High concentration of urokinase-type plasminogen activator receptor in the serum of women with primary breast cancer

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Aim of the study was to assess the concentration of urokinase-type plasminogen activator receptor (uPAR) in the serum of 103 women with breast cancer. Commonly recognized prognostic factors were taken into account, including age, histological grade of malignancy, stage of clinical advancement of the disease, status of local axillary lymph nodes and the size of the primary tumour.

Material and methods: The concentration of uPAR was assessed using an enzyme-linked immunosorbent assay (R&D Systems).

Results: The concentration of uPAR in women with breast cancer was found to be higher than in a control group and the difference was statistically significant. The concentration of uPAR was found to increase in line with increasing disease stage and this too was of statistical significance. Raised levels of uPAR were found in women with breast cancer both with and without metastases to the lymph nodes of the axilla. A positive relationship was also found between the concentration of the tested receptor and the size of the primary tumour. No significant relationship, however, was found between the concentration of uPAR and the histological grade of malignancy of the tumour. No statistically significant results were obtained regarding the menopausal status of the women, that is, whether they were pre- or postmenopausal.

Conclusions: Concentration of uPAR in serum of women with breast cancer is positively correlated with the stage of advancement of the disease. Thus, the assessment of this parameter can be useful in the clinical evaluation of women with breast cancer.

Key words: fibrinolysis, metastasis, breast cancer, uPAR, plasminogen activation system.

Introduction

A significant role in the growth of malignant tumours and in the formation of metastases is played by new blood vessels formed by the process of neoangiogenesis [1, 2]. Substances which play roles in the process arise from the vascular endothelial cells, from the tumour cells, and from the extracellular matrix (ECM). The many components produced have various functions, in which proteases have a regulatory role, such as inhibitors and receptors of the urokinase plasminogen activation system, including urokinase-type plasminogen activator (uPA), its receptors (uPAR – urokinase-type plasminogen activator receptor) and inhibitors PAI-1 and PAI-2 (plasminogen activator inhibitors) [3]. These components of the system not only take part in digestion, thus mobilising the endothelial cells into formation of new vessels, but also stimulate cancer cells to migrate and to form new remote metastases. One of the proteins of the plasminogen activation system which plays an important role in metastasis is urokinase (uPA), arising from the inactive precursor pro-uPA [4]. The functioning enzyme, whose role is to convert plasminogen into plasmin, is formed when urokinase binds with its specific membrane bound receptor – uPAR [6]. The uPAR receptor is a glycoprotein, of molecular weight 45–60 kDa, comprising 283 amino acids. The gene for this receptor is localised on chromosome 19q13.2, and is formed from 7 exons divided by 6 introns. In structure, the *N*-terminal fragment is bound with uPA and the *C*-terminal fragment is bound with the cell membrane by a glycosyl-phosphatidylinositol (GPI) chain [6]. To date, uPAR receptors have been identified on the surface of monocytes, granulocytes, fibroblasts, keratinocytes, vascular endothelial cells and cancer cells [7]. The expression of this receptor has also been observed in populations of macrophages and intravascular neutrophils. It has been shown that, on the surface of these cells, the uPAR takes an insoluble form, whilst the soluble form known as suPAR may be found in the plasma, in urine and in effusions from malignancies [7]. Scientific works in recent years have described increased expression of this receptor in cancers of the stomach, large intestine, ovary, endometrium and in cases of melanoma [8–12]. The authors of these studies noted that both the receptor (uPAR) and its complex with urokinase (uPA/uPAR) bring about changes regarding the invasiveness of cancer cells into the tissues surrounding the tumour. This is mostly through degradation of the ECM by these complexes, by stimulation of angiogenesis and by regulation of cell migration [12]. Recently it was suggested that the high concentration of uPA and the uPAR noted in the bodily fluids of many cancer patients may be of use in the diagnosis and prognosis of malignant diseases [12]. The purpose of this study was to assess the concentration of

uPAR in the serum of breast cancer patients and its dependency on various commonly accepted prognostic factors, such as age, disease advancement, grade of tumour malignancy, the status of local axillary lymph nodes and the size of the tumour.

This study is a continuation of our previous studies into the role of the fibrinolytic system in women with primary breast cancer.

Material and methods

The concentration of urokinase-type plasminogen activator receptor was assessed in the serum of 103 women with breast cancer. Patients with primary breast cancer, before first surgery, were included in the study. Patients who used neoadjuvant chemotherapy were excluded from the study group. The women were aged between 29 and 89 years (average age 56 years) and were treated in the Department of Oncology Surgery of the Poznan University of Medical Sciences. In each case, the diagnosis had been confirmed by histopathology tests carried out in the Department of Tumour Pathology, also of the Poznan University of Medical Sciences. A group of 40 healthy women, aged between 24 and 75 years (average 47 years), comprised the control group. The authors obtained the agreement of the Bioethics Committee of the University of Medical Sciences, in order to carry out the study. Clinical characteristics of the breast cancer patients are presented in Table 1.

Approximately 5 ml of venous blood was collected into clotting tubes from each patient. After about 30 minutes, the samples were centrifuged at 1000 rpm for 10 minutes. After centrifugation, the serum was isolated into 0.5 ml tubes and frozen at –20°C. The prepared tubes were stored in this manner until the time of testing, but not for more than six months. The concentration of uPAR was assessed using a "sandwich" type enzyme-linked immunosorbent assay (ELISA) from R&D Systems.

Statistical analysis

The obtained uPAR concentrations were subjected to statistical analysis using Statistica 8.0 software. Prior to analysis the variables were tested for normal distribution using the Shapiro-Wilk W test. For the purposes of identifying differences between the tested groups the Mann-Whitney U test was applied. Statistical hypotheses were accepted where the level of significance was $p < 0.05$.

Results

In the group of 103 women with breast cancer the median concentration of urokinase-type plasminogen activator receptor (uPAR) was more than 2.5 times greater than in the control group, and this difference was found to be statistically significant (Table 2, Fig. 1). The analysis of results also showed that the mean concentration of uPAR in the serum of post-menopausal women was significantly higher than in pre-menopausal patients (Table 2). The median concentration of uPAR was also found to increase in line with disease advancement (Table 2, Fig. 2). The highest median concentration of uPAR was found in the serum of women in stage

III of disease advancement and this was found to be statistically significant in comparison with the levels found in women whose disease was in stage I or II (Table 2). A significant difference was also found between uPAR levels in patients in stage II of disease advancement, when compared to those in stage III. Another statistically significant difference was identified when comparing the levels of uPAR in the serum of women with metastases to the axillary lymph nodes to those without metastases (Table 2, Fig. 3). Further analysis showed that there is no relationship between the grade of histological malignancy and median uPAR concentration (Table 2). There is, however, a relationship of statistical significance between the concentration of uPAR in the serum of women whose tumour is sized less than 20 mm, between 20 mm and 50 mm, or greater than 50 mm in diameter (Table 2, Fig. 4).

Discussion

The causes of the high coefficient of mortality in this disease are the lack of effective detection and diagnosis of this cancer, as well as the metastatic character of the disease [15]. At the time of diagnosis, around two thirds of patients already have metastases to the local lymph nodes and, in a considerable percentage of patients, there may also be micrometastases in remote organs. From the available data in the literature, it appears that a major factor in the formation of remote metastases is disturbance of the fibrinolytic system [16]. Substances produced by vascular endothelial cells and by tumour cells take part in this process [17]. An area of some interest, for many research centres, is the role of urokinase-type plasminogen activator (uPA) and its receptor in the process of metastasis in women with breast cancer [18]. So far, it has been shown that these substances are, above all, responsible for the conversion of plasminogen into plasmin. Plasmin is the main enzyme involved in the degradation of the vascular basement membranes, which facilitates migration and the adhesion of cancer cells to the surrounding tissues [17, 18]. Experimental work of recent

Table 1. Clinical characteristics of patients with breast cancer

Clinical characteristic	Number of patients	Percentage of tested patients (%)
Age		
pre-menopausal	31	30.1
post-menopausal	72	69.9
Stage of clinical disease advancement according to TNM		
I	47	45.6
II	38	36.9
III	18	17.5
Status of local axillary lymph nodes		
pN0	51	49.5
pN1	52	50.5
Size of the primary tumour		
pT < 20 mm	54	52.4
pT ≥ 20 ≤ 50 mm	40	38.9
pT ≥ 50 mm	9	8.7
Histological grade of malignancy		
G1	11	10.7
G2	50	48.5
G3	42	40.8

Table 2. Concentration of uPAR in patients with breast cancer and its relationship to age, stage of clinical advancement of disease, status of lymph nodes, tumour size and histological malignancy

Patient characteristic	uPAR	
	Median uPAR concentration [pg/ml]	uPAR concentration range [pg/ml]
Control group $n = 40$	2039.8	1010.2–3231.5
Breast cancer patients $n = 103$	4660.0*	1020.4–14124.0
Pre-menopausal	3901.8*	1020.4–14057.3
Post-menopausal	4882.2*	1803.2–14124.0
Stage of clinical disease advancement according to TNM		
I $n = 47$	2901.3*	1020.4–8831.2
II $n = 38$	5263.8*&	3189.4–10804.1
III $n = 18$	9327.6*&#	4071.5–14124.0
Axillary lymph node status		
pN0 $n = 51$	3189.4*	1020.4–8636.4
pN1 $n = 52$	6005.6*▼	2709.4–14124.0
Tumour size		
pT < 20 mm $n = 54$	3543.2*	1020.4–8327.9
pT ≥ 20 < 50 mm $n = 40$	5246.8*♦	1853.4–13676.1
pT ≥ 50 mm $n = 9$	10986.1*♦■	4705.0–14124.0
Histological grade of malignancy		
G1 $n = 11$	3429.3	1120.8–9001.2
G2 $n = 50$	4202.1*	1020.4–14057.3
G3 $n = 42$	5588.6*	1901.6–14124.0

n – number of tested women
*statistically significant difference for uPAR in comparison to control group, $p < 0.05$
&statistically significant difference for uPAR in comparison to the group of women in stage I of disease advancement, $p < 0.05$
#statistically significant difference for uPAR in comparison to the group of women in stage II of disease advancement, $p < 0.05$
▼statistically significant difference for uPAR in comparison to women without metastases to the axillary lymph nodes, $p < 0.05$
♦statistically significant difference for uPAR in comparison to women whose tumour measured < 20 mm, $p < 0.05$
■statistically significant difference for uPAR in comparison to women whose tumour measured ≥ 20 < 50 mm, $p < 0.05$

years has brought information regarding the increased activity of uPA and uPAR in neoplastic tissues and in the bodily fluids of cancer patients [18, 19].

Our earlier studies showed increased uPA activity in women with breast cancer. It may be supposed that increased activity of uPA accelerates the processes of proliferation, migration and adhesion, not only in endothelial cells but also in tumour cells. Urokinase-type plasminogen activator takes its effects through binding with its specific uPAR, forming the uPA-uPAR complex which accelerates extracellular conversion of plasminogen into active plasmins. The enzyme directly catalyses the destruction of the basement membranes and cell matrices, including fibronectins, laminins, vitronectins and fibrins [18]. Increased production of plasmins also leads to activation of metalloproteinase, which, as the only enzyme involved in the processing of type IV collagen, is responsible for the formation of the skeleton of the vascular basement membranes. As a consequence of raised urokinase activity and increased plasmin production, there is increased degradation of the extracellular matrix surrounding the tumour,
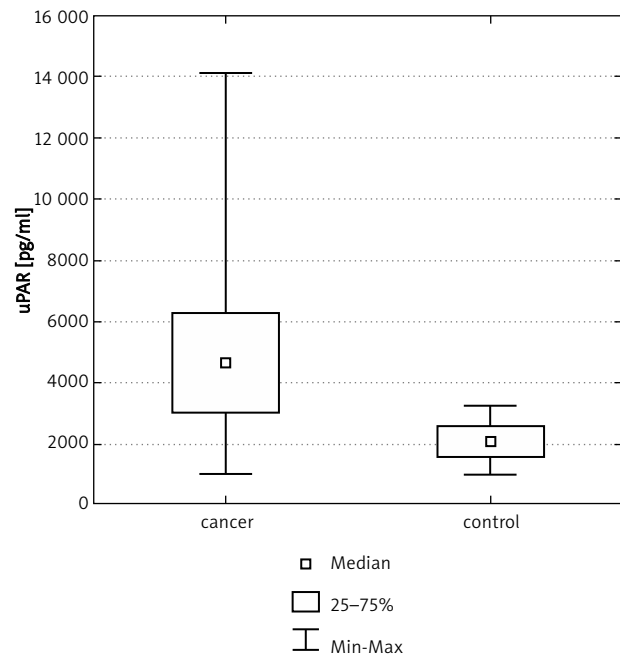

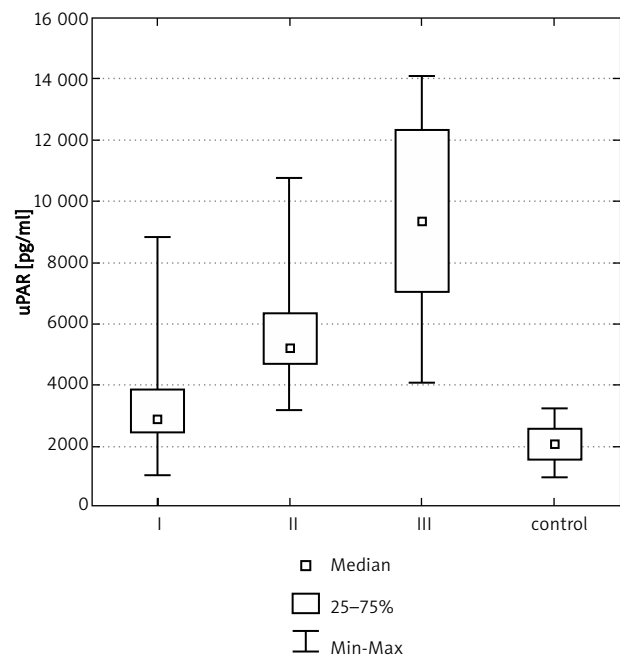**Fig. 1.** Concentration of uPAR in the serum of women with breast cancer

Fig. 2. Concentration of uPAR in the serum of women with breast cancer in relation to stage of clinical advancement of the disease

release of tumour cells from the primary tumour mass and their migration to the vessels. This makes it possible for tumour cells to invade remote organs [19]. The positive correlation between the activity of urokinase and the concentration of uPAR is a necessary condition for the process described above [20, 21]. The binding of uPA to the uPAR present on the surface of the tumour cells, thus forming the uPA-uPAR complex, is a condition for the formation of remote metastases.

In our study, we detected an increased level of uPAR in the serum of women with breast cancer, in comparison to the concentrations obtained from a control group.
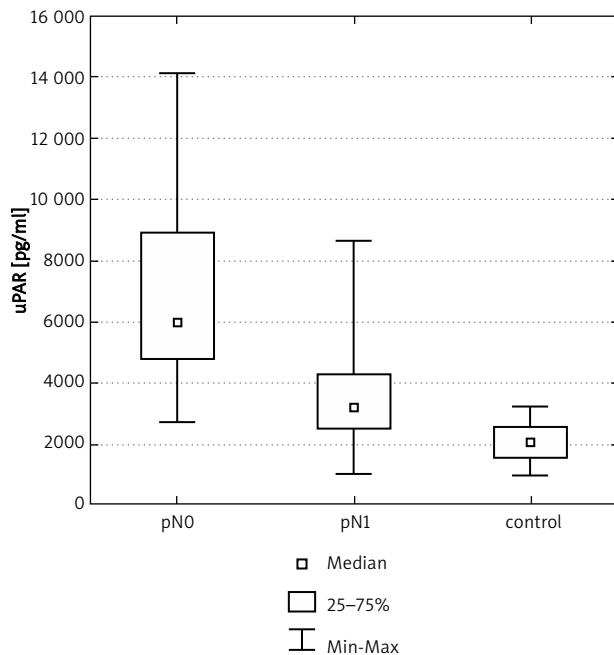
Fig. 3. Concentration of uPAR in the serum of women with breast cancer in relation to lymph node status
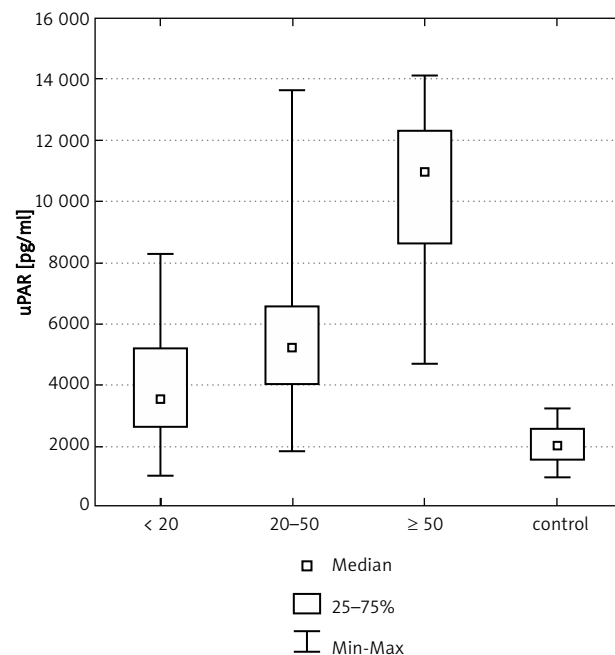

Fig. 4. Concentration of uPAR in the serum of women with breast cancer in relation to tumour size

In our group of 103 patients, 71 showed increased levels of uPAR. Similar observations were made by Witte *et al.*, who found a statistically significant difference between the concentrations of uPAR in the plasma of breast cancer patients and the values for that receptor in a control group. Those authors also obtained raised results for the concentration of the uPA/uPAR complex and positive correlations between these parameters [22]. Similar findings were obtained by Risbro and colleagues, who simultaneously tested blood sera and homogenised breast cancer tissue [23]. Foekens and colleagues not only determined the concentrations of uPAR and uPA in the serum, but also demonstrated that high expression in homogenised tissues can be correlated with shortened survival and increased relapse rates [24]. From the available literature it may be concluded that expression of the uPAR is dependent on the presence of various cytokines, most of which are produced by Th1 lymphocytes. The cytokines interferon α (INF-α) and interleukin 2 (IL-2) increase the expression of uPAR and the activity of uPA, while the interleukins IL-4 and IL-13 increase the activity of urokinase and reduce the expression of the uPAR [25]. In their studies, Meng *et al.* observed high expression of uPAR in cancer tissues from the breast. Increased expression of the receptor was seen mainly in the outermost layers of the tumour, which, according to some authors, may be related to the presence of uPA on the surface of tumour cells [26]. The determination of disease stage is of particular importance in the prognosis of, and in selection of suitable treatments for, cancer patients. In our study we observed a relationship between the concentration of the uPAR and the stage of disease advancement. Disease stage, according to the TNM classification, rose in association with significantly raised uPAR levels in the serum of our group of breast cancer patients. We have found no results in the literature which relate the assessment of uPAR concentration in breast cancer patients to disease staging. Only Gong and co-workers, testing for uPAR in homogenised breast cancer tissue using an ELISA method, found a statistically significant relationship between the level of uPAR in women and stage (I or II) of clinical disease advancement [27]. Suzuki, using an *in situ* hybridization method, determined that expression of uPAR is increased in about 30% of cases of adenocarcinoma and in about 85% of cases of cancer of the large intestine; and that this increase in expression rises in line with increasing stage of advancement according to the Dukes scale [28]. Based on the findings of the study, that author also proposed that expression of the receptor was likely to be associated with the transformation of adenocarcinoma into invasive cancer [28]. In their experimental work, carried out on the serum of patients with multiple myeloma, Dmoszyńska and colleagues also noted high concentrations of uPAR. The results were significantly higher than those obtained from a control group. That study did not, however, confirm a relationship between the stage of disease advancement and the uPAR level, probably because of the small size of the studied group [29]. Another important prognostic factor in the survival of, and treatment selection for, patients with breast cancer, is the status of the axillary lymph nodes [30, 31]. Specialist oncologists believe that there is a good chance that patients whose disease is discovered sufficiently early, prior to the formation of metastases, can be permanently cured. The results of this study showed a statistically significant difference between levels of uPAR in patients with metastases to the lymph nodes and the level of the activator in patients without metastases. In their group of patients, Grondhal-Hansen obtained no statistically significant difference between levels of uPAR and the presence of metastases to the axillary lymph nodes [32]. Gong *et al.* made similar observations [27]. Kaneko's results, based on a study involving more than 100 patients with stomach cancer, showed that there

was a positive relationship between the expression of the receptor and metastasis to the lymph nodes [33].

The analysis of our own results also included a comparison of serum uPAR concentrations to the degree of histological malignancy. We found no statistically significant differences between uPAR levels in patients with G1, G2 or G3 graded tumours. A lack of related findings in the literature meant that we were unable to compare our findings with those of other authors.

A significant prognostic parameter is the size of the tumour. The risk of disease progression and death rises in line with the size of the tumour. Small tumours are not, however, a reliable factor in a good prognosis, as even tumours measuring less than 10 mm can give rise to remote metastases. Our analysis showed that increasing tumour size goes hand in hand with increasing concentration of uPAR in the serum of women with breast cancer. We found statistically significant differences between the levels of uPAR in the control group, in patients with tumours measuring less than 20 mm, in patients whose tumours measured between 20 mm and 50 mm, and in those whose tumours measured greater than 50 mm. Little work has been carried out regarding the relationship between uPAR levels and tumour size, and so this parameter was also not compared with the findings of other researchers. On the basis of the available literature, we must accept that the plasminogen activation system plays an important role in the development of malignant tumours and the formation of metastases [34, 35]. The results of experimental studies, and of our own work, suggest that fibrinolysis may affect metastasis not only through the direct activation of plasmin, which is responsible for the degradation of vascular basement membranes and ECM, but also indirectly by the enzymatic activation of plasminogen [36, 37]. Among the main proteolytic enzymes are urokinase and tissue-type plasminogen activator (tPA). Earlier studies in our Laboratory Diagnostics Department showed raised levels of this activator in patients with breast cancer [38]. This enzyme not only directly takes part in the digestion of vascular basement membranes, but also activates metalloproteinases, thus facilitating the invasion of remote organs by cancer cells. It is presently believed that the binding of the uPAR, on the surface of tumour cells, to uPA, initiates an intracellular signalling cascade and plays an important role in the remodelling of the tissues surrounding the tumour and thus in the progression of the disease [38]. The formation of D-dimers is a result of the activation of the fibrinolytic system. In serum of patients with cancer an elevated concentration of this parameter has been observed. It is considered that determination of D-dimers is useful in the detection of latent intravascular activation of the coagulation system in patients with cancer [39, 40].

The relationship between tumour development and the activity of components of the fibrinolytic system gives hope that regulation of these processes may lead to new anticancer treatments [41]. Inhibition of the activities of the components of the fibrinolytic system is presently the subject of many studies.

In conclusion, increased levels of the uPAR was demonstrated in the serum of women with breast cancer. The level of this receptor was significantly higher in comparison to the level of uPAR in a control group. The presented results may indicate that increased activity of the fibrinolytic system and the action of its proteolytic components are involved in the formation of remote malignant metastases. It appears that the positive relationship between the concentration of the uPAR in women with breast cancer and advancing stage of disease may give us a valuable additional tool in the clinical assessment of women with this disease.

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