Diagnostic test for ovarian cancer composed of ovarian cancer symptom index, menopausal status and ovarian cancer antigen CA125

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Summary

The objective of the study was to evaluate accuracy of the diagnostic test composed of the ovarian cancer symptom index, ovarian cancer antigen CA125 and menopausal status. *Methods:* A case-control study consisting of 75 women - 24 patients with ovarian cancer, 20 patients with benign ovarian diseases, and 31 age-matched healthy controls. *Results:* Sensitivity and specificity for the ovarian cancer symptom index alone was 83.3% and 48.3%, respectively. Specificity improved up to 70.9% when menopausal status was added. When CA125 (at cut-off level of 21 U/ml) was added to the ovarian cancer symptom index, the highest sensitivity and specificity was achieved resulting in 79.1% and 100.0%, respectively. *Conclusions:* The ovarian cancer symptom index could be used as a first-step screening tool in combination with serum biomarkers followed by TVS examination with an acceptable sensitivity and specificity. However, further prospective studies with larger sample size are needed to reach clear conclusions.

Key words: Ovarian cancer; Symptoms; Screening.

Introduction

Due to lack of specific symptoms and effective screening, a majority of patients with ovarian cancer are diagnosed at advanced stages. However, recently attention has turned again to the development of the ovarian cancer symptom index which was first described by Goff *et al*. in the USA in 2007 [1]. A correlation was found between ovarian cancer and eight symptoms with defined duration and frequency. Then, in 2007, a consensus statement from the American Cancer Society, the Gynecologic Cancer Foundation, and the Society of Gynecologic Oncologists recommended that women discuss the following symptoms with a physician: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency). Although these symptoms can be caused by conditions other than ovarian cancer, women who experience these symptoms almost daily for more than a few weeks are encouraged to see their physicians, preferably a gynecologist [2].

Previous studies showed a sensitivity and specificity of the ovarian cancer symptom index comparable to ovarian cancer antigen CA125 alone – 64% and 88%, respectively [3]. The main role of the ovarian cancer symptom index is still to select patients for referral to gynecological consultation and further investigations.

Material and Methods

Ethical approval was given for this study by the Ethics Committee of Riga Stradins University. A case-control study consisting of 75 women - 24 patients with ovarian cancer in Group A, 20 patients with benign ovarian diseases in Group B, and 31 age-matched healthy controls in Group C. Patients were divided into the two study groups after surgery according to final histological diagnosis. Group B consisted of patients thought to have had ovarian cancer before the operation.

Patients with severe co-morbidities, previous or other coexisting malignancies were not included in the study. In both study groups tumors arising only from epithelial origin were included. In study Group A most of the patients had serous type ovarian adenocarcinomas, in addition also one patient with mucinous and one with an endometroid adenocarcinoma subtype were included. In study Group B, the majority of patients similarly had serous type cystadenomas, but also three endometroid and five mucinous benign ovarian cystadenomas were included.

For the control group serum samples were taken after transvaginal ultrasonographic (TVS) examination to ensure there was no gynecological pathology.

Before entering the study all women were asked about the frequency and duration of eight symptoms (pelvic pain, abdominal pain, increased abdominal size, abdominal bloating, difficulty in eating, feeling full quickly, urinary urgency and urinary frequency). Symptoms were considered positive, if any of them were present for < 1 year and had occurred > 12 days per month. All questions were asked by the doctor ensuring that all patients had understood the asked questions. In this questionnaire patients were not asked about symptom severity.

In the control group women were chosen who attended gynecologists in an outpatient clinic.

Tumor marker CA125 was detected in patient's serum by standard enzyme-labeled chemiluminescent immunometric assay ADVIA Centaur CA125 II™, Multi-Diluent 1, Bayer, using Siemens analyzer Immulite-2000 [4, 5].

Sensitivity, specificity and positive predictive value (PPV) for the ovarian cancer symptom index together with women's menopausal status and ovarian cancer associated antigen CA125 among study and control groups were calculated using the Vassarstat statistical program [6].

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Table 1. — *Comparison of sensitivity and specificity of the ovarian cancer symptom index in combination with menopausal status and ovarian cancer antigen CA125 at different cut-off levels.*

	Group A/ Group C	Group B/ Group C	Group A/ Group B
Ovarian cancer symptom index alone	83.3%/48.3%	55.0%/48.3%	83.3%/45.0%
Menopausal status alone	54.1%/70.9%	40.0%/77.5%	54.1%/60.0%
CA125 (> 21 U/ml) alone	95.8%/100.0%	55.0%/100.0%	95.8%/45.0%
combined with CA125 (> 21 U/ml)	79.1%/100.0%	25.0%/100.0%	79.1%/75.0%
combined with CA125 (> 35 U/ml)	70.8%/100.0%	20.0%/100.0%	70.8%/80.0%
combined with CA125 (> 65 U/ml)	70.8%/100.0%	20.0%/100.0%	70.8%/80.0%
combined with menopausal status and CA125 (> 21 U/ml)	50.0%/100.0%	20.0%/100.0%	50.0%/80.0%
combined with menopausal status and CA125 (> 35 U/ml)	45.8%/100.0%	15.9%/100.0%	45.8%/85.0%
combined with menopausal status and CA125 (> 65 U/ml)	45.8%/100.0%	15.9%/100.0%	45.8%/85.0%

Sensitivity and specificity of the ovarian cancer symptom index combined with serum antigen CA125 was calculated at cut-off levels of 21 U/ml, 35 U/ml and 65 U/ml. Individually sensitivity and specificity of the ovarian cancer symptom index was calculated after addition of menopausal status as an independent factor and after that in combination with CA125 at different cut-off levels. A statistically significant correlation or difference between variables and groups were accepted at the level of 0.05.

Results

Sensitivity and specificity for ovarian cancer antigen CA125 alone was higher than for the ovarian cancer symptom index alone or in combination with other variables – 95.8% and 100.0%, respectively (Table 1).

In Group A and B there were 15 menopausal women in each group and 22 menopausal women in Group C. Addition of menopausal status to the ovarian cancer symptom index alone improved specificity of the diagnostic test. The highest rates of sensitivity and specificity were observed when the ovarian cancer symptom index was used in combination with ovarian cancer biomarker CA125 elevated above 21 U/ml without addition of menopausal status. Sensitivity and specificity of the ovarian cancer symptom index remained low when applied for discrimination of patients with benign ovarian tumors from the control group women. The highest sensitivity and specificity for ovarian cancer patient isolation from patients with benign ovarian tumors was observed when ovarian cancer antigen CA125 was added to the ovarian cancer symptom index at the cut-off level of 21 U/ml. Specificity improved by 5% for each factor when menopausal status and higher cut-off level for ovarian cancer antigen CA125 was applied with remarkable decrease in sensitivity (Table 1).

PPV for the ovarian cancer symptom index alone was 0.06% at a sensitivity and specificity of 83.3% and 48.3%, respectively, but when combined with serum CA125 elevated above 21 U/ml, it was 3.06% at test sensitivity and specificity of 79.1% and 100% with an estimated average disease prevalence of 0.04%.

Discussion

Previously it was thought that ovarian cancer has no specific symptoms, especially for early-stage detection. Recently, researchers from the USA observed that symptoms, in combination with their frequency and duration, had a sensitivity of 56.7% for identifying early-stage disease and 79.5% for identifying advanced-stage disease with specificities ranging from 86% to 90%. In that study the symptom index performed similarly to CA125 for detecting any stage of the disease [7]. In similar studies the ovarian cancer symptom index revealed sensitivity and specificity ranging from 64.0%-68.0% and 84.7%-95.0%, respectively, among all stages [8-10].

At first it was observed by Goff *et al*., in a particular study where more pronounced symptom expression between ovarian cancer patients compared to patients with benign ovarian diseases; control group patients were also found [1]. A correlation between the ovarian cancer symptom index and stage among ovarian cancer patients was not statistically significant, but in other studies a positive symptom index prevalence of 44.8-56.7% for patients with Stage I/II disease and in 72.9-79.5% for patients with Stage III/IV disease was found [1, 7]. Moreover no statistically significant correlation was observed between the ovarian cancer symptom index and ovarian cancer antigen CA125. The reason for this might be a quite frequent expression of symptoms among control group women. Particular control groups do not reflect the average symptom distribution in the whole population. Average distribution of a positive ovarian cancer symptom index in the population was reported to be about 3% [11]. Regardless of control group selection bias, a positive ovarian cancer symptom index was observed up to 51.6% of control group women without finding any ovarian cancer. Even more - six women from the control group had three and more frequently repeating symptoms that had appeared during the previous 12 months.

Despite attempts to eliminate distribution bias of ovarian cancer antigen CA125 among ovarian cancer patients, they were normally distributed before and after exclusion of patients with ovarian cancer antigen CA125 exceeding 1000 U/ml, but a correlation between the ovarian cancer symptom index was still not achieved. Irrespectively of a high prevalence of the positive ovarian cancer symptom index in the control group, a strong correlation between the ovarian cancer symptom index and study groups was observed.

Overall, the sensitivity and specificity of the symptom index alone was 83.3 and 48.3, which is not similar to the data reported before. In a case control study by Mi-Kyung *et al*. consisting of 116 women with epithelial ovarian

cancer and 209 control group women sensitivity and specificity were 65.5% and 84.7%, respectively [8]. Specificity of the diagnostic test improved with addition of menopausal status and ovarian cancer antigen CA125, because none of the control group women had elevated CA125 and specificity reached 100% with slightly decreasing sensitivity. The highest sensitivity/specificity of the ovarian cancer symptom index according to our study data was achieved after addition of only one parameter – CA125 at a cut-off level of 21 U/ml which corresponds to other studies. Andersen *et al*. reported even higher diagnostic values for the combined symptom index with CA125 - sensitivity and specificity of 80.6% and 83.5% for early-stage ovarian cancer and 95.1% and 83.5% for late-stage cancers, respectively [8]. The addition of menopausal status to the ovarian cancer symptom index with simultaneously elevated serum ovarian cancer antigen decreased test sensitivity because there were a lot of ovarian cancer patients at premenopausal age which were lost with such approach. In the same study the symptom index identified cancer in 50% of the affected women who did not have elevated CA125 levels and 11.8% of the high-risk women without cancer also received a positive symptom index score [8].

According to our data, PPV for the ovarian cancer symptom index alone was lower than previously published, but when applied in combination with serum concentration of CA125, it was even higher than reported before. The estimated positive predictive value of the symptom index or symptoms meeting the consensus criteria was 0.6%-1.1% overall and less than 0.5% for early-stage disease in the study of 812 case patients and 1,313 population-based control subjects [12].

It is estimated that there is only one ovarian cancer patient found among 100 patients with the ovarian cancer symptom index. Historically the goal of a screening test has been to achieve a PPV greater than 10% to be considered cost effective and have an acceptable risk for the population being screened. Results from one of the largest trials on ovarian cancer symptom research suggest that there are a lot of women with false-positives with the ovarian cancer symptom index and that the test could be improved with addition of some other biomarkers. In the same study most case patients had a positive ovarian cancer symptom index result within five months before diagnosis [12]. That means that despite a rather short period between symptom appearance and diagnosis, it still remains a significant period in context of optimal debulking surgery.

Conclusions

The ovarian cancer symptom index could be used as first-step screening tool in combination with serum biomarkers followed by TVS examination with an acceptable sensitivity and specificity. However, further prospective studies with a larger sample size are needed to reach clear conclusions.

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