in vivo *18*: 831-836 (2004)

Serum CA 125 Combined with Transvaginal Ultrasonography for Ovarian Cancer Screening

ZOI ROUPA[1], EFTHIMIOS FAROS[2], VASILIOS RAFTOPOULOS[3], GEORGIOS TZAVELAS[4], EVANGELIA KOTROTSIOU[1], PENELOPE SOTIROPOULOU[1], EVRIDIKI KARANIKOLA[1], EVDOXIA SKIFTA[1] and ALEXANDROS ARDAVANIS[1]

[1]Department of Nursing, Faculty of Health Care Sciences, High Technological Education Institute, Larissa; [2]General Hospital of Larissa; [3]Hellenic Centre for Infectious Diseases Control, Syndromic Surveillance, Olympic Games ATHENS 2004, Athens; [4]High Technological Educational Institute, Piraeus; [5]Laiko General Hospital, Athens; [6]Agios Savvas Anticancer Hospital, Athens, Greece

Abstract. *Background: The aim of this study was to evaluate the combination of serum CA125 and Transvaginal Ultra Sonography (TVUS) score, as a screening procedure for ovarian cancer in premenopausal and postmenopausal women. Patients and Methods: A retrospective case-control pilot study was conducted. The files of 120 women with ovarian neoplasia detected by TVUS and increased CA125 level, within the framework of a prevention program, were reviewed. The relationship between the above tests and epithelial malignancy was investigated using the SPSS-12 program for Windows. Results: The combination of CA125 value exceeding 30U/ml and a TVUS score ≥35 had a sensitivity of 81.7% and specificity of 100% in predicting ovarian cancer. Mathematical analysis of the logistic model of our variables revealed a mathematical model that can calculate the likelihood of ovarian cancer detection, by using a combination of CA125≥30U/ml and TVUS score≥35. Conclusion: By combining TVUS and CA125, an accurate prediction for the presence of ovarian cancer may be achieved. Further investigation in a larger population is warranted.*

Ovarian cancer is a major cause of mortality and morbidity in developed countries. It is the most frequent cause of death from gynaecological malignancy in the USA, accounting for 14,500 deaths in 1999 and 25,200 estimated new cancer cases (1). According to the US National Cancer Institute (2), the prevalence of ovarian cancer is 20/100,000 in 30 to 50-year-old women and increases in older women. Ovarian cancer has the worst prognosis of all gynaecological malignancies, primarily because it tends to present at an advanced stage. As a result, early diagnosis is crucial to improve prognosis.

Several tumour marker blood tests have been used to detect ovarian cancer (3-9). CA125 is a tumour-associated high molecular weight glycoprotein, recognized by the monoclonal antibody OC125 and expressed by more than 80% of non-mucinous epithelial ovarian carcinomas (10). Serum levels are elevated in the majority of women with advanced ovarian cancer, although other conditions such as endometriosis, pregnancy and pelvic inflammatory cysts are also associated with increased serum levels (11-14). CA125 is currently the established tumour marker for the early detection of ovarian cancer recurrence, though a role for screening has not been demonstrated so far (15).

Transvaginal Ultra Sonography (TVUS) combined with serum CA125 level measurements have been evaluated in the United Kingdom (16, 17), Sweden (18) the United States (19) and in Europe (20). TVUS can detect ovarian cancer with a sensitivity approaching 100%, but it is insufficiently specific for use as a first-line screen (21, 22). This means that TVUS can detect not only ovarian cancers, but also women with benign disease. The cost-benefit analysis of isolated screening for epithelial ovarian cancer using a combination of CA125 and ultrasound techniques, even in women at high risk for the disease, would suggest that such screening is not cost-effective at this time (13).

Screening decisions based on CA125 most commonly use a single-threshold screening rule that refers a woman to ultrasound if her CA125 concentration exceeds 30 units/ml when postmenopausal, or 25 units/ml when premenopausal (10). Several trials of screening for ovarian cancer indicate that using a CA125 cut-off value of 30 U/ml has adequate

Correspondence to: Zoi Roupa, Egosthenon 86, Galatsi, Athens, Greece. Tel: +30 210 2924940, e-mail: zoeroupa@yahoo.gr, v_raftop@yahoo.gr

Key Words: CA125, transvaginal ultrasonography, ovarian cancer screening, menopausal status.

specificity for detecting preclinical disease (6, 14, 16, 23, 24). Alagoz *et al.* support an upper limit of normal of 20 U/ml and they encourage further research on the clinical impact of this new definition (15). Bese *et al.* suggested a lower level of 20 U/ml as a cut-off value prior to second-look laparotomy in evaluating women with known epithelial ovarian cancer (25). TVUS as a second-step test in women with elevated CA125 levels improves specificity, as does use of a mathematical algorithm which analyses rates of change of CA125 (14, 26). According to Berek and Bast, the serial measurement of CA125 has a high sensitivity, specificity and positive predictive value for the early detection of ovarian cancer (27).

Recently, Skates *et al.* have shown that preclinical detection of ovarian cancer using serial CA125 levels interpreted according to the risk calculation significantly improves screening performance compared with a fixed cut-off for CA125 (28). A majority of researchers use the widely accepted reference level of 35 U/ml (8, 18, 29, 30). However, using a CA125 cut-off value of 35 U/ml may not be appropriate for screening as women with naturally increased levels of CA125 experience many false - positives and probably do not reach 35 U/ml until at an advanced stage of their cancer (22, 31).

In their review, Carlson *et al.* reported that the sensitivity of TVUS for the detection of ovarian cancer in screening studies ranged from 50% to 100% (32), while the specificity ranged from 76% to 96.6%. Berek *et al.,* in their study of women with known ovarian cancer, have shown a sensitivity ranging from 83% to 99.7% (27). Screening studies with CA125 radioimmunoassay showed sensitivity and specificity ranging from 53% to 100% and 98.8% to 99.4%, respectively; moreover, the reported sensitivity for women with known or suspected ovarian cancer ranged from 61% to 96% (23, 25). CA125 has a positive predictive value of less than 10% as a single marker, but the addition of ultrasound screening to CA125 measurement has improved the positive predictive value to about 20% (33, 34).

In the largest published research conducted in England, the apparent sensitivity of CA125 was between 53% to 89% (24). The authors concluded that both transvaginal sonography and CA125 used alone are not specific enough; however, when the decision rule for surgical referral requires that both tests are positive, the predictive value of their combination is 27%. In Sweden the predictive value was found to be 13% (18).

Transvaginal sonography has a high sensitivity but its usefulness is limited by its specificity. In an older study, TVUS was sensitive in as many as 100% of cases, while specific in about 98% (21). Van Nagell *et al.* concluded that TVUS sensitivity was 81%, specificity was 98.9% and positive prediction value was 9.4% (35). Since cancer is rare compared to benign ovarian diseases, a specificity of 99.6% is required to achieve a predictive value of 10% (33). In a large screening study, TVUS gave positive predictive value and sensitivity in 6.7% and 86%, respectively (36).

Other researchers examined the predictive value of the combination of CA125 with other antigens such as CASA (Cancer Associated Serum Antigen) (37) and TPS (Tissue polypeptide specific antigen) (38) for the early detection of ovarian cancer.

Table I. *Sample characteristics.*

Variable	N	%
Education		
Elementary	60	50
High School	47	39.2
College/University	13	10.8
Marital Status		
Single	13	10.7
Married	106	88
Separated	2	1.3
Past Occupation		
Blue collar	7	5.7
White collar	28	23.3
Agriculture	12	10
Housewife	73	60.7
Population		
Urban	26	21.3
Semi-urban	40	33.3
Rural	54	45.3

Patients and Methods

In order to assess the sensitivity, specificity and positive predictive value of combined serum CA125 and TVUS, we reviewed the files of 120 consecutive women examined in the framework of a prevention program from a single health institution (Gynaecology-Obstetrics Unit, General Hospital of Larissa, Greece) over a period of five years, after the approval of the local Ethics Committee. The inclusion criteria for the selection of files appropriate for the study were the following: (1) age 20-80 years old, (2) positive TVUS for an ovarian tumour, (3) increased serum CA125 (≥30U/ml), (4) no family history of ovarian cancer, (5) no synchronous or metachronous diagnosis of cancer in another organ, (6) no active inflammatory or other peritoneal disease associated with CA125 increase, (7) no pregnancy, (8) no history of endometriosis surgery and (9) a complete pathologic documentation.

A structured record form of 25 points, divided into two parts, the first one including demographic information and somatometric data and the second part with health and gynaecological history, was used for chart audit. The smoking attitude defined whether the woman was currently smoking at least one pack of cigarettes. The postmenopausal status was defined as more than one year of amenorrhea, or women who had had a hysterectomy. All the other women, who did not meet these two criteria, were defined as being of premenopausal status.

Table II. *Chi-squared test results of variables with the presence or not of ovarian cancer.*

Variable	x^2	DF	*P*-value
Marital status	4.28	2	0.117
Years of education	7.304	4	0.121
Profession	3.06	2	0.216
Place of residence	1.905	2	0.386
Inflammation	0.001	1	1.0
Menopausal status	1.628	1	0.252

Table III. *Statistical characteristics of laboratory variables.*

	Mean	SD	KS test[1]	*p*-value[2]
HcT	36.39	4.33	2.141	0.000
Hb	12.25	0.77	1.781	0.004
WBC	7,864	6,265	2.899	0.000
PLT	226,566	86,111	1.741	0.005
RBC	3.96	0.43	1.608	0.007
Glucose	87.58	20.21	1.750	0.004
CA125	40.48	47.26	2.844	0.000
TVUS score	40.86	23.29	2.123	0.000

[1]Kolmogorov-Smirnov test
[2]For Kolmogorov-Smirnov test

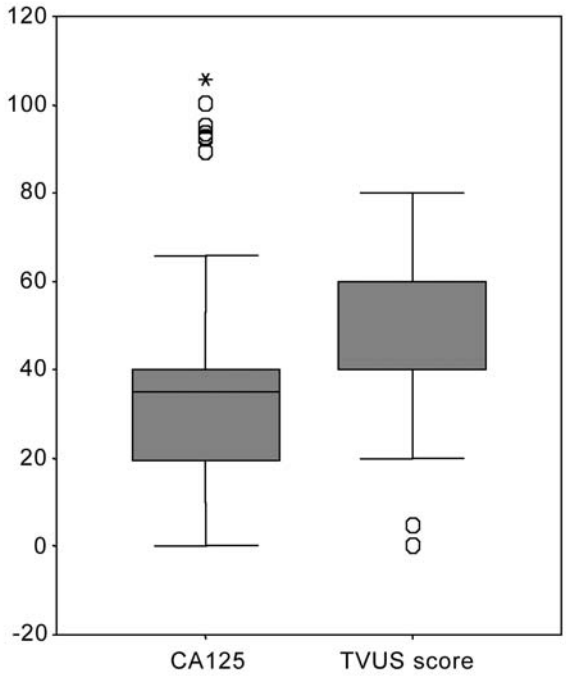

Figure 1. *Box plot of CA125 and TVUS score.*

The screening protocol included first the CA125 serum level of each woman. Women with a concentration of ≥30U/ml were referred for transvaginal ultrasonography in order to detect an ovarian mass. Echo pattern classification of ovarian cancer was done according to the system classification of the Department of Obstetrics and Gynaecology of the University of Tokyo, Japan. If TVUS gave abnormal results, surgical investigation was arranged. The malignancy of each pelvic mass was documented. The relationships between TVUS score positivity, CA125 levels and the diagnosis of ovarian epithelial malignancy as well as the above variables were, thereafter, investigated.

Our primary aim was to evaluate the CA125 and TVUS algorithm for the detection of ovarian cancer. A secondary aim was to develop a mathematical model that could generate our findings in order to develop a useful tool for health care professionals to estimate the risk of ovarian cancer when the serum CA125 level and TVUS score are known.

Statistics. SPSS-12 (Statistical Package for Social Sciences) was used for statistical analysis of the obtained data. The Pearson correlation coefficient was used to calculate the linear correlation of two continuous variables. The Chi-squared test was used between two nominal variables. The *t*-test assesses whether the means of two groups are statistically different from each other. Logistic regression was used as a categorical modelling in order to explore variables that correlate with the presence of cancer. The Kolmogorov-Smirnov test was used to test normal distribution (39). Values less than 0.05 were considered statistically significant, unless otherwise stated. We developed a model for the prediction of ovarian cancer detection and we tested its prediction with ROC analysis methodology. The frequency and 95% confidence interval of false-positive test results were determined.

Results

A total of 120 women were enrolled in the study. In 90 of these women (72%) a benign pathology of the ovary was diagnosed; in the remaining 30 women (28%) some histological type of epithelial malignancy was found. The interval from initial approach to surgical intervention and definitive diagnosis was 15 days to 12 months (median 2 months).

The mean age of the sample population was 50.83±14.30 years. The mean weight was 75.95±13.96 Kg. The population characteristics are shown in Table I.

The vast majority of the women (88%) were married. A large proportion (54.7%) was premenopausal and the rest 45.3% were postmenopausal. The majority of the women (60%) reported three pregnancies in the past. Sixty percent had two children and 56% of the women declared no abortion. A high percent of patients were smokers (88%). The mean general health status at the time of diagnosis was judged to be good by the investigators. Thirteen percent of women reported abdominal infections, mostly in the intragenitalia area. No pregnancy was reported at the time of initial or definitive diagnosis.

The Chi-squared test showed no correlation between the various demographic variables and the presence or not of ovarian cancer (Table II).

In Table III, the statistical characteristics of all laboratory variables used in the survey are shown. The Kolmogorov-

Table IV. *Pearson correlation coefficients between the various parameters and detection of ovarian cancer.*

	ACT	HB	WBC	PLT	RBC	CLUC	CA125	TVUS
HcT	1	0.383[b]	0.029	0.269[a]	0.058	0.077	0.013	-0.075
HB		1	0.031	0.046	0.115	0.328[b]	0.063	-0.092
WBC			1	0.123	0.205	-0.099	-0.077	-0.154
PLT				1	0.003	0.119	-0.073	-0.031
RBC					1	0.151	0.109	0.043
CLUC						1	0.366[b]	0.065
CA125							1	0.290[a]
TVUS								1

[b] Correlation is significant at the 0.01 level (2-tailed).
[a] Correlation is significant at the 0.05 level (2-tailed).

Table V. *Variables of logistic model (coefficients and p-values).*

Variable	Coefficient	*p*-value
Smoking	2.180	0.218
Number of abortions	0.986	0.168
Menopausal status	-1.458	0.228
HcT	-0.008	0.966
HB	-0.925	0.397
WBC	0.001	0.512
PLT	0.001	0.058
RBC	0.398	0.694
Glucose	0.067	0.101
CA125	0.061	0.008
TVUS score	0.048	0.047
Constant	-7.201	0.001

Smirnov test indicates that none of these indicators follows normal distribution.

In Figure 1, the box plot of CA125 and TVUS scores are shown. It is evident that distribution is not symmetric and there are outliers.

We tested whether or not there is a statistically significant correlation between certain laboratory variables used in the survey and CA125 or TVUS score. As can be seen in Table IV, there was only a moderate correlation among the level of CA125, glucose value ($r=.366$, $p<0.01$) and TVUS score ($r=.290$, $p<0.05$). There was no significant correlation between CA125 value and sample variables. In order to compare the mean effect of menopausal status on certain variables, *t*-tests and Levene's test of equality of variance were calculated. The data indicated that there were differences between three variables. We concluded that the difference between mean CA125 value ($p=.036$), mean glucose ($p=.000$) and mean blood pressure ($p=0.050$ for $p=0.1$) for premenopausal and postmenopausal women was significant. Postmenopausal CA125, glucose and blood pressure mean values were higher (Table IV).

A model for logistic regression analysis was used. The presence or not of ovarian cancer was the dependent variable while the laboratory variables, CA125, TVUS score, smoking, menopausal status and the number of abortions were used as independent variables. As seen in Table V, only CA125 and TVUS score were predictive indicators of ovarian cancer.

Mathematical analysis of the logistic model of these variables is as follows:

$$p=\frac{e^{0.035*CA125+0.039*TVS-4.67}}{1+e^{0.035*CA125+0.039*TVS-4.67}}$$

In this logistic model p is the likelihood of ovarian cancer detection, by using a combination of CA125≥30U/ml and TVUS Score≥35. For $p=0.2$ we conclude that (0.35x CA125) + (0.039xTVUS) =3.2837. The ability of model prediction is determined by the area under the distressed line. If the area is different from 0.5, then the model is statistically significant. The significance of the test is $p<0.00$. If p is above a certain critical value then the case is categorized as a cancer case. According to the ROC curve (Figure 2), we took as most optimal $p=0.2$, for which the percentage of positive prediction is 66.6%. The percentage of women with a true-positive, false-positive and false-negative result is shown in Table VI. The sensitivity of CA125 for detecting ovarian cancer in our sample was 93.3%.

Discussion

The development of a solid prognostic model for the early detection of ovarian cancer has not been feasible to date. CA125 alone has a limited clinical use for detecting some ovarian benign neoplasms or mucinous carcinomas (6). When considering alternatives, it must be remembered

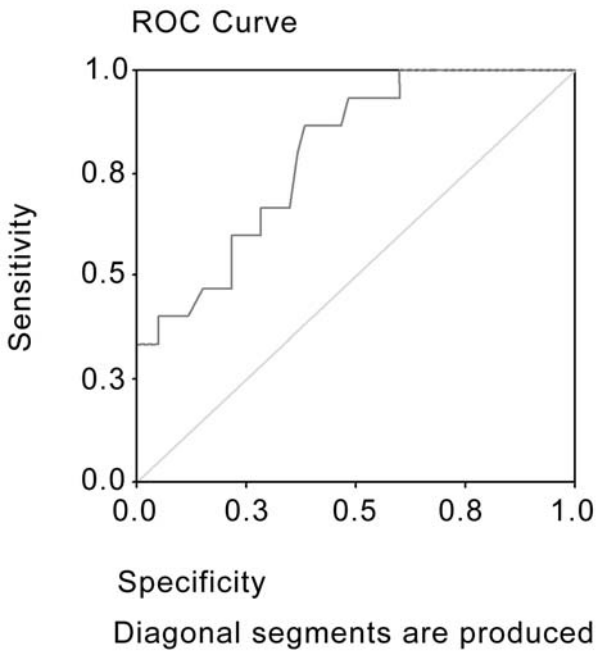

Figure 2. *ROC analysis.*

that TVUS costs four times more than CA125 (31). An efficient model is imperative in order to avoid unnecessary surgery as well as late intervention. Although several investigators have proposed various models of prediction, neither a consistent nor standard approach exists. In the present study, we explored the hypothesis that the combination of a positive TVUS and an elevated CA125 might reliably predict for an ovarian epithelial malignancy.

Among all laboratory variables used in our research, only CA125 and TVUS score correlated with the presence of ovarian cancer. Our data suggest that CA125 values exceeding 30U/ml or a TVUS score ≥35 are associated with a high likelihood of an ovarian cancer diagnosis. In our sample of women without a family history of ovarian cancer, the predictive value of CA125 was found to be 48% in the control group and that of the TVUS score was 46.6%. Jacobs *et al.* found a positive predictive value equal to 20.7% (24). The screening protocol of Jacobs *et al.* achieved a specificity of 99.9%, a positive predictive value of 26.8%, and an apparent sensitivity of 78.6% and 57.9% at one- and two-year follow-up respectively (16).

Bast *et al.* reported that, to detect 75% of ovarian cancers with a positive predictive value of 10% (equivalent to the diagnosis of one case of ovarian cancer per 10 laparatomies performed), a specificity of 99.6% must be attained (29). Our protocol has a predictive value of 66.6%, indicating that it is a useful tool for ovarian cancer detection.

Table VI. *Effectiveness of screening for ovarian cancer with serum CA125, TVUS or combination, for premenopausal and postmenopausal women.*

Variable	True-positive	False-positive	False-negative	Correct classification
CA 125>30 U/ml	93.3%	60%	40%	57% (1:1.32)
TVUS score	100%	70%	30%	45% (1:0.82)
For p=0.2*	100%	81.7%	18.3%	35% (1:0.53)
Menopausal status	60%	71.7%	28.3%	69.3% (1:2.3)

* p is the logistic model that combines CA125 and TVUS score

The risk calculation significantly improved the area under the curve from 84% to 93% compared with a fixed cut-off for CA125 (p=0.01). In another investigation for target specificity of 98%, the risk achieved a sensitivity of 86% for preclinical detection of ovarian cancer, whereas CA125 achieved a sensitivity of 62% (28). A combination of CA125 and ultrasonography in screening for ovarian cancer was used by other investigators in an older study (3, 16); their screening protocol achieved a specificity of 99.9%, a positive predictive value of 26.8% and an apparent sensitivity of 78.6% and 57.9% at one- and two-year follow-up, respectively. Another recent study using TVUS screening reported sensitivity 100%, specificity 98.9% and positive predictive value 9.4% (35). The cut-off level of CA125 in postmenopausal as compared with premenopausal women was determined in a relatively recent study; in postmenopausal women a cut-off level of 35U/ml gave a specificity of 98% (8).

The achievement of a high predictive value from a positive screening test is crucial for the early detection of often fatal diseases if diagnosed in advanced stage. The findings of the present retrospective study suggest that a combination of TVUS score and serum CA125 level may yield an accurate prediction of underlying epithelial ovarian cancer. Our findings are in accordance with those of the reviewed literature (22, 24, 38, 39). In view of these results, we are currently conducting a prospective trial in a large population from the same geographical area.

In conclusion, we propose that the combination of a TVUS score >35 and CA125 >30U/ml may reliably discriminate benign from malignant diseases of the ovary.

References

1 Landis SH, Murray T, Bolden S and Wingo PA: Cancer statistics 1999. Ca-A Cancer J Clin *49* (1), 1999.

2 The Surveillance Program, Division of Cancer Prevention and Control. Cancer Statistics Review 1973-1987. Washington DC; National Cancer Institute, 1988.

3 Jacobs I, Stabile I, Bridges J *et al*: Multimodal approach to screening for ovarian cancer. Lancet *1*: 268-71, 1988.

4 Jacobs I and Bast RC Jr: The CA125 tumor associated antigen: a review of the literature. Human Reprod *4*: 1-12, 1989.
5 Skates SJ and Singer DE: Quantifying the potential benefit of CA125 screening for ovarian cancer. J Clin Epidemiol *44*: 365-80, 1991.
6 Tamakoshi K, Kikkawa F, Shibata K *et al*: Clinical value of CA125, CA19-9, CEA, CA72-4 and TPA in borderline ovarian tumor. Gynecol Oncol *62(1)*: 67-72, 1996
7 Eagle K and Ledermann JA: Tumor markers in ovarian malignancies. Oncology *2*: 324-329, 1997.
8 Crump C, McIntosh MW, Urbal N, Anderson G and Karlan BY: Ovarian cancer tumor marker behavior in asymptomatic healthy women: implications for screening. Cancer Epidem Biomark Prevent *9*: 1107-1111, 2000.
9 Petricoin E, Ardekani A, Hitt B, Levine P *et al*: Use of proteomic patterns in serum to identify ovarian cancer. Lancet *359*: 572-77, 2002.
10 Pauler DK, Menon U, McIntosh M, Symecko HL, Skates SJ and Jacobs I: Factors influencing serum CA125II levels in healthy postmenopausal women. Cancer Epidem Biomark Prevent *10*: 489-493, 2001.
11 Niloff JM, Knapp RC, Schaetzl E *et al*: CA125 antigen levels in obstetric and gynaecologic patients. Obstet Gynecol *64(5)*: 703-7, 1984.
12 Haga Y, Sakamoto K, Egami H, Yoshimura R and Akagi M: Evaluation of serum CA125 values in healthy individuals and pregnant women. Am J Med Sci *292(1)*: 25-9, 1986.
13 Schwartz PE and Taylor KJ: Is early detection of ovarian cancer possible? Ann Med *27(5)*: 519-28, 1995.
14 Shuiqing MA, Keng S and Jinghe L: A risk of malignancy index in preoperative diagnosis of ovarian cancer. Chin Med J *116(3)*: 396-99, 2003.
15 Alagoz T, Buller RE, Berman M, Anderson B, Manetta A and DiSaia P: What is normal CA125 level? Gynecol Oncol *53(1)*: 93-7, 1994.
16 Jacobs I, Davies AP, Bridges J, Stabile I, Fay T, Lower A, Grudzinskas JG and Oram D: Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. BMJ *306(6884)*: 1030-4, 1993.
17 Menon U and Jacobs IJ: Ovarian cancer screening in the general population: current status. Int J Gynecol Cancer *11(Suppl 1)*: 3-6, 2001.
18 Einhorn N, Sjovall K, Knapp RC *et al*: Prospective evaluation of serum CA125 levels for early detection of ovarian cancer. Obstet Gynaecol *80(1)*: 14-18, 1992.
19 Gohagan JK, Prorok PC, Hayes RB and Kramer BS: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial of the National Cancer Institute: history, organization, and status. Control Clin Trials *21(6 Suppl)*: 51S-272S, 2000.
20 McNeil C: Ovarian cancer screening trials in progress [news]. J Natl Cancer Inst *87*: 1284, 1995.
21 Karlan BY: The status of ultrasound and color Doppler imaging for the early detection of ovarian carcinoma. Cancer Invest *15*: 265-9, 1997.
22 Urban N: Screening for ovarian cancer. We now need a definite randomised trial. BMJ *319*: 1317-8, 1999.
23 Jacobs I, Skates S, Davies A, Woolas R, Jeyerajah A, Weidemann P, Sibley K and Oram D: Risk of diagnosis of ovarian cancer after raised serum CA125 concentration: a prospective cohort study. BMJ *313*: 1355-58, 1996.
24 Jacobs I, Skates SJ, MacDonald N, Menon U, Rosenthal A and Prys DA: Outcome of a pilot randomized controlled trial of ovarian cancer screening. Lancet *253*: 2107-10, 1999.
25 Bese T, Demirkiran F, Arvas M, Oz AU, Kosebay D and Erkun E: What should be the cut-off level of serum CA125 to evaluate the disease status before second-look laparotomy in epithelial ovarian carcinoma? Int J Gynecol Cancer *7(1)*: 42-5, 1997.
26 Bell R, Petticrew M and Sheldon T: The performance of screening tests for ovarian cancer: results of a systematic review. Br J Obstet Gynaecol *105(11)*: 1136-47, 1998.
27 Berek JS and Bast RC Jr: Ovarian cancer screening. The use of serial complementary tumor markers to improve sensitivity and specificity for early detection. Cancer *76(10 Suppl)*: 2092-6, 1995.
28 Skates SJ, Menon U, MacDonald N, Rosenthal AN, Oram DH, Knapp RC and Jacobs IJ: Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmenopausal women. J Clin Oncol *21(10 Suppl)*: 206-10, 2003.
29 Bast RC Jr, Klug TL, St. John E *et al*: A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Eng J Med *309(15)*: 883-887, 1983.
30 O'Connell GH, Ryan E, Murphy KJ and Prefontaine M: Predictive value of CA125 for ovarian carcinoma in patients presenting with pelvic masses. Obstet Gynecol *70*: 930-2, 1987.
31 Urban N, Drescher C, Etzioni R and Colby U: Use of a stochastic simulation model to identify an efficient strategy for ovarian cancer screening. Control Clin Trials *18*: 251-70, 1997.
32 Carlson KJ, Skates SJ and Singer DE: Screening for ovarian cancer. Ann Intern Med *121(2)*: 124-132, 1994.
33 Jacobs I: Overview: progress in screening for ovarian cancer. *In*: Sharp F, Blackett A, Berek J, Bast R, ed. Ovarian Cancer 5. Oxford: Isis Medical Media, 1998.
34 Cohen LS, Escobar PF, Scharm C, Glimco B and Fishman DA: Three-dimensional power Doppler ultrasound improves the diagnostic accuracy for ovarian cancer prediction. Gynecol Oncol *82*: 40-48, 2001.
35 Van Nagell JR Jr, DePriest PD, Reedy MB, Gallion HH, Ueland FR, Pavlik EJ and Kryscio RJ: The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. Gynecol Oncol *77(3)*: 350-6, 2000.
36 De Priest PD: Transvaginal sonography as a screening method for the detection of early ovarian cancer. Gynecol Oncol *65*: 408-14, 1997.
37 Sehouli J, Akdogan Z, Heinze T, Konsgen D, Stengel D, Mustea A and Lichtenegger W: Preoperative determination of CASA (Cancer Associated Serum Antigen) and CA125 for the discrimination between benign and malignant pelvic tumor mass: a prospective study. Anticancer Res *23(2A)*: 1115-8, 2003.
38 Yeh LS, Hung YC, Kao A, Linn CC and Lee CC: Tissue polypeptide specific antigen (TPS) and carbohydrate antigen 125 (CA125) in the early prediction of recurrent ovarian cancer. Anticancer Res *22(6B)*: 3669-71.
39 Chakravarti, Laha and Roy: Handbook of Methods of Applied Statistics, Volume 1, John Wiley and Sons, 1967 pp.392-394.

Received April 14, 2004
Revised August 18, 2004
Accepted October 4, 2004