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THE CHANGE OF ARGINASE ACTIVITY IN BLOOD SERUM DURING BREAST AND PROSTATE CANCERS

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ABSTRACT

Breast cancer is the most common malignant tumor of women around the world. Prostate cancer contributes significantly to the overall cancer burden, being the most frequent malignant neoplasia in men. Therefore, great medical and scientific efforts are continually invested into understanding the disease's pathology and finding new methods for its diagnosis and treatment. It was interesting to investigate Arginase activity in blood serum during women breast and men prostate cancer.
In this study, a significant increase in blood serum arginase activity could be important for the early diagnosis of mentioned cancers and for their treatment. Taking into consideration that through inhibition of Arginase activity polyamine quantity is changed, which can have influence on the cancer cell metabolism, it can find practical application in medical practice.

Key words: *Breast cancer, prostate cancer, arginase, blood serum*

INTRODUCTION

Breast cancer is a malignant (cancer) tumor that starts in the cells of the breast [8]. It is found mostly in women, but men can get breast cancer, too. Breast cancer is one of the most common types of cancer accounting for 19% of all cancer-related mortality in women.
Prostate cancer has the highest incidence rate of any cancer among men in the several countries. Despite its high prevalence, the heterogeneous nature of prostate cancer makes it difficult to understand the molecular mechanisms controlling benign and malignant prostatic cell growth [1]. Therefore, it is important to continue to improve current diagnostic tools and determine new prognostic variables.
Cancer cells may differ from their normal counterparts in the activities or concentration of certain enzymes. That dif–ference may act as a useful biological marker of malignancy and aggressiveness in particular tumors. The application of measures correlating the activities of such enzymes may lead to elucidation of therapeutic approaches to cancer [1, 8].
It was interesting to investigate Arginase activity in blood serum during women breast and men prostate cancer, suggesting the enzyme activity as a test for cancer detection. Arginase (EC 3.5.3.1) is binuclear manganese metallo-enzyme that catalyzes the hydrolysis of L-arginine into urea and L-ornithine [7]. There are two known isoforms of this enzyme, arginase I (AI) and arginase II (AII) [5]. The AI enzyme is localized in the cytosol and is involved in the detoxification of ammonia as part of the urea cycle. The AII enzyme, found in the mitochondria, is involved in the biosynthesis of polyamines, glutamate, proline and NO [3, 7].

MATERIALS AND METHODS

Partisipants. This study was done at Yerevan State University at the Department of Biochemistry with 20 breast cancer (aged from 37-72, female) and 12 prostate cancer (aged from 45-78, male) patients who were hospitalized in the National Center of Oncology aft. V.A.Fanarjyan and with 7 healthy people (4 women and 3 men) aged from 34-69 (51±15). The chemoradiotherapy wasn't applied to any of the patients yet.
Colorimetric detrmination of arginase activity. The tissues homogenized in ice-cold 0.2*M* Glycine buffer, pH 9.5; by using Potter-Elvehjem Glass Tissue Homogenizer. The homogenate was centrifuged at 1500 *g* for 30 min at 4°*C*. In test-tube is added 1.5 *ml* glycine buffer, 0.5 *ml* supernatant, 0.2 *ml* $MnCl_2$ x $4H_2O$; 0.4 *ml* L-arginine. The control tube should contain the same, except of the 0.4 *ml* L-arginine. Enzyme catalysis interrupted with 1 *ml* 20% trichloroacetic acid. In sediment is determined the urea with Archibald's method with some modifications [2, 4]. Chemicals were obtained from Sigma Aldrich Co. Ltd. (Taufkirchen, Germany).
Statistical Analysis. Results expressed as means ± SD and means ± SE. Results examined by Student's t-test (single sample) using Statistica software (StatSoft 10.0).

RESULTS AND DISCUSSION

Arginase activity was determined in blood serum of patients with breast and prostate cancer in different stages. Among breast cancer group patients, 8 cases were stage I (56±9, $T_1N_0M_0$, 1-2 *cm*), 7 cases had stage II (48±11, $T_{1-2}N_1M_0$, 2-2.7 *cm*), 5 cases had stage III (56±12, $T_{2-3}N_{1-3}M_0$, 4.3-5.4 *cm*). Among prostate cancer group patients, 3 cases was stage I (62±7, $T_{1a}N_0M_0$), 5 cases had stage II (56±12, $T_{1-2}N_0M_0$), 4 cases had stage III (63±11, $T_3N_0M_0$) (*Table 1*).

Table 1. Demographic characteristics of patients with breast and prostate cancers.

Patients	Sex	Age	Cancer	Stage	TNM
4		50±8	-	-	-
8	Female	56±9	breast	I	$T_1N_0M_0$
7		48±11	breast	II	$T_{1-2}N_1M_0$
5		56±12	breast	III	$T_{2-3}N_{1-3}M_0$
3		56±7	-	-	-
3	Male	62±7	prostate	I	$T_{1a}N_0M_0$
5		56±12	prostate	II	$T_{1-2}N_0M_0$
4		63±11	prostate	III	$T_3N_0M_0$

Our studies have shown that in women breast cancer group of stage I activity of serum Arginase was increased by 28.8%, in group of stage II by 36.1% and group of stage III by 48.4% comparing to the healthy women group (*Fig. 1*, A).

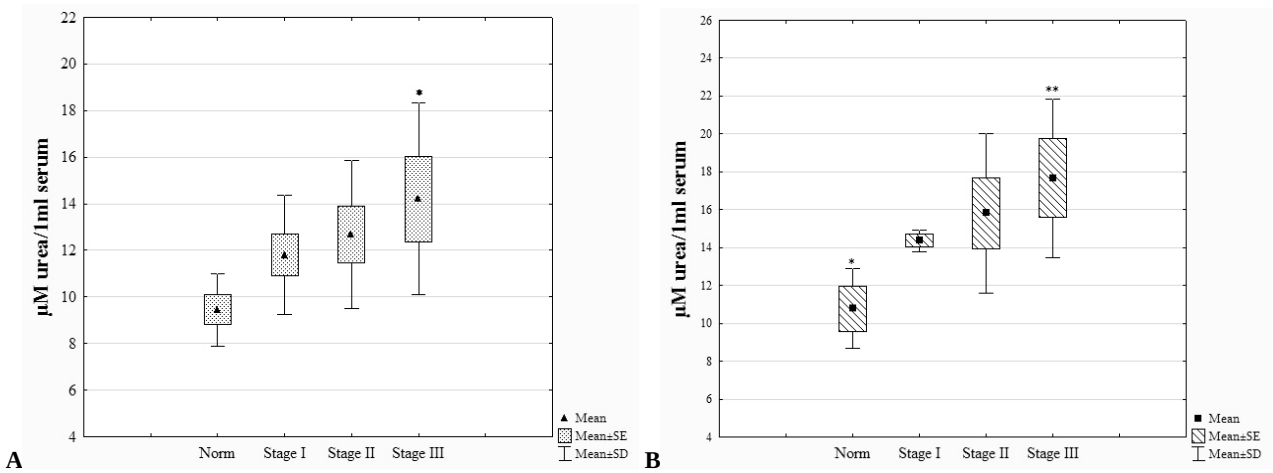

Fig. 1. The change of arginase activity in womens' serum during different stage of breast (A) and prostate (B) cancers ($p<0.001$).
(A) Breast cancer group patients: 8 cases were stage I ($T_1N_0M_0$), 7 cases had stage II ($T_{1-2}N_1M_0$), 5 cases had stage III ($T_{2-3}N_{1-3}M_0$).
(B) Prostate cancer group patients: 3 cases was stage I ($T_{1a}N_0M_0$), 5 cases had stage II ($T_{1-2}N_0M_0$), 4 cases had stage III ($T_3N_0M_0$).
* - $p=0.001$, ** - $p<0.05$.

In men prostate cancer group of stage I activity of serum Arginase was increased by 34.2%, in group of stage II by 46.7% and group of stage III by 59.3% comparing to the healthy men group (*Fig. 1, B*). Studies have shown that there is no correlation between human age and arginase activity changes: consistent pattern for stage 1-3 does not change (*Fig. 2*). Consequently, the more advanced the breast cancer, the higher the level of serum arginase activity.
It has been reported that the mean activity of arginase is high in the early stages and higher in the advanced states of the malignant group compared to those of the normal ones.

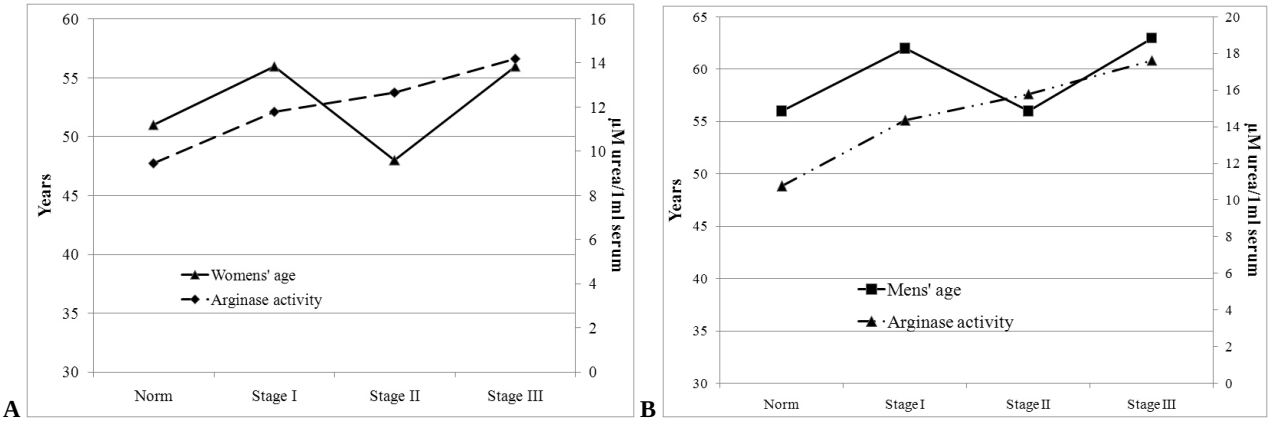

Fig. 2. The correlation between arginase activity, cancer stage and human age in blood serum at breast and prostate malignant tumors. (A) Breast cancer group patients: 8 cases were stage I ($T_1N_0M_0$), 7 cases had stage II ($T_{1-2}N_1M_0$), 5 cases had stage III ($T_{2-3}N_{1-3}M_0$). (B) Prostate cancer group patients: 3 cases was stage I ($T_{1a}N_0M_0$), 5 cases had stage II ($T_{1-2}N_0M_0$), 4 cases had stage III ($T_3N_0M_0$).

CONCLUSION

Our recent studies have shown that during inhibition of nonureotelic isoforms of arginase (AII) by N^G-hydroxy-L-arginine in brain and kidney of rats, the quantities of polyamines are decreased ratably [4]. Almost all cells can produce polyamines, but their production is especially high in rapidly growing cells. Polyamine (which includes putrescine, spermidine and spermine) concentrations are often increased in the blood of cancer patients (poor prognosis) [6].

We suggest that arginase inhibition may have some protective effects on breast cancer development as it inhibits ornithine levels, precursors of polyamines, and also polyamine levels. Our further investigations will be directed to answer to the mentioned questions.

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