

ROLE OF A COMBINED SOLUBLE INTERLEUKINE-2 RECEPTOR ALPHA (sIL-R2 α) AND CA-125 SERUM MARKER ASSAY FOR DETECTION OF OVARIAN CANCER

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Detection of ovarian cancer can be improved using a combined diagnostic test consisting of Ca-125 and serum interleukine-2 receptor alpha (sIL-R2 α) at a particular threshold. The objective of the study was to evaluate the accuracy of a diagnostic marker assay that combined Ca-125 and serum interleukine-2 receptor alpha. A case-control study of 38 patients with ovarian cancer, 40 patients with benign ovarian diseases and 31 age-matched healthy controls was designed. Ca-125 and sIL-2R α were detected in patients' serum by standardized chemiluminescent immunometric assays. For Ca-125, a standard cutoff level of 21 U/ml was applied and for sIL-2R α — two cutoff levels were calculated from women included in the control group — one as a mean concentration and the other as an upper limit of a 95% confidence interval. Mean serum concentrations among ovarian cancer patients for CA125 and sIL-2R α were 265.9 ± 40.2 U/ml and 651.0 ± 50.5 U/ml, respectively. The upper limit of the 95% confidence interval for a healthy control group of women was 304.5 U/ml for sIL-2R α . Sensitivity and specificity of 89.4% and 85.9% was achieved when CA125 was combined together with sIL-2R α at a threshold of 304.5U/ml with the condition that both markers are elevated. Sensitivity and specificity of 92.5% and 88.4% was observed when both biomarkers were applied to menopausal women. Serum sIL-2R α in combination with CA125 can be used as a differential diagnostic test for ovarian cancer at a specific threshold, especially among menopausal women.

Key words: ovarian cancer, Ca125, interleukine-2 receptor alpha, screening, diagnostics.

INTRODUCTION

A variety of modalities have been investigated to differentiate the primary nature of adnexial masses (either benign or malignant); however, none of the current facilities has been shown to have adequate sensitivity or specificity to be accepted as a good indicator of malignant potential of ovarian diseases.

Interleukin-2 is a serum polypeptide, produced after activation of T lymphocytes by interaction of specific T-cell antigen receptors with antigen presented by the major histocompatibility complex (Altman *et al.*, 1990). Interleukin-2 is one of the most important cytokines transferring signals for T cells and natural killers, and is involved also in other immunological reactions (Smith, 1988). Signal transferred by interleukin-2 to T cells ensures proliferation and differentiation of effector cells (Mills *et al.*, 1991; Waldmann, 1991).

IL-2 receptor is a complex of three non-covalently associated polypeptide chains: IL-2R α (CD25), IL-2R β (CD122), and IL-2R γ . IL-2R α appears on the surface only after activation of T cells, while IL-2R β and IL-2R γ are expressed permanently (Waldmann, 1991). IL-2R α then is released into the blood stream only after cell proliferation begins (Rubin *et al.*, 1985; 1990). The appearance of sIL-2R α in blood is thought to be one of the most accurate predictors of lymphocyte activation (Rubin *et al.*, 1990). High levels of sIL-2R α have been found in sera from patients with different types of tumours (Brunetti *et al.*, 1999; Lissoni *et al.*, 1990; Rubin *et al.*, 1990).

Barton *et al.* was the first one who published results on serum and ascitic levels of sIL-2R α and their correlation with CA-125 levels (Barton *et al.*, 1993). Almost at the same time, a similar study was conducted by Owens *et al.*; these results were in accordance with the previously published data. Both studies compared serum and ascitic concentra-

tions of sIL-2R α and Ca125 and concluded that the ascitic concentration of sIL-2R α was significantly higher than in sera (Barton *et al.*, 1993; Owens *et al.*, 1993). Later data was published on concentrations of sIL-2R α in sera, ascitic fluid and within the cystic fluid. The study showed that sIL-2R α values were higher in ascitis compared with those in sera, and the concentrations in sera and cyst fluids were comparable. They also noted that the assessment of serum sIL-2R α levels showed potential complementary value to CA125 for the detection of early stage ovarian carcinoma, but a 9% false positive rate limited the significance of cumulative value for a combination of these circulating markers (Sedlacek *et al.*, 2002).

Gebauer *et al.* (1999) established a cutoff level at the 95th percentile of the sIL-2R α concentration distributed in patients with benign diseases at 1200 U/ml. According to their results, 35% of ovarian cancer patients had elevated concentrations, and concentrations of sIL-2R α increased with FIGO stage. Moreover, FIGO-stage III patients with highly elevated sIL-2R α concentrations tended to have better prognosis than those with sIL-2R α levels within the normal range (Gebauer *et al.*, 1999). This may indicate the role of the immune system as well as sIL-2R α in the process of carcinogenesis, which was confirmed in another study in which patients with higher pretreatment serum sIL-2R α levels (more than 1200 U/ml) were found to have longer survival ($P < 0.02$), possibly explained by the presence of activated lymphocytes and a better immune surveillance (Pavlidis *et al.*, 1995).

In the literature there is a gap of approximately ten years in publications about sIL-2R α in ovarian cancer patients, but recently sIL-2R α has been investigated as a prognostic marker in the case of head and neck cancer (Meyer *et al.*, 2010), soft tissue sarcomas (Bien *et al.*, 2010) in patients with Non-Hodgkin's lymphomas (Jo *et al.*, 2010) and there is a lately published article in which ovarian cancer stage was associated with tryptophan degradation and a subsequent strong correlation with sIL-2R α was observed (Sperner-Unterweger *et al.*, 2011).

Currently, a novel approaches using biomarker combinations in cancer diagnostics are being developed; therefore, we consider that the diagnostic abilities of sIL-2R α in combination with other markers can contribute to improved ovarian cancer diagnostics.

The aim of this study was to evaluate whether a diagnostic test consisting of serum soluble interleukine-2 receptor alpha at particular cutoff levels improves ovarian cancer detection when used in combination with ovarian cancer antigen CA125, to test the previously established cutoff levels, and to search for possible correlations of these two antigens.

MATERIAL AND METHODS

A case-control study was conducted, which involved 109 women — 38 patients with ovarian cancer in the 1st study

group, 40 patients with benign ovarian diseases in the 2nd study group, and 31 age-matched healthy controls. All patients were observed at our hospital between January and December 2009. In the 1st study group there were six patients with stage I/II and 32 patients with stage III/IV ovarian cancers. Tumour differentiation was as follows: eight cases with low grade, 14 cases with intermediate, and 16 cases with high-grade differentiation.

Women with severe co-morbidities, previous or co-existing malignancies other than epithelial ovarian carcinoma were excluded from the study. In the first study group only women with ovarian malignancies of epithelial origin were included. In the second study group four women with benign sex cord / stromal and four women with benign germ cell tumours also were included. The control group included women who visited a gynecologist for a routine prophylactic visit and who had undergone a transvaginal ultrasonographic investigation to verify that they did not have any gynecological disease or suspicious adnexial mass.

In the morning of the planned surgery day, serum samples from patients were collected into two Becton and Dickenson 6 ml serum vacutainers. The vacutainers according to protocol were shaken 6–8 times, left 60 to 120 minutes for clot formation and centrifuged for 10 minutes at 1300 rpm. Then serum was aliquoted, divided and transferred into nine 0.5 ml eppendorfs for storage at -80°C . For the control group women, serum samples were taken after transvaginal ultrasonographic examination. The tumour markers CA125 and sIL-2R α levels were determined in patient serum by standard enzyme-labelled chemiluminescent immunometric assay using a Siemens analyzer Immulite 2000 and commercial kits with corresponding antibodies (Immulite Operator's Manual, 2002).

Sensitivity and specificity analysis for single biomarker and combinations of both were calculated in the Vassarstat website. Sensitivity and specificity for menopausal women was calculated separately. Other statistical calculations were performed using SPSS 17.0. To compare sensitivity and specificity of single and combined biomarker diagnostic tests, multivariate regression analysis was performed and a predictive model used to produce a ROC curve. Patients with concentrations of ovarian cancer antigen CA125 exceeding 1000 U/ml and sIL-2R α concentrations exceeding 1500 U/ml were excluded from descriptive analyses for mean biomarker concentration calculations in the groups and their comparison. Standard errors of the mean were calculated. To determine significant differences for variables in the study groups, an ANOVA test was performed and for correlation Pearson's correlation analysis was applied. Ovarian cancer antigens Ca125 and sIL-2R α were compared between groups also using the nonparametric Mann-Whitney test at different thresholds. For Ca125, a standard cutoff level of 21 U/ml was applied. Two cutoff levels for sIL-2R α were calculated from control group patients — one as a mean concentration of the group and the other as the upper limit of the 95% confidence interval for sIL-2R α concentration observed in the group. Microsoft Excel was used

for data collection. Statistically significant correlations and differences between means were accepted at the level of 0.05. The study was approved by the Ethics Committee of Riga Stradiņš University on 12 February 2009.

RESULTS

There were no age differences between study groups and the control group and there were similar proportions of menopausal women within each group (ANOVA; $P > 0.05$). Both biomarker concentrations were significantly higher in ovarian cancer patient groups (ANOVA, One-way; $P < 0.001$). Similarly, biomarker concentrations were higher in ovarian cancer patients even after exclusion of patients with extremely high biomarker concentrations (ANOVA, One-way; $P < 0.001$ for both markers).

There were 11 ovarian cancer patients from the same group with concentrations of CA125 ranging from 1394 to 10 000 U/ml and two patients with sIL-2R α concentrations of 3338 and 4716 U/ml. After exclusion of patients with extremely high biomarker concentrations, mean serum concentrations of CA125 and sIL-2R α in the 1st study group were 265.9 ± 40.2 U/ml and 651.0 ± 50.5 U/ml, respectively.

The area under the curve was higher for CA125 than for sIL-2R α alone or in combination with CA125 (Fig. 1). Addition of IL-2R α and CA125 decreased sensitivity of the diagnostic test at fixed specificities (Table 1). Sensitivity and specificity of 89.4% and 85.9% were achieved when CA125 was combined together with sIL-2R α at a threshold of 304.5 U/ml, with the condition that both markers have to be elevated (Table 2). The highest sensitivity and specificity was observed when both biomarkers were elevated among women in menopause. There were 13.8% patients from the 1st study group and 57.5% patients from the 2nd study group with serum sIL-2R α concentrations below the threshold (349.5 U/ml, upper limit of 95% CI) calculated from control

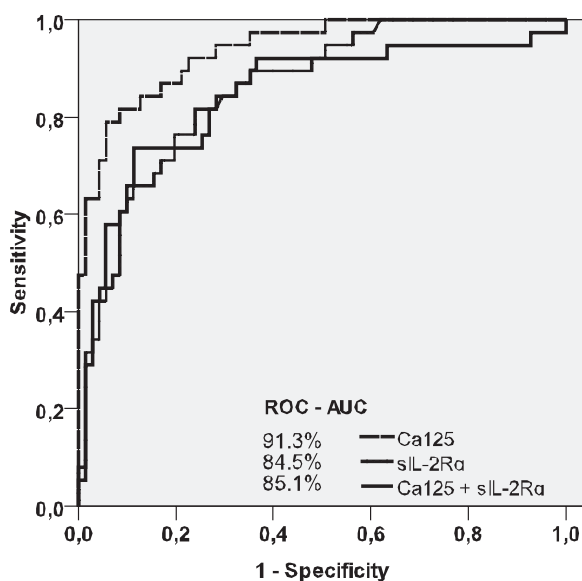


Fig. 1. Performance of the diagnostic test applied for pre- and post-menopausal women taken together.

group patients. If the mean concentration of sIL-2R α derived from the control group is applied for discrimination of patients suffering from benign or malignant diseases, only 5.5% patients from the 1st and 32.5% patients from 2nd study group had serum sIL-2R α concentrations below the threshold, and 64.5% of women from the control group would be diagnosed as having ovarian cancer.

A stronger correlation between Ca125 and sIL-2R α serum concentrations was observed when the analysis was performed without patient exclusion with high serum biomarker concentrations (Pearson Correlation, 2-tailed; 32.3% vs. 28.0%); both of the obtained correlations were statistically significant (Fig. 2).

DISCUSSION

The serum concentration calculated as the threshold for sIL-2R α in our study was significantly lower than that proposed previously — 349.5 vs. 1200 U/ml (Gebauer *et al.*,

Table 1

PERFORMANCE OF SERUM CA125 AND SIL-2R α ALONE AND IN COMBINATION CALCULATED SEPARATELY FOR WOMEN IN MENOPAUSE AND FOR ALL WOMEN TAKEN TOGETHER AT FIXED SPECIFICITIES

Among all women*	AUC (95% CI)	Cross validated sensitivity at specificity		
		90%	95%	98%
CA125	91.3% (85.5–97.2)	74.1%	59.3%	48.1
sIL-2R α	85.1% (77.8–92.4)	61.1%	38.9%	27.8%
CA125 + sIL-2R α	84.5% (76.0–93.0)	65.8%	44.7%	28.9%
Among menopausal women*				
CA125	95.3% (89.6–100.0)	85.0%	80.0%	75.0%
sIL-2R α	85.0% (76.2–93.8)	48.0%	44.0%	28.0%
CA125 + sIL-2R α	84.8% (73.8–95.7)	74.1%	70.4%	48.1%

* Calculations are performed between 1st study group and 2nd study group taken together with control group

Table 2

DIAGNOSTIC PERFORMANCE OF SINGLE AND COMBINED BIOMARKER TEST CONSISTING OF SERUM CA125 AND SIL-2R α AT DIFFERENT THRESHOLDS

Biomarkers and combinations	Among all women		Among menopausal women	
	sensitivity	specificity	sensitivity	specificity
CA125(>21 U/ml)	92.1%	76.0%	92.5%	80.7%
sIL-2R α (>304.5 U/ml)	94.7%	46.4%	96.2%	42.3%
sIL-2R α (>349.5 U/ml)	86.8%	66.1%	88.8%	61.5%
CA125 (>21 U/ml) or sIL-2R α (>304.5 U/ml)	97.3%	36.6%	96.2%	34.6%
CA125 (>21 U/ml) or sIL-2R α (>349.5 U/ml)	97.3%	54.9%	96.2%	53.8%
CA125 (>21 U/ml) and sIL-2R α (>304.5 U/ml)	89.4%	85.9%	92.5%	88.4%
CA125 (>21 U/ml) and sIL-2R α (>349.5 U/ml)	81.5%	87.3%	85.1%	88.4%

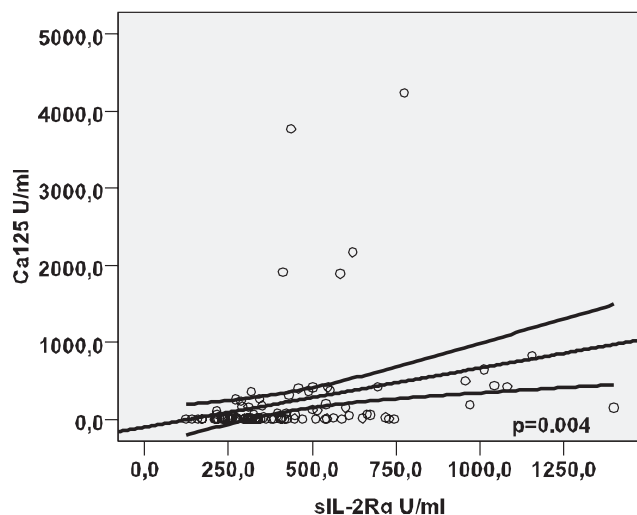


Fig. 2. Correlation between levels of Ca125 and sIL-2R α after patient exclusion with high serum concentrations (Ca125 1000 U/ml; sIL-2R α 1500 U/ml) with 95% confidence interval of mean concentrations (Pearson Correlation, 2-tailed).

1993). This explains why only 35% cancer patients had elevated serum concentration of sIL-2R α in comparison to 86.2% when a threshold of 349.5 U/ml was applied. Another discrepancy is in calculation of the threshold using control group patients. Gebauer *et al.* suggested using the 95th percentile, which is similar, but not exactly the same as the upper limit of the 95% of confidence interval of the mean control group serum concentration, which was used in our study.

To avoid mistakes that may arise from unequal distribution, extremely high concentrations were excluded from some calculations, but, even without exclusion of those ovarian cancer patients, serum sIL-2R α concentration was lower than in reports published previously — 828.7 ± 135.3 for all stages versus 1631 ± 274 and 2596 ± 384 U/ml for stage I/II and stage III/IV epithelial ovarian cancer (Hurteau *et al.*, 1995). Similarly, lower serum sIL-2R α concentrations among benign ovarian tumours were observed — 387.7 ± 33.3 versus 1507 ± 82 U/ml (Hurteau *et al.*, 1995). The results from our study are similar to data published by Bruijn *et al.*, in which ovarian cancer patients had higher serum levels of soluble interleukin-2 receptor alpha compared to patients with benign ovarian tumours or healthy blood donors (means of 750 vs. 469 and 390 U/ml, respectively, $P < 0.001$) (Bruijn *et al.*, 1998). Our data resulted in higher diagnostic performance, because 86.2% and 92.1% of ovarian cancer patients had elevated serum sIL-2R α (> 349.5 U/ml) and Ca125 (> 21 U/ml) concentrations, respectively, whereas in another study 79.6% and 77.8% patients with epithelial ovarian cancer had elevated serum levels of sIL-2R α ($> \text{or} = 71$ U/ml) and CA 125 ($> \text{or} = 83$ U/ml), respectively (Ferdegini *et al.*, 1993).

42.5% and 7.9% of patients with benign disease had also elevated serum levels of sIL-2R α (> 349.5 U/ml) and Ca125 (> 21 U/ml), which were significantly higher proportions

than those in another report on raised serum levels of sIL-2R α and CA 125: 11.6 and 7.0% of patients with benign ovarian diseases, respectively (Ferdegini *et al.*, 1993). Hurteau *et al.* reported elevated serum levels of either sIL-2R α or CA125 in eleven of 12 patients (92%) with potentially curable stage I/II disease and elevations of both sIL-2R α and CA125 in 8 of 12 (67%) (Hurteau *et al.*, 1995). According to our study, a diagnostic algorithm using elevation of either sIL-2R α or CA125 had sensitivity of 97.3% with an unacceptably low specificity of 36.6% — 54.9%, depending on the cutoff level applied. The same algorithm was applied by Ferdegini *et al.*, who reported a sensitivity of 88.9%, and the association of sIL-2R α and CA 125 had a specificity of 98.4% for epithelial ovarian cancer (Ferdegini *et al.*, 1993). In our population, performance of the diagnostic test showed similar high values, reaching sensitivity and specificity of 89.4% and 85.9%, when elevated serum concentrations of sIL-2R α and CA125 above 304.5 U/ml and 21 U/ml were applied at the same time. Another algorithm using simultaneously elevated biomarkers with a higher threshold for sIL-2R α (349.5 U/ml) had lower test sensitivity (81.5%). In contrast, the specificity reported by Hurteau *et al.* was low for the combination of CA 125 and soluble IL-2R alpha, reaching 27.1% at sensitivity of 88.5%, respectively (Hurteau *et al.*, 1995). The wide differences in the values reported can be explained by the various threshold levels applied.

The high diagnostic ability of our diagnostic algorithm may be explained by homogeneity of the control group, as there were no patients with and elevated Ca125 concentration above 21 U/ml. Moreover, even higher diagnostic performance was achieved when the same algorithm was applied for women at menopausal age, resulting in sensitivity and specificity of 92.5% and 88.4%, respectively.

Ca125 had the largest area under the curve when compared to sIL-2R α or when both markers were combined. Also diagnostic sensitivity and specificity of Ca125 was higher when compared to sIL-2R α in a population consisting of both pre- and postmenopausal women (92.1% and 76.0%) and also among menopausal women only (92.5 % and 80.7%). However, specificity was lower when compared to the developed diagnostic algorithm that achieved sensitivity and specificity of 89.4% and 85.9% in a population consisting of both pre- and postmenopausal women and 92.5% and 88.4% in a menopausal women population.

A stronger correlation between Ca125 and sIL-2R α serum concentration was observed when the analysis was performed without patient exclusion with high serum biomarker concentrations (Pearson correlation, 2-tailed; 32.3% vs. 28.0%); both of the obtained correlations were statistically significant (Fig. 2). In two separate studies, correlation between serum Ca125 and sIL-2R α was not observed when evaluated in serum and ascites (Hunter *et al.*, 1990; Barton *et al.*, 1993). The correlation in our study was weak, which may indicate the effect of other factors such as host immune responsiveness to tumour burden. Higher serum concentrations of sIL-2R α are associated with poor responsiveness to

treatment, which obviously suggests the impact of immune response on the level of sIL-2R α (Lauria *et al.*, 1992). Higher levels of sIL-2R α have been observed in malignant and autoimmune diseases, which may indicate impaired host immunity, but not tumour spread (Chilosi *et al.*, 1987; Symons *et al.*, 1988). Further evaluation of the proposed algorithm among other benign and malignant gynecological diseases is necessary.

In conclusion, addition of serum sIL-2R α level to ovarian cancer antigen CA125 levels improves ovarian cancer diagnostics. However, further prospective studies with larger sample sizes are required to confirm our findings.

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SERUMA ŠĶĪSTOŠĀ INTERLEIKĪNA 2 RECEPTORA ALFA (sIL-R2 α) UN CA-125 KOMBINĒTAIS TESTS OLNĪCU VĒŽA DIAGNOSTIKAI

Olnīcu vēža diagnostiku var uzlabot, izmantojot kombinēto diagnostikas testu, kas sastāv no olnīcu vēža biomarkiera Ca125 un serumā šķīstošā interleikīna 2 receptora alfa. Pētījuma mērķis bija novērtēt diagnostiskā testa precizitāti olnīcu vēža diagnostikā. Gadījumu kontroles pētījumā bija iesaistītas 38 pacientes ar olnīcu vēzi, 40 pacientes ar labdabīgu olnīcu audzēju un 31 vecumam atbilstošas veselas sievietes kontroles grupā. Ar olnīcu vēzi asociētā antigēna Ca-125 un serumā šķīstošā interleikīna 2 receptora alfa koncentrācija tika noteikta, izmantojot standartizētu hemiluminiscences imunometriskās analīzes metodi. Kā robežvērtība biomarkierim Ca125 tika izmantota seruma koncentrācija 21 U/ml, biomarkierim sIL-R2 α tika izmantoti divi robežlielumi — aprēķinātā vidējā seruma koncentrācija un 95% konfidences intervāla augšējā robeža starp kontroles grupas sievietēm. Vidējā seruma koncentrācija olnīcu vēža pacientēm biomarkieriem CA125 un sIL-2R α bija atbilstoši $265,9 \pm 40,2$ U/ml un $651,0 \pm 50,5$ U/ml. Diagnostiskā testa jutīgums un specifiskums sasniedza 89,4% un 85,9%, kad CA125 tika kombinēts kopā ar sIL-2R α pie robežvērtības 304,5 U/ml ar nosacījumu, ka abām biomarkieru koncentrācijām serumā ir jābūt paaugstinātām. Menopauzē esošu sieviešu populācijā diagnostiskā testa jutīgums un specifiskums sasniedza 92,5% un 88,4%. Serumā šķīstošā interleikīna 2 receptora alfa koncentrācijas noteikšanu serumā kopā ar biomarkieri Ca125 var izmantot kā diagnostisko testu olnīcu vēža diferenciāldiagnostikai pie noteiktiem robežlielumiem, īpaši menopauzē esošu sieviešu populācijā.