ORIGINAL ARTICLE

Prostate biopsy and relation to prostate-specific antigen in patients diagnosed with benign prostatic hyperplasia


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Abstract

Background: Benign prostatic hyperplasia (BPH) is the most frequent benign tumor in men above 50 years of age. Initial suspicion of prostate cancer is based on a digital rectal examination with abnormal findings or elevated serum levels of prostate-specific antigen (PSA) (≥ 4 ng/mL); these patients must be evaluated in order to rule out prostate cancer.

Aims: The aim of the present study was to determine the association of ultrasound-guided prostate biopsy with prostate cancer diagnosis in patients presenting with clinical BPH diagnosis.

Methods: A descriptive analytic study was conducted within the time frame of January to July 2012. Patients diagnosed with BPH that underwent ultrasound-guided prostate biopsy were included. Data were analyzed through descriptive statistics, categorical variables were compared using the chi-square test, and odds ratio was used to determine association.

Results: The mean age of the BPH patients was 68.5 ± 9.9 years (39-93) and the mean PSA (standard deviation, SD) was 5.9 ± 6.4 ng/mL. Of these patients, 166 (47.8%) had normal PSA and in 181 (52.2%) it was abnormal. The patients with BPH had an odds ratio (OR) of 1.8 (95% CI = 1.5-2.6); ultrasound-guided prostate biopsy was performed if they had an abnormal PSA, regardless of digital rectal examination findings and age.

Conclusions: In our study, the patients clinically diagnosed with BPH underwent ultrasound-guided prostate biopsy based on PSA levels in the majority of the cases, to rule out prostate cancer. The patients that underwent the biopsy presented with significantly higher PSA levels (10.9 ± 6.6 vs. 4.6 ± 5.4 ng/mL, p=0.0001), but only 28 (32%) of them had a digital rectal examination, and free PSA and PSA density or velocity were not determined. The ultrasound-guided prostate biopsy requested by the urologists in the majority of the cases was not based on the recommendations of the clinical practice guidelines (CPG).

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Introduction

Benign prostatic hyperplasia (BPH) is the most frequent benign tumor in men above 50 years of age, due to an enlarged prostate that causes urinary flow obstruction and lower urinary tract symptoms. It is the second most common cause of hospital admission for surgical intervention and the main cause of urology service consultation. In 2005, the Instituto Mexicano del Seguro Social (IMSS) provided 63,874 medical consultations for this disease, on the national level. The prevalence of BPH increases linearly with age.1

Prostate-specific antigen (PSA) is a glycoprotein synthetized by prostatic epithelial cells, and for practical purposes it is organ-specific, but not cancer-specific. Thus serum levels can increase in the presence of BPH, prostatitis, and other non-malignant conditions. There is a direct relation between PSA levels and prostate volume, and patients with BPH are not at greater risk for prostate cancer.2 The Guidelines for Clinical Practice (GCP) for the Diagnosis and Treatment of BPH recommend that all patients that enter a treatment protocol should have a bladder and prostate ultrasound study with baseline residual urine measurement, as well as PSA determination.3

Initial suspicion of prostate cancer is based on abnormal digital rectal examination findings or on increased serum PSA levels (≥ 4 ng/mL), and patients should be evaluated to rule out cancer of the prostate.1 Ultrasound-guided prostate biopsy is recommended in a large number of patients when they present with abnormal PSA determination, and so, for improving its specificity, free PSA determination is recommended when the PSA values are between 4 and 10 ng/mL. If free PSA is under 20%, it is associated with a greater risk for prostate cancer.1

There has been an important increase in serum PSA determination for prostate cancer detection since its approval by the Food and Drug Administration (FDA) in 1986. Its widespread use is mainly based on the fact that it increases early-stage prostate cancer detection.4 Even though PSA determination has been significantly associated with a reduced prostate cancer-specific mortality rate,5 it can also be the cause of considerable damage, such as: unnecessary ultrasound-guided prostate biopsy, complications secondary to ultrasound-guided prostate biopsy, overdiagnosis (identifying prostate cancer that has never caused symptoms during the patient’s lifetime, possibly resulting in unnecessary treatment), overtreatment of prostate cancer, and patient anxiety. Thus, there is currently not enough evidence at hand for the indiscriminate or massive recommendation of PSA determination, given that the balance between benefit and harm is not well established due to the fact that its potentially beneficial effects are still uncertain.6-10 The aim of the present study was to determine the association between ultrasound-guided prostate biopsy and prostate cancer diagnosis in patients with clinically diagnosed BPH.
Methods

Study population
The district of Baja California that encompasses the cities of Tijuana, Ensenada, Tecate, and Rosarito, has a population of 402,000 that is insured by the IMSS. The Hospital General Regional No. 20 works together with 8 Family Medicine Units and has a Urology Service with 4 physicians. The urologists order between 150 and 200 PSA determinations monthly, both for patients with BPH symptoms that are referred by the family physician for the first time and for the follow-up of patients with an already established prostate cancer diagnosis. The PSA and ultrasound-guided prostate biopsy orders are performed outside of the hospital and a daily register of the ordered studies is kept, along with a database that contains the name of the patient, his social security number, the date of the order, diagnosis, and the cost per study.

Procedures
The databases containing the information on PSA determination and ultrasound-guided prostate biopsy performed within the time frame of January to July 2012 were reviewed. The electronic clinical case records with the evaluation of the following variables were also reviewed: age, family history of first-degree relatives with prostate cancer, diagnosis, digital rectal examination findings, PSA values in patients initially diagnosed with BPH, and the pathology report on the patients that underwent ultrasound-guided prostate biopsy. A serum PSA level ≥ 4.0 mg/mL was regarded as abnormal.

Statistical analysis
Data analysis included descriptive statistics with means and standard deviation (SD) for the continuous variables. Prevalence and frequency were expressed in percentages. Categorical variables were compared through the chi-square test and numerical variables through the Student’s t test. The association between an abnormal PSA result and the performance of ultrasound-guided prostate biopsy was evaluated through odds ratio (OR) with a 95% confidence interval (CI). Statistical significance was set at a p ≤ 0.05. Data capture and analysis were carried out using the SPSS® version 16 program (SPSS Inc., Chicago IL).

Results
From January to July 2012, 661 PSA studies were ordered by the urologists; 173 (26.2%) in patients with an already established prostate cancer diagnosis and 486 (73.8%) in patients that had been referred to the Urology Service for the first time with a probable BPH diagnosis; of these 486 PSA studies ordered, 347 patients (71.3%) went to a family physician for the first time and for the follow-up of patients with an already established prostate cancer diagnosis. The PSA and ultrasound-guided prostate biopsy indications are: 1) patients with an unsuspicious digital rectal examination, but with an alteration in the PSA level between 4 and 10 ng/mL, with free PSA under 20%, density above 0.15, velocity greater than 0.75ng/mL/year, and a duplication time under 3 months after the initial PSA study. The values were lower in 63 (70.8%) patients, higher in 25 (28.1%), and remained the same in one (0.3%) patient.

Initial PSA determination
The mean age of the patients with BPH was 68.5 ± 9.9 (39-93), the mean PSA (SD) was 5.9 ± 6.4 ng/mL. Of these patients, 166 (47.8%) had normal PSA and it was abnormal in 181 (52.2%) (normal value was regarded as < 4.0 ng/mL). There was a higher frequency of abnormal PSA (57.7%) than of normal PSA (42.3%, p=0.19) in patients 75 years old or older, but with no statistical significance.

Ultrasound-guided prostate biopsy performance
Of the 347 patients clinically diagnosed with BPH, 86 patients (24.7%) had an ultrasound-guided prostate biopsy; BPH was histologically diagnosed in 84 of them and prostate cancer in 2. Eighty-three (96%) patients had an abnormal PSA result and 3 of the patients had abnormal digital rectal examination and normal PSA results. Digital rectal examination was carried out on 28 patients and was abnormal in 21 (75%). The patients with BPH had an odds ratio (OR) of 1.8 (95% CI=1.5-2.6) of undergoing an ultrasound-guided prostate biopsy if they had abnormal PSA, regardless of their digital rectal examination findings and age (table 1).

The ordering of 2 or more PSA studies
PSA was repeated in 86 patients, at a mean 6.0 (± 3.8) months after the initial PSA study. The values were lower in 63 (70.8%) patients, higher in 25 (28.1%), and remained the same in one (0.3%) patient.

Prostate cancer
Two patients had histopathologic diagnosis of prostate cancer. The first patient was 67 years old and did not have a digital rectal examination. His initial PSA was 19 ng/mL and when repeated at 3 months, was 15 ng/mL. Biopsy revealed a Gleason score of 6. The second patient was 57 years old and he did not have a digital rectal examination. His initial PSA was 10 ng/mL and repeat PSA at 5 months was 23.95 ng/mL, with a Gleason score of 4.

Discussion
Initial suspicion of prostate cancer is based on abnormal findings in a digital rectal examination together with elevated PSA levels, which are indications for ultrasound-guided prostate biopsy. In our study, the order for ultrasound-guided prostate biopsy in order to rule out prostate cancer in patients with a clinical diagnosis of BPH was based on PSA levels in the majority of cases. The patients that underwent ultrasound-guided prostate biopsy had significantly higher PSA levels (10.9 ± 6.6 vs. 4.6 ± 5.4 ng/mL, p=0.0001), but only 28 (32%) had a digital rectal examination and none of them had free PSA or PSA density or velocity determinations; those determinations improve specificity for early prostate cancer detection when serum PSA values are between 4 and 10 ng/mL.11,12 Based on the CPG for the Diagnosis and Prevention of Prostate Cancer at Secondary and Tertiary Care Centers, ultrasound-guided prostate biopsy indications are: 1) patients with an unsuspicious digital rectal examination, but with an alteration in the PSA level between 4 and 10 ng/mL, with free PSA under 20%, density above 0.15, velocity greater than 0.75ng/mL/year, and a duplication time under 3 months after the initial PSA study.
months; 2) no clinical suspicion in the digital rectal examination and a serum PSA level above 10ng/mL; and 3) all patients with normal PSA values, but with abnormal digital rectal examination findings. Studies have shown an important decrease in ultrasound-guided prostate biopsy in patients that have had free PSA determination. Likewise, patients 70 years old or older, with a PSA under 15 ng/mL and normal digital rectal examination, have been observed to have a low prostate cancer incidence, no association with general or prostate cancer-specific mortality, and a significant reduction in ultrasound-guided prostate biopsy of up to 20%; this could be taken into consideration when it is not possible to determine free PSA or PSA density.

For the purpose of selecting patients that are candidates for ultrasound-guided prostate biopsy and of histologically differentiating the risk factors associated with aggressive vs. indolent prostate cancer, a study was conducted that included patients without prostate cancer, with indolent prostate cancer, and with aggressive prostate cancer, finding that age, body mass index, a family history of prostate cancer, abnormal digital rectal examination, and PSA density were significantly associated with more aggressive prostate cancer. It was concluded that prostate biopsy should be performed in men with a PSA density > 0.1 ng/mL/cc or with abnormal digital rectal examination; men with a PSA density < 0.1 ng/mL/cc and a positive family history of prostate cancer would also be candidates for biopsy.

A family history of prostate cancer in first-degree relatives is a well established risk factor for prostate cancer. If a first-degree relative has the disease, the risk is doubled; if two or more first-degree relatives are affected, the risk increases 5 to 11-fold. Nevertheless, upon reading the medical notes in the case records, it was apparent that the majority of patients had not been asked about a family history of prostate cancer. A study that evaluated the knowledge family physicians and urologists have about the history of prostate cancer in first-degree relatives showed that up to 40% of the family physicians and urologists did not take a family history of prostate cancer into consideration and their knowledge of a family history of prostate cancer and its relation to prostate cancer were suboptimal.

The CPG are of invaluable help to the physician because they aid the professional in making better decisions and provide guidelines aimed at homologating treatment. In the last few decades, there has been great interest worldwide in CPG development and in the evidence-based medicine movement. CPGs have become a health system proposal for improving the quality and reducing the heterogeneity of medical attention and managing resources in a more organized and efficient manner. However, many physicians do not follow the CPGs. This could be because they are unaware of their existence or are unfamiliar with them; or perhaps physicians are aware of them, but do not use them in their daily practice due to a lack of time or to the pressure of work. In other words, they do not form part of the daily work routine of the physician.

### Conclusions

In our study, the decision to order a prostate biopsy by urologists, in the majority of cases, was not based on CPG recommendations, suggesting they are not used or not adhered to in the decision-making process. This lack of
adherence to the CPGs has also been documented in other studies, finding that the evaluation and treatment of BPH varies widely among urologists.\textsuperscript{18-20} A multicenter study conducted in Italy reported that the treatment of 53% of the patients diagnosed with prostate cancer was not based on the recommendations of the American Urological Association or the European Association of Urology.\textsuperscript{21}

**Conflict of interest**

The authors declare that there is no conflict of interest.

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**References**


