ROLE OF PROSTATE-SPECIFIC ANTIGEN AND DIGITAL RECTAL EXAMINATION IN THE DETECTION OF PROSTATE CANCER

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Prostate-specific antigen (PSA) is a kallikrein-like serine protease that is secreted exclusively by the epithelial cells of all types of prostatic tissue, benign and malignant. Its serum concentration is raised in men with prostatic disease including cancer. We have evaluated its usefulness in the diagnosis of prostate cancer by measuring serum PSA concentrations in 260 men aged 50 years or over. All had abnormalities at digital rectal examination (DRE) involving suspected cancer, signs and symptoms of benign prostatic hyperplasia and equivocal findings on DRE, and miscellaneous other conditions, including hematospermia, chronic prostatitis and microscopic hematuria. Transrectal prostatic needle biopsies were performed in the men with abnormal findings on DRE or elevated serum PSA (above 4 ng/ml). Serum PSA ranged from 4.0 to 9.9 ng/ml in 14 (5%) of the 260 men. Four of the men in this group (31%) who underwent prostatic biopsy had prostate cancer. Serum PSA levels greater than or equal to 10.0 ng/ml were found in 8 (3%) of the 260 men. 5 of these 8 (63%) who underwent prostatic biopsy had cancer. If DRE alone had been used to screen the men having biopsies, 4 of the 10 cancers (40%) would have been missed. If PSA alone had been used to screen these men, only 1 of the 10 cancers would have been missed. Serum PSA measurement was more reliable than DRE for detecting prostate cancer. Since these two methods do not always detect the same malignant tumor, the combined use of DRE and PSA testing affords a more complete evaluation of the prostate gland for malignant involvement.

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INTRODUCTION

Prostate-specific antigen (PSA) is a serine protease isolated from prostatic tissue by Wang et al.[1] in 1979. This unique glycoprotein is specific for, and produced by, all types of prostatic epithelial tissue. Since the initial identification and characterization of this prostatic marker, numerous researchers have investigated the clinical significance of serum PSA concentrations. An increased serum PSA was found to be a more sensitive indicator of prostatic cancer than an increased serum prostatic acid phosphatase, the previous "standard" serum marker for prostatic malignant involvement.[2,3] Thus, serum PSA has replaced serum prostatic acid phosphatase for detecting prostate cancer. Currently, serum PSA is widely accepted in clinical practice as a sensitive marker and has been proposed as a means of monitoring the response of prostate cancer to therapy.[4]

A recent study by Catalona et al. also suggested that measurement of serum PSA is a useful diagnostic tool for detecting prostate cancer.[5] Measurement of serum PSA concentrations has several advantages over rectal examination or transrectal prostatic ultrasonography in screening for prostate cancer and is more acceptable to patients than other screening procedures.[5] In order to determine the predictive significance of PSA and digital rectal examination (DRE) in the diagnosis of prostate cancer, we performed this prospective study.

MATERIALS AND METHODS

Between January 4, 1991 and February 26, 1993, we measured serum PSA in 260 ambulatory men, aged 50 years or over, who had abnormalities at rectal examination involving suspected cancer, signs and symptoms of benign prostatic hyperplasia and equivocal findings on rectal examination, and miscellaneous other conditions, including hematospermia, chronic prostatitis, urolithiasis and microscopic hematuria. Blood samples were withdrawn before biopsy and before or at least 1 week after DRE, since this procedure may raise the serum PSA concentration. PSA was determined by EIKEN PSA radioimmunoassay (EIKEN CHEMICAL CO., LTD., Tokyo, Japan). The normal reference range was 0–4.0 ng/ml. Catalona et al. reported that 67% of men with serum PSA values > 10 ng/ml were found to have prostate cancer.[5] Thus, we have subdivided our patients into 3 groups according to their serum PSA (4.0, 4.0–9.9, ≥ 10 ng/ml, respectively).

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The indications for prostatic biopsy were an abnormal result on DRE or an elevated serum PSA (above 4.0 ng/ml). These patients then underwent transrectal ultrasonography. If a hypoechoic area was found, biopsies were obtained with ultrasound guidance. The patients were given enemas containing sodium phosphate and sodium biphosphate and antimicrobial prophylaxis (oral cefaclor, 250 mg) for three days after biopsy. The biopsy was performed using an automatic biopsy gun (Bard) fitted with an 18-gauge biopsy needle.

Clinical staging consisted of rectal examination, determination of serum prostatic acid phosphatase levels, and radioisotope bone-scanning with confirmatory radiography, if necessary. If the tumor was judged to be confined to the organ, it was described as stage B; if it was judged to have extended through the capsule, but not to have metastasized, it was described as stage C; if it was judged to have metastasized, it was described as stage D. Correlation coefficients were calculated to evaluate the relationship between age, log serum PSA, and the diagnosis of cancer. The chi-squared test was used to compare the incidence of cancer, findings on rectal examination and PSA levels. The sensitivity, specificity, positive and negative predictive values and overall accuracy of the serum PSA measurement and rectal examination as diagnostic tests for prostate cancer were evaluated.

RESULTS

For the 260 men participating in the study, the initial serum PSA values were < 4.0 ng/ml in 238 (92%), 4.0–9.9 ng/ml in 14 (5%), and > 10.0 ng/ml in 8 (3%). Table 1 shows these results together with the age distribution.

A total of 22 men with serum PSA values less than 4.0 ng/ml underwent biopsy when only 1 (4.5%) was found to have prostate cancer. Fourteen men with serum PSA values of 4.0–9.9 ng/ml underwent biopsy and 4 (31%) were found to have prostate cancer. The 8 men with serum PSA values > 10.0 ng/ml underwent biopsy and 5 (63%) were found to have cancer (Table 1). Ten men were diagnosed as having prostate cancer (overall detection rate, 3.8%). Age did not correlate significantly with either serum PSA or the diagnosis of cancer.

Table 2 shows the relationship between the findings on DRE and the diagnosis of cancer. The percentage of men who proved to have cancer and a suspicious DRE was not significant. Table 2 also shows the relationship between serum PSA and the diagnosis of cancer. The finding of a suspicious result was significantly related to cancer ($X^2 = 4.31$, $p = 0.05$). If DRE alone had been used to screen the men who had biopsies, 4 of the 10 cancers (40%) would have been missed. If PSA alone had been used to screen these men, only 1 of the 10 cancers would have been missed.

Table 3 shows the sensitivity, specificity, and overall accuracy of rectal examination and serum PSA measurement. The advantage of the latter as a sole diagnostic test derives from its greater sensitivity, specificity and overall accuracy. Serum PSA measurement also had a higher positive and negative predictive value than DRE.

One man with a serum PSA less than 4.0 ng/ml and normal findings on DRE had stage D2, poorly differentiated, adenocarcinoma. This patient

Table 1. *Serum PSA concentrations and the incidence of cancer in 260 men.*

Age (yrs)	No of men (% of total)	Serum PSA concentration (ng/ml)					
		< 4.0		4.0–9.9		> 10.0	
		No	No with cancer /No with biopsy	No	No with cancer /No with biopsy	No	No with cancer /No with biopsy
50–59	40 (15)	39	0/1	1	0/1	0	0
60–69	100 (38)	91	0/8	4	1/4	5	3/5
70–79	89 (34)	79	1/9	7	2/7	3	2/3
80–90	31 (12)	29	0/4	2	1/2	0	0
All	260	238	1/22	14	4/14	8	5/8

Table 2. *Relationship between the results of rectal examination and PSA and the diagnosis of cancer in men who had prostate biopsies.*

Diagnosis	No of men		Normal		Suspicious	
	Rectal exam.	PSA	Rectal exam.	PSA	Rectal exam.	PSA
Cancer	10	10	4	1	6	9
No cancer	34	34	10	21	24	13

Table. 3. *Accuracy of rectal examination and serum PSA measurement in detecting prostate cancer on first biopsy.*

Measure*	Rectal examination (%)	Serum PSA (%)
Sensitivity	60	90
Specificity	29	62
Positive predictive value	20	43
Negative predictive value	71	95
Overall accuracy	36	68

**Sensitivity was determined by dividing the number of true positive results by the number of true positives plus the number of false negatives, specificity by dividing the number of true negative results by the number of true negatives plus the number of false positives. Positive predictive value was determined by dividing the number of true positive results by the number of true positives and false positives combined. Negative predictive value was determined by dividing the number of true negative results by the number of true negatives and false negatives combined. Overall accuracy was determined by dividing the number of true positive and true negative results by the total number tested.*

underwent biopsy because urinary cytology revealed adenocarcinoma. Four men with serum PSA levels in the range 4.0–9.9 ng/ml had clinical stages B2, D1, D2, and D2. Of 5 men with serum PSA > 10 ng/ml, 3 had disease confined to the prostate, as determined by pathological examination, and the others had metastatic bone cancer. No correlation was found between serum PSA and tumor stage.

DISCUSSION

Our findings suggest that serum PSA measurement is an useful addition to DRE and transrectal ultrasonography for detecting prostate cancer. Although all three tests have the ability to predict cancer, serum PSA was best. For example, among the 10 men in our study group who had cancer, DRE alone would have missed 4 (40%). However, if PSA measurement alone had been used to screen the men who had biopsies, only 1 patient would have been missed.

Serum PSA measurements are sufficiently sensitive to be used alone as a screening test for prostate cancer (Table 3). The specificity of PSA for screening is limited because it is elevated in men with benign prostatic hyperplasia or prostatitis.[3,6] However, PSA, measured in conjunction with DRE, is the tool which allows the urologist to diagnose clinically significant prostate cancer at an early stage. It is likely that PSA will play an important role in identifying men with potentially curable lesions.

Several large-scale studies have been conducted recently examining the role of PSA as a screening test for prostate cancer.[5,7,8] As mentioned in the introduction, Catalona et al. have evaluated 1,653 healthy, asymptomatic men, 50 years of age or over, with the help of their serum PSA concentrations. Thirty-seven were diagnosed as having cancer (overall detection rate, 2.2%).[5]

In addition, Brawer et al., in a study of 1,249 symptom-free men, also 50 years of age or over, without a family history of prostate cancer, identified 32 cases of prostate cancer (detection rate, 2.6%).[7]

Finally, Labrie et al. evaluated the ability of PSA to detect prostate cancer in 1,002 men, 45–80 years of age, who had been selected randomly from the electoral rolls of Quebec City and the surrounding area. Using a cut-off of 3.0 ng/ml (Tandem-R assay), they obtained a 4.6% detection rate.[8]

All these rates are somewhat better than the 1.3–1.5% reported with DRE. In the Catalona study, 32% of cancers identified would have been missed had DRE alone been used and in our own series, 40% of cancers would have been missed if DRE alone had been used for screening. Brawer's group found that 38% of their cancers would not have been detected if DRE had been used. We can conclude, then, that routine PSA testing of men in the age range at risk of developing prostate cancer increases the detection rate of this malignancy.

But PSA is not perfect. This is shown by Catalona's report,[5] in which a comparison group of 300 men underwent prostate biopsy for a variety of clinical conditions, including induration, asymmetry, equivocal DRE, hematospermia, and chronic prostatitis. Serum PSA was measured in 235 of them before biopsy. Cancer was found in 61 (26%) and of these, 13 (21%) had a serum PSA in the reference range (which for the Tandem-R assay is 0.0–3.9 ng/ml). These cancers would not have been identified had PSA been used to select patients for biopsy.

Cooner et al. observed similar findings in a series of 1,807 men, 50–89 years of age, who attended one urology practice for prostate evaluation.[9] Using DRE, PSA, and transrectal ultrasonography, the investigators found cancer in 263 men. Of these, 52 (20%) had a normal serum PSA (measured by Tandem-R assay).

Japanese investigators have demonstrated that mass screening using PSA and DRE in the Gunma Prefecture of Japan is successful in detecting early prostate cancer. The reported detection rate was high.[11]

In the Labrie study,[8] in which all patients were also evaluated using DRE, PSA and transrectal

ultrasonography, 16 of 57 (28%) patients found to have cancer had a serum PSA of 4.0 ng/ml or less. Reliance on serum PSA alone would have meant that these 16 cancers would have gone undetected. In our present study, only 4 of 10 patients with prostate cancer (10%) had a normal PSA level.

The data from these large investigations and our own results indicate that, although PSA can identify more cancers than DRE, not all prostate cancers are associated with an elevated serum PSA. In fact, approximately 20% of all identified prostate cancers are accompanied by a normal serum PSA.

In conclusion, PSA can identify some cancers not detectable by digital rectal examination; conversely, this examination can identify cancers not detectable from the serum PSA concentration. Neither PSA nor DRE is sufficiently sensitive or specific on its own to be an ideal screening test for early prostate cancer. Therefore, cost-effective evaluation of the prostate gland is best achieved when both PSA concentration and DRE are used. Transrectal ultrasonography is more costly and does not contribute appreciably to the detectability when the results of both the DRE and PSA determinations are normal. Transrectal ultrasonography is best reserved for patients who have an abnormal DRE or an increased serum PSA.

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