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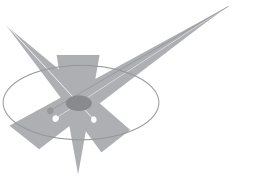

Original Paper

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Plasma total antioxidant status in breast cancer women in relation to lymph node involvement and HER-2/neu expression

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Oxidants can act at several stages of malignant transformation. To protect against toxic effects of oxidants and to modulate physiological effects of their action organisms have developed antioxidant defence systems. Plasma total antioxidant activity (TAS) measures peroxyl-scavenging capacity of the extracellular antioxidant system.

Aim The goal of this pilot study was to evaluate the plasma total antioxidant status in breast cancer women in relation to lymph node metastases and HER-2/neu expression.

Materials/Methods Newly diagnosed consecutive breast cancer patients (n=26) were recruited before any treatment and matched with controls (n=24) randomly selected from benign breast disease patients. Cancer progress was established according to lymph node involvement: No or N+. HER-2/neu was considered as either negative (0 or 1+) or positive (2+ or 3+). The plasma total antioxidant status (TAS) was measured by colorimetric test (RANDOX). HER-2/neu oncogene expression was determined in breast cancer tissue using the immunohistochemical method (Hercep Test).

Results The study demonstrated a significant decrease in the mean TAS level (mmol/L) in the breast cancer group (1.42±0.22) in comparison to the control group (1.56±0.18; $P<0.01$). The mean TAS concentration was found not to differ significantly between breast cancer subgroups in relation to the progress of the disease. Although the mean TAS concentration was not significantly different in regard to the HER-2/neu expression, there was a tendency observed towards higher TAS in the HER-2/neu negative subgroup (1.46±0.20) than in the HER-2/neu positive one (1.41±0.25).

Conclusions The results of the study suggest increased consumption of plasma antioxidants in response to enhanced oxidants production in breast cancer patients. Changes in TAS level do not seem to correspond with the progress of the malignancy but might be related to HER-2/neu expression.

Key words antioxidant status • breast cancer • plasma • cancer progress • HER-2/neu expression

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Background

Oxidants, i.e. reactive oxygen and nitrogen species, generated during both metabolic and inflammatory processes can attack DNA bases or deoxyribose residues to produce damaged bases and strand breaks. Alternatively, oxidants can oxidize protein and lipid molecules, and thus produce intermediates that react with DNA to form adducts. This damage leads eventually to mutation or apoptosis. Oxidants can act at several stages of malignant transformation. They induce permanent DNA sequence changes and can trigger epigenetic pathways which participate in the regulation of growth and differentiation [1]. On the other hand, cancer cells are reported to produce large amounts of reactive oxygen species, especially hydrogen peroxide [2].

To protect against toxic effects of oxidants and to modulate physiological effects of their action organisms have developed antioxidant defence systems. Both extracellular (mostly proteins and low molecular weight substances) and intracellular (mostly enzymes) defence systems consist of multiple interdependent components. A fine balance among many antioxidants appears to be more important for the overall protective capacity of the defence system than the activity or concentration of a single constituent [3].

Oxidative stress is defined as an imbalance between oxidants and antioxidants favouring reactive oxygen and nitrogen species.

Plasma total antioxidant activity (TAS) measures peroxyl-scavenging capacity of the extracellular antioxidant system, comprised of sulphydryl groups (mostly albumin), urate, ascorbate, carotenoids, retinol, á-tocopherol, bilirubin and proteins. TAS reflects residual antioxidant capacity after the consumption of reactive oxygen species [4,5]. To the best of our knowledge, there are only a few reports concerning oxidant-antioxidant status stress in regard to breast cancer progress or to HER-2/neu expression.

Aim

The goal of this pilot study was to evaluate the plasma total antioxidant status in breast cancer women in relation to lymph node metastases and HER-2/neu expression.

Materials and Methods

Materials

Newly diagnosed consecutive breast cancer patients were recruited before any treatment and matched with controls randomly selected from benign breast disease patients admitted to the 1st Ward of Surgical Oncology, Great Poland Cancer Centre in Poznań. On the basis of complete clinical examination those with the following conditions – alcohol abuse, chronic liver and renal disorders, any inflammatory process, diabetes mellitus, advanced atherosclerosis of any location, malabsorption or malnutrition syndrome, and malignancy other than breast cancer – were excluded from the study. The studied individuals were not taking any micronutrient supplementation. Smokers were asked not to smoke overnight before the blood collection. In the analyzed group there were 50 patients: 26 with breast carcinoma and 24 with benign breast diseases (Table 1).

Blood samples were collected from women with breast cancer and female controls after overnight fasting and stored at –80°C until assayed.

Cancer progress was established as: local (without any lymph nodes involved, No, and without any distant metastases, Mo) and meta (with the presence of lymph nodes involved and without any distant metastases, Mo). HER-2/neu was considered as either negative (0 or 1+) or positive (2+ or 3+).

All patients were informed of the study purpose and gave written consent. The reported study was approved by the Ethics Committee of

Table 1. Clinical characteristics of patient groups: with breast cancer and benign breast disease (control group).

Study group/subgroup	Number of patients
Breast cancer group	26
Age	54.7±8.0
Menopausal status	
pre	4
post	22
HRT	7
Histology type	
ductal	24
lobular	2
Clinical stage:	
a) Dcis	3
T1	16
T2	7
b) N0 (local)	18
N+ (meta)	8
Hormonal receptors status	
ER+	25
ER–	1
PG+	24
PG–	2
Smoking history (positive)	4
Control group	24
Age	58.8±9.4
Menopausal status	
pre	8
post	16
HRT	8
Histology type	
fibroadenoma	8
mastopathia fibrosa and cystica	11
adenosis sclerosans	2
hyperplasia ductalis	3
Smoking history (positive)	5

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Methods

The plasma total antioxidant status (TAS) was measured with the ABTS reagent (2,2'-azino-di-[3-ethylbenzthiazoline sulphate]) by colorimetric test (RANDOX Laboratories Ltd, Crumlin, United Kingdom) on StatFax™ 1904 Plus (Awareness Technology, Inc, Palm City, FL, USA).

HER-2/neu oncogene expression was determined routinely in breast cancer tissue using the immunohistochemical method (Hercep Test, DAKOCytomatin Company, Carpinteria, Ca, USA) in Great Poland Cancer Centre, Poznań.

Statistical analysis was performed using Statistica 6.0 for Windows (StatSoft). The results are expressed as means ± standard deviations. The distribution of values was verified by Shapiro-Wilk test. The comparisons between groups and subgroups were performed using non-parametric Mann-Whitney test. The statistical significance for the differences was accepted at the level $P<0.05$.

Table 2. Plasma total antioxidant activity (TAS) in breast cancer and benign breast disease (control) groups, also in relation to progress of the malignancy and HER-2/neu expression. The results are expressed as means ±SD.

Study group/subgroup	TAS [mmol/L]
Breast cancer group	1.42±0.22*
local (No)	1.42±0.23
meta (N+)	1.42±0.20
HER-2/neu negative (–)	1.46±0.20
HER-2/neu positive (+)	1.41±0.25
Control group	1.56±0.18

* significantly different from the control group, $P<0.01$.

Results

The study has demonstrated a significant decrease in the mean TAS level in the breast cancer group in comparison to the control group. The mean TAS concentration was found not to differ significantly between breast cancer subgroups in relation to the progress of the disease. Although the mean TAS concentration was not significantly different in regard to HER-2/neu expression, there was a tendency observed towards higher TAS in the HER-2/neu negative subgroup than in the HER-2/neu positive one (Table 2).

Discussion

The present study revealed changed plasma total antioxidant status in women with breast cancer as has already been reported. Decreased plasma TAS level in patients affected with malignancy suggests enhanced consumption of plasma antioxidants in response to increased production of reactive oxygen species. Thus, the finding supports the hypothesis of oxidative stress involvement in malignant process in the breast.

The results of other studies showed that the levels of superoxide radical and malonyldialdehyde

(MDA) – one of the lipid peroxidation markers – and the activities of some antioxidant enzymes (SOD – superoxidae dismutase, GPx – glutathione peroxidase, and GRx – glutathine reductase) in blood of patients with breast cancer were higher than in the controls, while the levels of vitamin C and both reduced and oxidized glutathione were decreased. The findings also confirm increased consumption of plasma antioxidant micronutrients and on the other hand upregulation of erythrocyte antioxidant enzymes activities, which does not protect macromolecules (e.g. lipids) from the consequences of enhanced oxidative stress [6]. Similarly, a study on oxidant-antioxidant status in breast cancer tissue revealed increased concentration of lipid peroxidation markers (MDA, hydroperoxides and conjugated diens) along with SOD and GPx activities in comparison to adjacent normal tissues and to fibroadenoma [7,8]. Moreover, higher concentrations of plasma total antioxidant status (measured with a different method than in the present study) and plasma micronutrients or metabolite with strong antioxidant properties, e.g. β-carotene, retinoid and bilirubin, were already observed to be associated with reductions in breast cancer risk [9].

The findings of the present investigation failed to demonstrate any difference in the plasma TAS level between the localized breast cancer subgroup and that with lymph nodes involved. Similarly, F. Tas et al. reported that tissue oxidant-antioxidant profile did not differ between breast cancer patients of various stages of the malignancy: I and II versus III and IV [7]. On the contrary, changes in tissue oxidant-antioxidant status were observed to be more pronounced in clinical stage III than in I and II [8]. The above discrepancies might result from various types of oxidative stress markers investigated and the relatively small number of patients.

The present research showed no significant changes in plasma TAS level in regard to HER-2/neu expression, although a tendency towards lower TAS level in HER-2/neu positive (+) in comparison to HER-2/neu negative (–) was found. An increase in GPx activity in HER-2/neu positive (+) compared to HER-2/neu negative (–) was described in breast cancer tissue, while other oxidant-antioxidant status markers (MDA, SOD, CAT-catalase) remained unchanged [7]. The above findings may suggest that oxidative stress might be related to HER-2/neu expression, and thus there is a need for further investigation.

Conclusions

The results of the study suggest increased consumption of plasma antioxidants in response to enhanced oxidant production in breast cancer patients. Changes in TAS level do not seem to correspond with the progress of the malignancy but might be related to HER-2/neu expression. Future research is needed to evaluate plasma TAS level along with oxidative damage markers to give better insight into oxidant-antioxidant imbalance in breast malignancy and on larger groups of patients.

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