ORIGINAL ARTICLE
Frequency of Prostate Cancer in Men with Low Percent Free Prostate Specific Antigen in the Serum

MEHNAZ JABEEN[1], RABEEA SALEEM[2], SHIREEN PIYARALI[3], PARDEEP KUMAR MAHESHWARI[4], SYED RAFIUDDIN UDDIN SHAH[5], ASAD SHAHZAD HASAN[6]
[1,4]Assistant Professor Urology, Sindh Institute of Urology and Transplantation, Karachi
[2,3]Senior Lecturer of Urology, Sindh Institute of Urology and Transplantation, Karachi
[5]Post fellow Trainee of Urology, Sindh Institute of Urology and Transplantation, Karachi
[6]Professor of Urology, Sindh Institute of Urology and Transplantation, Karachi
Corresponding author: Mehnaz Jabeen, Email: dr.meha@gmail.com, Cell: 0321 3938129

ABSTRACT
Introduction: Prostate cancer is the utmost communal type of cancer in adult men. Assessment of serum total prostate specific antigen (PSA) is broadly cast-off as a screening assistance in the prompt diagnosis of cancer of prostate. Irrespective of the prostate size or patient's age, 25% cut off value is set or less free PSA level in percentage is suggested for cases with values of PSA amid 4.1 and 10 ng/ml; This helps in detecting prostate cancers in 95% of cases and prevent 20% of unnecessary biopsies. The greater the free PSA percentage, the less jeopardy of cancer. This analysis was designed to evaluate the incidence of prostate cancer in patients with a low percentage of free PSA. If the scale is found to be higher, aggressive strategies and early treatment can lead to good progress.
Aim: To determine the frequency of prostate cancer in males with a low percentage of serum free PSA.
Study Design: This is a descriptive, cross-sectional study lasting 6 months from July 2020 to December 2020 at the Urology Department of the Sindh Institute of Urology and Transplantation.
Subject and method: 149 total individuals with symptoms of lower urinary tract were included in the research. All patients who came to the urology clinic (OPD); free PSA were examined with the same technique as the surgical patient and the result was recorded as proforma.
Results: - The prostate cancer Incidence in males with decreased free serum PSA in percentage is noted in 128(85.91%) patients.
Conclusions: Our study showed that prostate-specific free antigen plays an important role in the analysis of cancer of prostate**.**
Keywords: Serum prostate specific antigen**,** Prostate cancer**,** percentage of free PSA

INTRODUCTION
The cancer of the Prostate is the utmost communal type of cancer in adult men in their 50s. It is the frequently diagnosed neoplasm after lung cancer in the USA and is the most common reason of cancer death. There is no population data on the frequency and pervasiveness of prostate cancer in Pakistan. Some research based on regional hospitals or regional cancer registries shows that the prevalence of cancer of prostate in Pakistan is comparatively low at around 7%. The possible clarification for this is the low overall expectancy of life and the lack of researches on prostate cancer in Pakistan. It is the fifth most common cancer in Karachi province, affecting 7.3% of all men. 3. To reduce the number of deaths from cancer of prostate, it is important to identify the ailment primarily when it is limited to one organ. Thus, it can be treated with radiotherapy or radical surgery.

Serum is widely used in the measurement of total prostate specific antigen (PSA) in the early analysis of cancer of prostate and reduces prostate cancer death by 20% (4). Previously, the recommended limit of serum PSA levels was used to recommend prostate biopsy between 4.1 and 10 ng / ml, and approximately 30% to 70% of prostate cancer cases were detected when biopsy was performed [5]. However, the latest research shows that with PSAs ranging from 4.1 to 10 ng / ml, this standard approach can lead to miss not only 20% of prostate cancer cases, but also false positive results. In fact, only between 25% and 35% of high PSA levels are due to cancer; In most cases the cause is a slight enlargement of the prostate or inflammation and discharge (6, 7). Christensson et al. in one study, the PSA serum sensitivity in detecting prostate cancer was 66% [8]. Although the biopsy itself is a gold standard in the analysis of cancer of prostate, the percentage of free PSA that can be used as the probability that the biopsy will prove the cancer.

If PSA ranges 4.1 to 10 ng / ml, it is recommended to limit free PSA to 25% or less, irrespective of the prostate size and patient's age; Although it helps to detect 95% of prostate cancer and prevent 20% of unnecessary biopsies, only about 5% of prostate cancer is missing (8). The greater the free PSA percentage, the less jeopardy of cancer. If the free PSA percentage is above 25%, the probability of cancer of prostate drops to 8%. Rendering to the American Cancer Society and the National Cancer Institute, men with a PSA percentage of 7% or less should have a biopsy. If the biopsy is negative, but the free PSA is low, a new biopsy is recommended (9). Catalonia et al. (10). a multi-center study was conducted to evaluate men with prostate needle biopsy guided by the ultrasound and total PSA between 4.0 and 10.0 ng / ml. A total of 773 people were examined, of whom 379 (19%) eventually developed cancer. The total PSA in cancer patients has been shown to be higher, and in men who have not had a biopsy, the proportion between free PSA and total PSA is higher significantly. In subjects with less than 25% free / total PSA, 95% of the tumor was detected by prostate biopsy.

Local and international data are not available; therefore, the analysis was designed to evaluate the incidence of cancer of prostate in patients with a low percentage of free PSA. If on a larger scale, aggressive strategies can be used to assess this patient as quickly as possible so that prompt treatment can make a good prognosis.

MATERIAL AND METHOD

This was a Descriptive, Cross-sectional study, held in the department of Urology, Sindh Institute of Urology and Transplantation for the period of six months from July 2020 to December 2020. Consecutive, non-probability Randomized Sample Technique was used to collect the data. Keeping the cancer detection rate of 95%, Confidence level 95%, and margin of error 3.5%, the sample size came out to be 149 according to Raosoft sample size calculator.

Inclusion Criteria:

- Men **above 50 years** of age with lower urinary tract symptoms
- Duration of symptoms **more than 3 months**
- Total serum prostatic specific antigen in the range of 4.1-10 ng/ml
- Percent free PSA in serum less than or equal to 25%
- TRUS guided biopsies have been performed

Exclusion Criteria:

- Ejaculation within 24 hours of testing
- Instrumentation in urethra with in last one week
- Patients with in situ Folly's catheter
- Recent prostate surgery
- Patients on testosterone prescription
- Patients suffering from urinary tract infections
- Percent free serum PSA more than 25%
- Digital rectal examination performed in 2-3 days before taking blood test

Ethical Consideration: Written informed agreement was taken from patients or their attendants. Their autonomy, anonymity and beneficence were given highest importance. Their privacy was firmly preserved. They were completed liberty not to answer any question or leave at any time throughout the study. Ethical approval was acquired from ethical review committee of SIUT before starting the study.

Data Collection Procedure: The study included all patients who came to the SIUT Urological Emergency Room (OPD) with symptoms of the lower urinary tract and met the inclusion criteria. Selected patients were examined with a brief history of biopsy to diagnose prostate cancer, if they met the operative definition. The free PSA test was performed using a similar technique to that performed by a surgical patient and the result was recorded on the form.

Statistical analysis: All collected data was entered into SPSS version 17.0 for statistical analysis. Descriptive statistics were used as a frequency (percentage) for categorical variables such as lower urinary tract symptoms and prostate cancer (yes / no). Standard deviation (SD) and Means were documented for continuous variables such as age, total PSA, and symptom duration. Stratification was achieved to minimize the impact of modifiers such as age, symptom duration, education level,

and economic status. The chi-square test was used and the P value <0.05 was measured significant.

RESULTS

149 total patients with symptoms of lower urinary tract were registered in the study. Most of the patients were between 51 and 70 years of age as shown in Figure 1. The patients average age was 60.15±6.58 years (95%CI: 59.08 to 61.21) as shown in table 1. Average total PSA and duration of symptoms was 6.37±1.52 and 7.12±3.15 months as presented in table 1. Most of the patients were belonged to poor and middle economic status as shown in figure 2. Similarly 79.19% education status of the patients were metric and below metric as presented in figure 3. Regarding obstructive symptoms, hesitancy was commonest (80.5%) and irritative symptoms nocturia was the found commonest symptom that was observed in (50.3%) cases as presented in table 3.

Frequency of prostate cancer in males with low percent free PSA in the serum to be found 128(85.91%) cases as presented in figure 4. Rate of prostate cancer was insignificant among different age groups as shown in table 3. Similarly rate of prostate cancer was observed insignificant among duration of symptoms, educational status and educational status as presented in table 4, 5 and 6.
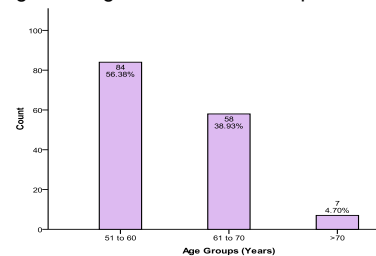
Figure 1: Age distribution of the patients.

Table 1: Descriptive Statistics of Characteristics of Patients

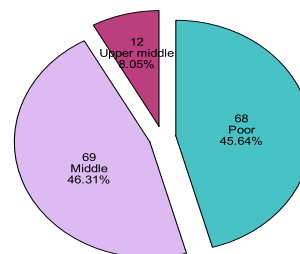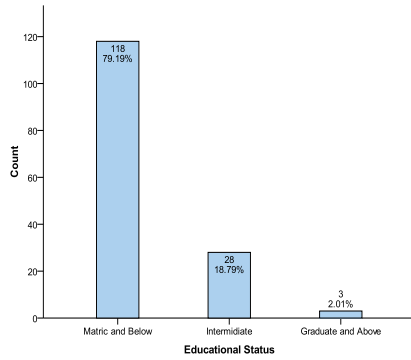| Descriptive Statistics		Age (Years)	Total PSA	Duration Symptoms (months)
Mean		60.15	6.37	7.12
95% Confidence Interval for Mean	Lower Bound	59.08	6.13	6.61
	Upper Bound	61.21	6.62	7.63
Median		59	6	6
Std. Deviation		6.58	1.52	3.15
Minimum		50	4	4
Maximum		78	10	19
Interquartile Range		9	2.9	3

Figure 2: Economical Status Of The Patients n=149

Figure 3: Educational status of the patients

Table 2: Obstructive and irritative symptoms

| Symptoms		Frequency	Percentage
Hesitancy	Difficulty in initiating the urinary stream	120	80.5%
Poor stream	Loss of caliber and force of urinary stream	80	53.7%
Double voiding	Urinating a second time within 2hours of the previous void	50	33.6%
Post void dribbling	Passing >4 drops of urine after urination	82	55.0%
Sensation of incomplete bladder emptying	Patient feels the urine is still in bladder	70	47.0%
Nocturia	Wakes up more than 2 times at night to pass urine	75	50.3%
Frequency	Pass urine more than 6 times a day	60	40.3%
Urgency	Urgent desire to pass urine	62	41.6%
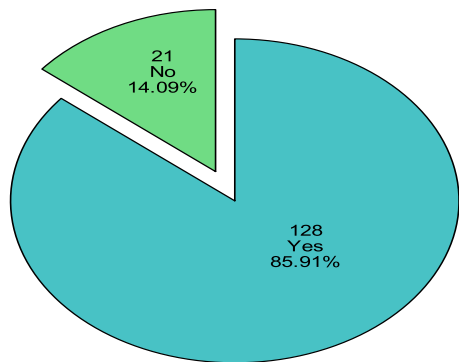
Figure 4: Frequency of prostate cancer in men with low percent free psa in the serum n=149

Table 3: Frequency of prostate cancer in men with low percent free psa in the serum with respect to age groups

| Age Groups (Years) | PROSTATE CANCER | | Total | Chi-Square with P-Values |
	Yes n=128	No n=21		
51 to 60	75(58.6%)	9(42.9%)	84	Chi-Square=1.93 P=0.38
61 to 70	47(36.7%)	11(52.4%)	58	
>70	6(4.7%)	1(4.8%)	7	

Table 4: Frequency of prostate cancer in men with low percent free psa in the serum with respect to duration of symptoms

| DURATION OF SYMPTOMS (Months) | PROSTATE CANCER | | Total | Chi-Square with P-Values |
	Yes n=128	No n=21		
4 to 6 months	74(57.8%)	9(42.9%)	83	Chi-Square=5.28 P=0.73
7 to 12 months	47(36.7%)	8(38.1%)	55	
>12months	7(5.5%)	4(19%)	11	

Table 5: Frequency of prostate cancer in men with low percent free psa in the serum with respect to Economic status

| EDUCATIONAL STATUS | PROSTATE CANCER | | Total | Chi-Square with P-Values |
	Yes n=128	No n=21		
Poor	58(45.3%)	10(47.6%)	68	Chi-Square=0.35 P=0.83
Middle	59(46.1%)	10(47.6%)	69	
Upper Middle	11(8.6%)	1(4.8%)	12	

Table 6: Frequency of prostate cancer in men with low percent free psa in the serum with respect to educational status

| Educational Status | PROSTATE CANCER | | Total | Chi-Square with P-Values |
	Yes n=128	No n=21		
Metric and Blow	100(78.1%)	18(85.7%)	118	Chi-Square=0.88 P=0.64
Intermediate	25(19.5%)	3(14.3%)	28	
Graduate and Above	3(2.3%)	0(0%)	3	

DISCUSSION

Prostate cancer is the utmost communal cancers in men. In Wales and England, the new cases of cancer of prostate augmented by 180% between 1971 and 1998 (10). In 2001, 198,100 new cases approximately and 31,500 demises from prostate cancer had been occurred, an increase that will increase as a result of an aging population (11). The actual incidence in Pakistan is not recognized. In one analysis, the prostate cancer incidence was lower in northwestern Pakistan than other malignancies and ranked eighth on the list of malignancies. This low prevalence may be because of absence of male responsiveness, low literateness, and a lack of a prostate cancer screening program. There is no age limit, also younger men can become victims of prostate cancer (13, 14).

The utmost significant advancement in improving the action of PSA as a tumor marker is the detection of different molecular forms of PSA [15]. Numerous researches have revealed that the percentage of free PSA (free PSA to total PSA ratio) is much beneficial than whole PSA in differentiating prostate cancer from nodular hyperplasia in patients with a safe level of total PSA [16, 17].

The majority of patients in this study were amid 51 and 70 years of age, with 60.15 ± 6.58 years mean age. Comparable outcomes were gained in a study by Iqbal and Chaughtai. In this study, the majority of patients ranged in age from 60 to 90 years, with 68 ± 10 years mean age. A Jamaica study exhibited that the mean age at analysis was 72 (18). Due to the large population of men around the

world, prostate cancer needs a special opportunity in diagnosis and treatment.

High PSA levels are of great importance in the prostate cancer diagnosis. However, when PSA levels in serum are low, i.e., 2.5–10 ng / ml, their importance in cancer detection decreases (18). The PSA is present in many molecular forms. Most inhibitors of serum proteins and serum PSA complexes, i.e., 70–90%, bind alpha 1 antimotrypsin [9]. The free form is called a specific prostate-free antigen.

In this study, the incidence of prostate cancer was 128 (85.91%) in men with a low percentage of serum-free PSA. Similar results can be found in many other studies. Hanif et al. (5) In a sample of 93 patients with prostate cancer, 74 (79.6%) had PSA levels (> 4 ng / ml), and normal PSA (<4 ng). / ml) in 19 (20.4%) cases.

Catalonia et al. (19) conducted a multi-center study to evaluate males with a total 4.0 to 10.0 ng / ml PSA who performed an ultrasound needle biopsy of the prostate gland. A total of 773 people were examined, of whom 379 (19%) eventually developed cancer. The total PSA in cancer patients has been shown to be higher, and in men who have not had a biopsy, the proportion between free PSA and total PSA is significantly higher. In patients with less than 25% free / total PSA, 95% of the tumor was detected by prostate biopsy.

Christension et al. (20) assessed total PSA and free PSA in 121 cases with prostate cancer and with nodular hyperplasia in 144 patients. The free PSAs percentage was suggestively lower in patients with nodular hyperplasia compared to patients with prostate cancer. Prompt recognition of cancer of prostate shows a 90% sensitivity and an 18% reduction in the percentage of free PSAs. Lilja et al. (21) have shown that the percentage of free PSA in prostate cancer patients is significantly lower than in nodular hypertrophy. Compared with the mean PSA of 28% of patients with nodular hypertrophy, the mean PSA of 18% of patients with cancer was found to be average. A study by Stefan and colleagues in Germany showed that the FPSA / TPSA ratio can better differentiate prostate cancer patients from BPH patients when serum PSA is below 10.0 ng / ml. (22) Klaus et al. Early detection of prostate cancer in all other serum studies showed an advantage over the FPSA / TPSA ratio [23, 24]. Global Cancer Recognition Rate Catalon (10) et al. Brawer et al. In a study by Iqbal and Chaughtai (7), prostate cancer was detected in 19–4.0.0 ng / ml PSA values in 19% of men. Schmitt et al. (25); Gann et al. (26) also showed similar results. As a result of this study and other studies, it can be concluded that the FPSA / TPSA ratio for the detection of prostate cancer in patients with a PSA value of 2.5–10 ng / ml and prevents the patient from behaving unnecessarily. surgery.

Other studies have yielded similar results. The increase is moderate in most patients with BPH, but it is estimated that between 3% and 21% of patients have PSA values> 10 ng / ml (28, 29).

We compared the increase in age of patients with prostate cancer with PSA levels and found that 58.6% of patients ranged in age from 50 to 60 years. However, Hanif et al. (5), 54.4% of patients were aged 60–69 years. Dijkman (31) et al. In 1996, he reported that prostate cancer is a serious age-related cancer that affects 50% of patients between the ages of 61 and 70.

CONCLUSION

Our research has shown that free prostate-specific antigens play a significant part in the analysis of prostate cancer. This can result in decrease number of unnecessary prostate biopsies in males. Strategies can be established to assess this patient as soon as possible so that prompt treatment has a good prognosis.

REFERENCES

1. Siegal R, Naishaham D, Jemal A. Cancer statistics 2012. CA Cancer J Clin. 2012;62:10-29.
2. Ahmed Z, Qureshi A, Idrees R, Aftab K. Prostatic carcinoma: a pakistani perspective. Asian Pacific J Cancer Prev. 2009;10:323-4.
3. Barakzai MA, Mubarak M, Kazi JI. Histopathological lesions in transrectal ultrasound guided biopsies of prostate in patients with raised serum prostate specific antigen: a preliminary report. Nephro-Urol Mon. 2011;3:186-90.
4. Rafi T, Sattar A, Asif N, Dawood MM, Aamir M, Rehman Z. The Comparison of Percent Free PSA with total PSA in the diagnosis of Prostate Cancer. J Pak Med Assoc. 2003;53:233-6.
5. Hanif M, Zaidi P, Kamal S, Idrees S, Rasool SA. Significance of prostate specific antigen in Prostate cancer patients and in non-cancerous prostatic disease patients. J Pak Med Assoc. 2007; 57:248-51.
6. Aly M, Wiklund F, Gronberg H. Early detection of prostate cancer with emphasis on genetic markers. Acta Oncologica. 2011;50:18-23.
7. Iqbal N, Chaughtai N. Evaluation of the diagnostic use of free prostate specific antigen/total prostate specific antigen ratio in detecting prostate cancer. J Pak Med Assoc. 2005;55:318-20.
8. Christensson A, Björk T, Nilsson O, Dahlén U, Matikainen MT, Cockett AT, et al. Serum prostate specific antigen complexed to α1antichymotrypsin as an indicator of prostate cancer. J Urol. 1993;150:100-5.
9. Lieberman S. Can percent free prostate specific antigen reduce the need for prostate biopsy?. Eff Clin Pract. 1999;2:266-71.
10. Majeed A, Babb P, Jones J, Quinn M. Trends prostate cancer incidence, mortality and survival in England and Wales 1971-1996. Br J Urol. 2000;85:1058-62.
11. Greenlee RT, Hillharmon MB, Murray T, Thun M. Cancer statistics 2001. CA Cancer J Clin. 2001;51:15-36.
12. Khan SM, Gillani J, Nasreen S, Zai S. Cancer in North West Pakistan and Afghan refugees. J Pak Med Assoc. 1997;47:122-4.
13. Wingo PA, Tong T, Bolden S. Cancer statistics. Cancer J Clin. 1995;45:8-30.
14. Smith CV, Bauer JJ, Connelly RR, Seay T, Kane C, Foley J, et al. Prostate cancer in men age 50 years or younger. Urology. 2000;164:1964-7.
15. Woodrum DL, Brawer MK, Partin AW. Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer. J Urol. 1998;159:5-12.
16. Vashi AR, Wojno KJ, Henrick BA. Determination of reflex range and appropriate cut points for percent free prostate specific antigen in 413 men refered for prostatic evaluation using the AxSYM system. Urology. 1997;49:19-27.
17. Lauderer A, Chen YT, Soriano TF. Measurement of the proportion of free to total prostate specific antigen improves diagnostic performance of prostate specific antigen in the diagnostic gray zone of total prostate specific antigen. Urology. 1995;46:187-94.

18. Coard KCM. Prostate cancer at the University Hospital of the West Indies in Jamaica. A clinicopathological profile at the time of needle biopsy diagnosis. West Indian Med J. 2002;51:40-3.
19. Catalona WJ, Parlin AW, Skawin KM, Brawar MK, Flanigan RC, Patel A, et al. Use of percentage of free prostate specific antigen to enhance differentiation of prostate cancer from benign prostate disease: a prospective multicenter clinical trial. JAMA. 1998; 279:1542-7.
20. Christenssen A, Bjork T, Nilsson O. Serum prostate specific antigen complexed to α1antichymotrypsin as an indicator of prostate cancer. J Urol. 1993;150:100-5.
21. Lilja H, Christensson A, Dahlen U. Prostate specific antigen in serum occurs predominantly in complexes with a 1 antichymotrypsin. Clin Chem. 1991; 37:1618-25.
22. Stefan E, Christian PP, Manfred PW. Clinical significance of the determination of non-complexed prostate specific antigen as a marker for prostate carcinoma. Urology. 1996;47:525-8.
23. Klaus J, Brigitte B, Michae L. Determinate of alpha-1 anti-chymotrpsin. PSA complex in serum does not improve the differentiation between BPH and carcinoma prostate compared to total and percentage free PSA. Urology. 1999;53:1160-8.
24. Elgamed AA, Cornille FJ, Van Popell HP, Van De Voorde WM, Mc Cabe R, Baret LV. Free to total prostate specific antigen ratio as a single test for detection of significant T1c prostate cancer. J Urol. 1996;56:1042-7.
25. Smith DS, Catalona WJ and Herschman JD. Longitudinal screening for prostrate cancer with prostate specific antigen. JAMA. 1996;276:1309-15.
26. Gann PH, Hennekens CK and Stampfer MJ. A prospective evaluation of plasma prostate specific antigen for detection of prostate cancer. JAMA. 1995;273:289-94.
27. Bernstein LH, Rudolph RA, Pinto MM, Viner N, Zuckerman H. Medically significant concentrations of prostate-specific antigen in blood assessed. Clin Chem. 1990;36:515-8.
28. Ercole CJ, Lange PH, Mathisen M, Chiou RK, Reddy PK, Vessella RL. Prostatic specific antigen and prostatic acid phosphatase and staging of patients with prostatic cancer. J Urol. 1987;138:1181-4.
29. Armitage TG, Cooper EH, Newling DW, Robinson MR, Appleyard I. The value of the measurement of serum prostate-specific antigen in patients with benign prostatic hyperplasia and untreated prostate cancer. Br J Urol. 1988; 62:584-9.
30. Palken M, Cobb DE, Warren BH, Hoak DC. Prostate cancer correlation of digital rectal examination, transrectal ultrasound and prostate specific antigen levels with tumor volume in radical prostatectomy specimens. J Urol. 1990;143:1155-62.
31. Dijkman GA, Debruyne FM. Epidemiology of prostate cancer. Eur Urol. 1996;30:281-95.