrioid carcinoma, but without statistical significance when compared to other diagnoses. Ca 15.3 can well discriminate malignant tumors from other tumor types.

Women with malignant tumors had the highest levels of CEA. The significantly highest levels of CEA were in women with mucinous adenocarcinoma and in the group of of ''other malignant tumors". (Stated as meant?) Nevertheless, there were no significant differences in the levels of CEA within the group of malignant tumors or between women who had benign and borderline tumors.

The literature shows that combined multiple tumor markers can improve overall diagnostic accuracy [8]. The sensitivity of a serum-marker combination was significantly greater than the sensitivity of the Ca 125 assay alone in patients with all stages of primary ovarian epithelial tumors of different histotypes. When used as single markers, however, only the Ca-125-II assay could distinguish invasive Stage I tumors in apparently healthy women [25]. A combination of serum and molecular markers, such as serum Ca 125, Ca 19 and mRNA for survivin gene, could allow for better triage between endometriosis and malignant adnexal masses [26]. HE 4 in combination with Ca 125 appears to be the most effective tool for the early diagnosis of ovarian carcinoma [19]. Different risk models and screening algorithms that combine and evaluate tumor markers together have been developed, with the aim of improving the specificity and sensitivity of diagnostic tests to allow for an effective triage of women to appropriate institutions for their care. The Risk of Ovarian Malignancy Algorithm [ROMA] is most commonly used, and it utilizes the dual marker combination of HE 4 and Ca 125 to stratify both postmenopausal and premenopausal women into high- and low-risk groups [19]. This model has achieved the highest sensitivity and specificity. Furthermore, some researchers advise that in patients with an undiagnosed tumor in the pelvis, the Ca-125/CEA ratio may be used to preoperatively identify a substantial fraction of patients with ovarian and non-ovarian malignancies [27]. We also confirmed that Ca 125 and HE 4 should be used together in order to most accurately predict the nature of adnexal masses. We also obtained (Change to "looked at"?) another model that combined CEA and HE 4. (Did you study this one? What were your conclusions about it?)

Since severe consequences can occur if a malignant tumor is not recognized, higher sensitivity of the tested tumor marker is needed [6,9]. Our results show that the combination of Ca 125 and HE 4 had the highest sensitivity. When separate markers were evaluated, the most appropriate was Ca 125. (Do you mean that Ca 125, when evaluated alone, had the highest sensitivity? If not, what was it most appropriately used for?) HE 4 levels were correctly associated with the highest percent of cases.

In conclusion, higher levels of Ca 125, HE 4 and Ca 15.3 are correlated with malignant tumors. Women with malignant tumors have significantly higher levels of Ca 125, CEA and HE 4 than women with other tumor types. Ca 19.9 is the highest in mucinous adenocarcinoma and the lowest in granulosa-cell tumors. The highest levels of CEA were found in women with mucinous adenocarcinoma and the group of ''other malignant tumors". There are no significant differences for levels of CEA within the malignant tumors or between women who had benign and borderline tumors. Ca 125, HE 4 and Ca 15.3 can discriminate well between malignant tumors and other tumor types. The highest sensitivity in the preoperative prediction of the tumor nature was achieved by the combination of Ca 125 and HE 4. A significant model for the likelihood of cancer that combines HE 4 and CEA has been shown? in this study.

According to our results, blood levels of tumor markers can be good predictors of the nature of the adnexal masses, but, unfortunately, none? of them can accurately predict the exact diagnosis of the adnexal tumor. For the most precise preoperative prognosis of the nature of adnexal tumors, a combination of tumor markers should be used.

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## Conflict of interest statement

Authors state no conflict of interest.

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