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RESEARCH ARTICLE

Influence of Autoantibodies to Estradiol and Progesterone on the Blood Serum Hormones Concentrations in Postmenopausal Healthy Women and Breast Cancer Patients

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Abstract

Background: It is known that antibodies to steroid hormones are associated with some human diseases (systemic lupus erythematosus, thrombosis, recurrent pregnancy loss, autoimmune dermatitis et al.). There were no any data about action of specific autoantibodies on the sex hormones in hormone-dependent cancer patients. **Objectives:** The purpose of this study was to investigate the probable links between estradiol (Es) and progesterone (Pg) levels and autoantibodies of A-class specific to these hormones (IgA-Es and IgA-Pg) in the blood serum of healthy women and breast cancer patients. **Patients and Methods:** There were examined 521 nearly diagnosed breast carcinoma patients from Regional Clinical Oncology Dispensary (Kemerovo, Russian Federation) and 143 healthy women from Kemerovo (Russian Federation). The serum concentration of Es and Pg were analyzed by competitive immunoassay using specific monoclonal antibodies. The serum IgA-Pg and IgA-Es were analyzed by solid-phase non-competitive immunoassay using Pg and Es conjugated with bovine serum albumin as adsorbed antigens. The data analysis was performed using software STATISTICA 8.0 (Stat Soft Inc., USA). **Results:** We discovered that low ratios Pg/Es<4.3 were associated with breast cancer. Personal IgA-Pg/IgA-Es ratios negatively correlated with Es levels and positively correlated with Pg levels and Pg/Es ratios in compared groups. The influence of IgA-Pg/IgA-Es ratio on the hormones levels and their ratio in heathy women was more strong than in breast cancer patients. **Conclusions:** Our clinical results correspond to the known experimental data about influence of specific antibodies on the levels of steroid hormones in immunized animals. Human autoantibodies to Es and Pg could stimulate or inhibit promotion of carcinogenesis by influence on Pg/Es ratio depending on individual IgA-Pg/IgA-Es ratio.

Keywords: Estradiol- Progesterone- Autoantibodies- Breast cancer

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Introduction

It is well known that estradiol (Es) and progesterone (Pg) play an important role in the promotion of the breast carcinogenesis by influence on the proliferation of mammary cells. In addition, Es acts as initiator of carcinogenesis by the formation of mutagenic adducts with DNA [1-3]. On the other hand immunization of animals against Es and Pg resulted in elevated blood serum hormones levels and modulation of their biological actions [4-10]. Caldwell et al. (1971) [11] revealed that immunization of rats by Es conjugated with bovine serum

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albumin (Es-BSA) induced regression of Es-sensitive mammary adenocarcinoma. They were confident that the neutralization of the circulating Es by antibodies (Abs) was the primary cause of extended survival time and longer interval between implantation and tumor growth.

The low-weight Es adducted with macromolecular carrier could induce the synthesis of specific antibodies as a hapten. There were found the associations of anti-Es Abs with some human diseases: systemic lupus erythematosus [12] and thrombosis in women on oral contraceptives [13]. Anti-Pg Abs was associated with recurrent pregnancy loss [14] and autoimmune dermatitis [15]. The specific immune reaction on both Es and Pg were revealed in women with premenstrual syndrome [16, 17] and recurrent pregnancy loss [18]. Autoantibodies to Es-receptor were markers of systemic lupus erythematosus [19] and systemic sclerosis [20]. They acted as Es-agonists in mammary carcinoma cell culture [21,22] and their serum levels correlated with breast cancer cell proliferation [23].

There were no any data about action of specific autoantibodies on the sex hormones in hormone-dependent cancer patients.

Previously we have proposed that Abs to Es and Pg could stimulate or inhibit hormone-sensitive carcinogenesis according to individual features of their formation [24-26]. In the present study, we explored the influence of autoantibodies to Es and Pg on the blood serum hormones levels in postmenopausal healthy women (HW) and breast cancer patients (BCP).

Materials and Methods

Patients

The study was performed in 664 non-smoking postmenopausal women, of which 521 women were primarily diagnosed with invasive breast cancer (BC) in the Regional Clinical Oncology Dispensary (Kemerovo, Russian Federation). Each case diagnosis was confirmed morphologically in the oncology dispensary. Data related to tumor size, grade, and stage were collected from surgical pathology reports. All cases were unilateral - 267 (51.2%) right breast, 254 (48.8%) left breast. The histopathological subtype of the all cases was ductal carcinoma. Most cases belonged to differentiation grade II (247, 47.4%), followed by grade I (185, 35.5%), grade III (86, 16.5%) and grade IV (3, 0.6%). 143 HW without breast pathology were included for comparison. The median ages of participants were 63 (ranging from 42 to 85) for BCP and 58 (ranging from 43 to 80) for HW.

The study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by ethics committee of Institute of Human Ecology of Siberian Branch of Russian Academy of Sciences (protocol №46/1). All women provided informed consents.

Inclusion and exclusion criteria

Inclusion criteria: for BCP group – patients with primarily diagnosed invasive breast cancer, non-smoking postmenopausal women, patients were aged over 40 years old; for control group - healthy postmenopausal women without breast pathology, non-smoking, women were aged above 40 years old.

Exclusion criteria: patients with other types of tumor, patients without any treatment (chemotherapy, X-ray therapy, hormone replacement therapy, surgery); smoking women, young women under 40 years old.

Immunoassay of Antibodies to Estradiol and Progesterone

Abs to Es and Pg were detected by solid phase non-competitive enzyme-linked immunosorbent assays. Microtiter wells were coated with 2 μg/ml Es or Pg conjugated with bovine serum albumin BSA (Amresco, USA) in 100 μl phosphate-buffered saline (PBS) pH 7.4 (Amresco, USA) at room temperature overnight. The Es-BSA conjugate was received from Sigma-Aldrich (Germany). Pg-BSA conjugate was obtained by conjugation of hemi-glutarate of 21-hydroxyprogesterone (Sigma-Aldrich, Germany) and BSA by the carbodiimide method. Coated wells were blocked for 30 min in blocking buffer saline (0.5% BSA in PBS, 0.05% Tween 20). The serum samples were diluted at 1/20 in blocking buffer saline and were incubated with coated antigens (100 μl/well) for 1 h at 37◦C. Bound Abs were detected by goat anti-human IgA antibody labeled with horseradish peroxidase (1/10000 dilution, Novex, USA). After each assay steps wells were washed 4-5 times with 250 μl/well of washing buffer saline (PBS, 0.05% Tween 20). The amounts of bound Abs were determined through enzymatic reaction with the chromogenic substrate TMB (Vector Corp., USA). The reaction was then terminated by addition of 2 N HCl and absorbance was measured at 450 nm. All measurements were conducted in duplicate.

The levels of Abs to Es or Pg were expressed in arbitrary units and calculated based on the following formula:

$$IgA\text{-}X = (OD_{X\text{-}BSA} - OD_{BSA})/OD_{BSA}$$

where X were Es or Pg; $OD_{X\text{-}BSA}$ was the absorbance of the binding to hapten–BSA conjugate, OD_{BSA} was the absorbance of the binding to BSA.

Steroid Hormones Determination

The concentrations of Es and Pg were determined using commercial kits “ImmunoFA-Estradiol”, “ImmunoFA-PG” (“Immunotech”, Russia) according to the instructions for use.

Statistical Analysis

All statistical analyses were conducted using STATISTICA version 8.0 (StatSoft Inc., USA). Normality was evaluated by Shapiro-Wilk’s W-test. The Mann–Whitney U-test and χ^2 with Yates’ correction were used for comparison of non-parametric data. The results are expressed as medians (Me), interquartile range (IQR). The relationship between the antibodies levels and the steroids hormones was assessed using the Spearman’s rank correlation analysis. All statistical analyses were two-sided, $p<0.05$ were considered statistically significant. To determine the threshold values of Abs and steroid

hormones (cut-off) ROC analysis was performed [27]. Odds ratio (OR) was determined with 95% confidence interval (95% CI).

Results

Associations of the serum Es and Pg levels with the breast cancer in postmenopausal women

Breast cancer is typically Es- and Pg-dependent women malignant tumor. Interactions of Es and Pg with mammary cellular receptors are complicated. Incidence rates and risk factors for breast cancer differ according to Es- and Pg- receptors status [28]. It was revealed that Pg inhibited Es-mediated growth of Es-receptor α cell line xenografts and primary breast tumor explants, and had increased anti-proliferative affects when coupled with Es antagonist [29].

Here we studied the blood serum Pg and Es levels and calculated the individual Pg/Es ratios in 143 HW and 521 BCP. The results are shown in Figure 1. The Pg levels were significantly less but Es levels were high in BCP that in HW ($p<0.0001$). The Pg/Es ratio in BCP was less than in HW ($p<0.0001$). There were no any differences on these parameters between BCP according to Pg- and Es-receptors presence (data not shown).

The cut-off between compared groups on these parameters was calculated using ROC-analysis. The frequencies of cases with the low (<) and high (≥) hormones levels and ratios in HW and BCP were determinated. The high levels of Es (>200 pmol/L) were revealed in BCP more frequently than in HW (66.8% vs 44.1%; $\chi^2=23.6$; $p<0.0001$). The high levels of Pg (≥900 pmol/L) were found more rarely in BCP than in HW (30.9% vs 58.7%; $\chi^2=36.2$; $p<0.0001$). The high Pg/Es ratios (≥4) were revealed in BCP more rarely than in HW (31.5% vs 55.9%; $\chi^2=27.8$; $p<0.0001$). It means that high levels of Es (>200 pmol/L) were associated with high BC risk ($p<0.0001$; OR=2.6; 95% CI=1.8-3.7) and high Pg levels (≥900 pmol/L) as well as high Pg/Es ratios (≥4.3) were not associated with BC risk ($p<0.0001$; OR=0.3; 95% CI=0.2-0.5 and OR=0.4; 95% CI=0.2-0.5 correspondingly). But low levels of Pg (<900pmol/L) and low Pg/Es ratios (<4.3) were associated with BC risk ($p<0.0001$; OR=3.2; 95% CI=2.2-4.7 and OR=2.8; 95% CI=1.9-4.0 correspondingly).

Influence of Abs to Es and Pg on the levels of these hormones in the blood serum of HW and BCP

Taken into attention the possibility of model antibodies against steroids to elevate the levels of sex hormones in immunized animals we studies the influence of autoantibodies to Es and Pg on their levels in the blood serum of HW and BCP. There were searched the specific antibodies of A class based on their known possibility to bind and transport the corresponding hormones into epithelial target cells. In the Table 1 the correlations between IgA-levels to Pg and Es (IgA-Pg and IgA-Es) and IgA-Pg/IgA-Es, on the one hand, and Pg and Es levels, and Pg/Es ratio, on the other hand, in compared groups are shown.

In HW the Es levels, but not Pg levels and Pg/Es ratio positively correlated with the IgA-Es levels. The Pg levels but not Es levels and Pg/Es ratio positively correlated with the IgA-Pg. The levels of Es (negatively) and Pg (positively) and Pg/Es ratio (positively) correlated with the IgA-Pg/IgA-Es ratio.

In BCP correlations of Es, Pg and Pg/Es with the IgA-Es were not revealed. The levels of Es negatively correlated with IgA-Pg and with IgA-Pg/IgA-Es. The levels of Pg and Pg/Es ratio correlated positively with IgA-Pg levels and IgA-Pg/IgA-Es ratio.

The study of Es and Pg concentrations and Pg/Es ratios in HW and BCP with the low (<1) and high (≥1) levels of IgA-Es and IgA-Pg and IgA-Pg/IgA-Es ratio are shown in Table 2. The average Es-concentration decreased from 213 pmol/L in HW with low IgA-Pg/IgA-Es ratio to 138 pmol/L with high IgA-Pg/IgA-Es ratio (i.e. on 35.2%). The respective decline in BCP was only 5.2%. The average Pg- concentration increased from 862 to 1414 pmol/L in HW (i.e. on 64%), but only on 13.3% in BCP. The average Pg/Es ratio increased from 3.6 in HW with low IgA-Pg/IgA-Es ratio to 12.5 with high IgA-Pg/IgA-Es ratio (i.e. on

Table 1. Correlations Equations between IgA-levels and IgA-ratio (x) and Hormones Concentrations and Hormones Ratio (y) in Breast Cancer Patients and Healthy Women

(x)	(y)	Breast cancer patients		Healthy women	
Abs levels, Abs ratios	Hormone levels, ratios	r_s (p)	y=α*x+b	r_s (p)	y=α*x+b
1. IgA-Es	Es	-0.01 (0.91)	----	0.21 (0.01)	y=0.02x+0.2
	Pg	0.04 (0.33)	----	-0.01 (0.95)	----
	Pg/Es	0.03 (0.47)	----	-0.17 (0.06)	----
2. IgA-Pg	Es	-0.13 (0.004)	y=-0.01x+0.3	-0.05 (0.55)	----
	Pg	0.19 (<0.0001)	y=0.05x+0.8	0.31 (0.0001)	y=0.1x+0.9
	Pg/Es	0.20 (<0.0001)	y=0.5x+3.9	0.15 (0.07)	----
3. IgA-Pg/IgA-Es	Es	-0.15 (0.0007)	y=-0.04x+0.3	-0.35 (<0.0001)	y=-0.2x+0.4
	Pg	0.18 (<0.0001)	y=0.2x+0.8	0.50 (<0.0001)	y=0.6x+0.6
	Pg/Es	0.21 (<0.0001)	y=1.9x+3.6	0.45 (<0.0001)	y=6.1x+4.1

r_s - Spearman's rank correlation, $p<0.05$ was statistically significant

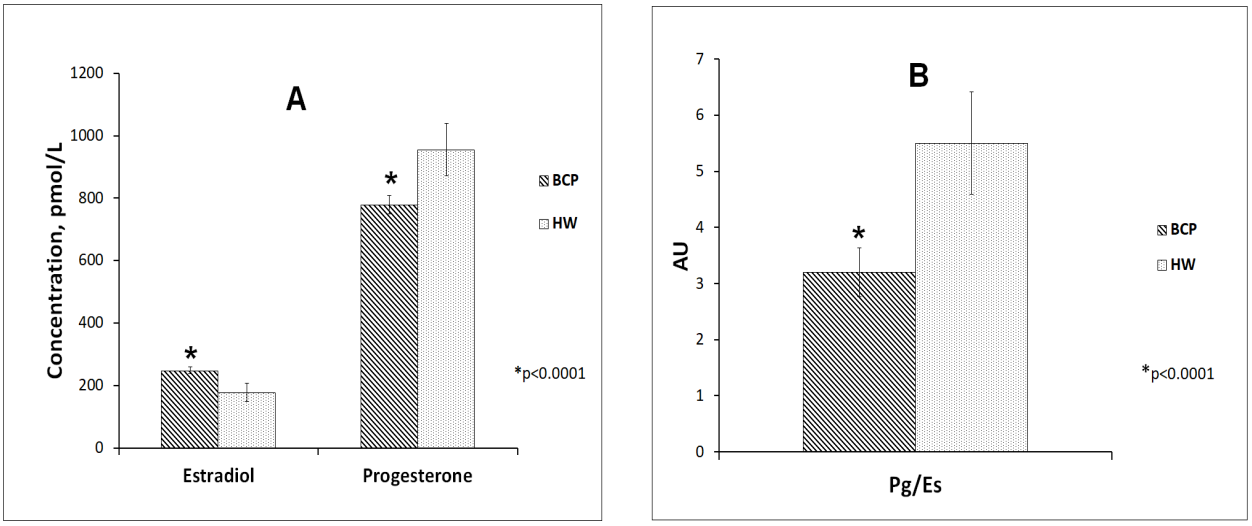

Figure 1. Medians of Estradiol and Progesterone Concentrations (A) and Pg/Es Ratios (B) in Breast Cancer Patients (BCP) and Healthy Women (HW)

Table 2. Medians (Me) and Interquartile Range (IQR) of Estradiol (Es) and Progesterone (Pg) Concentrations (pmol/L) and Pg/Es Ratios at Low (<) and High (≥) IgA-Pg/IgA-Es Ratios in Blood Serum of Healthy Women and Breast Cancer Patients

Antibodies ratios	Es Me (IQR)	Pg Me (IQR)	Pg/Es Me (IQR)
Healthy women			
1.1. IgA-Pg/IgA-Es<1	213(121-355)	862 (711-1119)	3.6 (1.9-10.6)
1.2. IgA-Pg/IgA-Es≥1	138 (91-187)	1414(1110-1797)	12.5 (7.9-17.9)
p-value	0.001	<0.0001	<0.0001
Breast cancer patients			
2.1. IgA-Pg/IgA-Es<1	249 (185-411)	760 (649-920)	3.0 (1.8-4.6)
2.2. IgA-Pg/IgA-Es≥1	236 (146-291)	861 (706-1345)	3.7 (2.7-9.02)
p-value	0.006	0.0002	0.0001

p<0.05 was statistically significant

247.2%). The respective raise in BCP was only on 23.3%.

Discussion

In the present study the influence of specific auto Abs in human on the blood serum Es and Pg concentrations was shown for the first time.

It was found that the average Es-levels in BCP was higher than in HW and the average Pg-levels was lower in the corresponding groups. These data confirm that Es could stimulate but Pg could inhibit the promotion of carcinogenesis in mammary gland.

The positive correlations between Es and IgA-Es levels and between Pg and IgA-Pg were revealed in HW. IgA-Es correlated neither with Es nor with Pg in BCP. IgA-Pg positively correlated with Pg and negatively with Es in BCP. It means that specific autoantibodies could influence on the Es and Pg levels as well as in model experiments.

The personal Pg/Es ratio was calculated in compared group. ROC-analysis has conducted to determine the odds ratio (OR) for these parameters. The frequency of cases with high Pg/Es ratio (≥4.3) was higher in HW that in BCP (OR=0.4; 95%CI=0.2-0.5). Such hormonal state could be marked as "hormonal balance". The frequency of cases with low Pg/Es ratio (<4.3) was corresponding higher in BCP than in HW (OR=2.8; 95%CI=1.9-4.0) and such hormonal state could be marked as "hormonal disbalance".

We have proposed that hormonal balance/disbalance depended on individual IgA-Pg/IgA-Es ratio. It was marked as "immunological disbalance".

There were positive correlation between IgA-Pg/IgA-Es ratio and Pg/Es ratio in HW and in BCP. It means that immunological and hormonal balance (disbalance) are interconnected and interdependent.

The average value of Pg/Es ratio was low (hormonal disbalance) in HW with IgA-Pg/IgA-Es ratio<1 (immunological disbalance). And average value of Pg/Es ratio was high (hormonal balance) in HW with IgA-Pg/IgA-Es ratio ≥1 (immunological balance). But in BCP with IgA-Pg/IgA-Es ratio ≥1 (immunological balance) the state of hormonal disbalance was remained (average value of Pg/Es ratio was low). It means that immune-

hormonal relationships in HW were strong but in BCP were weak. These differences could be explained by the strong affinity of Abs to Es and Pg in HW and weak affinity of corresponding Abs in BCP.

The proposal mechanism of immunomodulation of steroid-dependent carcinogenesis by specific auto-Abs needs the further investigations. First, the study of anti-idiotypic Abs to hormones has to be explored because they take part in hormone-antibody interaction and could influence on the cell behavior through the membrane steroid receptors [22, 23, 30-34].

Secondly, it's need to study Abs to the chemical carcinogens because their metabolites interact with Es-receptors [35-38] Abs to carcinogens were found in the blood serum of healthy donors and cancer patients [39-42] the levels of Abs to steroid hormones correlated with levels of Abs to chemical carcinogens in human [24].

In conclusions, the levels of Es and Pg in the blood serum of postmenopausal women depend on the levels of specific autoantibodies. The individual IgA-Pg/IgA-Es ratios influence on the Pg/Es ratios in HW more strong than in BCP. The comprehensive analysis of auto-Abs to endogenous steroids and environmental carcinogens together with corresponding anti-idiotypic Abs will be helpful for the further study of immune-hormonal disbalance in human carcinogenesis.

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Conflict of interest

The authors declare that they have no conflict of interest.

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