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Hormonal status and distribution of the ABO system phenotypic groups in menopausal and postmenopausal women with breast tumors

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Breast cancer is one of the most frequent neoplastic diseases within the female population worldwide. Hormonal imbalance and the ABO system group antigens are among the numerous risk-factors which provoke the development of breast benign and malignant tumors. Here, we have investigated the following sex-steroid hormones: estradiol (E2), progesterone (P), testosterone (T)), non-sex hormones (thyroxin (fT4), thyroid-stimulating hormone (TSH) and prolactin (PRL), and the distribution of the ABO system phenotypic groups in the menopausal and postmenopausal women with breast tumors (benign, malignant). Enzyme-linked immunosorbent assay (ELISA) was used for quantitative determination of hormones. The immune-serological methods were used for investigation of the ABO system phenotypic groups. Our present investigations in menopausal and postmenopausal women with breast tumors have revealed significantly higher expression of sex-steroid hormone estradiol, but decreased progesterone, and also significantly increased testosterone levels. Thyroid gland revealed hypofunction, which confirms the decrease of thyroxin, and increase of prolactin and TSH in the blood. According to our findings, carriers of A(II) phenotypic groups showed high risk for breast tumors development in women during both stages, menopausal and postmenopausal.

Keywords: Breast adenocarcinoma, Cancer, Estradiol, Fibroadenoma, Prolactin, Thyroid-stimulating hormone (TSH), Thyroxin (fT4)

Breast cancer is one of the four most common causes of cancer deaths. Among women, it ranks second (14%) next only to lung and bronchus cancer. While in USA, it is estimated to be 14.38% of total 40,610 cancer deaths in 2017, the cancer country profile 2014 of WHO reports 15.5 and 19.1% in Georgia and Serbia, respectively[1-3]. Apart from the risk-factors *viz*., alcohol consumption, tobacco smoking, overweight or obesity, hormonal imbalance also provoke the development of breast benign and malignant tumors[2,4,5]. The balance between the estrogens and the androgens play major role in non-transformed tissue homeostasis and represent the critical factor that regulates mammary cell proliferation, both in the non-transformed and cancerous tissues[5,6]. Furthermore, hormones are unavoidable and important regulators of the human physiology[7].

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Steroid hormones [estrogens (estrone and estradiol) and androgens, (testosterone, androstendione, dehydro epiandrosterone and progesterone)] which are synthesized by ovaries play prominent role in the growth, development differentiation, and pathological processes of breast glands[8]. Presumably, the imbalance between estrogen and progesterone is crucial for the breast cancer initiation and progression[9]. During the period of menopause (~50-65 years), the production ability of estradiol by ovaries gradually decreases, and eventually its concentration becomes minimized. During the same period, adrenal gland represents the source of androgens[8,10]. However, during the post-menopausal period (above 65 years), ovaries do not produce estrogens (because of follicule absence), but preserve the androgens (mainly the synthetic ability of androstendione). The androstendione together with androgens of adrenal gland reaches in the breast gland adipose tissues (in the peripheral tissue), where the androstendione transforms into estrone (E1) by action

of enzyme aromatase. Then, 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) transforms E1 into the estradiol (E2)[8]. The activity of enzyme aromatase has been detected in the breast gland normal tissues as well as in malignant tissues. Presumably, the estrogens originated from the breast tissues (based on overexpression of enzyme aromatase) are sufficient enough to transform into metabolites with genotoxic feature. The overexpression of estrogens may be crucial factor for the initial phase of breast cancer development. The levels of estrogen and estrogen receptor (ER) are used as the diagnostic and prognostic parameters for this disease.

Besides ovaries, hypophysis and thyroid gland hormones may also influence the formation, functional activity, and pathogenesis of breast cancer[11,12]. Thus, the majority of the breast gland tumors (both benign and malignant), are hormone-dependent tumors[13]. In this context, demonstration of hormonal abnormalities that potentially promote the development and progression of breast cancer pathology assumes interest.

The ABO system group antigens are known to stimulate the development of some malignant tumors, such as the tumors of female reproductive system. The ABO antigens play crucial role in the function of immune system. Their association between the ABO system antigens and development of various tumors has been reported already[14-17] and are used as prognostic and diagnostic markers for different tumor types[18]. Moreover, the ABO system antigens represent main antigens in humans, which are present on the surface of erythrocyte and other epithelial cells[19]. The majority of reproductive organs and breast derived tumors originate from the epithelial cells. It is also established that the ABO system genes are frequently altered in various tumors[20]. These changes in glycosyltransferase reflects to the expression of group antigens on the epithelial cells, which may be connected to the metastatic processes and tumor development and progression. Nakagoe *et al.*[21] showed that the altered expression of the ABO system's antigens may be connected with the neoplastic transformation and the processes of metastasis. In most tumors, the glycosylation processes have been changed in the genes of the ABO system[22]. Altered glycosylation may possibly play prominent role in signal transduction and apoptosis processes in the malignant cells[23].

In this study, we investigated sex-steroid hormones estradiol (E2), progesterone (P) and testosterone (T) in menopausal and postmenopausal women with breast tumors for any association between them. Also, we studied characteristics of the functional condition in the thyroid gland (hypofunction), quantitative alterations of thyroid hormone thyroxin (fT4), and amount of the anterior pituitary gland hormones thyroid-stimulating hormone (TSH) and prolactin (PRL) in menopausal and postmenopausal women with breast tumors (benign, malignant). Further, we studied the distribution of the ABO phenotypic groups in menopausal and postmenopausal women to ascertain the association between the alteration of hormonal homeostasis and distribution of the ABO phenotypic groups among women with breast tumors.

Materials and Methods

These research investigations have been performed between 2011 and 2013. For the assessment of hormonal status, we used the blood samples of menopausal (50-65 years) and postmenopausal (65-75 years) women with benign (fibroadenoma) and malignant tumors of breast gland. All the patients belonged to Adjara region population (Georgia). The clinical stages of the disease were estimated by exploring the cytological, morphological, ecosophical and computer methods. The clinical specimens were collected from the Adjara Oncology Centre, and the experiments were carried out at the Laboratory of Immunogenetics (Shota Rustaveli State University) and Laboratories of Immunology and Biochemistry (Oncology Centre).

In the control group, we examined 30 healthy donor patients (15 menopausal and 15 postmenopausal). We also examined 60 diseased women, 30 menopausal women (15 with benign tumor, 15 with malignant) and 30 postmenopausal women (15 with benign tumor, 15 with malignant tumor). Therefore, each study groups (i.e., control, benign tumor and malignant tumor) included 15 patients in case of the separate age group (menopause or postmenopause), respectively. Each age group had respective control group consisted of the women with similar age. Therefore, the liquid biopsy specimens (venous blood samples) were taken on day 20th of the regular menstrual cycle and serum specimens were utilized for the test. Thereafter, the serum samples stored at 2-8°C for 24 h, and were frozen at −20°C or lower for the longer periods. Enzyme-linked immunosorbent assay (ELISA) was performed for the quantitative determination of hormones using the kits (Monobind,

Inc., Lake Forest, CA, USA). We calculated the mean absorbance value (A_{450}) for each set of the reference standards, controls, and the test samples.

Blood specimens from the women with either benign or malignant breast cancers were tested for the analysis of the ABO system antigens. For the ABO system assessment, the number of patients were: 20 females in each group (benign and malignant) with age group. The same number of blood samples of healthy women served as the control. Blood samples were collected by finger puncture approach. The internationally acknowledged immune-serological methods were used, i.e., the immunoserologic ABO phenotype was determined by the agglutination reactions of the individual's red cells using the anti-A, anti-B, and anti-A,B antisera test system (Gemostandart Ltd., Moscow, Russia).

The data thus obtained were processed using the standard statistical methods, i.e., the variance method by means of Graphpad Prism 6 software. P <0.05 was regarded as statistically significant value.

Our research study was strictly performed according to the Medical Ethics Committee of Oncology Centre (Ajdara, Georgia), and the Committee-approved written informed consent was obtained from each and every patients.

Results

First of all, we determined the level of estradiol (E2) in menopausal women with breast benign and malignant tumors. We found that the level of E2 was increased (~1.2 fold) in the benign tumors and ~1.7 fold in the malignant tumor types as compared to the control group (Fig. 1A). As for the levels of antiestrogenic hormone, the levels of progesterone (P) were found decreased in the order, control group → benign tumor (~1.6 fold) → malignant tumor (~2.07 fold) (Fig. 1B). In the menopausal women, the amount of testosterone (T) was increased (~1.6 fold) in the benign tumor and very high (~4.4 fold) in breast cancer group (Fig. 1C).

Secondly, we measured the levels of E2, P, and T in the postmenopausal women within the above mentioned tumor and control groups. Experimental results demonstrated that the level of E2 was significantly increased. In the benign and malignant breast cancers, we detected increased levels of E2 (~2.3 fold; ~2.5 fold, respectively) [Fig. 1A(i)]. The concentration of P was notably decreased in the benign tumor group (~1.2 fold), and also in the malignant tumor (~2 fold) cases as compared with the control group [Fig. 1B(i)]. The level of T was increased (~1.7 fold) in benign tumor as compared with the control group, which was significantly higher (6.07-fold) in breast cancer among the postmenopausal women [Fig. 1C(i)].

The control group of menopausal women compared with patients in reproductive period, the level of E2

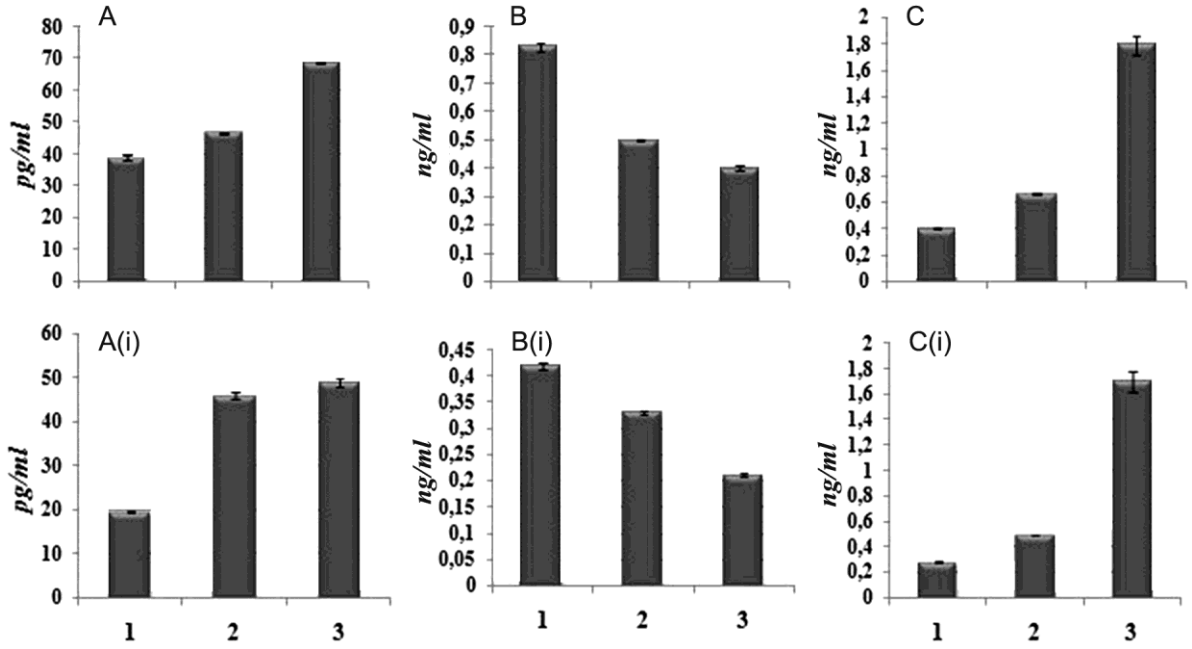

Fig. 1 — Sex-steroid hormones estradiol (E2), progesterone (P) and testosterone (T) levels in menopausal (A, B & C, respectively) and postmenopausal (A(i), B(i) & C(i), respectively) women with breast tumors. [1, control group; 2, benign tumor; and 3, malignant tumor]

was decreased, but not statistically significant. In contrast, in the control group of postmenopausal women, the level of E2 was decreased significantly as compared with the control groups of reproductive and menopausal ages.

Further, we measured the levels of thyroid hormone fT4 and also the levels of anterior pituitary hormones: TSH and PRL among the menopausal and postmenopausal women with breast tumors (benign and malignant). The fT4 level was low in the menopausal women with malignant tumor as compared to the control group. But the levels of fT4 did not change significantly in the benign tumor group (Fig. 2A). The TSH levels were increased in breast cancer patients as compared to the control group (Fig. 2B). In the menopausal women, the control and breast benign tumors groups, the levels of PRL did not change significantly (~1.07 fold), but its levels were ~2 times higher in the breast malignant cases (Fig. 2C).

The levels of fT4 and TSH in postmenopausal women with breast tumors were decreased in breast cancer patients, particularly with benign tumors. The changes in the dynamics of free thyroxin followed the pattern: control group → benign tumor → malignant tumor [Fig. 2A(i)]. The TSH levels were increased in both the study groups, i.e., benign and malignant tumors, but the trend of increase was significantly higher in the malignant tumors cases [Fig. 2B(i)]. The increase of thyrotrophic hormone in breast cancer patients followed the pattern: postmenopausal women to menopausal women**.** In women with benign tumor, the alteration dynamic of TSH rose from menopausal age group (Fig. 2B) to the postmenopausal age group [Fig. 2B(i)]. The PRL levels were increased within the breast cancer cases. The highest level of PRL was detected in the menopausal women with malignant breast tumor, while the lowest levels were detected in postmenopausal women [Fig. 2C(i)].

In the distribution of the ABO system phenotypic groups among the menopausal and postmenopausal women, the O(I) phenotypic group was characterized with highest distribution frequency among the menopausal women of the control group. The frequency of A(II) phenotypic group was higher as compared to the O(I) phenotypic group. The frequencies of B(III) and AB(IV) groups were nearly ~14 fold lower than the O(I), and approximately ~5 fold lower than that of the A(II) phenotypic group (Table 1). In the menopausal women with breast tumours, we found a decreased frequency of the O(I) phenotypic group. The frequency distribution of A(II) phenotypic group was increased compared to the control group. Also, we noticed a significantly higher frequency of the AB (IV) group in women with benign tumors (Table 1).

In the menopausal women with breast malignant tumor, we found lower rates of the O(I) phenotypic

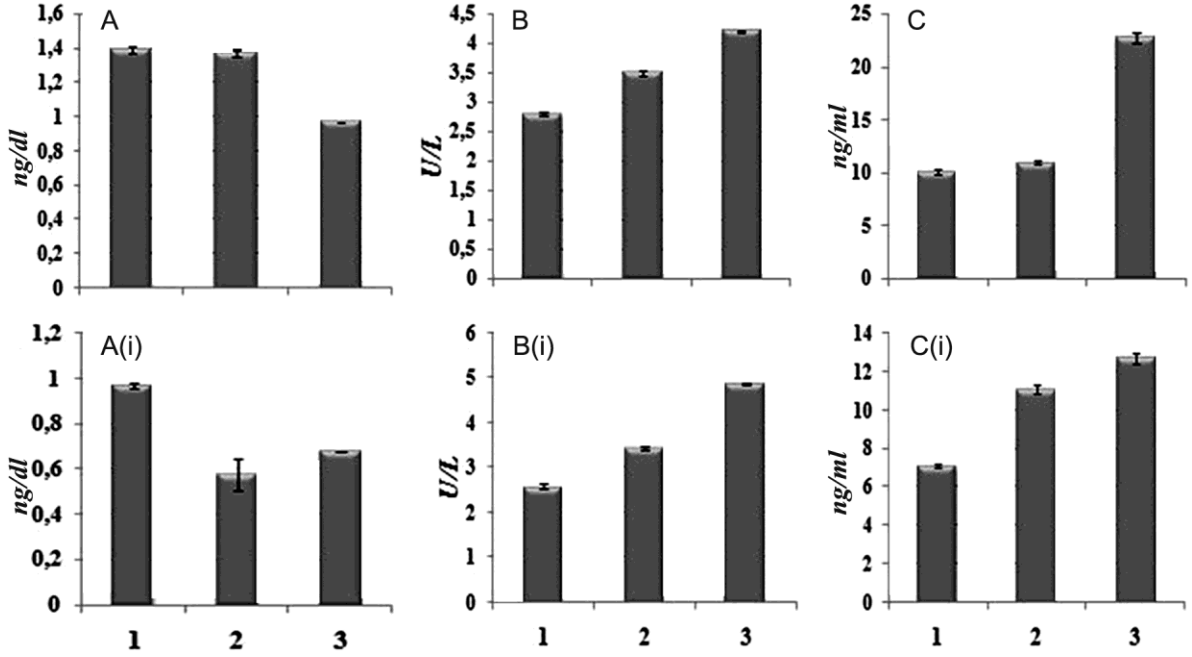

Fig. 2 — Non-sex hormones free thyroxin (fT4), thyroid-stimulating hormone (TSH) and prolactin (PRL) in menopausal (A, B & C, respectively) and postmenopausal (A(i), B(i) & C(i), respectively) women with breast tumors. [1, control group; 2, benign tumor; and 3, malignant tumor]

Table 1 — Percentage distribution (%) of the ABO phenotypic groups in menopausal and postmenopausal women \with breast tumors (benign and malignant)

Phenotype groups of the ABO System	Menopause			Postmenopause		
	Control group	Benign tumor	Malignant tumor (cancer)	Control group	Benign tumor	Malignant tumor (cancer)
O(I)	70±10.6	40±10.2	45±11.1	50±11.1	25±10.2	20±8.9
A(II)	20±10.2	45±11.1	45±11.1	45±10.2	60±10.5	70±10.6
B(III)	5±4.8	5±4.8	10±6.7	5±4.8	5±4.8	0±0
AB(IV)	5±4.8	10±4.8	0±0	0±0	10±4.8	10±4.8

n=20 (The number of the patients in each group)

group as compared to the control group. Interestingly, frequency of the A(II) phenotypic group was significantly higher when compared with the control group, but the AB(IV) phenotypic group was not observed in the malignant tumors.

The frequency of distribution of the ABO phenotypic groups were also studied within the post-menopausal breast cancer patients. Our investigations revealed that the ABO system phenotypes in the control group of post-menopausal women had the following pattern: O(I) → A(II) → B(III). Notably, the AB(IV) phenotypic group was not observed in the control group (Table 1). Interestingly, in the post-menopausal women with benign and malignant tumors, the frequency distribution of the A(II) phenotypic group was found to be the highest. The frequency of O(I) was lower as compared to the control group. With regard to the B(III) phenotypic group, this was not observed among the post-menopausal women with breast malignant tumor whereas the AB(IV) phenotypic group distribution was relatively lower in both the groups i.e., benign and malignant tumors (Table 1).

Discussion

As noted earlier, the biosynthesis of estrogens is placed mainly in follicular cells of the ovaries[8,24]. At the same time, during the reproductive age, biosynthesis of estrogens occurs through androgens' secretion from the adrenal glands. For the menopausal women, there is lowering of the functional activities of ovaries, but during the postmenopausal age, the ovaries in general discontinue the production ability of estrogens because of the absence of follicles. Therefore, the levels of estrogens among the control group of menopausal women was found to be decreased and also significantly lowered among the control group of the postmenopausal women. It is notable that the level of estrogens are maintained at certain threshold by the secretion of estrogens from the adrenal gland cortex and breast adipose tissues.

As expected, in benign and malignant tumors as compared to the control group, the high level of estrogens in the menopausal and postmenopausal period may due to the conditioned over-expression/ biosynthesis of androgens (in particular, androstenedione) by the cortex of the adrenal glands. Taking into considerations, we assume that the level of cholesterol sharply increased during the above mentioned period[25]. It is well known that cholesterol represents the precursor of steroid hormones, i.e., the background of increased cholesterol may cause elevated biosynthesis of estrogens. Other studies have also shown that the activity of enzyme aromatase was increased among certain tumors[26]. This condition may reflect an increased biosynthesis of estradiol as supported by our findings as well. Also, it is noticed that during the menopausal and postmenopausal age, decreased levels of progesterone is observed in the blood of tumor with the disease [Fig. 1 B and B(i)], and similar pattern for increasing estradiol level [Fig. 1 A and A(i)].

Thus, we have demonstrated the imbalance of progesterone and estradiol. It is possible that in breast malignant tumors of the menopausal and postmenopausal women, overexpression of estrogens and its antagonist hormone, i.e., decrease of progesterone, may promote imbalance of the target tissues growth and differential regulation[24], which may represent the main reason of breast cancer development. Toniolo and colleagues[27] reported a positive correlation between the levels of estradiol and breast cancer. Thus, estrogens play crucial role in promoting the proliferation processes and evolution of breast cancers. Also, *in situ* metabolism of estrogens, aromatase-mediated pathway may predominantly be connected to the development of these types of tumors in the above age groups.

The elevated testosterone levels in breast malignant tumor of menopausal and postmenopausal women [Fig. 1 C and C(i)] may presumably be linked with the increased secretion of estrogens. Possibly, high levels

of T among the women with breast malignant tumors may directly stimulate proliferation of breast gland cells division and with neoplastic transformation[11]. In the peer-reviewed literature, the correlations between the T levels and breast cancer pathology are still controversial. Based on some of the peer-reviewed literature data, there is correlation between the T levels and breast cancer formation, while some others studies show the opposite[28,29]. In our current study, testosterone and estradiol were found to be significantly higher in postmenopausal women with breast tumors (benign, malignant) as compared with the control groups. It is possible that the increased levels of estrogens and androgens are contributing factors towards the development of breast cancer. Also, based on the other studies, high level of sex-steroid hormones increased the risk of breast cancer development[4,11]. Thus, in the menopausal and postmenopausal women with breast malignant tumor, we found significantly increased level of sex steroid hormone estradiol on the background of sharply decreased progesterone (and also increased testosterone). This imbalance may initiate the increased proliferation of breast gland cells by estradiol.

As observed here**,** both the sex-steroid hormones and the non-sex hormones influence the formation and functional activity of mammary glands, and also, among them the following hormones: free thyroxin (fT4) of thyroid gland, thyroid-stimulating hormone (TSH) and prolactin (PRL) of the anterior pituitary gland. The thyroid hormones are known to have regulatory effects on the morphogenesis and the functional differentiation of breast gland epithelial cells. Also, thyroid hormones participate in the biosynthesis of steroid hormones, and the processes of metabolism in both the reproductive as well as in menopausal ages[30]. Therefore, a normal thyroid function is essential for numerous reproductive functions. Thus, the changes in thyroid gland function and activity significantly influences the condition of the reproductive system[31]**.**

According to our current findings, we believe that the observed significant decrease of thyroxin in women of menopause and postmenopause ages may be caused by the differential damage of hormone synthetic cells such as deficiency in iodine, the autoimmune diseases of thyroid gland, etc.[32]. But, the deficiency of thyroid hormones (decrease of thyroxin production) by negative feedback mechanism may cause the reinforcement of TSH production and increase its level in the blood[33] as also supported by our findings.

We demonstrated the hypofunction of thyroid glands among the menopausal and postmenopausal women [Fig. 2 A and A(i)]. Possibly, the reported alterations of thyroid hormones (non-sex hormones) may play some important role in the development of breast cancer. Our previous studies also expressed hypofunction in women of reproductive ages with breast tumors (benign and malignant)[34]. The relationship between breast tumors and thyroid hormone has always been controversial. Thyroid disorders may or may not be characteristic of women with breast cancer[35]. Thyroid hormones play important role in many cellular metabolic activities such as co-regulation of cell proliferation, processes of apoptosis, and differentiation[36]. Therefore, any alteration of thyroid hormones may participate in the breast cancer development.

As shown in Fig. 2 C and C(i), the increase of PRL in women with breast malignant tumor of the menopausal women could be conditioned by the expressed hypofunction of pituitary gland largely due to the increased secretion of hypothalamus releasing hormone by the feedback mechanism, i.e., enhancement of both hormones thyrotrophic and prolactin secretion. On the other hand, reduction of thyroxin production may be responsible for the decrease in dopamine synthesis and correspondingly intense synthesis of prolactin[37]. In our previous investigation on breast tumor women of the reproductive age, we noticed an increased levels of PRL[34]. It is well known that PRL hormone is involved in normal breast development, and experimental evidence suggests that PRL can promote cell proliferation, increase cell motility, and support tumor vascularization. Tworoger & Hankinson[38] have shown in postmenopausal women, there is positive correlation between the level of PRL and risk of breast cancer development. Also, higher levels of circulating prolactin are known to be associated with higher incidence of *in situ* breast carcinoma[39].

Thus, in menopausal and postmenopausal women with breast tumors (benign and malignant) we found wide spectrum of hormonal alterations, which were significantly overexpressed in malignant tumors subjects. The observed alterations include quantitative levels of sex steroid hormones and non-sex hormones. These alterations are connected with the regulatory mechanisms and various signaling pathways that can repress the cell immunity. Therefore, this imbalance

may promote the formation of tumors deepening of the complex alteration mechanisms.

Among the menopausal women, we showed high frequency of the O(I) and A(II). In case of the post-menopausal women, we noticed high frequency of the A(II) phenotypic group, whereas in the B(III) and AB(IV) phenotypic groups of the menopausal and postmenopausal age women, the observed phenotypic frequency was lower (Table 1). It is possible that these phenotypic groups have relatively lesser chance to develop breast benign and malignant tumors.

We argue that menopausal and postmenopausal women with the A(II) phenotypic group may have higher risk for the development of breast cancer. It is notable that the frequent distribution of the A(II) phenotypic group was high in both tumors (benign, malignant) as compared to the control group in above mentioned age groups. Thus, in our present investigation, the A(II) phenotypic group was found to be associated with potentially higher risk of developing breast benign and malignant tumors. Furthermore, it is also known that carrier of A blood groups may have the potential for increased risk of breast cancer development[15,17].

Conclusion

Based on our above findings, it can be concluded that in menopausal and postmenopausal women with breast tumors, there was significantly expressed sex-steroid hormone (estradiol) and on the background decreased progesterone and increased testosterone. The overexpression of estradiol play important role in the stimulation of proliferation and create suitable condition for the development of breast cancer in these periods. Thyroid glands were found to be as hypofunction, which confirms the decrease in thyroxin and increase of prolactin and thyroid-stimulating hormone in the blood. Alterations in sex-steroid and thyroid hormones (non-sex hormones) also play important role in the development of breast cancer. Furthermore, carriers of the A(II) phenotypic groups had higher risk for breast tumors development in both periods. On the other hand, in menopausal and postmenopausal women with the O(I) phenotypic groups, there is less tendency for breast cancer development.

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