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ORIGINAL ARTICLE

Prostate-specific antigen in breast disease

Bee Hoon POH *MBBS*, Gita JAYARAM *MD (Path), FRCPath*, Pavai STHANESHWAR *MD* and Cheng Har YIP* *FRCS, FAMM*

*Departments of Pathology and *Surgery, University Malaya Medical Centre, Malaysia*

Abstract

The aim of this study is to assess tissue and serum prostate-specific antigen (PSA) in breast lesions; to compare tissue PSA with serum PSA; to compare tissue PSA in benign and malignant lesions and to compare PSA with known prognostic factors in breast carcinoma. Tissue PSA immunoreactivity in twenty women with breast carcinoma was compared with PSA in twenty-three women with benign breast lesions. Tissue PSA was also compared with known prognostic indicators such as tumour size, axillary nodal status, histological type, histological grade, oestrogen receptor status, progesterone receptor status and c-erbB-2 oncoprotein over-expression. Serum free PSA levels from these women were measured pre- and post-operatively and an attempt was made to correlate serum PSA with tissue PSA expression. 40% and 43% of malignant and benign breast lesions respectively showed tissue PSA immunoreactivity. No significant difference was observed in the tissue PSA expression between these two groups as also between tissue PSA and known prognostic indicators. As serum PSA levels were below the detection limit (< 0.004 ng/ml) in all except two benign cases, no statistical evaluation was done for the latter. Tissue PSA expression did not correlate with other prognostic markers and detectable serum PSA levels were present in too few cases for statistical analysis. Although no definitive conclusion is possible in this preliminary study regarding the role of PSA in breast disease, it stimulates interest in further research in this direction.

Keywords: Tissue prostate-specific antigen, serum prostate-specific antigen, breast neoplasms.

INTRODUCTION

Prostate specific antigen (PSA) is a 33 kD glycoprotein that was initially reported to be prostate-specific.[1] Located on chromosome 19,[2] its main function is to cleave seminal coagulum.[3] PSA has also been reported in other tissues,[4] biological fluids[5-6] and a variety of tumours.[7] PSA has been documented to be present in normal breast tissue as well as in benign and malignant breast tumours[8-12] and tissue PSA has been considered as a good prognostic marker for breast cancer.[13-17]

Serum PSA is a valuable marker for the diagnosis and monitoring of prostatic carcinoma. Detectable serum PSA has also been demonstrated in women with and without breast diseases.[18-20] PSA secreted into mammary ductal system is the likely source of circulating PSA in women. Ultra-sensitive immunoassays have demonstrated that at least 50% of normal female sera contain detectable PSA[18] but the concentration of serum PSA is 100-500 times lower in females as compared to males. Studies correlating serum PSA with circulating steroid hormone levels are on record.[21] Elevated serum PSA levels have been observed in endocrine-dependent disorders including breast carcinoma and fibrocystic condition.[20, 22]

Serum PSA exists in free form as well as complexed form (complexed with anti-chymotrypsin and α-2 macroglobulin). The latter is the major fraction of serum PSA in normal women[17-19] while the free form predominates in breast cancer.[17-20] This leads to the conjecture that free PSA may have clinical application as a circulating tumour marker either alone or in combination with other diagnostic markers.

MATERIALS AND METHODS

The study group comprised 43 consecutive women, 19 to 71 years of age. They were admitted to the University Malaya Medical Centre, Kuala

Address for correspondence and reprint requests: Dr Bee Hoon Poh, Department of Pathology, Faculty of Medicine, University Malaya Medical Centre, Jalan 59100 Kuala Lumpur, Malaysia. Email address: pohbh73@hotmail.com

Lumpur, between February and May 2004 for breast surgery that ranged from excision to modified radical mastectomy with axillary clearance. 23 were diagnosed pre-operatively as benign breast lesions (BBL) and 20 as malignant based on clinical findings, mammography, fine needle aspiration cytology, core needle biopsy and/or varying combinations of these. The pre-operative blood samples for PSA estimation were taken on the day of surgery and the post-operative samples one week after. The 10 control serum specimens were taken from women with no evidence of breast disease. All serum samples were stored at -20ºC until further analysis.

Tissues in all 43 cases were subjected to gross inspection, description, fixed in buffered formalin and processed routinely for histopathological study. 3 μm thick sections were cut and stained with Haematoxylin and Eosin. In all cases of carcinoma, one section was selected for oestrogen receptor (ER) protein, progesterone receptor (PR) protein, c-erbB-2 (Her2/neu) and PSA staining. Immunohistochemical staining for PSA was performed using anti-mouse antibody against PSA at 1:100 working dilution (following the protocols recommended by *Neomarkers, Fremont A 94539, USA)*. The detection system employed was a labeled avidin-biotin-complex system based reagent. The reaction was visualised with diaminobenzidine chromogen and a brown cytoplasmic precipitate seen on microscopical examination confirmed the presence of PSA in the tissue. Sections of benign prostatic tissue from nodular prostatic hyperplasia were used as positive control.

Free PSA in the serum was estimated using DPC-Immulite PSA kit and Immulite analyzer that has a detection limit of 0.02 ng/ml. The serum samples were lyophilized-concentrated using the previously described technique of *Huland et al.*[23] After lyophilization, a standardized quantity of 160 µl of distilled water was added to the dry powder to produce 200 µl of a five-fold concentrated serum needed to increase the clinical detection limit to > 0.004 ng/ml.

Scoring system for tissue-PSA

Semi-quantitative assessment of the percentage of cells expressing immunoreactivity to PSA was formulated. Scores of 1 to 4 were given corresponding to ≤ 25% cells, 26-50% cells, 51-75% cells and > 75% cells showing positive staining. Qualitative evaluation of the intensity of PSA staining was given scores ranging from 0 to 3 (denoting negative, mild, moderate and strong staining respectively). The total score was the sum of the semi-quantitative and qualitative scores. Possible total scores ranged from 0 (the minimum score obtainable) to 7 (maximum score).

Statistical Analysis

Correlation of tissue PSA with known prognostic factors (tumour size, histological type, histological grade, nodal status, ER status, PR status and c-erbB-2 oncoprotein over-expression) was done by Fisher's exact test. P-values of < 0.05 were considered statistically significant.

RESULTS

The age distribution of the cases studied ranged from 19 to 71 years. 17 of 23 cases in the benign group had diagnoses of fibroadenoma or

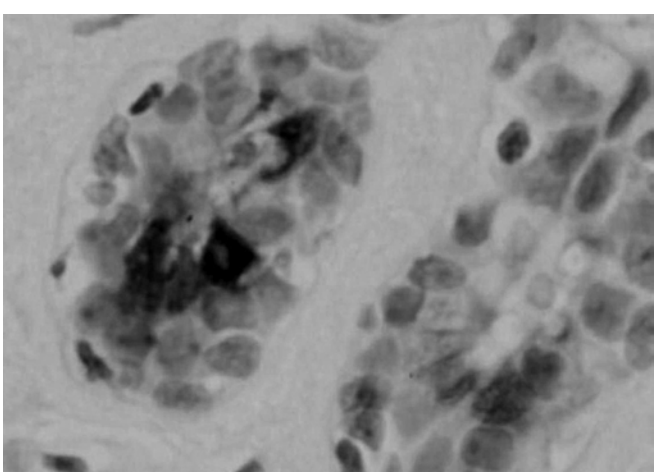

FIG. 1: Cells of fibroadenoma expressing 3+ tissue-PSA positivity. PSA x 400.

fibroadenomatoid mastopathy. 10 of 23 benign cases (43%) showed tissue PSA positivity (Figure 1) of variable distribution and intensity (ranging from score 1 to score 3). There was luminal accentuation of the staining pattern (Figure 2) in many. 8 of 10 positive cases were fibroadenomas or fibroadenomatoid mastopathy while the remaining two were tubular adenoma and complex sclerosing lesion. In both cases with fibrocystic condition, the material within cyst lumina was PSA-positive (Figure 3).

Pre- and post-operative serum PSA levels could be analysed in only 12 benign cases where serum samples were adequate for lyophilization concentration. 10 of 12 patients had serum PSA below the detection limit (< 0.004 ng/ml) in both pre and post-operative samples. In two cases where serum pre-operative PSA was 0.08 ng/ml and 0.05 ng/ml respectively, (fibrocystic condition and intraductal papilloma), post-operative values returned to below-detection levels. Table 1 shows the correlation of histological diagnosis with tissue and serum PSA.

85% of malignant lesions were infiltrating ductal carcinoma (IDC), not otherwise specified (NOS), of histologic grade 2 or 3. One was a multifocal carcinoma. 8 of 20 cases (40%) of all carcinomas showed tissue-PSA positivity. 12 of 20 cases (60%) were positive for ER and 11 of 20 cases (55%) for PR. 10 cases (50%) expressed both ER and PR. 9/20 cases (45%) over-expressed c-erbB-2.

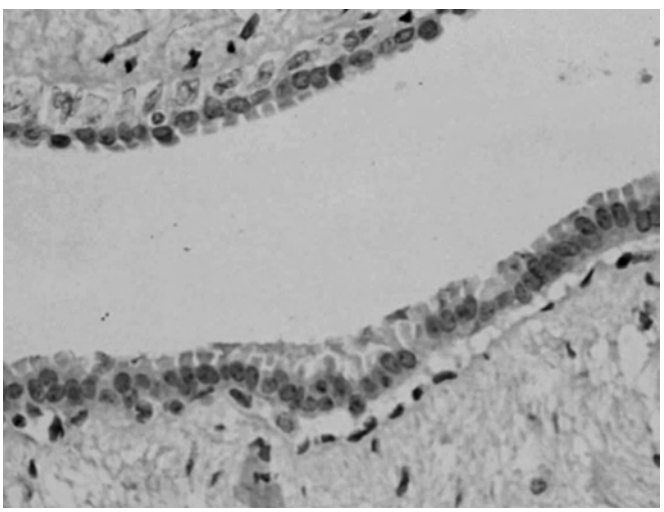

FIG. 2: Luminal accentuation of PSA in cells of fibroadenoma. PSA x 200.

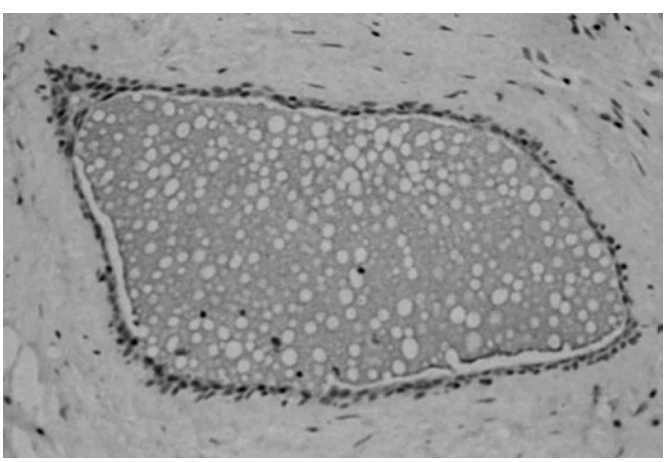

FIG. 3: Intraluminal staining pattern of PSA in fibrocystic condition. PSA x 100.

TABLE 1: Histological diagnoses correlated with tissue PSA status and serum PSA in 23 patients with benign breast disease

No	Histological Diagnosis	Tissue PSA			Serum PSA (ng/ml)	
		Percentage Score	Intensity Score	Total	Pre-op	Post-op
1	Fibroadenoma	4	2	6	< 0.004	NA
2	Fibroadenoma	3	2	5	NA	NA
3	Fibroadenoma	1	3	4	< 0.004	< 0.004
4	Fibroadenoma	3	1	4	< 0.004	< 0.004
5	Fibroadenoma	1	1	2	< 0.004	< 0.004
6	Fibroadenoma	1	1	2	< 0.004	< 0.004
7	Fibroadenoma	1	1	2	< 0.004	NA
8	Fibroadenoma	0	0	0	< 0.004	< 0.004
9	Fibroadenoma	0	0	0	< 0.004	NA
10	Fibroadenoma	0	0	0	< 0.004	< 0.004
11	Fibroadenoma	0	0	0	NA	NA
12	Fibroadenoma	0	0	0	NA	NA
13	Fibroadenoma	0	0	0	NA	NA
14	Fibroadenomatoid mastopathy	2	2	4	< 0.004	< 0.004
15	Fibroadenomatoid mastopathy	0	0	0	< 0.004	< 0.004
16	Fibroadenomatoid mastopathy	0	0	0	< 0.004	< 0.004
17	Fibroadenomatoid mastopathy	0	0	0	< 0.004	NA
18	Fibrocystic condition	0	0	0	0.08	< 0.004
19	Fibrocystic condition	0	0	0	NA	NA
20	Intraductal papilloma	0	0	0	0.05	< 0.004
21	Intraductal papilloma	0	0	0	< 0.004	< 0.004
22	Tubular adenoma	4	2	6	< 0.004	NA
23	Complex sclerosing lesion	1	4	5	NA	NA

NA: Not available

Pre- and post-operative serum PSA levels could be analysed in only 10/20 malignant cases where serum samples were adequate for lyophilization concentration. In all 10 cases analysed, serum PSA was below the detection limit (< 0.004 ng/ml). Histological diagnosis correlated with the known prognostic markers, tissue and serum PSA is given in Table 2.

Categorizing the benign and malignant cases into two groups each, (PSA-positive group and PSA-negative group), no statistically significant difference was found (Table 3). The PSA histoscores were grouped into three categories. Scores of 2-3 were categorized as 'low,' scores of 4-5 as 'intermediate' and 6-7 as 'high.' While larger numbers of benign cases showed higher scores ('intermediate' or 'high'), malignant cases mostly scored in the 'low' range (Table 4).

75% of breast carcinomas were ≤ 3 cm in size and 60% of them had positive lymph nodes. 8/17 (47%) IDCs showed tissue-PSA positivity. The malignant cases were grouped based on prognostic indicators such as tumour size (≤ 3cm versus > 3cm), lymph node status (positive versus negative) and histological type (IDC versus special types), hormone receptor status (positive versus negative) and c-erbB-2 oncoprotein over-expression (positive versus negative). Table 5 shows the correlation of tissue PSA with known prognostic markers of breast carcinoma. Statistical evaluation showed no significant correlation between tissue-PSA and various prognostic indicators.

As serum PSA levels were below the detection limit (0.004 ng/ml) in all but two benign cases, no statistical evaluation was done.

DISCUSSION

Immunofluorometric and immunohistochemical studies, western blotting, chromatographic analysis and molecular analysis have shown that PSA is expressed in breast milk, breast cyst fluid and in benign and malignant breast tumours.[5, 10, 12, 24-25] Breast cancer is the leading cause of morbidity and mortality in many developed countries,[26] as well as in Malaysia.[27-28] Emerging new diagnostic and prognostic markers may help greatly in early detection of malignancy as well as in developing newer therapeutic protocols that may reduce morbidity and mortality. The presence of PSA in some breast cancer cells has prompted investigations into the clinical applications of this marker as an adjunctive tool in the prognostic assessment and management of breast carcinoma.[29]

Only 2 of 22 cases in the present study showed detectable serum PSA levels (possibly due to the small sample specimen). Our observation of PSA expression in 40% of breast cancer tissues by immunohistochemical method is comparable to other studies.[12, 30-31] Our present and other studies[12, 30-31] showed no correlation between the presence of PSA in breast carcinoma tissue and known prognostic indicators, contrary to the immunofluorometric analysis on tumour cytosols which demonstrated significant correlation.[10-11, 32] This could possibly be due to the larger number of cases and more accurate estimation of PSA in the cytosol in the latter compared to semi-quantitative nature of evaluation of tissue-PSA and the small number of cases in the former.

In the present as well as in *Howarth et al's* study,[8] PSA staining in breast tissue was found to show a luminal accentuation pattern. As the luminal border is the active secretory part of the cell, there may be a tendency for PSA to be concentrated here before being secreted into the acinar or ductal lumen. Another interesting observation in the present study was that in both cases of fibrocystic condition, the secretion within the cyst lumina showed positive staining reaction for PSA, a feature that has been previously described.[24, 33-34] This could be due to concentration of PSA in the cystic secretions before its excretion into the general circulation. *Bradshaw et al.*[33] showed that estimation of the ratio of free/complexed PSA in cyst fluid may offer utility in breast cyst classification. Since the ratio is higher in type I cysts, (of apocrine/ secretory type), that have a higher risk for breast cancer, this investigation may have some clinical significance.

Categorising benign and malignant breast lesions into 'tissue PSA positive' and 'negative' groups showed no statistically significant difference between the two groups in the present study. The differences in the degree of tissue PSA expression (as manifested by PSA histoscore) was however apparent between these two groups, with most benign breast lesions showing a higher degree of expression of tissue-PSA as compared to breast carcinoma. *Yu et al*,[9] reporting similar findings, postulated that the differences in tissue- PSA expression could most likely be due to alteration of balance between steroid hormones, their receptors and various growth factors.[11, 35-38] Alteration in the gene/genes that govern the hormonal and growth factor activities may also play a role in the differential expression of PSA in benign and malignant lesions. Since

TABLE 2: Histological diagnoses correlated with ER, PR, c-erbB-2 oncoprotein, tissue PSA and serum PSA in 20 patients with malignant breast disease

No	Histological diagnosis	Grade	Tumour size	lymph node status	ER	PR	c-erbB-2	Tissue PSA			Serum PSA (ng/ml)	
								Percentage Score	Intensity Score	Total Score	Pre-op	Post-op
1	IDC	2	3cm	+	+	+	+	4	1	5	< 0.004	NA
2	IDC	2	4cm	+	+	-	+	2	2	4	< 0.004	< 0.004
3	IDC	3	2.5cm	+	+	+	+	2	1	3	< 0.004	< 0.004
4	IDC	2	4.5cm	+	+	+	-	2	1	3	< 0.004	NA
5	IDC	3	2cm	+	-	-	-	2	1	3	< 0.004	< 0.004
6	IDC	3	2.5cm	-	-	-	+	1	2	3	NA	NA
7	IDC	3	2.5cm	+	-	-	-	1	2	3	< 0.004	< 0.004
8	IDC	2	2.3cm	+	+	+	+	1	1	2	< 0.004	< 0.004
9	IDC	2	3cm	+	+	+	+	0	0	0	< 0.004	< 0.004
10	IDC	2	5cm	-	+	+	-	0	0	0	< 0.004	< 0.004
11	IDC	2	1.4cm	-	+	+	-	0	0	0	NA	NA
12	IDC	3	3cm	+	-	-	+	0	0	0	NA	NA
13	IDC	3	2cm	-	-	-	+	0	0	0	< 0.004	< 0.004
14	IDC	2	2cm	-	+	-	-	0	0	0	NA	NA
15	IDC	3	4cm	+	-	+	-	0	0	0	< 0.004	NA
16	IDC	2	1.5cm	-	-	-	-	0	0	0	NA	NA
17	IDC	3	3.5cm	+	-	-	-	0	0	0	NA	NA
18	ILC	2	2cm	+	+	+	-	0	0	0	NA	NA
19	PC	NG	2.5cm	-	+	+	-	0	0	0	< 0.004	< 0.004
20	TC	NG	2cm	-	+	+	+	0	0	0	< 0.004	< 0.004

IDC: Infiltrating ductal carcinoma; ILC: Infiltrating lobular carcinoma; PC: Papillary carcinoma; TC: Tubular carcinoma
+: Positive; -: Negative; NA: Not available; NG: Not graded

TABLE 3: Tissue PSA correlated with histology (benign versus malignant)

Sample (N=43)	PSA positive No. (%)	PSA negative No. (%)	p-value
Benign	10 (43.0%)	13 (57.0%)	
Malignant	8 (40.0%)	12 (60.0%)	1.00 (NS)

NS: not significant

TABLE 4: Correlation between histological diagnoses (benign or malignant) and PSA histoscore

		Degree of PSA Histoscore				Total
		N	L	I	H	
Diagnosis	**Benign**	13 (56.6%)	3 (13%)	5 (21.7%)	2 (8.7%)	23
	Malignant	12 (60%)	6 (30%)	2 (10%)	0 (0%)	20
Total		25	9	7	2	43

N: Negative; L: Low; I: Intermediate; H: High

TABLE 5: Correlation between PSA and prognostic factors in breast cancer

Characteristics	PSA positive No. (%)	PSA negative No. (%)	p-value
Tumour size			
≤ 3 cm (15)	6 (40.0%)	9 (60.0%)	
> 3 cm (5)	2 (40.0%)	3 (60.0%)	NS
Axillary nodal status			
Positive (12)	7 (58.0%)	5 (42.0%)	
Negative (8)	1(12.0%)	7 (78.0%)	NS
Histological type			
Infiltrating ductal carcinoma (NOS) (17)	8 (47.0%)	9 (53.0%)	NS
Special types (3)	0 (0.0%)	3 (100%)	
Histological Grade			
Grade 2 (9)	4 (44.4%)	6 (55.6%)	
Grade 3 (8)	4 (50.0%)	4 (50.0%)	NS
Receptor status			
ER positive (12)	5 (41.0%)	7 (59.0%)	
ER Negative (8)	3 (37.5%)	5 (62.5%)	NS
PR positive (11)	4 (36.0%)	7 (64.0%)	
PR Negative (9)	4 (44.0%)	5 (56.0%)	NS
c-erbB-2 oncoprotein over-expression			
Positive (9)	5 (55.6%)	4 (44.4%)	
Negative (11)	3 (27.0%)	8 (73.0%)	NS

NS: Not significant; NOS: not otherwise specified

genetic and physiological mechanisms behind PSA gene regulation by steroid hormones is still unclear, it may need more research for further elucidation.

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