

Original Article

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Use of Free-Total Prostate Specific Antigen Ratio in Screening Prostate Cancer in Men with Specific Elevations of Prostate Specific Antigen

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Background: To evaluate the diagnostic performance of free-total PSA (Prostate Specific Antigen) ratio using the criteria of total PSA > 4.0 ng/ml as the cut-off for prostate cancer diagnosis in men.

Method: A total of sixty patients (58.03±9.8 years) were recruited as test subjects from the cancer unit of National Obstetric Fistula Center (NOFIC), Nigeria. All the patients had total PSA value above 4.0ng/ml. Free and total PSA estimations were performed using the principle of Enzyme Linked Immunosorbent Assay (ELISA).

Results: Free-total PSA ratio indicated high sensitivity (98.2% and 98.2%), specificity (87.9% and 82.9%) and positive predictive values (93.3% and 90%) for detecting undiagnosed prostate cancer at cut-offs of 0.25 and 0.19 respectively. High sensitivity (97.6%) and moderate specificity (61.7%) and positive predictive value (70.0%) were observed at cut off of 0.10. Using the free-total PSA ratio cut-off of ≤ 0.10 for prostate cancer, 70% of the test subjects were diagnosed of prostate cancer, on the other hand when a cutoff of > 0.25 was used, 6.7% of the test subjects were diagnosed of a possible benign prostatic hyperplasia.

Conclusion: Free-total PSA ratio is a highly sensitive, specific and useful diagnostic tool alternative to total PSA assay for the screening of undiagnosed prostate cancer. Furthermore, it is highly predictive of the risk for developing prostate cancer at specific cutoff levels.

Key words: Prostate-Specific Antigen, Free-Total PSA Ratio, Prostate Cancer

Introduction

Prostate-specific antigen (PSA), a protein produced by cells of the prostate gland (both normal cells and cancer cells produce PSA) is used to screen men for prostate enlargement be it benign or malignant (1). Serum PSA exists in a free form as well as complex with a number of protease inhibitors (2-6). Most PSA is bound to Alpha-1-antichymotrypsin (ACT), and assays for total PSA measure both this bound fraction and free PSA (4, 7). Men with prostate cancer have a greater fraction of complex, or bound serum PSA and a lower percentage of PSA that is free compared (Free PSA) to men without prostate cancer (3, 4). Empirical evidence has shown that cancer patients

have a higher percentage of PSA bound to ACT than normal controls (4, 8, 9).

Although prostate specific antigen (PSA) assay is widely considered as the most useful tumor marker for detecting cancer, however, its use as an effective test for prostate cancer has been controversial. Clinical practice recommendations from the American Cancer Society and the American Urologic Association have suggested annual cancer screening with both PSA and digital rectal examinations (10, 11). On the other hand, some advisory groups such as the National Cancer Institute, the American College of Physicians and the US Preventive Services

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Task Force, have recently recommended against the use of PSA test to screen for prostate cancer because the benefits if any are small and the harm can be substantial (12-14). For example, when used in screening, the PSA test can help detect small tumors that do not cause symptoms. Detecting tumors that are not life threatening is called 'over-diagnosis' while treating these tumors is called 'overtreatment' (1). Secondly, PSA test lacks specificity and may give false positive or false negative results, thus leading to many unnecessary prostate biopsies particularly for PSA values between 4.0 and 10.0 ng/ml (1, 2). A recent study has shown that some men with normal PSA levels below 4.0 ng/ml have prostate cancer, while others with higher levels do not have prostate cancer but have shown to have benign prostatic hyperplasia (BPH) (15). Furthermore, there is no evidence that PSA testing reduces disease specific morbidity or mortality (13-14).

The above facts call for a need to develop strategies that can improve the specificity of PSA. Most investigators have recommended the use of free-total-PSA ratio calculated from the measurement of free and total PSA in place of total PSA for prostate cancer screening (6, 9, 16). Several studies from different institutions, evaluating a considerable number of different assays, have confirmed the ability of percent free-PSA to improve specificity in detecting prostate cancer with no loss of sensitivity (17-20). Recent studies have also shown that free-total PSA ratio can be used in clinical practice to discriminate between PSA elevation secondary to benign prostatic disease and prostate cancers thus making better decisions about risks of prostate cancer (17, 18). Free-total PSA ratio is superior to total PSA assay in distinguishing primary carcinoma of prostate (CaP) from benign prostate hyperplasia (BPH) in patients with increased total PSA. In addition, its value is effective in reducing the rate of unnecessary biopsies in men with total PSA higher than 4 ng/mL (21). Research has shown that men who were screened with free-total PSA ratio had a lower rate of death from prostate cancer (22). In this cross-sectional study, we aimed at evaluating the diagnostic performance (sensitivity, specificity, positive predictive value) of free-total PSA ratio by using the criteria of total PSA > 4.0 ng/ml as the cut off for prostate cancer diagnosis in men who reported at the prostate cancer screening unit of National Obstetric Fistula Center (NOFIC) Abakaliki, Ebonyi State, Nigeria.. We also determined the incidence of undiagnosed prostate cancer (PSA level > 4 ng/ml) at different risk levels in this suspected group of men.

Study Design

Sixty men aged 40 years and above, who reported at the cancer screening unit of National Obstetric Fistula Center (NOFIC) Abakaliki, Ebonyi State, Nigeria, were recruited for this study. Those included in the study as test subjects were male patients who attended the prostate cancer screening at the NOFIC, aged ≥ 40 years and had total PSA values > 4.0 ng/ml after PSA estimation. The consent of all the subjects was sought prior to participation in the study. Subjects were allowed to withdraw at any point of the research. This study was approved by the ethical committee of Medical Laboratory Science Department, EBSU.

Sample Collection and Analysis

About 5ml blood samples were collected into plain container from the subjects in a relaxed mood without any prior prostate manipulation. The blood was centrifuged and serum used for PSA analysis. The serum was used for the analysis the same day and none was stored beyond 24 hours before use. Free and total PSA estimation was done using the principle of Enzyme Linked Immunosorbent Assay (ELISA) by BioCheck Inc: Cat number BC1019. Free-total PSA ratio was calculated.

Data Analysis

Descriptive data was expressed as mean $\pm$ standard deviation for continuous variables and as percentages for categorical variables. Comparative analysis involving two variables was performed using independent sample t-test. Correlation analyses between variables were determined using Pearson's bivariate correlation test. ROC curve analysis was used to determine the diagnostic performance of free-total PSA ratio for detecting prostate cancer. Statistical significance was set at $P < 0.05$. All statistics were done using IBM-SPSS statistical software (version 20).

Results

Table-1 shows the mean values of total PSA, free PSA and free-total PSA ratio for the subjects. Table-2 indicates frequency distribution of test subjects according to the level of risk of prostate cancer. Data shows that among the sixty subjects queried for prostate cancer, 42 (70%) had free-total PSA ratio values ≤ 0.10 ; 12 (20%) had free-total PSA ratio values between 0.11 – 0.18; 2 (3.3%) had values that fell between 0.19-0.25 and 4 (6.7%) had free-total PSA ratio > 0.25.

Table-2: Total PSA, free PSA and free-total PSA ratio for the subjects.

Variables	Test Subjects
Total PSA	24.88 ± 31.05
Free PSA	2.39 ± 4.1
Free-Total PSA Ratio	0.09 ± 0.08

Table-2: Frequency distribution of test subjects with specific elevations of prostate cancer (PSA level ≥ 4.0 ng/ml) according to free-total PSA ratio categories.

Prostate Ca risk level to Free-Total PSA ratio	No. of subjects with PSA level ≥ 4 ng/ml	%
≤ 0.10	42	70
0.11 – 0.18	12	20
– 0.25	2	3.3
> 0.25	4	6.7
Total	60	100

Table-3: Classification of subjects according to free-total PSA ratio cut-offs and the sensitivity, specificity, positive predictive value and relative risk of elevated PSA levels (≥ 4.0 ng/ml)

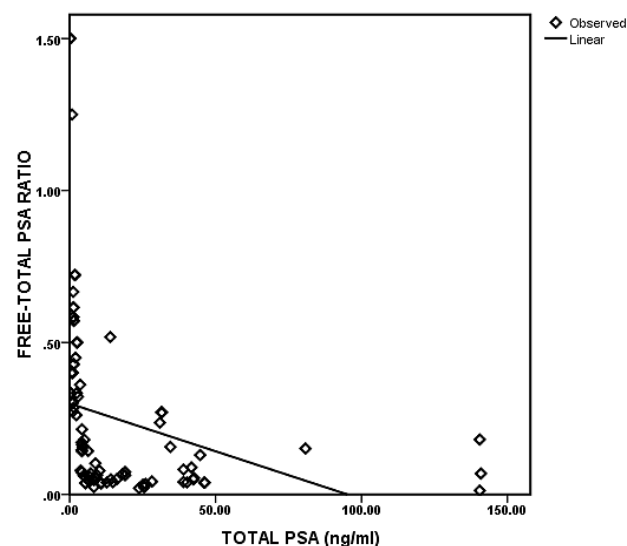
FREE-TOTAL PSA RATIO CUT-OFF	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	RELATIVE RISK (95% CI)
0.25	98.2	87.9	93.3	28.0 (6.8-153.8)*
0.19	98.2	82.9	90.0	27.0 (6.3-150.6)*
0.10	97.6	61.7	70.0	20.5 (4.3-116.8)*

*Significant association ($p < 0.0001$)

Table-3 shows the sensitivity, specificity and positive predictive value for detecting undiagnosed prostate cancer at free-total PSA ratios of 0.25, 0.19, and 0.10 respectively. As the cutoff level of free-total PSA ratio decreased, the sensitivity, specificity and positive predictive values increased. Similarly, the relative risk of developing prostate cancer also decreased with decrease in free-total PSA ratio cutoff level and indicated significant associations ($p < 0.001$) with undiagnosed prostate cancer at all cut-off levels.

Free-total PSA ratios indicated high sensitivity, specificity and positive predictive values for detecting undiagnosed prostate cancer at cut-offs of 0.25 (98.2%; 87.9%; and 93.3%) and 0.19 (98.2%; 82.9% and 90%) respectively. High sensitivity (97.6%) and moderate specificity (61.7%) and positive predictive value (70.0%) were observed at cut off of 0.10. Further investigation revealed that at cut off level of 0.25, fifty six test subjects had free-total PSA ratio < 0.25 while 4 persons had values ≥ 0.25 . At cutoff level of 0.19, fifty four test subjects had values < 0.19 while 6 subjects

had values ≥ 0.19 . At cutoff level of 0.10, forty two test subjects had values < 0.10 while 18 subjects had values ≥ 0.10 .

**Figure-1:** Scatter plot of individuals according to their free-total PSA ratio and total PSA levels.

Pearson's bivariate linear correlation indicated significant and inverse relationship ($R = -0.296$; $p = 0.005$) between free-total PSA ratio and total PSA.

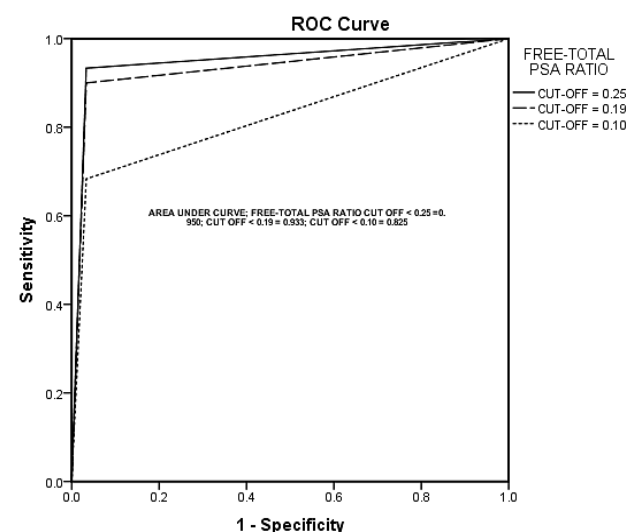
**Figure-2:** ROC plot for free-total PSA ratio as a diagnostic indicator of undiagnosed prostate cancer at each possible free-total PSA ratio cutoff level.

Figure-2 represents the ROC plot for free-total PSA ratio as a diagnostic indicator of undiagnosed prostate cancer at each possible free-total PSA ratio cutoff level. Area under the curve (AUC) revealed a high predictive value for free-total PSA ratio in detecting undiagnosed prostate cancer at cut offs of 0.25, AUC = 0.950; 0.19, AUC=0.933; 0.10, AUC= 0.825 respectively.

Discussion

The PSA assay was considered the most useful tumor marker for detecting prostate cancer until the advisory groups refused to recommend it as a routine screening test for prostate cancer. This is because; there is no evidence that PSA testing reduces disease specific morbidity or mortality (13, 14). Similarly, the lack of specificity by PSA test which leads to unnecessary prostate biopsies is another major concern to clinical practitioners. A previous study reports that PSA test has very poor positive predictive value (23).

In this study, we demonstrated that free-total PSA ratio is both sensitive and specific for detecting undiagnosed prostate cancer. The area under the curve of the ROC plot revealed a high performance of free-total PSA ratio as a useful diagnostic tool for detecting undiagnosed prostate cancer at different cut offs. Our data further indicates a significant association between free-total PSA ratio values and presence of prostate cancer thus demonstrating the predictive capacity of free-total PSA ratio for prostate cancer. Percent free PSA improves sensitivity and specificity in detecting prostate cancer. This agrees with previous studies that free-total PSA ratio may be used to decrease the number of prostate biopsies in patients with serum PSA levels of 4.0 to 10.0 ng/mL. (17- 20, 24, 25) The present findings show that the use of free-total PSA ratio in the diagnosis and screening of prostate cancer is an improved way to distinguish cancerous from benign and inflammatory conditions of the prostate gland. The specificity of using PSA to detect prostate cancer lies in free-total PSA ratio and this further nullifies the lack of specificity, unnecessary prostate biopsies and harm often associated with PSA test (12-14).

It is noteworthy that the free-total PSA ratio cut-offs at 0.25 and 0.19 identified a large proportion of the study population with undiagnosed prostate cancer and are at great risk of developing prostate cancer (RR = 28; 95% CI, 6.82-153.8 and RR = 27; 95% CI, 6.31-150.6). Eighteen test subjects with initial PSA level ≥ 4 ng/ml were found not to have prostate cancer when free-total PSA ratio cut-off of <10 was used. These findings demonstrate the clinical utility of free-total PSA ratio in detecting men with an elevated PSA level who do not turn out having prostate cancer and vice versa.

The free-total PSA ratio of < 0.25 is a marker of prostate cancer while free-total PSA ratio ≥ 0.25 is an indicator of benign prostatic hyperplasia. Probability of benign disease is seen in free-total PSA ratio of ≥ 0.25

while probability of malignant disease is seen in free-total PSA ratio of ≤ 0.10 (26). Of all the sixty test subjects who were seen at the prostate cancer unit in NOFIC with suspected prostate cancer, 70% had prostate cancer risk (at free-total PSA ratio ≤ 0.10) while 6.7% presented benign prostatic hyperplasia as determined by Free-total PSA ratio of > 0.25 . A multicenter study group assessing the diagnostic performance of free PSA evaluated 1081 men and found that among men diagnosed with prostate cancer, 4% had a free-total PSA ratio of > 0.25 , while only 2% of men with BPH had a free-total PSA ratio of < 0.07 (24), this suggests potential clinical utility for free-total PSA ratio.

Conclusion

Free-total PSA ratio is a highly sensitive, specific and useful diagnostic tool alternative to total PSA assay for the screening of undiagnosed prostate cancer. A free-total PSA cut off at 0.25 and 0.19 could identify more individuals with undiagnosed prostate cancer at great risk of developing prostate cancer. Using the free-total PSA ratio cut off of ≤ 0.10 for prostate cancer, 70% of the test subjects were diagnosed of prostate cancer risk. At the cutoff of > 0.25 was used, 6.7% of the test subjects were diagnosed of a possible benign prostatic hyperplasia.

Conflict of Interest

The authors declare that no conflict of interest exists in publishing this article.

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