The antioxidative role of selenium in pathogenesis of cancer of the female reproductive system

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Selenium, as a component of few antioxidant enzymes, participates indirectly in elimination of reactive oxygen species and in antioxidative defense of the organism. There is a correlation between the concentration of selenium, activity of glutathione peroxidases (GSH-Px), and other parameters of antioxidative defense in blood components. The above mentioned factors were suggested to play an important role in etiopathogenesis of neoplastic diseases. Therefore, the aim of our present study was to compare the selenium status and GSH-Px activity in the plasma of 22 healthy women, 50 individuals suffering from cancer of uterine cervix, uterine corpus or ovary, and 49 women diagnosed with benign neoplasia of the uterine corpus or ovary. In addition, the selenium concentration was measured in postoperative cancer tissues, benign tumors, and histopatologically healthy surgical margins of the aforementioned patients.

An average selenium concentration and GSH-Px activity in blood plasma of cancer patients and benign neoplasia patients was significantly lower than in the plasma of healthy women. It suggests that lower overall selenium status and lower selenium-dependent antioxidative capacity of the organism might partly contribute to development of neoplastic diseases of reproductive system.

Postoperative tissues of patients revealed significantly higher selenium concentrations in cancer tissues of uterine cervix and corpus, and benign tumors of uterine corpus, as compared to corresponding healthy tissue margins. Higher accumulation of selenium in these neoplastic tissues might reflect a compensatory up-regulation of antioxidant defense systems in tumors that often undergo a persistent oxidative stress.

Key words: selenium, glutathione peroxidase, reactive oxygen species, carcinogenesis, cancer of reproductive system

Reactive oxygen species (ROS) are the most common factors involved in pathogenesis of neoplastic diseases [1]. They are produced in human organism as by-products of the aerobic metabolism and react with all bio-molecules, causing damage to lipid membranes proteins and nucleic acids [2]. The attack of ROS on DNA may bring most serious biological consequences since they cause double and single strand breaks, as well as chemical nucleobase modifications which may result in mutations and trigger carcinogenesis [2]. Aerobic organisms developed defense mechanisms against detrimental effects of ROS. They include antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and non-enzymatic antioxidants (e.g. vitamins A, E, C, glutathione, and uric acid) [3,4]. Glutathione peroxidases are enzymes that reduce hydrogen peroxide and lipid hydroperoxides to water and organic alcohols, respectively [5]. Since they contain amino acid selenocysteine, their biosynthesis is dependent on the presence of selenium in a diet. Thus, selenium indirectly participates in ROS elimination [6,7].

In early 1970's first reports indicated that people with various cancer types demonstrated low concentration of selenium in blood [8]. This observations induced the epidemiologic studies focused on the associations between geographical distribution of selenium in the soil, the amount of selenium consumed by humans, and cancer mortality. Shamberger et al. [9, 10] compared a dietary selenium consumption with the

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mortality of various cancer types in different USA towns and states. They proved that there is a statistically significant negative correlation between cancer mortality in different parts of the country with high, medium and low concentration of selenium in the soil and, thus, between the amount of selenium consumed in a diet. Clark et al. [11] examined a content of selenium in agricultural tillage in every part of USA and compared it with the mortality of various cancer types (lung, oesophagus, colon, rectal, urinary bladder, pancreas, breast, ovarian and uterine cervix). They reported that the cancer mortality is high in those parts of the country which are characterized with low contents of selenium in the soil. Widespread studies on the correlation between the amount of selenium in a diet, its concentration in the human blood, and the incidence of cancer were performed by Schrauzer et al. [12, 13]. Using WHO data about the dominating food products available in different countries the authors estimated the amount of selenium consumed by inhabitants every year [13]. They correlated those data with the mortality caused by cancer of intestine, pancreas, lungs, prostate, breast, ovary, and urinary bladder.

The results concerning twenty studied countries showed statistically significant negative correlation between selenium dietary intake and the frequency of cancer. They reported also a negative correlation between selenium concentration in blood and the mortality evoked by several cancer types.

Selenium, as a component of few antioxidant enzymes, participates indirectly in elimination of reactive oxygen species and in antioxidative defense system of the organism. There is a correlation between the concentration of selenium, the activity of glutathione peroxidases, and other antioxidant molecules of the blood [14]. The afore mentioned factors play probably an important role in etiopathogenesis of neoplastic diseases. Therefore, the aim of our current study was to compare the selenium status and glutathione peroxidase activity in blood plasma of healthy women and women with cancer or benign tumors of uterine cervix, uterine corpus, or ovary. A selenium concentration in postoperative neoplastic tissues and healthy tissue margins was also investigated.

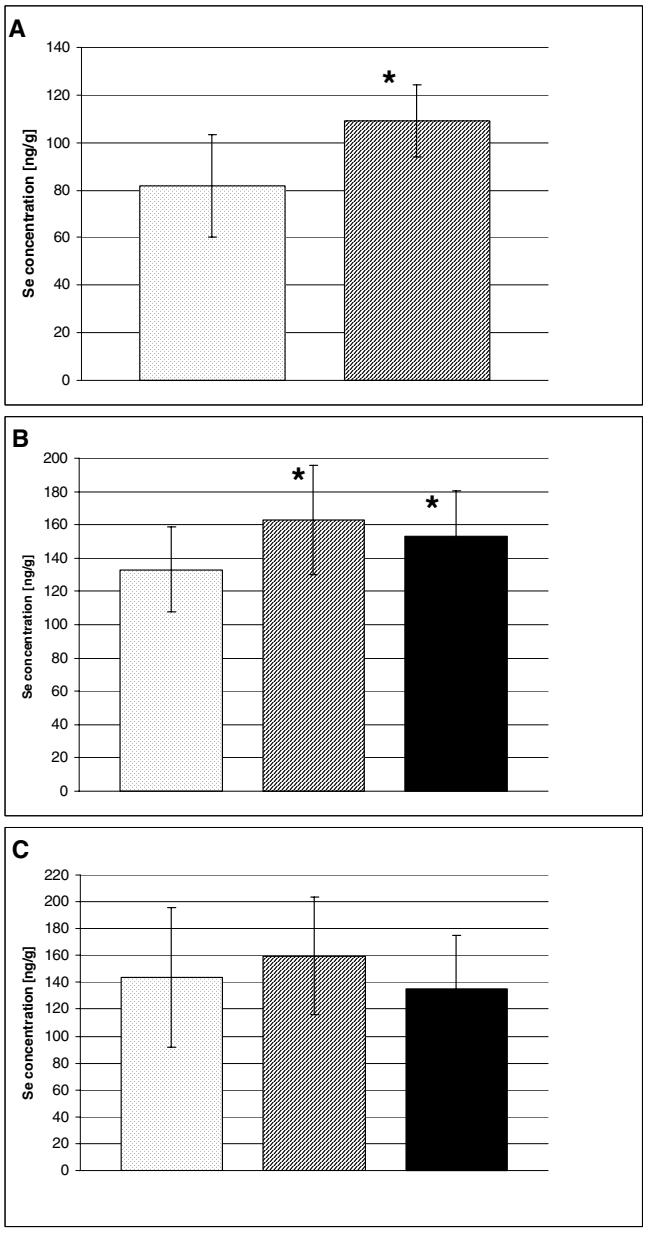

Figure 1. The average selenium concentration in uterine cervix tissues [A] corpus of uterus [B], and in ovary [C]
non-neoplastic tissues , cancer tissues , benign tumor tissues
*** statistically significant difference at p<0.05 as compared to non-neoplastic tissue**

Materials and methods

The tissues and blood samples were taken from 50 women with reproductive system cancer (medium age = 48 ± 9.2 years) and from 49 women with benign neoplasia (medium age = 45 ± 7.3 years). All were patients of the Department of Oncological Gynecology, Cancer Center in Bydgoszcz (Poland). In addition, the blood was taken from 22 healthy women (a control group; medium age = 38 ± 5.4 years) undergoing a preventive examination in gynecological clinic.

Blood plasma was isolated by centrifugation and the concentration of selenium by the method of Watkinson [15] and the activity of glutathione peroxidase using the method of Paglia and Valentine [16] were determined. The fragments of cancer or benign tumor tissues of the ovary, uterine cervix or uterine corpus, as well as fragments of corresponding non-neoplastic healthy tissue margins were isolated immediately after operation and kept in the liquid nitrogen until analyzed for the selenium concentration with the fluorometric method of Watkinson using 2,3-diaminonaphtaline [15] with some modifications [17].

Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA) was used for all statistical calculations.

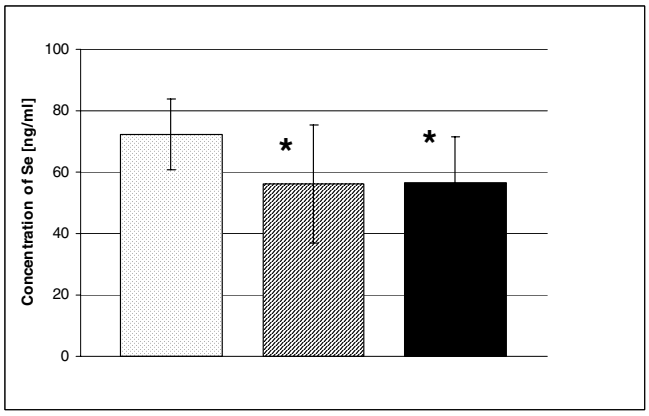

Figure 2. The average selenium concentration in plasma : control group, cancer patients, patients with benign tumors of reproductive organs * statistically significant difference as compared to control group (p<0.05)

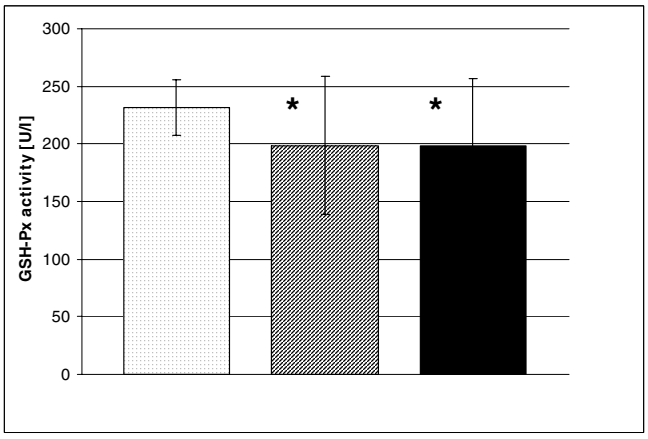

Figure 3. GSH-Px activity in blood plasma of women: control group, cancer patients , patients with benign tumors of reproductive organs * statistically significant difference as compared to control group (p<0.05)

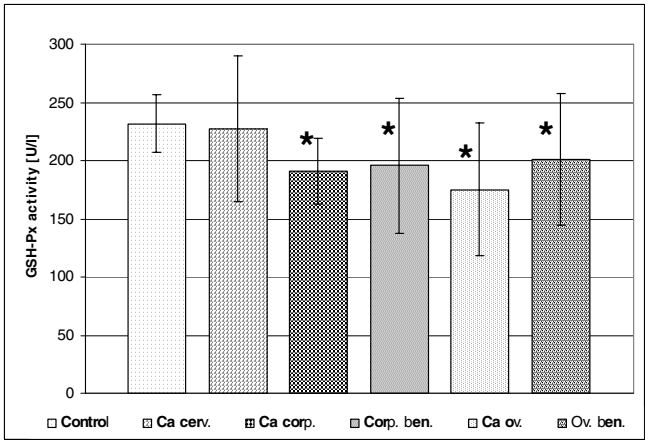

Figure 4. GSH-Px activity in blood plasma of women with cancer and benign tumors of various reproductive organ tissues compared to control healthy women * statistically significant difference as compared to control group (p<0.05)

The studies have been approved by the local Bioethical Committee at the Collegium Medicum of Nicolaus Copernicus University, Bydgoszcz, Poland.

Results

In all studied organs (ovary, cervix and the corpus of uterus) the concentration of selenium in neoplastic tissues was higher compared with non-neoplastic tissues (Fig. 1). In cancer tissue of uterine cervix the selenium level was about 24.9% higher ($p<0.001$) than in healthy tissue margin (81.9 ± 21.5 ng/g tissue). In uterine corpus the selenium concentration in cancer tissue (163 ± 33.0 ng/g) and in benign tumor (153 ± 27.3 ng/g) were significantly higher ($p < 0.01$ and $p > 0.05$, respectively) compared with healthy part of the corpus (133 ± 25.5 ng/g). In cancerous ovarian tissue the concentration of selenium (159 ± 43.8 ng/g) was 9.7% higher compared with healthy ovary (144 ± 52.1 ng/g) and about 15% higher than in benign tumor tissue but these differences did not approach statistical significance.

In the blood plasma of the same individuals the average concentration of selenium was significantly lower (cancer patients: 56.3 ± 19.3 ng/ml and benign tumor patients: 56.4 ± 15.1 ng/ml) compared with selenium concentration of healthy women (72.3 ± 11.6 ng/ml) ($p < 0.001$) (Fig. 2). The average activity of GSH-Px in blood plasma of women suffering from all three cancer types (199 ± 60.0 U/l) and benign tumors of these organs (198 ± 58.7 U/l) were significantly lower ($p<0.02$ and $p<0.01$, respectively) compared with that determined in plasma of healthy women (231 ± 24.0 U/l) (Fig. 3). A comparison of mean GSH-Px activity in plasma of patients grouped according to type of neoplastic disease and its localization revealed that only in women with cervical carcinoma the activity of this enzyme (228 ± 62.7 U/l) didn't differ significantly from the abovementioned values in the control group (Fig. 4). All other subgroups of patients demonstrated significantly lower GSH-Px activity than healthy individuals ($0.001 < p < 0.05$) (Fig. 4).

Discussion

Reactive oxygen species (ROS) and their adverse effects on the organism have been widely investigated in last decades. The reason for this interest was an increasing evidence that ROS are involved in development of many diseases, among them even neoplasms [1]. The insufficiency of antioxidative defense systems that function in the cells plays an important role in etiopathogenesis of neoplastic diseases.

Selenium has a fundamental significance in antioxidative defense. It intensifies the ROS elimination as an integral part of selenoenzymes that posses an antioxidant activity.

The protective effects of selenium and selenoproteins against development of neoplastic diseases has been well documented [18, 19]. In 1970 a negative correlation was observed between the amount of selenium consumed and the incidence of disease and mortality due to various cancer types [13, 20].

Our results show significantly lower concentration of selenium in blood plasma of women suffering from cancer of reproductive organs (Fig. 2) and they are in agreement with findings of Torun et al. [21]. These authors studied the concentration of selenium in blood serum of the people with various cancer types and reported that the average concentration in blood serum of all studied patients' groups was about 26.5% lower compared with control group of healthy individuals. These values are in agreement with our findings which show that the concentration of selenium in plasma of women having cancer of reproductive organs is 22.3% lower than in control group (Fig. 2).

The efficiency of antioxidative systems depends mainly on the level of low – molecular weight compounds and on the activity of antioxidative enzymes, among them seleno-dependent glutathione peroxidases. GSH-Px protects the lipids of cell membranes from peroxidation by decomposing H_2O_2 and organic hydroperoxides [5].

Selenium incorporated in GSH-Px in the form of selenocysteine was proved to be a crucial component of the active centre of GSH-Px and from that discovery turned the attention to the role of selenium as an anticarcinogenic micronutrient.

Lower activity of glutathione peroxidase reported in our studies (Fig. 3,4) may result in the insufficient elimination of reactive oxygen species produced during normal metabolic processes in the cells and may contribute to increased oxidative damage to biomolecules.

Several years ago other authors also confirmed significantly lower activity of GSH-Px in plasma of women with cancer uterine cervix and corpus [22,23].

The findings of our current study show that antioxidative system is weakened in women with cancer of reproductive organs. It is very important for the antioxidative system to be efficient to counteract the activity of damaging factors leading to carcinogenesis. Although there are a few different mechanisms neutralizing free radicals, the enzymatic system is thought to play the most important role.

In plasma of all studied cancer patients the selenium concentration was lower compared with healthy women. However, in neoplastic tissues the level of selenium was higher compared with non-neoplastic surrounding tissues (Fig. 1). The metabolism in neoplastic tissue is changed when opposed to healthy tissue. In neoplastic tissue of uterine cervix the concentration of selenium was 33.4% higher ($p<0.001$), in uterine corpus – 22.5% ($p<0.01$), and in ovary – 10.8% ($p>0.05$). The tendency of neoplastic tissues to accumulate more selenium was observed in the middle 1960'-ties [24]. Higher selenium levels in neoplastic tissues compared with non-neoplastic surrounding tissues were also observed by other authors in other human organs. In breast [25] and pulmonary [26] neoplastic tissues the selenium concentration was determined to be 2 and 1.7-fold higher than in healthy tissue, respectively. Both neoplastic tissues demonstrated also higher GSH-Px activity. The reason of accumulating more selenium in neoplastic tissue is unknown. Some authors [27] suggest that selenium is used for the synthesis of selenoproteins that participate in neutralization of carcinogenic agents [28]. This hypothesis seems to be likely since the activity of seleno – dependent GSH-Px in neoplastic tissue is higher compared with healthy tissue [25, 26].

In conclusion, higher selenium contents in neoplastic tissue of uterine cervix and corpus might reflect an increased synthesis of selenoproteins of antioxidative activity.

A decreased selenium level in blood plasma of women with cancer of reproductive organs compared to healthy ones may have a significant meaning in neoplastic disease development. A decreased levels of selenium and glutathione peroxidase activity in cancer patients may indicate that selenium, as a component of antioxidative enzymes, plays an important role in protection against reactive oxygen species and prevents neoplasia.

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