

Evaluation of prostatic cancer prevalence in patients with prostatic-specific antigen between 4 and 10 and normal digital rectal examination

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Abstract

Background: Prostate cancer is one of the most common male cancers. The prevalence of prostate cancer is different due to genetic and environmental factors. Diagnosis of prostate cancer is by biopsy due to prostate-specific antigen (PSA) and Digital Rectal Examination (DRE). Controversy about decision making for prostate biopsy in PSA between 4 and 10 and normal DRE, is one of the problems in this time. In this study we evaluated the prevalence of prostate cancer in males with PSA between 4 and 10 and normal DRE. We also evaluated the PSA density and percent of free PSA in patients with prostate cancer.

Materials and Methods: A total of 121 males with PSA between 4 and 10 and normal DRE, were evaluated. Then, transrectal ultrasonography (TRUS) and prostate biopsy from 12 points of peripheral zone, was done. These data were analyzed by Chi-square, *t*-test and ANOVA and Roc curve.

Results: In this study, the prevalence of prostate cancer in PSA between 4 and 10 and normal DRE, was evaluated, 29.8%. With use of Roc curve, PSA density cutoff point was calculated 0.12 and percent of free PSA cutoff point, was calculated, 18%.

Conclusion: In males with PSA between 4 and 10 and normal DRE, PSA density smaller than 0.12-0.15, and percent of free PSA greater than 18%, the prevalence of prostate cancer is very few and we can safely ignore the TRUS and prostate biopsy in these males and eliminate its costs and side effects.

Key Words: Benign prostatic hyperplasia, digital rectal examination, percentage of free prostate-specific antigen, prostate cancer, prostate-specific antigen, prostate-specific antigen density

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INTRODUCTION

Prostate cancer is one of the most common malignancies in men whose prevalence increases with age. Due to its importance and prevalence, screening tests are performed annually after the age of 50 and even at lower ages in people with a positive family history.^[1-3]

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Screening methods for prostate cancer include digital rectal exam (DRE) and the prostate-specific antigen (PSA) blood test.^[1,2]

Application of these methods leads to an early diagnosis of prostate cancer at lower clinical stages.^[1,4]

In DRE test, stony hard prostate and nodularity are important for diagnosis of prostate cancer. If prostate is hard and/or nodular, the patient is suspected of having prostate cancer, so PSA and TRUS-guided biopsy of prostate will follow.^[1]

Although hardness and/or nodularity of prostate can be suspected, sometimes the examination findings are borderline and cannot be used for a final diagnosis.

PSA, a protein produced in prostate, is another means for prostate cancer diagnosis.

Normal level of PSA which varies with age is as follows:

Up to 49 years: 2.5 ng/dl

Up to 59 years: 3.5 ng/dl

Up to 69 years: 4.5 ng/dl

Up to 79 years: 6.5 ng/dl.

In clinical trials, values more than 4 are routinely suspicious and the patient undergoes prostate biopsy. PSA higher than 10 ng/dl shows more probability for prostate cancer and in this case, prostate biopsy has to be done. However, values 4-10 are suspicious and other subsidiary parameters such as percentage of free PSA (the ratio of free PSA to total PSA), PSA velocity, and PSA density, contribute to the diagnosis and decision making about prostate biopsy.^[1,5-8]

Various studies have reported final diagnosis of prostate cancer with PSA of 4-10 in 25% of patients. However, there have not been many studies on PSA of 4-10 and normal DRE.

The prevalence of prostate cancer in different parts of the world varies, especially in PSA between 4-10, due to different reasons including genetic and racial issues and also different dietary habits.^[1]

This study was conducted to examine the frequency of prostate cancer in Isfahan, Iran, in order to provide patients with better and more appropriate management.

Moreover, chronic prostatitis is a rather common diagnosis for PSA between 4-10; in various studies, patients undergo a treatment cycle of oral antibiotics for one month to eliminate its effect and then, PSA

is again measured and its rate becomes the basis for whether to do prostate biopsy.^[9,10]

PSA density less than 0.15, PSA velocity less than 0.75 ng/dl and percentage of free PSA higher than 18% may indicate a benign prostate problem and probably do not warrant biopsy. However, different studies have reported various values for the above parameters, which vary in different parts of the world.^[1]

Therefore, performing prostate biopsy for people with PSA between 4-10 is controversial, which may be due to the following reasons:

- Possibility for diagnoses like chronic prostatitis and benign prostatic hyperplasia (BPH) in patients with PSA between 4-10 and normal DRE
- The existence of different errors in laboratorial measurement, measurement techniques, and laboratorial kits that reduce the reliability of the results and make judgment about PSA velocity difficult
- Probable side effects of biopsy such as septicemia, bleeding, and damage to rectum bladder, etc
- The existing costs for patients and insurance system
- Lack of consensus on the exact values of percentage of free PSA and PSA density.

The conditions which increase PSA include prostate cancer, BPH, acute and chronic prostatitis, prostate manipulations like prostate massage, catheterization, and prostate biopsy.^[1]

Prostate manipulations and acute prostatitis are simply diagnosed from the patient's descriptions and experience, however, distinguishing BPH, prostate cancer, and chronic prostatitis would be more difficult especially when DRE shows no symptoms of prostate cancer such as hardness or nodularity of prostate.^[1,2]

Guram Karazanashvili *et al.*'s study, in England, considered the inflammation of prostate as one of the factors of increase in PSA up to 10 and suggested administration of antibiotics for a period of one month prior to deciding to do prostate biopsy. Then, PSA must be checked again and if it is high, prostate biopsy should be performed.

Klingler HC *et al.* in their study in England concluded that PSA density and the ratio of free PSA to total PSA (percentage of free PSA) were not much effective in reduction of number of negative biopsies and also determination of people in danger of prostate cancer, in PSA 4-10.

A study by William J. Catalona *et al.* in America considered the percentage of free PSA useful for distinguishing benign and malignant conditions of prostate and deciding to do prostate biopsy, in PSA 4-10 and regarded values less than 25% as indicator of benign conditions of prostate.

H.J. Luboldt *et al.*'s study, in Germany, found the percentage of free PSA helpful for deciding to do biopsy in PSAs 4-10 and normal examination of prostate and considered values of 16% and 25% for different ages.

H. Ballentine Carter *et al.* regarded the percentage of free PSA of 18% and PSA density of 0.15 as indicators of prostate cancer in PSAs 4-10.

The present study was conducted to examine the frequency of prostate cancer in PSA between 4 and 10 and normal DRE in order to perform diagnostic and therapeutic procedures for patients with prostate cancer and avoid unnecessary actions and associated complications and costs by determining the precision of these diagnoses in the studied region and also specifying the values of free PSA percentage and PSA density in cancer patients.

MATERIALS AND METHODS

Study design

Selection and description of participants

In this prospective descriptive analytical study, patients who came to the health centers of Isfahan University of Medical Sciences for their urinary symptoms and/or annual screening for prostate cancer in 2010, with PSA between 4 and 10 were selected to be examined. Their PSA and free PSA were again measured.

A total of 121 patients were included in the study whose PSA was between 4 and 10 with no evidences for prostate cancer such as hardness and nodularity of prostate and did not have a history of prostate manipulations, urinary retention, or acute prostatitis.

The studied population was selected from the available people through simple sampling.

Technical information

Bladder ultrasound was performed for all patients to determine the size of prostate by a sonographer using a specific ultrasound device for all patients. The size of prostate was used to determine PSA density.

From the night before biopsy, all the patients started liquid diet along with bisacodyl suppositories in order to prepare rectum for biopsy.

All the patients underwent antibiotic prophylaxis of ciprofloxacin (500 mg) and metronidazole (500 mg) as a

single oral dose before prostate biopsy. Also after biopsy, they took 500 mg ciprofloxacin tablet every 12 hours and 500 mg metronidazole every 8 hours for 3 days.

The TRUS-guided prostate biopsy was performed with biopsy needle (20 cm, 18G, GALINI) from 12 different points of basal, middle lobe, apex, and right and left lobes of the prostate. It was tried to sample from the peripheral area of the above points where the cancer risk was more than other areas.

Then, all the samples were delivered to a pathology laboratory to be analyzed.

In the next visit, the patients with their pathology results were divided into different groups based on the type of histological diagnosis, values of PSA density and percentage of free PSA, and also their age.

Statistics

Given that the pathology results of studied patients scientifically indicated that a prostate biopsy was required, the patients were enrolled in the study after signing informed written consent. The data were analyzed using Chi square test, ROC curve, T-test, and ANOVA test.

RESULTS

In this study, 121 patients with PSA between 4 and 10 and normal DRE underwent prostate biopsy. The age of patients was 59-80 years and their mean age was 69.8 years. The independent *t*-test showed no significant difference between the mean age of healthy participants and patients with prostate cancer (*i*-value = 0.1). Among the studied patients, 36 (29.8%) patients were diagnosed to have prostate cancer. [Figure 1, Table 1] Among the patients with prostate cancer, 84.4% had PSA density was greater than or equal to 0.15, with sensitivity of 58% and specificity of 95%.

In 97.3% of the patients with prostate cancer, the ratio of free PSA to total PSA (percentage of free PSA) was less than 0.18 with the sensitivity of 100% and specificity of 98%.

The present study found that the higher value of PSA was directly associated with prevalence of prostate cancer in those patients ($P < 0.001$) [Table 2, Figure 2].

Table 1: Prevalence of cancer in different ages

Age	Count	Percent	Cancer patients	
			Count	Percent
59-65	37	30/6	7	18/9
66-74	53	43/8	19	35/8
75-80	31	25/6	10	32/3
Total	121	100	36	29/8

In this study, a cutoff point was calculated for the two following parameters, using ROC curve, of which percentage of free PSA was 0.18. [Figure 3] and the PSA density was 0.12 with sensitivity and specificity more appropriate than 0.15 (Sens. = 86%, Spec. = 93%) [Figure 4].

However, further studies are required to prove this result because of the limited number of patients.

There was no significant correlation between the age of patients and prevalence of prostate cancer ($P = 0.099$).

The smaller size of prostate of the patients was directly associated with the higher prevalence of

prostate cancer which was statistically significant ($P < 0.001$).

Although using ROC curve, PSA density was calculated 0.12 as a cutoff point with more favorable sensitivity and specificity, further studies are needed to prove the result because of the limited number of studied patients.

DISCUSSIONS

Prostate cancer is one of the prevalent cancers in men.

The suspicion for prostate cancer is caused by DRE and PSA more than 4, which would be proved by doing prostate biopsy.

There is a controversy in different references on the prevalence of prostate cancer in PSA between 4 and 10 and normal DRE and proper diagnostic and therapeutic actions in these conditions and also additional diagnostic parameters.

Table 2: Prevalence of cancer in different PSAs

PSA	Total count	Cancer patients	Percent of cancer patients
6-4	35	2	5/7
6/1-7/9	48	12	25
8-10	38	22	57/9

PSA: Prostate-specific antigen

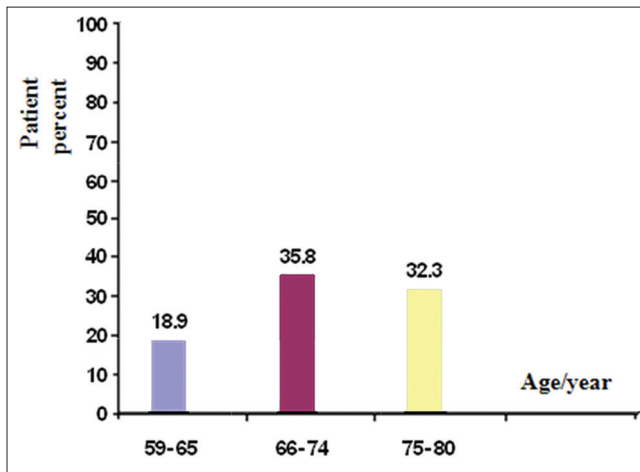


Figure 1: Prevalence of prostate cancer in different ages

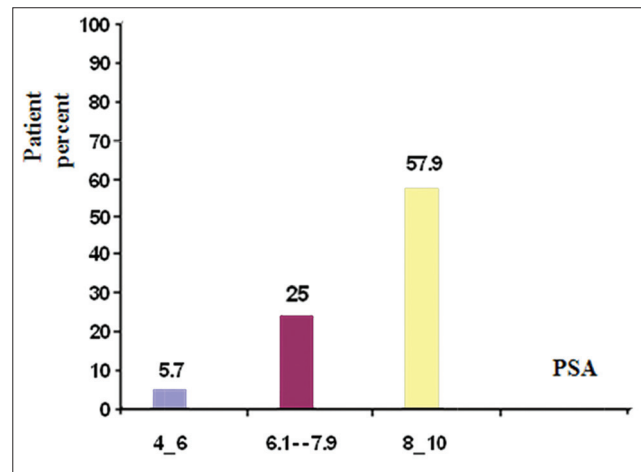


Figure 2: Prevalence of prostate cancer in different prostate-specific antigens (PSAs)

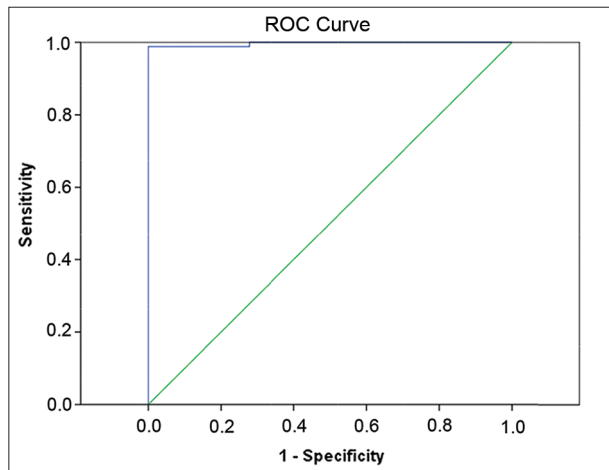


Figure 3: ROC curve of free PSA percent

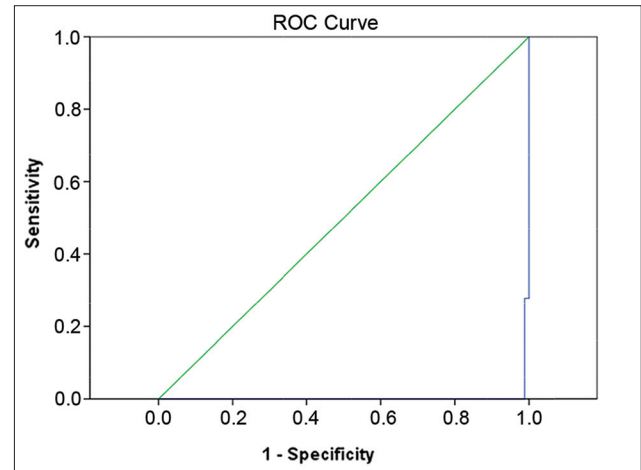


Figure 4: ROC curve of PSA density

In these conditions, other subsidiary parameters such as PSA density, percentage of free PSA may be used to decide for doing prostate biopsy and other therapeutic actions.

In this study, the prevalence of prostate cancer in the studied region was determined as 29.8%.

Moreover, it can be said that PSA density more than 0.15 and percentage of free PSA less than 18%, with a rather appropriate sensitivity, may contribute to make a diagnostic suspicion and a decision for doing prostate biopsy.

Haluk, Ozen *et al.* in their study in America, reported the prevalence of prostate cancer as 25% in PSA between 4 and 10 and considered the use of free PSA and PSA density useful for a proper decision-making and doing biopsy when required.

Although PSA density was calculated 0.12 as a cutoff point with more favorable sensitivity and specificity than 0.15 by using ROC curve, further studies are required due to the limited number of studied patients.

Limitations of the present study include variations in laboratorial kits even in one special laboratory in different times, and in devices for measuring PSA that might interfere with accurate assessments.

Furthermore, as the ultrasound test is an operator-dependent procedure, the ultrasound test was performed by one sonographer in order to eliminate the confounding factor in measurement of the size of prostate.

Based on the results of the present study, the patients with PSA between 4 and 10, normal DRE, PSA density less than 0.15, and percentage of free PSA more than

18% can ignore doing prostate biopsy with a rather appropriate reliability in order to reduce unnecessary biopsy tests and prevent its side effects.

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