

# EXPRESSION PATTERNS OF PSA IN FEMALE BREAST TUMORS

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## REZUMAT

**Obiective:** Investigarea expresiei PSA în țesutul mamar normal și tumoral. **Material și metode:** Am studiat 52 cazuri de tumori mamare. Diagnosticul histopatologic a fost stabilit pe secțiuni colorate cu hematoxilină-eozin, iar evaluarea expresiei PSA s-a efectuat imunohistochimic. **Rezultate:** Pe secțiunile colorate cu hematoxilină-eozină am diagnosticat 41 tumori maligne, între care un caz de metastază cutanată de carcinom mamar și 11 tumori benigne. Adiacent țesutului tumoral, am identificat țesut mamar normal în 7 tumori benigne și 9 tumori maligne. Expresia PSA a fost identificată în 50% cazuri cu țesut mamar normal, 57% leziuni benigne și 63% carcinoame mamare și a fost apreciată în funcție de procentul de celule PSA- pozitive și intensitatea imunoreacției PSA. În țesutul mamar normal, am observat o reacție moderat pozitivă, cu un pattern granular citoplasmatic, heterogenă la nivelul acinilor. În cadrul leziunilor benigne, reacție intens pozitivă a prezentat metaplazia apocrină, moderat pozitive fiind fibroadenomul, hiperplazia lobulară și ductală. Dilatațiile chistice au prezentat reacție negativă. În cazul leziunilor maligne, reacție intens pozitivă au prezentat carcinoamele invazive lobulare și metastaza cutanată. Carcinoamele ductale invazive, carcinomul medular și mucinos au fost moderat pozitive. **Concluzii:** 50% dintre speciamentele cu țesut mamar normal, 54% dintre leziunile benigne și 63% din tumorile maligne au prezentat imunoreacție pozitivă pentru PSA. În țesutul mamar normal, PSA a fost heterogen distribuit numai la nivelul acinilor, țesutul normal, adiacent leziunilor benigne prezentând o imunoreacție mai intensă decât cel adiacent carcinoamelor. În cazul țesutului tumoral, rezultate intens pozitive am constatat în majoritatea carcinoamelor lobulare invazive și leziunilor de metaplazie apocrină, în timp ce adenoza, dilatațiile chistice, carcinoamele papilare și metaplazic au fost negative.

**Cuvinte cheie:** PSA, kaliceine, imunohistochimie, tumori mamare, glandă mamară normală

## ABSTRACT

**Objectives:** To investigate the prostate-specific antigen (PSA) expression in normal and tumoral mammary gland. **Material and methods:** We studied 52 cases of breast tumors. The pathological diagnosis was established on hematoxylin-eosin stained sections and the PSA expression was immunohistochemically assessed. **Results:** On hematoxylin-eosin stained samples we found 41 malignant tumors including also a skin metastasis of a breast carcinoma and 11 benign tumors. Adjacent to 7 benign tumors and 9 malignant tumors we found normal breast tissue. The PSA expression was identified in 50% of normal breast tissue, 54% of benign lesions and in 63% of malignant tumors and was quantified according to the percentage of PSA-positive cells and the intensity of the immunostaining. We noticed a moderately positive, heterogeneous reaction, with granular cytoplasm pattern in the secretory units of the normal breast tissue. The benign lesions with a moderate PSA expression were: fibroadenoma, lobular and ductal hyperplasia. The apocrine metaplasia was strongly positive. The dilated cysts were negative. The malignant lesions with moderate immunoreaction were: invasive ductal carcinoma, medullary carcinoma, mucinous carcinoma. The lobular invasive carcinoma and the skin metastasis of the breast carcinoma were highly positive. **Conclusions:** 50% of normal breast tissue, 54% of benign lesions and in 63% of malignant tumors were PSA-positive. In the normal breast tissue, PSA was heterogeneously distributed, only the acini being positive. The normal tissue adjacent to a benign lesion expressed PSA with greater intensity than the normal tissue adjacent to a carcinoma. A highly positive reaction expressed the lobular invasive carcinomas and the lesions of apocrine metaplasia. Metaplastic and papillary carcinoma, the adenosis and the cystic dilatations were negative.

**Key Words:** PSA, kallikreins, immunostaining, breast tumors, normal mammary gland.

## INTRODUCTION

Breast cancer continues to be a major health problem, being the second cause of mortality after the lung cancer.<sup>1</sup> Despite of extensive research,

the breast cancer etiology remains unclear.<sup>2</sup> One of the new directions in cancer research is to identify new biomarkers used in diagnosis, prognosis and pharmacodiagnosis.

Tissue kallikreins are encoded by 15 structurally similar steroid hormone-regulated genes that co-localize to chromosome 19q13.4, representing the largest cluster of contiguous protease genes in the entire genome. Recent data suggest that kallikreins may be involved in carcinogenesis, particularly in the tumor invasion and thus, may represent attractive drug targets.<sup>3,4</sup>

Prostate specific antigen (PSA) or human kallikrein 3 is a 33-kDa single-chain glycoprotein expressed at

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high levels in the epithelium of the human prostate gland. It is a serine protease with chymotrypsin-like activity and the main biological role of this protease is to liquefy the seminal fluid increasing the sperm motility. It was first described in seminal plasma and isolated from the prostate.<sup>5,6</sup> PSA was the first tumor marker allowed by Food and Drug Administration for use as a biochemical marker for the diagnosis and monitoring of prostate adenocarcinoma.<sup>7</sup>

Although prostate-specific antigen (PSA) is a well established tumor marker for the diagnosis and management of prostate cancer and its position is clear and incontrovertible, with the new sensitive methodologies, PSA has been detected in a variety of extraprostatic tissues, especially the breast tissues.<sup>8,9</sup> Breast PSA is identical in molecular weight and mRNA sequence to seminal PSA and PSA gene expression in breast tumors appears to be under hormonal control because in the steroid hormone receptor-positive breast cell lines T-47D and BT-474, the PSA production can be induced by androgens, progesterone, mineral corticoids and glucocorticoids.<sup>10-12</sup> The PSA expression is different in premenopausal and postmenopausal women due to the influence of the ovarian hormones.<sup>13</sup> DNA sequencing confirmed that no mutations were present in the coding region of PSA gene in breast tumors, but multiple mutations/polymorphisms were detected in the core promoter and enhancer region.<sup>14</sup> These mutations/polymorphisms may alter the steroid hormones regulation of the gene, affecting the PSA expression level.<sup>15</sup>

In the late years, a number of studies have been published regarding the extraprostatic sources of PSA. Of great interest was the immunohistochemical localization of PSA in the female breast, in normal and pathological conditions. The interest is due to the great incidence of the positive reaction in malignant tumors and to the possible correlations with the hormonal status.<sup>16-18</sup>

The aim of our study was to further investigate the expression of PSA in the normal breast tissue and in different types of benign and malignant breast tumors.

## **MATERIALS AND METHODS**

We studied 52 surgically obtained specimens from patients who underwent surgical resections or biopsies for breast cancer or suspected lesions, in the Clinical County Hospital in Timisoara, Surgery Clinics I, II and III. Ethical approval was obtained, and all patients gave informed consent.

The samples were formalin-fixed and paraffin-embedded, according to the routine procedure. The morphological and immunohistochemical analyses were performed in the Laboratory for Cytological, Histological and Immunohistochemical Techniques of the Victor Babes University of Medicine and Pharmacy, Timisoara. The pathological diagnosis and grading were established on hematoxylin-eosin samples and were based on the standard recommendations by AFIP in 2004 and the Scarff-Bloom-Richardson grading system.<sup>19-21</sup>

### **PSA expression**

Additional sections from every case were immunohistochemically stained for PSA, using rabbit anti-human prostate-specific antigen/HRP, in the EPOS working system provided by DakoCytomation, Denmark. After the sections were deparaffined and rehydrated, the next steps of the technique were: antigen retrieval by microwave heating in Dako target retrieval solution; blocking of endogenous peroxidase; washing with distilled water and Tris; incubation with anti PSA antibody for 30 minutes; washing with TBS; incubation with chromogenic substrate solution (DAB) for 10 minutes; washing with distilled water; counterstain with modified hematoxylin and mount with a cover slip. We used sections from 5 cases of prostate adenocarcinoma and 5 cases of prostate benign hyperplasia as positive control. For evaluating the non-specific staining, we used additional sections incubated without primary antibodies as negative controls.

We elaborated a quantification system for the PSA immunohistochemical expression in the breast tissue that was used as an internal standard for all our samples. We quantified the results according to the percentage of the PSA-positive cells, the distribution and the intensity of the immunostaining. The results were estimated as negative (-), weakly positive (+1), moderately positive (+2) and strongly positive (+3) in the following manner: negative when less than 10% cells were PSA-positive; weakly positive (+1) when less than 1/3 cells were PSA-positive, no matter the intensity, distributed heterogeneously; moderately positive (+2) - between 1/3 and 2/3 moderate or intensive PSA-positive cells, heterogeneously distributed; strongly positive (+3) - more than 2/3 intense PSA-positive cells, homogeneously distributed.

## **RESULTS**

The morphology of the studied specimens was represented by 11 benign lesions and 41 malignant

breast tumors, including a skin metastasis of a breast carcinoma. Adjacent to 7 benign tumors and 9 malignant tumors we identified normal breast tissue. The benign lesions were: fibroadenoma, ductal and lobular hyperplasia, fibrocystic disease, apocrine metaplasia, and adenosis. The malignant breast tumors that we found were: ductal and lobular carcinoma in situ, invasive ductal and lobular carcinoma, medullary carcinoma, mucinous carcinoma, metaplastic carcinoma, invasive papillary carcinoma and a skin metastasis of a breast carcinoma.

### PSA expression

The immunoreaction assessment considers the dominant lesion, the additional lesions and the normal breast tissue that was found on sections in some cases. Adjacent normal breast tissue was found in 16 cases, 9 adjacent to malignant tumors and 7 adjacent to benign lesions. From the 16 cases, 50% were PSA-positive. From the 9 cases adjacent to malignant tumors 4 (44.44%) were PSA-positive [3 weakly positive (+1) and 1 case moderately positive (+2)]. From the 7 cases adjacent to benign lesions, 4 (57.14%) were moderately positive (+2). (Table 1)

**Table 1.** The distribution of the PSA expression in the normal breast tissue.

Normal tissue	Number of cases	PSA expression			
		Negative	+1	+2	+3
Normal tissue adjacent to a benign lesion	7	3	0	4	0
Normal breast tissue adjacent to a malignant lesion	9	5	3	1	0

In the benign lesions, the reaction final product was found in 12 lesions (54%). From the 6 benign lesions adjacent to malignant tumors, 2 cases were moderately positive (+2) and 4 were negative. The lesions of apocrine metaplasia were positive (+3) in all the 4 cases that we found. (Tables 2, 3)

**Table 2.** The distribution of the PSA expression in the benign tumors.

The benign tumor	Number of cases	PSA expression			
		Negative	+1	+2	+3
Fibroadenoma	6	1	0	2	3
Cystically dilatations	4	4	0	0	0
Apocrine metaplasia associated	4	0	0	0	4
Adenosis	1	1	0	0	0
Ductal epithelial hyperplasia	1	0	0	1	0

**Table 3.** The distribution of the PSA expression in cancer adjacent lesions.

The invasive cancer adjacent lesion	Number of cases	PSA expression			
		Negative	+1	+2	+3
Ductal epithelial hyperplasia	2	0	0	2	0
Fibrocystic disease	3	3	0	0	0
Adenosis	1	1	0	0	0
<b><i>In situ ductal carcinoma</i></b>	<b>5</b>	<b>1</b>	<b>1</b>	<b>3</b>	<b>0</b>
<b><i>In situ lobular carcinoma</i></b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>3</b>

We found 41 malignant tumors, with 15 negative cases (36.58%) and 26 (63.41 %) PSA-positive; from the positive cases, 6 (14.63%) were intensively positive (+3), 14 (34.14%) moderately positive (+2) and 6 (14.63%) weakly positive (+1). The distribution of the lesions were: 2 cases of in situ ductal carcinoma [cribriform (+2) and papillary (negative)], 27 invasive ductal carcinoma [11 (41%) cases were negative and 16 (59%) cases were positive], 4 cases of invasive lobular carcinoma [3 cases (+3) and 1 (+1)], 2 cases of medullary carcinoma (+2), 2 cases of mucinous carcinoma (+2), 2 cases of papillary carcinoma (negative), 1 case of metaplastic carcinoma (negative) and a skin metastasis of a breast carcinoma (strongly positive, 3+). (Table 4)

**Table 4.** The distribution of the PSA expression in malignant tumors.

The malignant tumor	Number of cases	PSA expression			
		Negative	+1	+2	+3
In situ ductal carcinoma	2	1	0	1	0
Ductal invasive carcinoma, G <sub>1</sub>	4	1	0	2	1
Ductal invasive carcinoma, G <sub>2</sub>	17	7	4	5	1
Ductal invasive carcinoma, G <sub>3</sub>	6	3	2	1	0
Lobular invasive carcinoma	4	0	0	1	3
Medullary carcinoma	2	0	0	2	0
Mucinous carcinoma	2	0	0	2	0
Papillary carcinoma	2	2	0	0	0
Metaplastic carcinoma	1	1	0	0	0
Skin metastasis of a breast cancer	1	0	0	0	1

Between the PSA-positive invasive ductal carcinomas, 75% were G<sub>1</sub> (well differentiated), 59% were G<sub>2</sub> (moderately differentiated) and 50% were G<sub>3</sub> (poorly differentiated).

The positive outer control of immunohistochemical technique for PSA. For the estimation of PSA immunohistochemical expression we studied first the outer positive control samples, represented by 5 cases of benign prostate hyperplasia and 5 cases of prostate adenocarcinoma with Gleason score less than 8. We estimated the presence, distribution

and pattern of the reaction's final product and the reproducibility of the method in the same technical conditions. In the prostate benign hyperplasia we found an intense positive immunoreaction (+3) only in the cytoplasm of the secretory cells, with a granular pattern and intensification at the apical snout. The basal and stroma cells were not stained. The PSA immunoreaction was also highly positive (+3) in all the 5 cases of prostate carcinomas. The great majority of malignant cells were strongly stained in brown. The necrosis areas were not stained and occasionally we noticed macrophages moderately stained in the glandular lumen. This reaction was considered false positive and it was excluded from interpretation.

From these 10 cases of prostate tumors we performed many serial sections and we used them as outer positive control samples when we tested the anti-PSA reactivity of the mammary gland lesions.

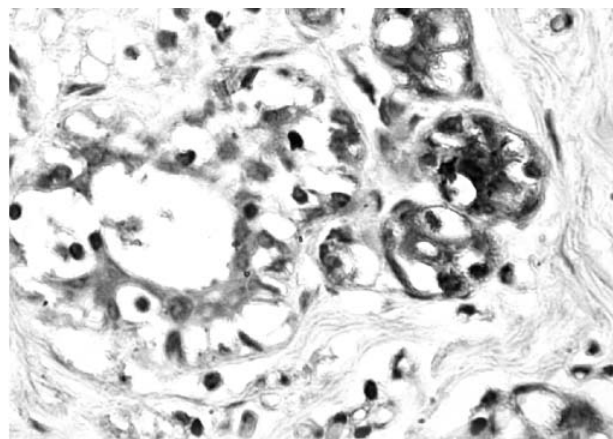
### The PSA expression in the normal female breast

In the normal breast we identified a positive PSA immunoreaction in the secretory duct-lobular units. The reaction was constantly heterogeneous for the same case and even for different zones in the same terminal tubule-lobular unit. We noticed the presence of highly stained acini together with negative acini in the same lobule.

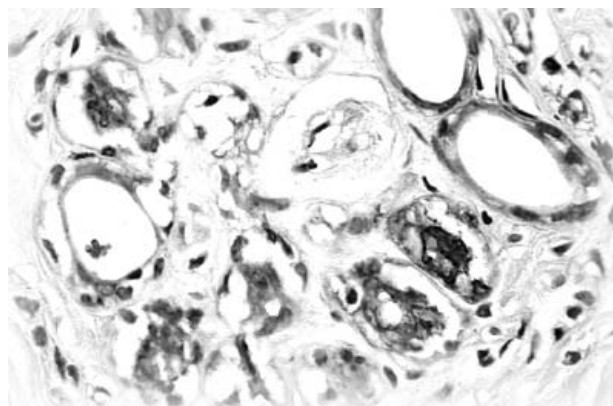
In many cases of normal mammary gland, we noticed a strong reaction similar with that of the prostate tissue but, unlike the prostate tissue, the reaction was heterogeneous, with diffuse granular pattern in the cytoplasm, either intralobular or in different lobules, pattern that we did not find on the outer positive control samples.

We noticed that, unlike the prostate, in the mammary gland only the acini were constantly positive, whereas the ducts were generally negative. This finding may have a high significance in the evaluation of the reaction for the malignant tumors of the breast, because in these conditions we expect a higher positive reaction for the lobular invasive carcinomas than for the ductal invasive carcinomas. These features of intralobular distribution of PSA are confirmed in the great majority of the cases with normal mammary tissue, but also in the apparently normal mammary tissue in the neighborhood of a benign or malignant tumor. (Fig. 1)

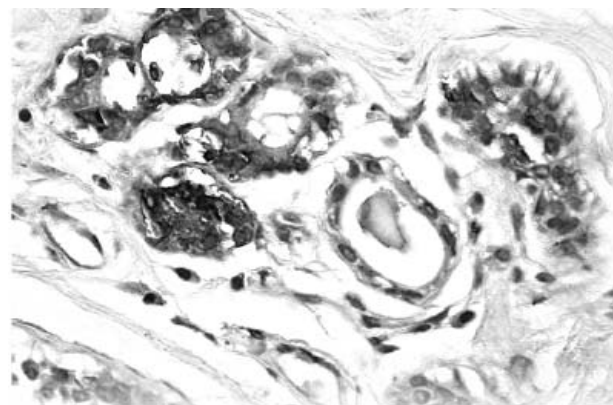
In the normal-appearing breast tissue adjacent to the malignant tumors, the intensity of the PSA immunoreaction was lower than in the normal-appearing breast tissue adjacent to the benign lesions. (Fig. 2, 3)



**Figure 1.** Normal breast tissue. Heterogeneous distribution of PSA final reaction's product. Positive acini for PSA, low or moderately stained; the duct is negative. PSA, EPOS, DAB, x400.



**Figure 2.** Atrophic lobule in the neighborhood of a breast carcinoma. PSA, EPOS, DAB, x400.

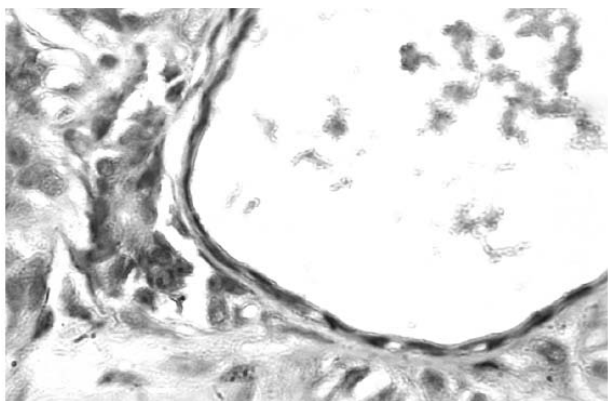


**Figure 3.** Atrophic lobule in the neighborhood of a fibroadenoma. Lobules adjacent to the fibroadenoma are of greater intensity than the intensity of PSA immunostaining of the lobules surrounding an invasive carcinoma. PSA, EPOS, DAB, x400.

### Fibrocystic Disease

The fibrocystic disease was characterized by the presence of the cysts of different sizes. Constantly, the cysts, especially the large ones, lined by a flattened epithelium were negative for PSA. These cysts were negative, even when the adjacent acini were positive. (Fig. 4) The exception was in the case of the large cysts

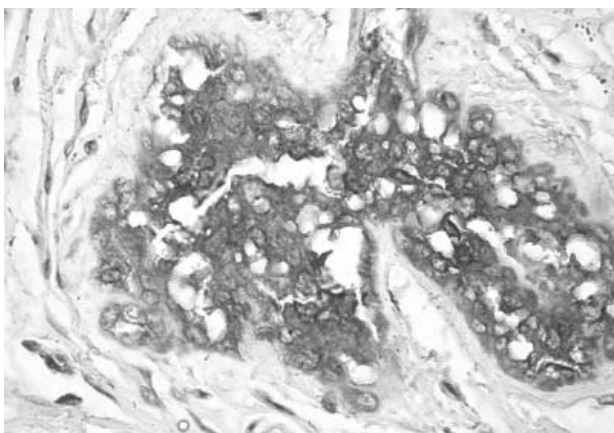
lined by apocrine-type epithelium. The individual cells with apocrine differentiation were highly positive for PSA.



**Figure 4.** Fibrocystic disease. Medium size cyst, lined by a flattened epithelium, negative for PSA. Adjacent glands with moderately positive PSA immunoreaction. PSA, EPOS, DAB, x400.

### Fibroadenoma

The PSA immunoreaction was limited to the glandular epithelial cells and was intensively expressed. (Fig. 5) The final reaction's product was homogeneously distributed, with the same intensity along the glands. Occasionally, in the glands luminae, we noticed an amorphous material strongly stained in brown. All the stroma components were negative.

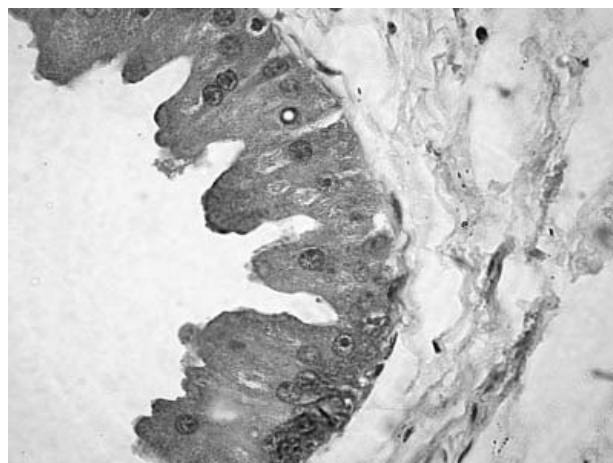


**Figure 5.** Fibroadenoma. The gland is compressed by the stromal components proliferation. The cells are moderately/intensively immunostained for PSA. PSA, EPOS, DAB, x400.

### Apocrine metaplasia

Apocrine metaplasia was constantly positive for PSA, even in the conditions when it was the only lesion detected in the normal or pathological tissue, negative for the same reaction. Most frequently the apocrine metaplasia was not a diagnosis by itself; it was especially associated to the fibrocystic disease. All the cells with apocrine differentiation were homogeneously and strongly stained, with intensification at the apical portion of the cytoplasm (the typical "apocrine

snout"). (Fig. 6) In the cases of apocrine metaplasia associated to the fibrocystic disease we noticed the presence of coalescent pseudopapillary projections, projecting into the glandular lumen. In concordance with the other cases, the cells with apocrine differentiation were positive for PSA. It was remarkable the fact that the presence of apocrine metaplasia at the large cyst epithelium induces the positivity of the PSA immunoreaction. This aspect was not observed in the cysts with flattened or cubical epithelium.

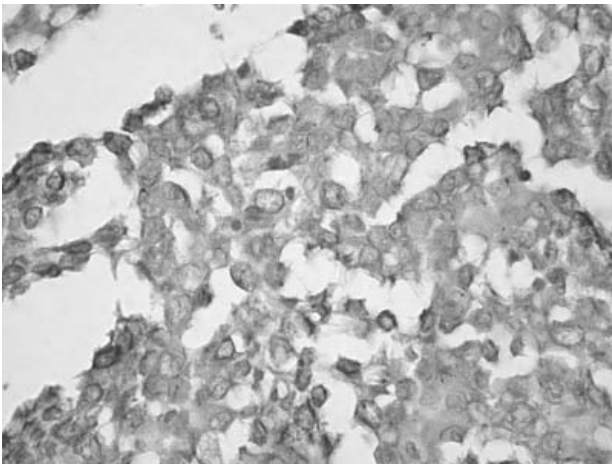


**Figure 6.** Apocrine metaplasia. Strong PSA immunostaining. It can be noticed the focal intensification of the reaction at the apical snout. PSA, EPOS, DAB, x400.

### Invasive ductal carcinoma

The invasive ductal carcinoma was the most frequently histopathological form of breast carcinoma. In the positive cases for PSA, we observed the heterogeneous distribution of the final reaction's product, but the intensity of the reaction was reduced or moderate, even in the conditions when we used the most sensitive working systems. (Fig. 7) In some cases, we noticed the presence of associated typical ductal hyperplasia lesions and, in these cases, the epithelial cells of these ducts were more intensively stained than the malignant cells.

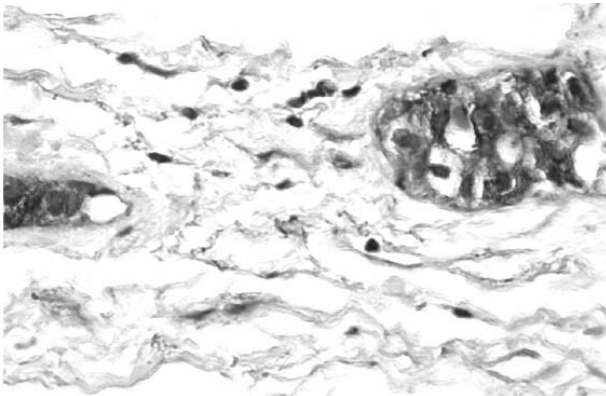
Only occasionally, we noticed some isolated, compacted groups of cells or atypical glands with intense PSA expression, but this aspect was the exception and not the rule. In some negative glands, we noticed the existence of rare isolate positive cells. When the reaction was positive, the final reaction's product was granular, diffusely distributed in the cytoplasm. Constantly, the normal ducts or those with minor morphological changes adjacent to the tumor were negative. In situ ductal carcinoma. If an invasive ductal carcinoma showed PSA staining, adjacent intraductal carcinoma that we found was stained positively, with a greater intensity.



**Figure 7.** Invasive ductal carcinoma. Moderate intensity of the reaction in malignant glands . PSA, EPOS, DAB, x400.

### Lobular invasive carcinoma

The cases with lobular invasive carcinoma expressed PSA constantly and intense, in concordance with assumed hypothesis after the evaluation of the epitope distribution at the terminal duct-lobular unit. In one case, we noticed the presence of the lobular in situ and invasive carcinoma on the same slide, and both were strongly, equally stained. In the majority of cases, the PSA immunoreaction was strongly positive in the cells with the typical Indian file pattern of growth. (Fig. 8)



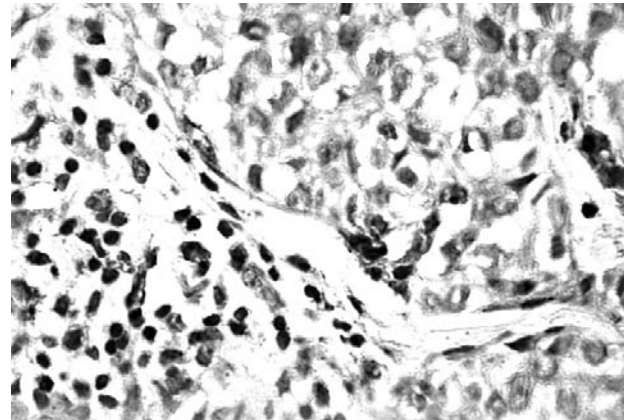
**Figure 8.** In situ and invasive lobular carcinoma. Highly positive cells for PSA. PSA, EPOS, DAB, x400.

### Medullary carcinoma

The medullary carcinoma represents a distinct entity from which we had, in the pure form, a reduced number of cases. Performing the PSA immunoreaction on these cases we found all the cases positive, the final reaction product being obvious in the majority of the cells. (Fig. 9)

In contrast with other malignant tumors, in these cases, we observed also a positive nuclear reaction besides the cytoplasmic pattern of distribution of the

final reaction product. The evaluation was repeated with other working systems and the results were the same. These aspects were not described in other studies and we have no explanation for this finding.



**Figure 9.** Medullary carcinoma. Moderate positive immunoreaction for tumor cells and negative for the surrounding lymphocytes and connective tissue. PSA, EPOS, DAB, x400.

### Skin metastasis of a breast carcinoma

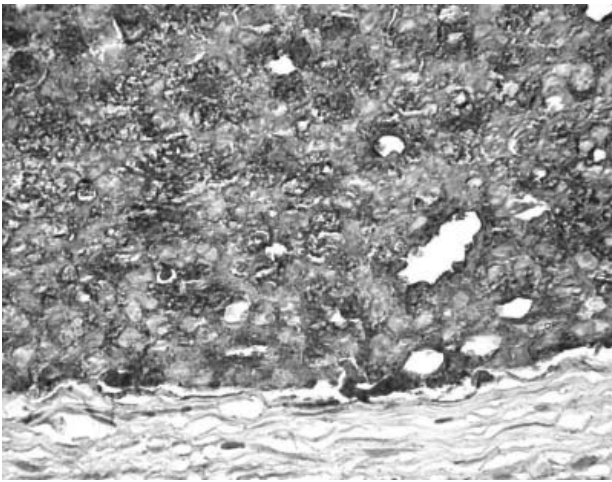
The malignant cells were disposed on solid masses and trabecular bars that infiltrated the dermal connective tissue. The PSA immunoreaction was homogeneous, diffuse and intense in the most majority of malignant cells. The connective tissue compounds and the epithelial cells surrounding the proliferation were not immunostained.

The number of positive cytoplasm stained granules was significantly higher in the cells that were grouped in pseudolumens. In the neighborhood of the connective septum, we observed cells stained with higher intensity. The amount of final reaction product varied from cell to cell, some were pale, with chromophobe cytoplasm.

Large areas of secondary tumor were characterized by the presence of malignant cell trabecular bars surrounded by thick bands of collagen fibers, looking like a local progression. In this organization manner, all the malignant cells were intensively stained for PSA.

An interesting aspect that we noticed and was not found in the literature was the disposition of the PSA positive tumor cells around the capillary vessels and postcapillary vein. (Fig. 10)

We noticed also the invasion of the vessel walls by the tumor cells. Only with these morphological observations we could not specify if these cells belonged to the metastasis contingent of the primary tumor or to the expansion clone of the secondary tumor.



**Figure 10.** Skin metastasis of a breast carcinoma. The arrangement of the PSA positive malignant cells around the capillary vessels and around a post capillary vein. PSA, EPOS, DAB, x400.

## DISCUSSIONS

Using polyclonal anti-PSA antibodies in EPOS working system, we noticed PSA positive immunoreaction in 50% of normal breast tissue, 54% of benign lesions and in 63% of malignant tumors. Bodey et al detected PSA positive in 100% of the malignant tumors, Howarth et al in 30% , Heyl et al in 49%, and Alanen et al in 32% of breast malignant tumors.<sup>18,22-24</sup> Yu et al found PSA positive in 33% of normal tissues, 65% of benign lesions and 28% of malignant tissues.<sup>25</sup> Another study, using immunohistochemistry on 75 breast cancers shows PSA positivity in only 7 cases.<sup>26</sup>

Like other authors, we observed intensely positive reaction for apocrine metaplasia and hyperplastic ductal and lobular epithelium.<sup>22</sup> Contrary to the findings of Howarth et al (1997), the lesions of adenosis and cystic dilatations that we found were negative.<sup>22</sup>

It was demonstrated that chromosomal alterations, inhibition of apoptosis, HER-2/neu amplification, and p53 mutations occur in histological benign tissues adjacent to breast carcinomas.<sup>11,27</sup> According to the hypothesis that specific aberrations may be present in cancer and normal-appearing adjacent tissues that precede the morphologically detectable neoplastic transformation, we studied not only the expression of PSA in breast cancer but also the PSA expression in the normal tissue and benign lesions adjacent to the carcinomas and also specimens who presented only benign lesions and normal mammary gland adjacent to these lesions.

We found normal-appearing lobules adjacent to PSA-positive fibroadenoma of greater intensity than the intensity of PSA immunostaining of the lobules surrounding an invasive carcinoma. Also, we noticed

that the cells of the ductal hyperplasia adjacent to the malignant glands were of greater intensity than the malignant cells. Sauter et al (2002) did not find a statistically greater PSA expression in the histological benign, but cancer-adjacent tissue than in malignant tissue.<sup>11</sup> They suggested that the difference might be significant if the analyses were not limited by sample size. The lesions of carcinoma in situ were stronger immunostained than the surrounding malignant cells of an invasive carcinoma and the PSA-positive benign lesions presented higher staining than the malignant lesions.

All the case of medullary carcinoma and mucinous carcinoma, carcinomas with better prognosis in their pure forms, were moderately positive in the most majority of the cells. Howarth et al also found PSA positive staining in better differentiated tumors, for example mucinous carcinoma.<sup>22</sup> Similarly, Yao et al (2004) reported that 55% of the 20 carcinomas with neuroendocrine cell differentiation, carcinomas with lower rate of malignancy, were PSA positive.<sup>28</sup> According with these authors, the majorities of breast carcinomas in our study were well (75%) and moderately differentiated (59%) and we also found an association between the PSA-positive reaction and the histopathological type. In opposite, Yu et al reported no correlation with histological type and grade.<sup>25</sup>

The role of extraprostatic PSA appears to be complex, poorly understood and of unknown clinical relevance. In this context, the results regarding the prognostic value of the PSA are controversial. Some authors did not notice significant survival differences.<sup>23,24</sup> On the contrary, other studies suggested that the patients with PSA-positive breast cancer had a superior survival rate, being associated with early disease stage, small tumors, the positivity of the hormonal receptor, especially progesterone and androgens, young age, low recurrence rate, low grading. PSA may be a marker of the endogenous hormone balance between androgens, progesterone and estrogen.

Furthermore, PSA may have a good prognostic value for relapse-free survival in patients with estrogen receptor-negative tumors, suggesting that might identify the group of patients with hormonal receptor-negative tumors witch would respond to endocrine therapy.<sup>25,29-31</sup> This hypothesis is in agreement with the studies that found no significant correlation between estrogen hormone receptors and PSA immunoexpression, PSA expression being androgen-dependent.<sup>32</sup> Foekens et al (1999) demonstrated that PSA expression in breast cancer correlated with poor

response to the adjuvant therapy with tamoxifen.<sup>33</sup> The significance of the PSA expression in the mammary gland remains to be clarified.

## CONCLUSIONS

We found PSA positive in 50% of normal breast tissue, 54% of benign lesions and in 63% of malignant tumors. The normal mammary tissue expressed, in opposite to the secretory cells of prostate, an intralobular heterogeneous reaction, with positive acini together with negative acini. The positive PSA cells that we found were only the glandular elements. The acini were positive, whereas the ducts were negative. The normal-appearing lobules adjacent to PSA-positive fibroadenoma were of greater intensity than the intensity of PSA immunostaining of the lobules surrounding an invasive carcinoma. The apocrine metaplasia was highly positive (+3). Adenosis and the cystic dilatations were negative. The lobular carcinomas were stained stronger than the ductal carcinoma. The papillary and metaplastic carcinomas were negative. The cases of medullary carcinoma and mucinous carcinoma, carcinomas with a better prognosis in their pure forms, were moderately positive (+2).

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