

Infection/Inflammation

# A Prospective Study of Reducing Unnecessary Prostate Biopsy in Patients with High Serum Prostate-Specific Antigen with Consideration of Prostatic Inflammation

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**Purpose:** We aimed to reduce unnecessary prostatic biopsy in patients with high prostate-specific antigen (PSA) by consideration of prostatic inflammation.

**Materials and Methods:** The investigation was conducted prospectively in 413 patients with a PSA level of 4 to 10 ng/ml from January 2004 to December 2009. All patients underwent the expressed prostatic secretion (EPS) or voided bladder urine 3 (VB3) test to be classified into two groups: positive group and negative group. Patients with a positive result on the EPS or VB3 test were treated with antibiotics for 2 months, and in cases in which the PSA level remained high, we performed prostate biopsy. In patients with a negative result on the VB3 test, we performed prostate biopsy directly.

**Results:** Of the 413 study patients, 215 (52%) patients had positive findings on the EPS or VB3 test. After 8 weeks of antibiotics therapy, 53 of the 215 men avoided prostate biopsy because their PSA level was normalized. The other patients (162 of 215) still had elevated PSA levels of more than 4 ng/ml, including 7 patients in whom the biopsy revealed cancer. Patients with negative findings (198 of 413) underwent prostate biopsy. Of the 198 patients, 41 were diagnosed with prostate cancer. The total prostate cancer detection rate was 11.6% in our subjects, where as it was 20.7% in the patients with negative findings on the EPS or VB3 and 3.3% in the patients with positive findings, respectively.

**Conclusions:** In cases in which the PSA level is increasing, if we first exclude prostatitis and carry out a serial diagnostic procedure, it may help to reduce unnecessary prostatic biopsy.

**Key Words:** *Biopsy; Prostate-specific antigen; Prostatic neoplasms; Prostatitis*

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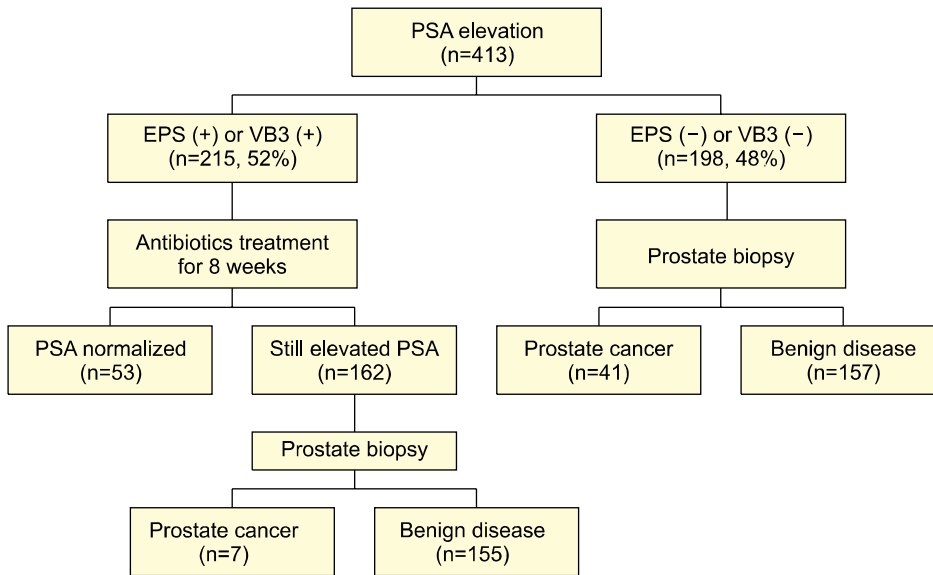
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## INTRODUCTION

The prostate-specific antigen (PSA) level has been an important diagnostic tool for detecting prostate cancer. It has been shown that an abnormal digital rectal examination (DRE) has markedly decreased and biochemical findings (elevated PSA) have increased over the past 20 years for the indication of prostate biopsy [1]. This means that evaluation of prostate cancer is more and more based on the PSA level rather than on suspicious DRE. However, cancer detection rates from biopsy in the presence of isolated PSA

elevation and a normal DRE range between 30% and 40% [1]. Also, a high concentration of PSA can be found in benign disorders such as benign prostatic hyperplasia (BPH), urinary tract infections, and bacterial prostatitis [2-5].

Histological prostatitis is a common entity in men without clinical prostatitis. Although it has been reported that acute inflammation is necessary to cause PSA elevation, there is growing evidence that subclinical inflammation may also contribute to rises in PSA levels [6-9]. Furthermore, several investigators have shown that treatment of chronic prostatitis, when identified, can decrease PSA,



**FIG. 1.** The process of prostate cancer detection considering PSA reduction after antibiotic treatment. PSA: prostate-specific antigen, EPS: expressed prostatic secretion, VB3: voided bladder urine 3.

which suggests that the use of anti-microbial or anti-inflammatory drugs may reduce the number of men who need prostate biopsies [10,11].

There is no doubt that symptomatic prostatitis needs to be treated, but uncertainty exists about the appropriate management of asymptomatic patients with elevated PSA and normal DRE.

The aim of our study was to investigate the possibility of reducing the number of prostate biopsies in patients with a high PSA level showing a PSA decrease or normalization after antibiotic therapy. This approach could be useful in patients for whom it is necessary to postpone biopsy and in patients with previous negative biopsies who are willing to avoid biopsy until further PSA increase.

## MATERIALS AND METHODS

This investigation was conducted prospectively among 413 patients with a serum PSA level of over 4 ng/ml to under 10 ng/ml from January 2004 to December 2009. Subjects were excluded if they had been treated by 5- $\alpha$  reductase inhibitor for more than 3 months or if they had a history of transurethral resection of the prostate. The PSA level was determined by using immunoenzymatic assay before DRE and transrectal ultrasonography (TRUS) to avoid false-positive results. To exclude prostatitis, all patients underwent the expressed prostatic secretion (EPS) or voided bladder urine 3 (VB3) test to be classified into two groups. One group had positive findings on the EPS or VB3 test and the other group had negative findings. The expressed prostatic secretions were collected on a glass slide. A cover slip was placed over the specimen and it was examined under high-power microscopy. A positive finding was defined as a white blood cell (WBC) count higher than 10 in the prostate secretion after EPS or WBC higher than 10 in VB3 urine after EPS. The patients with a positive result were treated with quinolone antibiotics for 2 months, and

they were asked to return for repeat screening 2 months later. If the PSA level was still higher than 4 ng/ml after 2 months, the patients underwent prostate biopsy. In the other cases, the patients avoided prostate biopsy. The patients with a negative EPS or VB3 test immediately underwent prostate biopsy. The subjects underwent at least 10 core biopsies with transrectal ultrasound-guided needle biopsy of the prostate. SPSS ver. 10.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis, and independent t-tests were used for analysis of the characteristics of both groups. P-values of less than 0.05 were considered significant.

## RESULTS

Of the 413 men studied, 215 (52%) patients had positive findings on the EPS or VB3 test. They received levofloxacin 100 mg tid daily. Antibiotic treatments were administered for a total of 8 weeks in 215 patients. After 8 weeks of antibiotic therapy, serum PSA screening was repeated. Of the 215 patients, 53 men avoided prostate biopsy because their serum PSA level had decreased to less than 4 ng/ml. The other patients (162 of 215) still had an elevated serum PSA level of more than 4 ng/ml, including 7 in whom the biopsy results revealed cancer. Patients with negative findings on the EPS or VB3 test (198 of 413) underwent prostate biopsy immediately (Fig. 1). Of these 198 patients, 41 were diagnosed with prostate cancer. The total prostate cancer detection rate was 11.6% in our subjects, whereas it was 20.7% in the patients with negative findings on the EPS or VB3 test and 3.3% in those with positive findings, respectively.

The mean age was significantly different between the positive group (65.0) and the negative group (71.2). There were no significant differences in the mean initial serum PSA level or prostate volume between the groups (Table 1).

**TABLE 1.** The characteristics of both patient groups according to the findings of the EPS or VB3 test

	Negative group (n=198)	Positive group (n=215)	p-value
Age (yr)	71.2±9.3	65.0±12.3	0.00
Prostate volume	42.5±23.0	39.8±16.9	0.17
Serum PSA	6.1±1.6	6.3±1.7	0.13
Prostate cancer detection rate (%)	40 (20.7)	7 (3.3)	0.00

Values are presented as mean±standard deviation or number (%). EPS, expressed prostatic secretion; VB3, voided bladder urine 3; PSA, prostate-specific antigen.

## DISCUSSION

Since PSA was introduced in the 1980s as a variable for detecting prostate cancer, the detection rate of prostate cancer has been increasing. It is true that an abnormal finding on a DRE or TRUS is an indication for prostate biopsy, but in the majority of cases, the PSA level is the most important factor in deciding whether we will proceed with prostate biopsy [2].

However, it is reported that 30 to 40% of patients who test positive for prostate cancer in prostate biopsy proceeded when only the PSA was increased without any abnormality in the DRE or TRUS [1]. The specificity and sensitivity of PSA can result in high values in other positive diseases. The PSA may increase not only in BPH but also in urinary tract infection and bacterial prostatitis. The PSA can increase in acute inflammation and silent infection [7-9,12]. Also, some researchers have reported that treatment with antibiotics and anti-inflammatory drugs for chronic prostatitis can decrease the PSA and the necessity for prostate biopsy [7,10,11].

Nadler et al. [6] reported that the size and infection of the prostate can be a chief cause of PSA increase in the case of patients not diagnosed with prostate cancer. But Irani et al. [13] reported that even if there is an infiltration of inflammatory cells in the prostatic interstitium, it is not related to the PSA increase in the blood if the glandular epithelial cell layer is not destroyed at the same time. Furthermore, it has been reported that the existence of inflammatory cells of the interstitium or glandular tissue in the prostate biopsy has no statistical affiliation with the concentration of PSA in the blood [14,15]. Carver et al. [16] argued that National Institutes of Health (NIH) category IV asymptomatic prostatitis increases the PSA concentration in the blood, but its clinical significance is not that great because the mean differences with the normal group are 2.3 ng/ml and 1.4 ng/ml, respectively. Pansadoro et al. [17] reported that there is an increase of the concentration of PSA in the blood in 71% of patients with acute prostatitis, 15% of patients with chronic prostatitis, and 6% of patients with nonbacterial prostatitis, but there was no PSA increase in patients who showed only symptoms of chronic

prostatitis. Hasui et al. [18] found a relation of the PSA concentration in the blood with acute and chronic prostatitis accompanied by clinical symptoms identified histologically, but no relation in the case of deactivated prostatitis. Chang et al. [19] investigated 223 patients who tested negative in a prostate biopsy by classifying the infection level and reached the conclusion that the whole size of the prostate is an important factor that contributes to the increase in the PSA concentration in the blood, but that there was no relation with the prostatitis level.

The relationship of prostatitis and the PSA increase continues to stimulate dispute, and we suggest that the findings mentioned above are not sufficient to explain the reason for the PSA increase in the case of NIH category IV asymptomatic prostatitis. Nadler et al. [20] investigated 421 patients with NIH category III chronic prostatitis and reported recently that the mean PSA concentration in the blood of the patients investigated was 1.97 ng/ml. Compared with the level in the normal group of 1.72 ng/ml, this was a statistically significant increase, but it is still below the normal PSA range. Also, f-PSA, percent f-PSA, and the [-2] pPSA isoform show some increase with prostate cancer, but they are inappropriate to be used as biomarkers of prostate cancer diagnosis because of their low specificity and sensitivity.

Treatment with antibiotics in the case of chronic prostatitis and increased PSA results in a very significant PSA decrease [11]. But any special bacteria is found in 90% of cases of prostatitis with or without symptoms. This kind of investigation of the changes in PSA after treatment with antibiotics or anti-inflammatory drugs for nonbacterial prostatitis is uncommon. According to the report of Potts [7] among 122 patients with an average PSA increase of 9.35 ng/ml, 51 (42%) patients were diagnosed with infection by urinalysis after a massage of the prostate or prostatic secretion (EPS). The patients were then treated with antibiotics for 4 weeks, and after 6 to 8 weeks they had a PSA examination. After the treatment, 22 of the 51 patients had a normal PSA concentration (average, 2.9 ng/ml) and they did not need a prostate biopsy. But there was a continuous increase of PSA in the remaining 29 patients, and among them, 9 patients were diagnosed with prostate cancer. In comparison with patients diagnosed with cancer in prostate biopsy after treatment with antibiotics, the PSA decrease in patients with benign biopsy results was significantly greater (-1.3% vs. -21.3%).

In the investigation carried out with 95 patients diagnosed with nonbacterial prostatitis and who showed an increase of PSA, Bozeman et al. [10] proceeded with prostate biopsy in patients in whom the PSA value did not decrease after 4 weeks of treatment with antibiotics and anti-inflammatory drugs. Among these, the PSA of 36.4% of patients decreased from 8.48 ng/ml to 5.39 ng/ml after treatment; in 44 patients (46.3%) the PSA decreased below 4 ng/ml, so they avoided prostate biopsy. In the remaining patients who underwent prostate biopsy, 13 patients (25.5%) were diagnosed with prostate cancer, 37 patients (72.5%) with

chronic infection, and 1 patient (1.05%) with BPH. Among the patients diagnosed with prostate cancer, just 4.8% of patients had shown a PSA decrease from 8.32 ng/ml to 7.92 ng/ml, which was not statistically significant. Therefore, the authors argued that chronic prostatitis is the chief cause of PSA increase and that treatment for prostatitis can decrease unnecessary prostate biopsy.

But Hochreiter [21] argued that although the authors of two investigations considered that the patients were not diagnosed with prostate cancer because the PSA was decreased to less than 4 ng/ml, it was difficult to conclude that the patients in fact had no cancer.

Our results should be interpreted with an understanding of our study limitations. It is not a certainty that PSA-normalized patients are cancer free after antibiotic therapy. Additional research is needed with pathologic confirmation for PSA-normalized patients.

## CONCLUSIONS

Chronic prostatitis may interfere with the interpretation of PSA levels for prostate cancer screening. There are no general guidelines that can be applied to all men with increased PSA before prostate biopsy. In cases in which the PSA level is increasing, if we first exclude prostatitis and carry out a serial diagnostic procedure, it may help to reduce unnecessary prostate biopsy.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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