



Soluble E-Cadherin in Prostate Cancer as a Serum Biomarker in Contrast to Prostate Specific Antigen

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Abstract

Histopathology is gold standard in diagnosis of prostate cancer but it is a cumbersome method. On the other hand, prostate specific screening has revolutionized in detection of prostate cancer but due to PSA's lack of sensitivity and as it is not cancer specific novel biomarkers are needed to improve risk assessment. To measure and compare the level of soluble E-cadherin and prostate specific antigen in the detection of prostate cancer, this cross-sectional study was conducted at the Department of Laboratory Medicine in collaboration with the Department of Urology, BSMMU, Dhaka, from March 2017 to February 2018. Total 70 patients were enrolled and divided into Group A (PCa) and Group B (BPH). Each group was consisted of 35 subjects who had histopathologically proven prostate cancer and benign prostatic hyperplasia. E-cadherin with a cut off value 7.3, 95% CI 0.91-1.00, had 74.3% sensitivity and 97.1% specificity for prediction of PCa. 80 kDa fragment of E-cadherin is more specific but was not available. Comparison of E-cadherin in prostate cancer without metastasis and with metastasis is recommended. Immunohistochemical examination of E-cadherin in biopsy sample is also recommended.

Keywords

Histopathology; Prostate cancer; Cumbersome method; Serum biomarker; Benign prostatic hyperplasia

Introduction

Prostate cancer is the major public health issue worldwide because of its increased mortality and morbidity rates. It is evaluated as a most frequently observed solid neoplasm. Environmental factors together with genetic predisposition plays vital role in prostate cancer development, however, its etiology remains unclear [1]. In developed countries, prostate cancer is now the most common male cancer, accounting for 11.9% of the annual cancer burden [2]. The incidence of prostate cancer has increased over the past 10 years, because of Prostate Specific Antigen (PSA) screening and public awareness [3]. Prostate cancer is killing over 10000 men in UK every year. In the year 2000, the number of prostate cancer was estimated about 5,13,000 worldwide [4]. Higher incidence has been observed among men with better socioeconomic circumstances and educational attainment [2].

It is common in northern Europe and the USA (particularly in the black population) but is rare in China and Japan. It rarely occurs before the age of 50 and has a mean age at presentation of 70 years [5]. In the last 20 years, with the widespread use of prostate specific antigen as a screening tool, a greater proportion of patients present with localized prostate cancer was identified [6]. However, there is no authentic statistical data in Bangladesh. National institute of cancer research and hospital, Dhaka recorded that the annual mortality rate per 1,00,000 people from prostate cancer has increased by 34.9% since 1990 to 2013, which is an average of 1.5% a year [7]. Prostate cancers tend to arise within the peripheral zone of the prostate and almost all are adenocarcinomas (Table 1). Metastatic spread to pelvic lymph nodes occurs early and metastases to bone, mainly the lumbar spine and pelvis, are common [5]. Prostate cancer rarely causes symptoms until it is advanced. So early detection of this cancer is critical [8].

Due to the biological heterogeneity of PCa and rapidly expanding treatment options, tumor-specific characteristics of the disease is required to optimize outcome and avoid overtreatment with unnecessary adverse effects [6,9]. Until now, Prostate Specific Antigen (PSA) remains the only clinically relevant diagnostic and follow-up biomarker [10]. Recent research has been aimed at finding markers to overcome the limitation of PSA, not only to diagnose PCa but also to distinguish between local and metastatic disease [11]. The detection of prostate cancer, its clinical staging and prediction of its prognosis remain topics of paramount importance in clinical management. The digital rectal examination, although once the "gold standard" has been largely supplemented by a variety of techniques including serum and tissue based assays. Methods of analysis of PSA have been improved and other tumor markers and biologic determinants are on the horizon. Advances in body imaging have also provided new capability for non-invasive assessment [12]. Marker detection in serum is attractive since sampling is simple and ideal for screening [13]. A panel of serum biomarkers known to be involved in inflammatory processes and tumor genesis of different types of cancer was evaluated for diagnostic and predictive potential in a cohort of patients with PCa. E-Cadherin, N-Cadherin, β -Catenin, Integrins, Focal adhesion kinase, Connexins and Matrix metalloproteinases all appear promising biological markers associated with the early stage metastatic process in prostate cancer [14].

PSA is a glycoprotein which is secreted exclusively by the prostatic epithelium. It is not a tumor specific antigen as it reacts with prostatic materials in benign and malignant tissues. It can transiently increase after the manipulation and the irritation of genitourinary tract (Table 2). An elevated level of serum PSA not only detects aggressive malignancy but it is also associated with benign prostate hyperplasia (BPH) and with mildly aggressive, slowly progressive neoplasia [14]. Nevertheless, PSA is expressed by the cancer tissue at 3 ng/ml/gram of cancer in blood, against 0.3 ng/ml/gm of tissue in BPH. The serum PSA levels are influenced by the patient's ages and prostatic sizes. In a healthy 60 years old man with no evidence of prostatic carcinoma, the serum PSA concentration increases by approximately 3.2% per year [15]. The concentration of PSA is a million times higher in prostatic fluid than in the blood and normally only small amount is absorbed into the blood stream [16]. Although PSA value of >4 ng/ml has 80% sensitivity detecting prostate cancer

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Table 1: Association between age with PCa and BPH (n=70).

Age (years)	Group A (n=35)		Group B (n=35)		p Value
	N	%	n	%	
51-60	9	25.8	14	40.0	
61-70	15	42.9	15	42.8	
71-80	6	17.1	3	8.6	
>80	5	14.3	3	8.6	
Mean ± SD	67.9 ± 10.7		64.7 ± 10.4		0.075 ^{ns}
Range (min, max)	50,90		41,87		

Ns: Not Significant
 Group A: Prostate Cancer (PCa)
 Group B: Benign Prostatic Hyperplasia (BPH)
 p value reached from unpaired t-test

Table 2: Comparison of E-cadherin finding with histopathological finding of PCa (n=70).

E.cad (cut off value)	Histopathological finding		Total
	+ve for PCa	-ve for BPH	
Positive (≥7.26)	26 (74.3%) (true positive)	1 (2.9%) (false positive)	27
Negative (<7.26)	9 (25.7%) (False negative)	34 (97.1%) (true negative)	43
Total	35	35	70

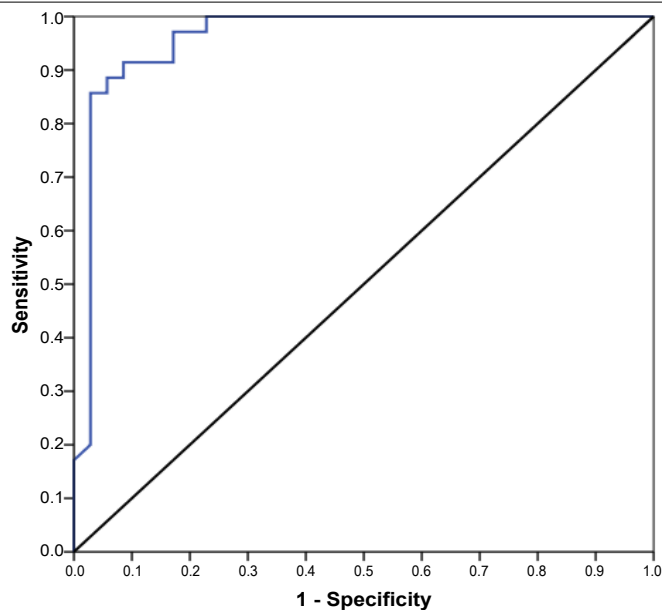
Cut off value of E-cadherin for PCa was set at calculated median of 7.26 µg/l with s.e. 0.21.
 s.e.: Standard Error

but specificity is only 20% [17]. The sensitivity and specificity of PSA are not sufficient to make it an ideal tumor marker for screening and early detection. All diagnosed patients will not require treatment and only patients at high risk of having a deadly cancer will require aggressive therapy. So, overtreatment must be avoided to prevent the unnecessary exposure to the risk of treatment related adverse events [9]. The prime mediator of epithelial cell-cell adhesion participates in the development and architecture maintenance of epithelial tissues. Cadherin superfamily consists of more than 40 members, which share common characteristics. Among cadherins, E-cadherin is the most important molecule. E-cadherin mediates lateral cell-cell adhesion in secretory tissues, like prostate. It is a type-1 calcium dependent cell adhesion molecule and is a major component of adherens junctions in epithelial cells [14]. It is expressed in epithelial tissues being involved in the formation and maintenance of the histoarchitecture. Loss of the function or/and the expression of any of the elements of the E-cadherin/catenins complex impair cell adhesiveness resulting to a loss of the normal tissue architecture [8]. Reduced/absent expression of E-cadherin has been found in a variety of human carcinomas including gastric, head and neck, bladder, prostate, colorectal and breast cancer [18].

In normal physiological condition, E-cadherin plays an important role in embryonic development, morphogenesis and maintenance of epithelial integrity. Furthermore, loss of E-cadherin expression correlated well with the *in vitro* invasive phenotype of cancer cell lines. In human cancers, E-cadherin expression in epithelium is correlated inversely with tumor grade [19]. There is no association between expression of E-cadherin fragment in serum and any of the following clinical parameters: age, preoperative prostate specific antigen, seminal vesicle involvement, surgical margin, tumor size, weight of prostate gland and race [3]. Loss of E-cadherin expression in cell is correlated inversely with tumor grade. There is aberrant expression of E-cadherin with increase grade of human prostate cancer [19]. Proteolytic cleavage of E-cadherin from cell surface may account for the soluble form which has been found in serum and urine with

elevated levels in patients with a variety of cancers [20]. The 120 kDa, full-length E-cadherin is known to be important for well-functioning cell-cell adhesion and its cleavage has been linked to the malignant progression of adenocarcinomas including prostate cancer [21,22]. To determine the frequency of E-cadherin expression, HECD1 antibody is detected which binds to an extracellular epitope of E-cadherin. There is a strong correlation between membrane and cytoplasmic E-cadherin immunoreactivity (P<0.01). E-cadherin expression is significantly higher in bone and soft tissue metastasis (P<0.01) [23]. Soluble E-cadherin yielded favorable discriminative ability over PSA for more aggressive tumors with a Gleason score>7 (P=0.01) [10]. In a recent study, an 80 kDa fragment of full length E-cadherin has been described as almost exclusively observed in the neoplastic aspect of prostate cancer tissue. There is significant expression of the E-cadherin in serum with local PCa and metastatic PCa (P<0.001) compared to healthy individuals and benign enlargement of prostate [3]. This 80 kDa fragment is exclusively seen in neoplastic prostate tissue and may represent a useful biomarker of prostate cancer disease progression [3]. The correlation between aberrant soluble E-cadherin (120 kDa) expression and local extension of tumor is highly significant (p<0.005) (Figure 1). The presence of metastatic tumor is significantly correlated with aberrant soluble E-cadherin (120 kDa) expression (P<0.001) [19]. The 80 kDa fragment of E-cadherin in serum is exclusively raised in prostate cancer. But due to unavailability of its measuring kit in world market, soluble full length (120 kDa) E-cadherin can also be measured as a serum biomarker for prostate cancer (Table 3). PSA is only a screening test and the histopathological study is an invasive procedure. Furthermore there is no study related to E-cadherin in prostate cancer in Bangladesh.

Therefore, the aim of this study is to evaluate full length soluble E-cadherin in prostate cancer and in benign enlargement of prostate and then compare its accuracy with PSA and histopathological findings in context to our population.



Diagonal segments are produced by ties.

Figure 1: Receiver-operator characteristic (ROC) curve of E-cad for prediction of PCa.

Based on the receiver-operator characteristic (ROC) curves PCa had the best area under curve, which is significantly associated to identification of PCa. Receiver-operator characteristic (ROC) were constructed using PCa value of the patient's E.cad with a best combination of sensitivity and specificity for prediction of PCa which gave PCa cut off value of 7.3 with 74.3% sensitivity and 97.1% specificity as the value and for identifying the E.cad for prediction of PCa.

Table 3: Comparison of E-cadherin finding with histopathological finding of BPH (n=70).

E-cadherin (cut off value)	Histopathological finding		Total
	+ve for BPH	-ve for BPH(PCa)	
Positive (≤ 6.27)	27 (77.1%) (true positive)	1 (2.9%) (false positive)	28
Negative (>6.27)	8 (22.9%) (False negative)	34 (97.1%) (true negative)	42
Total	35	35	70

Cut off value of E-cadherin for BPH was set at calculated median of 6.27 µg/l with s.e. 0.31.
s.e.: Standard Error

Materials and Methods

A cross-sectional study was conducted at the Department of Laboratory Medicine in collaboration with the Department of Urology, BSMMU, Dhaka, from March 2017 to February 2018. Total 70 patients were enrolled in this study and divided into Group A (PCa) and Group B (BPH). Each group was consisted of 35 subjects, who had histopathologically proven prostate cancer and benign prostatic hyperplasia. Sample size was calculated by using formula

$$n = \frac{(u+v)^2 (\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

(DANIEL's Biostatics, 9th edition). PSA and

E-cadherin in both prostate cancer and benign prostatic hyperplasia were measured by automated analyzer and Human E-cadherin ELISA kit respectively. Patient's with prostate cancer who received any cancer specific treatment, chronic inflammatory diseases of prostate, other epithelial carcinomas (Eg. Colon carcinoma, bladder carcinoma, oral carcinoma) were excluded. Data were collected by a predesigned proforma. Data were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences). The test statistics to be used for analysis of data were Mean $(\bar{X}) = \frac{x_1 + x_2 + \dots + x_n}{n}$, t

$$(\text{Unpaired}) = \frac{m_1 - m_2}{\sqrt{SE_1^2 + SE_2^2}}$$

, Student's t-test (for comparison of data

presented in quantitative scale), validity test with level of significance being set 0.05 and the Receiver Operating Characteristic (ROC) curve (Table 4). The accuracy of the screening test was judged against the histopathological diagnosis made on biopsy material taken from the lesion by validity test.

Results and Discussion

In this study, it was observed that the mean ± SD age was 67.9 ± 10.7 years in PCa group and 64.7 ± 10.4 years in BPH group. The difference was statistically not significant (p>0.05). Tsaur et al. showed the median age at tumor diagnosis was 65 years. Constantinou and Feneley [4] obtained in their study that aged ranged 60-74 years in prostate cancer. Sukesh et al. showed that most of the prostatic enlargements were in the age group of 60-79 years. In the present study, it was observed that the mean ± SD of PSA was 83.99 ± 48.76 ngm/l in PCa group and 7.49 ± 5.93 ngm/l in BPH group. The difference was statistically significant (p<0.05) between two groups. Tsaur Igor et al. showed that the median PSA level of prostate cancers with poor Gleason's score was 70.7 ng/ml. Ahmed and Naz et al.

showed in their study that mean \pm SD of PSA in prostate cancer 41.9 ± 38.7 ng/l and in BPH 13.5 ± 10.5 ng/l. In this current study, it was observed that the mean \pm SD of E-cad was 7.77 ± 0.80 μ g/l in PCa group and 4.08 ± 2.39 μ g/l in BHP group. The difference was statistically significant ($p < 0.05$) between two the groups. Kuefer et al. found that the mean \pm SD of E-cadherin in PCa was 9.46 ± 0.42 and in BPH was 6.27 ± 0.21 , which is nearly consistent with the present study. In the present study, E-cadherin was evaluated in the diagnosis of PCa with a cut off value ≥ 7.26 , by histopathological finding, true positive 26 cases (37.1%), false positive 1 case (1.4%), false negative 9 cases (12.8%) and true negative 34 cases (48%) were identified by histopathological finding. Umbas et al. [19] found that in patients with cancer tissue, E-cadherin expression was true positive in 32% and true negative in 42%, which is nearly consistent with this study.

In the current study, E-cadherin was evaluated in the diagnosis of BPH with a cut off value of ≤ 6.27 by histopathological finding, true positive 27 cases (38%), false positive 1 case (1.4%), false negative 8 cases (11.4%) and true negative 34 cases (48%) were identified by histopathological finding. This was observed to detect the sensitivity and specificity of E-cadherin in BPH. There is no such study was done before to compare the E-cadherin finding with histopathological findings of BPH. In the present study, PSA was evaluated in the diagnosis of PCa positive with a cut off value of ≥ 45 ng/ml, true positive 24 cases, false positive 23 cases, false negative 11 cases and true negative 12 cases were identified by histopathological finding. In this current study, it was observed that in PSA evaluation of BPH positive with a cut off value of ≤ 10 ng/ml, true positive 26 cases, false positive 25 cases, false negative 9 cases and true negative 10 cases were identified by histopathological finding. Comparison of PSA finding was done with the histopathological findings of both PCa and BPH to detect the sensitivity and specificity of PSA as per specific objective. But no such study was found to compare the PSA with histopathological finding.

In the present study, the validity of E-cadherin and PSA in the diagnosis of PCa had sensitivity 74.3% and 68.6%, specificity 97.1% and 34.3%, accuracy 85.7% and 51.4%, positive predictive values

96.3% and 51.1%, negative predictive values 79.1% and 52.2% respectively (Table 5). Sensitivity was higher in E.cad in evaluation of PCa with compared to PSA but the difference was not statistically significant ($p > 0.05$). However specificity, accuracy, positive predictive value and negative predictive value was significantly higher ($p < 0.05$) in E-cadherin with compared to PSA. Tsaour Igor et al. found that E-cadherin had specificity of 96% in clinically significant PCa, which is compatible with this study. In intermediate ranges of PSA (4–10 ngm/l), specificity is reported to be 20% with a sensitivity of 80% (Catalona). Thompson et al. showed that PSA had a specificity 20.5% and sensitivity 93% in prostate cancer, which is nearly compatible with this study. The validity of E-cadherin and PSA in the diagnosis of BPH positive had sensitivity 77.1% and 74.3%, specificity 97.1% and 28.6%, accuracy 87.1% and 51.4%, positive predictive values 96.4% and 51.0%, negative predictive values 81.0% and 52.6% respectively. Sensitivity was higher in E-cadherin in the evaluation of BPH with compared to PSA but the difference was not statistically significant ($p > 0.05$) however specificity, accuracy, positive predictive value and negative predictive value were significantly higher ($p < 0.05$) in E-cadherin with compared to PSA (Table 6). Schofield Kevin et al. showed that sensitivity and specificity of E-cadherin was 72% and 97% respectively, which is consistent with current study. Proteomic profiles of 154 men with PSA 2.5-15 ngm/l were 67% specific for discriminating between positive and negative biopsies of prostatic disease according to Ornstein et al. PSA value of > 4 ng/ml has 80.0% sensitivity detecting prostatic hyperplasia but specificity is only 20% (Ramirez et al.). This is consistent with the present study. In this present study based on the receiver-operator characteristic (ROC) curves E-cadherin had the best area under curve, which is significantly associated to identification of PCa with area under the curve 96.0% in this present study. E-cadherin with a cut off value 7.3, 95% CI 0.91-1.00, had 74.3% sensitivity and 97.1% specificity for prediction of PCa. In a study Kuefer et al. [22] reported that PCa had a mean E-cadherin concentration of 7.26 ± 0.21 , 95% CI 6.82–7.70. These findings were nearly consistent with our study.

Table 4: Validity test of E.cad and PSA for evaluation of PCa (n=70).

Validity test	Group A		p value
	E-cad (%)	PSA (%)	
Sensitivity	74.3	68.6	0.596
Specificity	97.1	34.3	0.001
Accuracy	85.7	51.4	0.001
Positive predictive value	96.3	51.1	0.001
Negative predictive value	79.1	52.2	0.05

Table 5: Validity test of E.cad and PSA for evaluation of BPH (n=70).

Validity test	Group B		p value
	E-cad (%)	PSA (%)	
Sensitivity	77.1	74.3	0.273
Specificity	97.1	28.6	0.001
Accuracy	87.1	51.4	0.001
Positive predictive value	96.4	51.0	0.001
Negative predictive value	81.0	52.6	0.05

Table 6: Receiver-Operator characteristic (ROC) curve of E-cad for prediction of PCa.

	Cutoff value	Sensitivity	Specificity	Area under ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
PCa	7.3	74.3	97.1	0.960	0.001	0.911	1.00

So, observations of this study were within international norms. Our data indicate that, soluble E-cadherin can be used as serum biomarker in diagnosis of prostate cancer.

Conclusion

This study was undertaken to measure and compare the level of soluble E-cadherin and prostate specific antigen in the detection of prostate cancer. Most of the sample age belonged to 7th decade in both groups. Our study showed that E-cadherin was found higher than the cut off value in prostate cancer than benign prostatic hyperplasia. Specificity and accuracy are more than PSA. The E-cadherin level below the cut off value will therefore exclude prostate cancer. No invasive procedure is required for detection of prostate cancer. So, E-cadherin can be used as a diagnostic tool to detect prostate cancer.

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