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Diagnostic value of measuring serum CA 15-3, TPA, and TPS in women with breast cancer

Izabela Śliwowska^{1BCDEF}, Zygmunt Kopczyński^{1ADEF},
Sylvia Grodecka-Gazdecka^{2ADF}

¹ Department of Laboratory Diagnostics, Chair of Oncology, Poznań University of Medical Sciences, Poznań, Poland

² Department of Surgery, Chair of Oncology, Poznań University of Medical Sciences, Poznań, Poland

Summary

Investigation:

The concentrations of CA 15-3, TPA, and TPS were determined in the serum of 90 women with breast cancer.

Material/Methods:

Serum CA 15-3 levels were determined by Abbott immunofluorescent tests, TPA concentration using the Byk-Roland immunoluminometric method, and TPS by the BEKI Diagnostics immunoenzymatic method.

Results:

In the diagnosis of breast cancer, the TPA test had the greatest diagnostic sensitivity. A strong correlation was found between the percentages of women with positive levels of all three markers and advanced stages of breast cancer.

A longitudinal evaluation of 42 women who underwent neoadjuvant chemotherapy showed clinical regression of the tumor and a statistically significant reduction in the concentrations of these markers.

Conclusions:

These results indicate that determining the serum levels of CA 15-3, TPA, and TPS may be used to establish the stage of disease and it provides useful guidance both in deciding whether to treat surgically and in estimating the efficacy of neoadjuvant chemotherapy in patients with breast cancer.

Key words:

breast cancer • tumor markers • CA 15-3 • TPA • TPS

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Author's address:

Dr. n. biol. Izabela Śliwowska, Department of Laboratory Diagnostics, Chair of Oncology, Poznań University of Medical Science, ul. Łąkowa 1/2, 61-878 Poznań, Poland; e-mail: izabela.sliwowska@oncology.am.poznan.pl

INTRODUCTION

The most frequent cancer amongst Polish women is breast cancer, and it is also the leading cause of death from cancer for women [16]. In the early diagnosis, treatment planning, and follow-up of breast cancer, several tumor markers may be helpful, including the antigen 15-3 (CA 15-3), tissue polypeptide antigen (TPA), and tissue polypeptide-specific antigen (TPS) [1,2,5,10,23,24,26]. Serum tumor markers are measured throughout cancer therapy to detect recurrences, the existence of metastases, and the progression of the disease [2,5,23,24,26]. Breast cancer therapy should be planned according to the stage of the disease, and various combinations of surgery, radiotherapy, chemotherapy, and endocrine therapy are commonly employed [13,14,18,19]. The essential method of curing breast cancer at an early stages is surgery. Locally advanced breast cancers without distant metastases need aggressive neoadjuvant treatment, usually consisting initially of chemotherapy or hormone therapy, followed by surgery. This multidisciplinary treatment increases the chances of recovery and of long-term, disease-free survival [7,12,13,18,19].

The aim of this study was to compare the values of serum CA 15-3, TPA, and TPS in women with breast cancer at various stages of the disease and to consider the usefulness of these tests in evaluating the efficacy of treatment.

MATERIAL AND METHODS

The concentrations of CA 15-3, TPA, and TPS were determined in the sera of 90 female breast cancer patients aged 32–85 years (average: 57.2 years) treated at the Chair of Oncology in Poznan. Of the women investigated, 48 (mean age: 62.5 years, range: 41–85 years) were diagnosed with primary operable cancer and 42 (mean age: 51.9 years, range: 32–73 years) as suffering from locally advanced cancer. All 42 women in the latter group received a course of neoadjuvant chemotherapy; 26 were then treated according to the CMF program, ten received the AC program, and the remaining 6 received the FAC program.

Benign breast disease was diagnosed in a group of 30 women, aged 34–87 years (average: 55.4 years), who served as a group for comparison.

Serum CA 15-3, TPA and TPS assay

Blood samples from all the patients with breast cancer were drawn one day before surgery. Serum samples were also obtained from those patients undergoing neoadjuvant chemotherapy before the first cycle of treatment.

The serum was obtained by centrifugation at room temperature and then stored in multiple aliquots at -20°C .

Serum CA 15-3 levels were determined by Abbott immunofluorescent tests, using a cut-off value of 28 U/ml. The TPA concentration was determined using the Byk-Roland immunoluminometric method, using a cut-off value of 75 U/l, and TPS by the BEKI Diagnostics immunoenzymatic method (cut-off: 80 U/l). Values above the cut-offs were considered positive.

Statistical analysis

The statistical analyses were carried out using STATISTICA 5.5 software. The serum levels of the examined markers are expressed as the mean \pm SD, the median, and the range. Data are presented as percentages of positive patients. All results underwent statistical analysis using non-parametric tests (Mann-Whitney and Wilcoxon). The level of statistical significance was set at $p < 0.05$.

RESULTS

Significantly higher median concentrations of CA 15-3, TPA, and TPS were found in the women with breast cancer than in the women with benign breast disease. Of the group of 30 women with benign breast disease, the concentration of CA 15-3 was above the cut-off point in 3 of them (10.0%), above that of TPA in 5 (16.7%), and that of TPS in 8 (26.7%).

The highest concentrations and frequency of occurrence were found in the women with breast cancer. In 40 patients (44.4% of this group) the CA 15-3 concentration was above the cut-off. The concentration of TPS was increased in 62 (68.9%) and that of TPA in 74 women (82.2%).

Table 1 summarizes the percentages of serum CA 15-3, TPA, and TPS positive patients with breast cancer, stratified on the basis of TNM status. A strong correlation was found between positive levels of all three markers and advanced stage of the disease.

In the diagnosis of breast cancer, the TPA test had the greatest diagnostic sensitivity (82%). The diagnostic sensitivities of the TPS and CA 15-3 levels were lower (69% and 44%, respectively) (Table 2). However, the CA 15-3 test had the highest diagnostic specificity (90%) compared with those for TPA (80%) and TPS (73%). The positive predictive values were 94% for TPA, 93% for CA 15-3, and 89% for TPS. The negative predictive values were 78%, 53%, and 65%, respectively. Combined evaluation of two serum markers demonstrated a complementary expression of the antigens. Evaluation of TPA with either CA 15-3 or TPS increased the diagnostic sensitivity to 90% (Table 2).

In the ROC curve analysis, TPA has the largest area (0.909) under the ROC curve, followed by TPS (0.873) and CA 15-3 (0.842) (Figure 1). These data show that TPA had the greatest diagnostic value in breast cancer of the three markers investigated.

Further analysis showed significantly lower median concentrations of CA 15-3, TPA, and TPS in the women with primary operable cancer compared with the women with primary inoperable breast cancer (Table 3). Analysis of the results also showed that, of the group of 48 women with primary operable cancer, the concentration of TPA was over the cut-off point in 35 of them (72.9%). The smallest percentage of high levels of TPS and CA 15-3 occurred in this group. Higher concentrations of CA 15-3, TPA, and TPS were found in the 42 women with locally advanced breast cancer. In 39 women in this group (92.9%), the concentration of TPA was over the cut-off value (Table 3).



Table 1. Summary of the evaluation of CA 15-3, TPA and TPS serum markers in breast cancer patients according to tumor stages

Clinical stage of breast cancer according to TNM classification	No of patients	CA 15-3 (>28 U/ml)	TPA (>75 U/l)	TPS (>80 U/l)
N 0	38	13 (34.2)	28 (73.7)	18 (47.4)
N 1	52	27 (51.9)	46 (88.5)	44 (84.6)
T 1	40	12 (30.0)	30 (75.0)	25 (62.5)
T 2	41	20 (48.8)	35 (85.3)	31 (75.6)
T 3	9	8 (88.9)	9 (100.0)	7 (77.8)
Total	90	40 (44.4)	74 (82.2)	62 (68.9)

Numbers in parentheses represent percentage

Table 2. Diagnostic sensitivity, specificity and predictive value of tests for CA 15-3, TPA and TPS in the diagnosis of breast cancer

Tumor marker or combination	Diagnostic sensitivity	Diagnostic specificity	Positive predictive value PV(+)	Negative predictive value PV(-)
CA 15-3	0.44	0.90	0.93	0.53
TPA	0.82	0.80	0.94	0.78
TPS	0.69	0.73	0.89	0.65
CA 15-3 + TPA	0.90	0.97	0.89	0.60
CA 15-3 + TPS	0.78	0.97	0.88	0.49
TPA + TPS	0.90	0.93	0.86	0.63

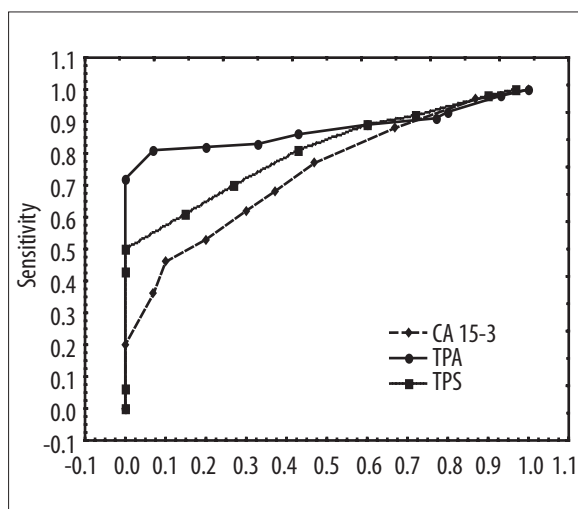


Figure 1. Receiver operating characteristic (ROC) curves of CA 15-3, TPA and TPS. Calculations based on values of the breast cancer group (n=90) and the group with benign breast disease (n=30). Area under the ROC curves: CA 15-3=0.842; TPA=0.909; TPS=0.873

A longitudinal evaluation of the 42 women with locally advanced disease, all of whom received neoadjuvant chemotherapy, was also performed (Table 4). The use of neoadjuvant chemotherapy caused clinical regression of the

tumor and a statistically significant reduction in the CA 15-3, TPA, and TPS concentrations.

A decrease in the concentration of TPA to 50% of the level before treatment was noted in 40 (95.2%), in the CA 15-3 concentration in 38 (90.5%), and of TPS in 37 (88.1%) of the 42 women with locally advanced breast cancer (Table 4).

DISCUSSION

CA 15-3, a recognized tumor marker, is routinely used in the diagnosis and monitoring of breast cancer patients [7,12,22,23]. The test for CA 15-3 is used in assessing the efficiency of first-line chemotherapy and in the early diagnosis of recurrence after radical treatment [11,14,23,26]. In the last decade of the 20th century, the interest of both clinicians and laboratory diagnosticians was focused on tissue polypeptide antigen (TPA), a marker representing the apoptosis of cancer cells, and tissue polypeptide-specific antigen (TPS), a marker reflecting the dynamics of the neoplastic process [1,2,6,10,25]. However, these tests are not widely used in Poland in the diagnostics of breast cancer.

Our results show essential differences between the median concentrations of CA 15-3, TPA, and TPS found in women with breast cancer and in women with benign disease. The finding of significantly higher median values for all these markers in malignant than in benign disease suggests that

Table 3. Concentration of CA 15-3, TPA and TPS in the serum of women with operable and locally advanced breast cancer

	Operable breast cancer n = 48			Primary inoperable breast cancer n = 42		
	CA 15-3 U/ml	TPA U/l	TPS U/l	CA 15-3 U/ml	TPA U/l	TPS U/l
Mean ±SD	24.7±8.7	108.9±63.2	104.9±47.7	29.8±13.2	156.9±59.7	132.0±65.6
Median	24.8	102.1	88.7	30.7*	163.4*	128.4*
Range	7.9–43.4	14.1–242.8	36.8–236.5	4.9–59.3	35.6–298.3	45.3–258.6
No of positive (%)	>28 U/ml 15 (31.2)	>75 U/l 35 (72.9)	>80 U/l 26 (54.2)	>28 U/ml 25 (59.5)	>75 U/l 39 (92.9)	>80 U/l 36 (85.7)

* p<0.05; Numbers in parentheses represent percentage

Table 4. Changes in serum CA 15-3, TPA and TPS levels in women with breast cancer undergoing neoadjuvant chemotherapy

Neoadjuvant chemotherapy	CA 15-3 U/ml			TPA U/l			TPS U/l		
	Mean ±SD	Median	Range	Mean ±SD	Median	Range	Mean ±SD	Median	Range
Before treatment	29.8±13.2	30.7	4.9–59.3	156.9±59.7	163.4	35.6–298.3	132.0±65.6	128.4	45.3–258.6
No of positive (%)	>28 U/m	25 (59.5)		>75 U/l	39 (92.9)		>80 U/l	36 (85.7)	
After treatment	22.4±10.7	20.2*	4.6–50.7	120.1±55.2	113.8*	30.8–238.0	96.8±59.3	79.6*	38.3–310.6
No of positive (%)	>28 U/m	14 (33.3)		>75 U/l	34 (80.9)		>80 U/l	20 (47.6)	
Stable disease (SD) (%)		38 (90.5)			40 (95.2)			37 (88.1)	
Partial Remission (%)		4 (9.5)			2 (4.8)			5 (11.9)	

* p < 0.05; Numbers in parentheses represent percentage

very high levels of serum CA 15-3, TPA, or TPS imply the presence of malignant disease. Similar results were reported by D'Allesandro and Seker [4,22].

The evaluation of serum samples obtained from 90 women with breast cancer revealed higher TPA levels in cases with more advanced disease. In fact, while only 53% of the patients with stage I breast cancer had positive serum TPA levels, this percentage rose to 95% in those women with stage III. These results indicate that high levels of CA 15-3 appear to be related to the tumor burden, whereas those of TPS to the lymph node status.

Further analysis of the results showed that a greater frequency of high levels occurred in the group of women with breast cancer. The highest level in the serum of patients with breast cancer was observed in the test for TPA (82%), a slightly lower level for TPS (69%), and the lowest for CA 15-3 (44%). By taking the area under the ROC curves as a measure of the diagnostic discriminatory power of the markers, TPA (0.909) was significantly better than TPS (0.873) and CA 15-3 (0.842). The areas under the ROC curves for TPA and CA 15-3, reported by Gion and Findeisen et al. were slightly smaller [8,9].

Combined evaluation of TPA and CA 15-3 serum levels demonstrated a complementarity of these two markers. A combination of two tumor markers has a higher sensitivity than each one alone. Thus, combining CA 15-3 and TPA produced positive levels of approximately 90%,

an increase over TPA sensitivity alone of approximately 12%. Similar results have been obtained by other authors [4,7,12,17,21,25].

Comparative analysis of the group of patients with primary operable cancer and of women with inoperable cancer showed significantly higher median concentrations and a greater frequency of increased levels of CA 15-3, TPA, and TPS in women with locally advanced disease. In this group of 42 patients, the concentration of TPA exceeded the cut-off value in 93% women, but this was only found in 73% of the group with primary operable cancer. A similar dependence was observed in the determination of CA 15-3 and TPS.

A comparison of the CA 15-3, TPA, and TPS levels and pre- and post-neoadjuvant chemotherapy, showed a correlation between response to therapy and reduction in serum marker levels. A decrease to 50% of the markers' initial levels, corresponding to stable disease (SD), was observed. With TPA this was found in 95.2% of the patients, with CA 15-3 in 90.5%, and with TPS in 88.1%. Increases in the concentrations of these markers were not observed in any of the patients. These results are in agreement with previous reports regarding the possible usefulness of CA 15-3, TPA, and TPS in evaluating the response to chemotherapy of patients with advanced breast cancer [3,15,20,28]. Tumor marker information may be used to change ineffective treatments and as an aid in individualizing therapy in patients with breast cancer [5,24].



CONCLUSIONS

1. The increased serum levels of CA 15-3, TPA, and TPS correlate with the clinical stage of disease, lymph node status, and tumor burden in breast cancer.

2. TPA is the most useful tumor marker in the diagnosis of breast cancer, particularly if combined with CA 15-3.

3. Determination of CA 15-3, TPA, and TPS together indicates the efficiency of neoadjuvant chemotherapy.

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