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Predictive power of sexual hormones and tumor markers in endometrial cancer

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Abstract
Objective The purpose of the present study was to investigate the predictive power of sexual hormones and tumor markers in endometrial cancer.
Methods A total of 135 healthy women were prospectively compared with 135 women who had histopathologically confirmed endometrial cancer. Both the groups of women were matched by age and body mass index.
Results When compared with healthy controls, women with endometrial cancer had significantly higher serum levels of CA-125, CA 19-9, prolactin and thyroid-stimulating hormone, whereas significantly lower serum concentrations of α-fetoprotein, CA 15-3, follicle-stimulating hormone and luteinizing hormone (LH). Tumor stage correlated positively and significantly with serum levels of prolactin, CA-125 and CA 19-9 as did tumor grade with serum concentrations of LH, estradiol, prolactin and CA-125. Serum CA-125 levels >35 U/ml were found to have a sensitivity of 42.2%, specificity of 87.4%, positive-predictive value of 77.0% and negative-predictive value of 60.2%. Besides endometrial cancer could be diagnosed with 16.3% sensitivity, 100.0% specificity, 100.0% positive- and 54.4% negative-predictive values with serum prolactin levels >30 ng/ml.
Conclusions Because serum concentrations of CA-125 can be elevated in various malignancies, it is obvious that it is neither specific nor accurately diagnostic for endometrial tumors. What is more, the distinct effects of physiological factors on prolactin secretion shadow the credibility of this hormone in early diagnosis of endometrial tumors. Thus, either prolactin or CA-125 is far from being utilized as the sole entity for screening endometrial cancer. Therefore, both parameters should be regarded as the components of a biochemical screening panel that is to be developed in future.

Keywords CA-125 · Endometrial cancer · Prediction · Prognosis · Prolactin

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Introduction

Addressed as the most common gynecologic malignancy in developed countries, endometrial cancer accounts for the majority of uterine corpus tumors [1]. Despite the significant advance in diagnosis and treatment of gynecological cancers, endometrial cancer associated mortality rate seems to increase in relation with the gradually rising annual incidence [2, 3].

Diagnostic failures and therapeutic difficulties have emphasized the significance of screening programs as well as clinical methods for prognostic evaluation. However, there is no efficient and reliable screening test for asymptomatic women with a moderate risk of endometrial cancer [4]. Because physical findings are normal in most women with early endometrial cancer, pelvic examination has limited diagnostic power. Similarly, Pap smear is of less value in determination of endometrial tumors. Despite being recommended for the evaluation of menopausal women with a high risk of endometrial cancer, endometrial biopsy is not used as a general screening test [5].

Thus, studies have focused on developing a biochemical panel that would indicate the early cases of endometrial cancer as well as subjects with poor prognosis. Serum levels of CA-125 have been shown to associate with the progression of endometrial cancer so that it can be used as an independent indicator for extra-uterine involvement of the disease [6–9]. Also, a significant relationship has been reported to exist between survival and serum concentrations of CA 15-3 and CA 19-9 in women with endometrial cancer [10].

Although many clinical trials have been conducted so far, no valid biochemical panel is available for either screening or prognostic evaluation of endometrial tumors. Therefore, it is not unwise to begin the pursuit of such a test with the sexual hormones and tumor markers which are frequently used in daily clinical practice. The present study aims to investigate the predictive power of sexual hormones and tumor markers in endometrial cancer.

Materials and methods

The present study was approved by the Institutional Review Board and Ethics Committee of Dr Zekai Tahir Burak Women Health Research and Education Hospital where the study was conducted at the Department of Gynecological Oncology between June 2007 and 2008. Written informed consent was obtained from each participant.

A total of 135 healthy women were prospectively compared with 135 women who had histopathologically proven endometrial cancer. Women with endometriosis, adenomyosis, pelvic inflammatory disease, peritoneal tuberculosis and thyroid disease were excluded as were women with a history of ovarian, cervical, tubal, breast, pulmonary, gastric, hepatic and intestinal cancer.

The age, height and weight of every participant was recorded to calculate the body mass index by the formula [weight (kg)/height^2 (m^2)]. After a complete physical examination was performed in each participant, a peripheral blood sample of 10 ml was drawn by standardized phlebotomy procedure. The collected samples were put into anticoagulant-free glass tubes which were kept at room temperature for 2 h. Sera were separated by centrifugation and immediately frozen to be stored at −80°C. No more than two freeze–thaw cycles were applied for any sample.

At the laboratories of the study center, electrochemoluminescence immunoassay was used to measure serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and prolactin (Roche Elecsys 1010/2010, Roche Diagnostics, Mannheim, Germany). On the other hand, serum levels of thyroid-stimulating hormone (TSH) levels were recorded by radioimmunoassay (DSL Diagnostic Systems Laboratories, USA). Meanwhile, serum levels of α-fetoprotein (AFP), carcinoembryonic antigen (CEA), CA-125, CA 19-9 and CA 15-3 were specified by electrochemoluminescence immunoassay (Roche Elecsys Kits, Roche Diagnostics, Mannheim, Germany).

Following FIGO guidelines, surgical staging was performed for every participant in whom endometrial tumor was detected by endometrial sampling techniques and confirmed histologically [11]. After the surgical specimens were conserved in 10% buffered solution of formaldehyde for 24 h, they were evaluated and defined histopathologically according to the FIGO classification [12].

The intra-assay coefficients of variation (CVs) were reported to be 5.3, 3.8, 7.8, 6.2, 5.0, 5.0, 6.2, 3.8, 5.3 and 4.7% while the inter-assay CVs were documented as 1.8, 1.5, 10.0, 5.7, 4.1, 4.0, 5.7, 1.5, 1.8 and 7.2% for FSH, LH, TSH, estradiol, prolactin, AFP, CEA, CA-125, CA 19-9 and CA 15-3, respectively. The normal range was ratified as 3–20, 5–20, 0.4–4.0 mIU/l, 25–75 pg/ml, 4–30, 0–10, 0–2.5 ng/ml, 0–35, 0–37 and 0–31 IU/ml for serum levels of FSH, LH, TSH, estradiol, prolactin, AFP, CEA, CA-125, CA 19-9 and CA 15-3, respectively. However, serum concentrations of CEA were accepted to differ between 0 and 5.0 ng/ml for smokers.

The collected data were analyzed by Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago, IL, USA) in computerized media. Data were expressed as mean ± standard deviation or percentages where appropriate. Parametric variables of two groups were compared by independent samples *t* test, while Mann–Whitney *U* test was used to compare those of three groups. Non-parametric variables of two groups were compared by one-way ANOVA, whereas Kruskal–Wallis test was utilized to compare those of three groups. In case statistical significance was detected by either Mann–Whitney *U* or Kruskal–Wallis test, post hoc test was applied. The possible relationship between a particular biochemical parameter and stage or grade was evaluated by Pearson correlation test. Predictive power of the gynecological hormones and tumor markers were determined by χ^2 test and the selectivity of these parameters were demonstrated by receiver operating characteristic (ROC) curves. $P < 0.05$ was considered to be statistically significant.

Results

The demographic and clinical data of women with endometrial cancer are compared with those of healthy controls in Table 1, while Table 2 compares the mean serum concentrations of sexual hormones and tumor markers of the control and patient groups. As shown in

Table 1 Demographic and clinical features of healthy controls and patients with endometrial cancer

	Endometrial cancer ($n = 135$)	Healthy control ($n = 135$)	P
Mean age (years)	54.3 ± 4.3	53.4 ± 4.9	0.142
Mean body mass index (kg/m^2)	24.08 ± 2.40	23.56 ± 2.53	0.082
Mean gravidity	1.4 ± 0.8	2.0 ± 1.0	0.001*
Mean parity	0.9 ± 0.5	1.4 ± 0.6	0.001*
Mean age at menarche (years)	11.0 ± 0.6	13.1 ± 0.8	0.001*
Endometriosis	12 (8.9%)	4 (3.0%)	0.030*
Menopause	107 (79.3%)	100 (74.1%)	0.315
Mean age at menopause (years)	45.1 ± 1.1	42.4 ± 1.3	0.001*
Hormone replacement therapy	58 (43.0%)	56 (41.5%)	0.796
Smoking	22 (16.3%)	17 (12.6%)	0.388
Hypertension	12 (8.9%)	5 (3.7%)	0.038*
Diabetes mellitus	6 (4.4%)	3 (2.2%)	0.044*

* $P < 0.05$ was accepted to be statistically significant

Table 2 Serum concentrations of sexual hormones and tumor markers in patients with endometrial cancer and healthy controls

	Endometrial cancer ($n = 135$)	Healthy control ($n = 135$)	P
Follicle-stimulating hormone (mIU/ml)	24.49 ± 11.15	28.02 ± 16.10	0.038*
Luteinizing hormone (mIU/ml)	20.81 ± 8.77	25.87 ± 13.77	0.001*
Thyroid-stimulating hormone (mIU/l)	2.63 ± 1.09	2.31 ± 0.97	0.012*
Estradiol (pg/ml)	29.56 ± 13.34	31.67 ± 16.66	0.252
Prolactin (ng/ml)	21.22 ± 9.35	18.12 ± 7.53	0.003*
Alpha-fetoprotein (ng/ml)	3.55 ± 2.07	4.24 ± 2.66	0.017*
Carcinoembryonic antigen (ng/ml)	2.29 ± 1.47	2.07 ± 1.35	0.212
CA-125 (IU/ml)	35.68 ± 11.05	26.79 ± 7.45	0.001*
CA 19-9 (IU/ml)	32.99 ± 7.50	23.55 ± 5.61	0.001*
CA 15-3 (IU/ml)	23.41 ± 7.37	25.63 ± 5.44	0.005*

* $P < 0.05$ was considered to be statistically significant

Table 3 Power of sexual hormones and tumor markers in predicting endometrial cancer

	Sensitivity (%)	Specificity (%)	PPV[a] (%)	NPV[b] (%)	χ^2	P
Follicle-stimulating hormone	79.3	27.4	52.2	56.9	72,593	0.001*
Luteinizing hormone	68.2	26.7	48.2	45.6	46,459	0.001*
Thyroid-stimulating hormone	8.9	97.8	80	51.8	213,333	0.001*
Estradiol	1.5	92.6	16.7	48.4	224,133	0.001*
Prolactin	16.3	100	100	54.4	189,170	0.001*
Alpha-fetoprotein	0.7	97	25	49.2	254,237	0.001*
Carcinoembryonic antigen	34.8	71.9	55.3	52.4	37,037	0.001*
CA-125	42.2	87.4	77	60.2	55,126	0.001*
CA 19-9	21.5	100	100	56	166,459	0.001*
CA 15-3	14.1	82.2	44.2	44.9	125,393	0.001*

* $P < 0.05$ was accepted to be statistically significant

[a] PPV: positive-predictive power

[b] NPV: negative-predictive power

Table 3 is the predictive power of the aforementioned biochemical parameters in distinguishing endometrial cancer patients. Figure 1 represents the ROC curves that were drawn to indicate the selectivity of (1) prolactin (2) CA-125 and (3) prolactin and CA-125 combination for endometrial cancer.

Within the reviewed patients with endometrial tumors, the most common histologic type was detected as

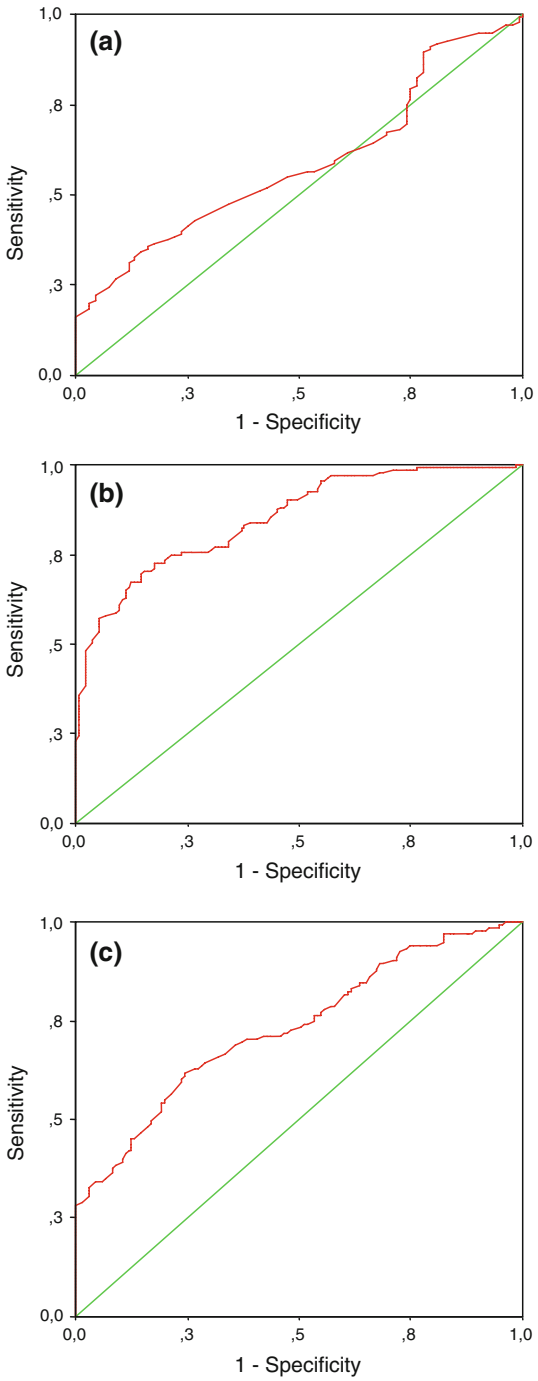

Fig. 1 ROC curves for **a** prolactin, **b** CA-125, **c** combined prolactin and CA-125

endometrioid adenocarcinoma (75.6%) which was followed by mixed type (9.6%), clear cell (5.3%), mucinous (4.4%) and serous papillary (3.7%) carcinoma. Squamous carcinoma and undifferentiated carcinoma was diagnosed in one patient each.

Eighty-two patients with endometrial cancer (60.7%) were assigned to stage I, whereas 21 patients (15.6%) had stage II endometrial tumor. Besides, stage III and stage IV endometrial cancer was specified in 26 (19.3%) and 6 (4.4%) patients, respectively. Table 4 demonstrates the mean serum concentrations of sexual hormones and tumor markers in the patients at different stages of endometrial cancer. To accomplish proper statistical analysis, patients with stage IV endometrial tumor were allocated with those at stage III. A positive and significant correlation was found to exist between the stage and mean serum prolactin levels (correlation coefficient 0.668, $P = 0.001$), CA-125 (correlation coefficient 0.233, $P = 0.007$) and CA 19-9 (correlation coefficient 0.227, $P = 0.008$).

On the other hand, grade-1 endometrial cancer was detected in 18.5% (25/135) of the reviewed patients, while grade-2 endometrial cancer was present in 66 (48.9%) and 44 (32.6%) subjects, respectively. Table 5 compares patients with grades 1, 2 and 3 tumors according to the serum concentrations of sexual hormones and tumor markers. Tumor grade correlated positively with LH (correlation coefficient 0.242, $P = 0.005$), prolactin (correlation coefficient 0.451, $P = 0.001$) and CA-125 (correlation coefficient 0.363, $P = 0.001$). However, tumor grade and estradiol was found to correlate negatively (correlation coefficient -0.221, $P = 0.010$).

Discussion

Modern practice of gynecological oncology considers endometrial cancer as a challenging disease due to the lack of a valid and non-invasive screening method [1, 5]. Hence, the present study seeks the answer to the question whether the commonly used sexual hormones and tumor markers can be adopted in a biochemical screening panel for endometrial tumors.

When compared with healthy controls, patients with endometrial cancer are found to have significantly lower levels of FSH, LH, AFP and CA 15-3 in the present study. Several studies have reported subdued values of FSH and LH which have been proposed to indicate a participating hypothalamic dysfunction in the pathogenesis of endometrial cancer. This hypothesis seems to be further supported by the moderate to high sensitivity of FSH and LH values so that both hormones seem to distinguish those with endometrial cancer within a group of asymptomatic women [13–15].

Although several previous studies documented that the expression of AFP and CA 15-3 is decreased in case of endometrial cancer, no reasonable theory has been proposed to explain the underlying mechanism [13–15]. In accordance with the literature, the present study has assigned a high specificity and a low to moderate sensitivity for both AFP and CA 15-3 so that both tumor markers may be recognized as molecules whose production

Table 4 Expression of sexual hormones and tumor markers according to stage in patients with endometrial cancer

	Stage I ($n = 82$)	Stage II ($n = 21$)	Stage III–IV ($n = 32$)	P
Follicle-stimulating hormone (mIU/ml)	23.68 ± 11.77	26.75 ± 10.05	25.10 ± 10.24	0.503
Luteinizing hormone (mIU/ml)	19.64 ± 8.96	22.75 ± 7.91	22.53 ± 8.56	0.157
Thyroid-stimulating hormone (mIU/l)	2.62 ± 1.09	2.65 ± 1.09	2.65 ± 1.13	0.987
Estradiol (pg/ml)	31.04 ± 14.01	27.97 ± 12.93	26.81 ± 11.55	0.264
Prolactin (ng/ml)	16.45 ± 7.09	24.51 ± 4.85	31.26 ± 7.72	0.001[a,*]
Alpha-fetoprotein (ng/ml)	3.28 ± 1.97	3.73 ± 1.99	4.10 ± 2.29	0.149
Carcinoembryonic antigen (ng/ml)	2.06 ± 1.28	2.42 ± 1.36	2.80 ± 1.85	0.048[a,*]
CA-125 (IU/ml)	33.32 ± 9.97	40.39 ± 13.26	38.65 ± 10.76	0.006[b,*]
CA 19-9 (IU/ml)	32.09 ± 6.71	32.76 ± 7.63	35.44 ± 8.91	0.099
CA 15-3 (IU/ml)	23.26 ± 7.31	24.09 ± 9.38	23.32 ± 6.19	0.898

* $P < 0.05$ was accepted to be statistically significant

[a] Statistical significance exists between stages I and III–IV

[b] Statistical significance exists between stages I and II

Table 5 Expression of sexual hormones and tumor markers according to grade in patients with endometrial cancer

	Grade 1 ($n = 25$)	Grade 2 ($n = 66$)	Grade 3 ($n = 44$)	P
Follicle-stimulating hormone (mIU/ml)	20.28 ± 13.76	25.51 ± 10.41	25.36 ± 10.28	0.112
Luteinizing hormone (mIU/ml)	15.89 ± 9.72	21.51 ± 7.98	22.57 ± 8.53	0.006[a,*]
Thyroid-stimulating hormone (mIU/l)	2.83 ± 1.10	2.50 ± 1.08	2.71 ± 1.11	0.363
Estradiol (pg/ml)	37.04 ± 17.21	28.12 ± 11.20	27.48 ± 12.64	0.007[b,*]
Prolactin (ng/ml)	20.26 ± 5.14	15.92 ± 7.60	29.71 ± 7.26	0.001[c,*]
Alpha-fetoprotein (ng/ml)	3.21 ± 2.30	3.25 ± 1.79	4.19 ± 2.21	0.040*
Carcinoembryonic antigen (ng/ml)	2.13 ± 1.63	2.08 ± 1.12	2.69 ± 1.76	0.086
CA-125 (IU/ml)	27.98 ± 7.65	35.77 ± 10.20	39.90 ± 11.74	0.001[a,*]
CA 19-9 (IU/ml)	32.44 ± 5.43	32.23 ± 7.62	34.42 ± 8.23	0.3
CA 15-3 (IU/ml)	23.88 ± 8.80	22.82 – 7.17	24.02 ± 6.90	0.663

* $P < 0.05$ was accepted to be statistically significant

[a] Statistical significance exists between grades 1 and 3

[b] Statistical significance exists between grades 1 and 2

[c] Statistical significance exists between grades 2 and 3

is greatly induced by a newly growing endometrial tumor. Right alongside with AFP and CA 15-3, the reviewed endometrial cancer patients are found to have significantly elevated serum concentrations of TSH, prolactin, CA-125 and CA 19-9. This predominance of protein hormones and markers may be attributed to the enhanced synthetic activity within the endometrial cells that are being exposed to carcinogenesis [13–15].

As notified by earlier studies including that of Yurkovetsky et al. CA-125 is defined to be highly specific and moderately sensitive for endometrial tumors [14–17], while prolactin is qualified to be favorably specific and sensitive [14, 15, 18].

However, the present study has been unable to verify this and exhibited a rather low sensitivity for prolactin. One possible explanation for the referred discrepancy may be the variances in serum prolactin levels; that is, prolactin secretion usually has an ovulatory cycle and follows a diurnal pattern, thus, leading to peak values during REM sleep, and in the early morning; also, serum prolactin levels can rise after exercise, meals, sexual intercourse, minor surgical procedures or following epileptic seizures [19].

To clarify the underlying molecular mechanisms, the present study further investigated the alterations in the serum concentrations of sexual hormones and tumor markers at each tumor stage and grade. Thus, tumor stage was shown to correlate positively with the serum prolactin, CA-125 and CA 19-9 levels in the reviewed patients.

In contrast with the findings of Levina et al. [15], serum prolactin concentrations are shown to increase as the tumor

stage advanced. In fact, it would be reasonable to anticipate excessive prolactin release from the cells that are involved in an endometrial tumor because this peptide hormone also acts as an inflammatory and angiogenetic cytokine. That is, prolactin triggers angiogenesis that essentially occurs during carcinogenesis and unrestrained neoplastic growth [20]. Thus, elevated levels of serum prolactin in ovarian and endometrial cancers have been reported recently, indicating a potential role for this peptide in carcinogenesis [15, 20, 21]. Moreover, serum prolactin levels were found to be significantly elevated in women with a strong family history of ovarian cancer as was the expression of prolactin receptors in case of endometrial hyperplasia [15, 22].

It has been lately documented that serum CA 19-9 levels increase in women with endometrial cancer, but, to our knowledge, no positive correlation has been reported to exist between this carbohydrate antigen and tumor stage. Thus, CA 19-9 may either reflect the invasive features of an endometrial tumor or act as a false-positive alarm as was the case in avoiding CA 19-9 for diagnosis of pancreatic cancer [6].

Another interesting finding of the present study is the significant relationship between tumor grade and serum levels of LH, estradiol, prolactin and CA-125. The inverse correlation between tumor grade and estradiol may suggest the lack of estradiol in the pathogenesis of endometrial cancer (currently called type B) endometrial tumors which are more likely to have higher grade and more aggressive behavior. On the other hand, low-estradiol levels can be caused by elevated LH concentrations which may result from a hypothalamic defect that is probably associated with endometrial carcinogenesis [13, 14, 21]. As opposed to the inverse correlation detected by the study of Levina et al. [15], the present study demonstrated a direct and significant relation between tumor grade and prolactin. Although several studies have favoured the adoption of prolactin as a powerful diagnostic marker [14, 15], the reliability of this peptide hormone should be the interrogated carefully as the represented data remind of the prominent physiologic influence on prolactin secretion.

Currently, CA-125 is one of the most reliable tumor markers that are commonly used to predict endometrial adenocarcinoma. Being a glycoprotein located on cellular surface, the elevated CA-125 levels may point out that tumor cells are shed and scattered within the peritoneal cavity, thus, indicating the aggressive tumor behavior, or in other words, tumor grade [23]. Also serum CA-125 levels have been shown to increase in parallel with the propagation of extrauterine disease and lymph node involvement, thus pointing out advanced stage and poor prognosis. Despite being addressed as an independent and cardinal prognostic indicator for endometrial cancer patients, a clinically significant number of patients would have more advanced disease than indicated by preoperative CA-125 values. Furthermore, low to moderate sensitivity of CA-125 establishes another adversity which can be eliminated by combining CA-125 with other biochemical entities [14–17].

Because serum concentrations of CA-125 can be elevated in various malignancies, it is obvious that it is neither specific nor accurately diagnostic for endometrial tumors. What is more, the distinct effects of physiological factors on prolactin secretion shadow the credibility of this hormone in early diagnosis of endometrial tumors. Thus, either prolactin or CA-125 is far from being utilized as the sole entity for screening endometrial cancer. Therefore, both parameters should be regarded as the components of a biochemical screening panel that is to be developed in future. Further prospective and controlled studies are required to investigate the power and reliability of sexual hormones and tumor markers in early diagnosis of endometrial tumors.

Conflict of interest statement None.

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