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Original Paper

Value of PSA (Prostate-specific Antigen) in the Detection of Prostate Cancer in Patients with Urological Symptoms. Results of a Multicentre Study

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The aim of this multicentre study was to assess the usefulness of prostate-specific antigen (PSA) as a diagnostic procedure for prostate cancer in patients with urological symptoms, and compare it with digital rectal examination (DRE). The study included 2054 urological patients, aged over 50 years, and PSA levels were measured using an automated enzyme immunoassay. In the 680 cases with PSA levels >3 μg/l and/or suspect DRE, transrectal ultrasound and prostate biopsy were also performed, leading to a diagnosis of cancer in 131 cases. The sensitivity of PSA was higher (95% and 73% for the cut-off values of 3 and 10 μg/l, respectively) than DRE (69%), both parameters being complementary. When DRE and PSA (>10 μg/l) were combined, 118 cancers were diagnosed, with a PPV of 37%. We recommend using PSA and DRE in combination as a diagnostic procedure for prostate cancer in urological patients, since both methods are complementary. Copyright © 1996 Published by Elsevier Science Ltd

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INTRODUCTION

PROSTATE-SPECIFIC ANTIGEN (PSA) is a glycoprotein with serine protease activity with an approximate molecular weight of 33 kd which, though not specific for prostate epithelial cells, does characterise them [1–3]. Routine PSA measurement has significantly improved the management of patients with prostate cancer, and its value in monitoring response to treatment is incontrovertible [4–5]. However, since not only malignant cells produce PSA, its diagnostic value is still far from being definitive. Nevertheless, in recent years, different authors have reported positive results suggesting that PSA levels are useful as a screening test in prostate cancer [6–9].

The purpose of this multicentre study was to assess the usefulness of PSA as a diagnostic procedure for prostate cancer in patients with urological symptoms, and compare its diagnostic efficacy to that of digital rectal examination (DRE).

PATIENTS AND METHODS

We performed a prospective study in which a total of 19 hospitals participated. 2054 male patients, aged over 50 years, who attended a urology department with or without urinary clinical symptoms, were included in the study; 73% of the patients had clinical symptoms. Patients with a previous history of prostate cancer, clinically suspected acute prostatitis, concomitant severe organic disease, or treated with corticosteroids, anti-androgens or LH-RH analogues within 3 months prior to inclusion were excluded from the study.

Serum levels of PSA were measured and DRE was performed in all patients. In all cases, blood samples were taken prior to DRE. PSA measurements were performed using an automated microparticle enzyme immunoassay in an IMx analyser (Abbott, Chicago, Illinois, U.S.A.). To ensure the quality of the results, external and in-house quality controls

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Table 1. Distribution of patients by age

Age group	Number	%
50–60	526	25.9
61–70	894	42.9
71–80	510	25.1
>80	124	6.1

were performed. The in-house quality control was based on the low and middle controls included in the kit, the mean concentration obtained for each being 4.01 and 15.23 μg/l and the coefficient of variation between centres 5.3 and 4.5%, respectively. The external quality control was performed with two commercial controls (Lyphochek, Biorad, Anaheim, California, U.S.A.), the mean values found for each being 6.63 and 73.9 μg/l, and the corresponding coefficients of variation between centres, 5.09 and 6.89%, respectively. DRE was performed by a urologist in all cases.

Although the definition of the upper normal limit for PSA has been controversial, most authors agree in using 4 μg/l as the normal limit. However, some series report that 6–10% of patients with PSA levels ranging from 3 to 4 μg/l show positive biopsies [7–10]. Therefore, in our study, we used PSA levels above 3 μg/l as the criterion for performing biopsy. Thus, subjects with PSA levels under 3 μg/l and DRE not suspicious of cancer (normal or abnormal, but benign) were not assessed further. Patients with PSA levels from 3 to 4 μg/l underwent a second measurement within 15 days and were assessed subsequently only if the PSA level was again above 3 μg/l. In patients with PSA levels above 3 μg/l and/or suspect DRE, transrectal ultrasound (TRUS) was performed, and a biopsy of the suspect nodes and six randomised biopsies (3 in the right lobe and 3 in the left lobe) were taken in all cases.

PSA density (PSA) was estimated in 488 of the patients who underwent biopsy (93 of the patients with cancer and 395 patients with a negative biopsy). To do this, the prostate volume was calculated from the three diameters of the prostate measured in TRUS. This calculation was performed using the ellipse formula ($L \times W \times H \times 0.5$).

The chi-squared test was used to compare the results qualitatively. The results for the different parameters assessed are expressed in terms of sensitivity and positive predictive value (PPV).

RESULTS

The mean age of the patients was 66.6 years, with a standard deviation of 8.5 and a range of 50–94 years. Table 1 shows the demographics of the study population.

DRE was not suspicious for cancer in 1830 (89.1%) of the patients, while PSA was ≤3 μg/l in 1412 (68.7%) of the cases. Table 2 shows the distribution of the results for PSA and DRE obtained in the total patients. In the 2054 patients studied, one or both tests were positive in 33.1% (680) of the cases, with urinary clinical symptoms in 85%. In 587 of these patients, ultrasonography and biopsy were performed and, therefore, compliance with the protocol was 86%. No biopsy was performed in 4 patients with PSA levels under 3 μg/l (but with positive DRE), in 35 patients with PSA levels from 3 to 4 μg/l (1 with a positive DRE), in 39 patients with PSA from 4.1 to 10 μg/l (4 with positive DRE), and in 15 patients with PSA above 10 μg/l (8 with positive DRE). Prostate cancer was diagnosed in 131 of the patients who underwent biopsy, and the cancer detection rate was 6.27% in the total population.

Table 2. PSA and DRE results in patients included in the study

	Number	%
DRE negative/PSA ≤3 μg/l	1374	66.9
DRE negative/PSA >3 μg/l	456	22.2
DRE positive/PSA ≤3 μg/l	38	1.9
DRE positive/PSA >3 μg/l	186	9.1

Table 3 shows the PSA results in patients who underwent biopsy. Using 3 μg/l as the cut-off value, no significant differences were seen ($P = 0.55$) in the distribution of patients based on the biopsy results. Thus, 95% of patients with a positive biopsy and 94% with a negative biopsy had PSA levels above 3 μg/l. By contrast, the difference was significant ($P < 0.05$) when the cut-off value was set out at 4 μg/l, the level being exceeded by 92% of the patients with a positive biopsy and 84% of those with a negative biopsy. 73% with a positive biopsy had a PSA level above 10 μg/l.

DRE was suspicious in 69% (90/131) of patients with a positive biopsy and in 25% (116/456) of patients with a negative biopsy, with a statistically significant relationship between suspect DRE and cancer ($P < 0.001$).

Table 4 shows the results obtained combining PSA (using different cut-off values) and DRE. The combination of both methods increased the diagnostic sensitivity obtained with either test alone, even when 3 μg/l was used as the PSA cut-off value.

The number of cancers diagnosed, number of negative biopsies, PPV and cancer rate for PSA (cut-off values of 3, 4 and 10 μg/l), DRE and different combinations of both parameters are shown in Table 5. With the diagnostic scheme followed in this study (PSA >3 and/or DRE+), 131 cancers were diagnosed (only 2 more than with the marker PSA >4 and/or DRE+), PPV was 22% and the number of negative biopsies was 456. The highest PPV (70%) was seen for the marker PSA >10 and DRE+, although the same marker showed the lowest number of diagnosed cancers (68).

PSAD exceeded the cut-off value of 0.15 in 86.0% of the patients with prostate cancer, a percentage significantly higher ($P < 0.001$) than the 45.8% of increases seen in the group of patients with a negative biopsy (Table 6), and PPV was 31%. Table 7 shows the results obtained for PSAD in patients with negative DRE and PSA levels ranging from 3 to 10 μg/l. Biopsy was positive in only 3 of the 84 patients with PSAD levels above 0.15, PPV being 3.57%.

Table 3. PSA levels in patients undergoing biopsy

	Biopsy +		Biopsy –	
PSA (μg/l)	Number	%	Number	%
<3.1	6	4.6	28	6.1
3.1–4	4	3.1	45	9.9
4.1–10	25	19.1	271	59.4
>10	96	73.3	112	24.6
Total	131	100	456	100

Table 4. Combined PSA (using cut-off values of 3, 4 and 10 μg/l) and DRE in patients with prostate cancer

DRE	PSA >3	Number	%
–	+	41	31.3
+	–	6	4.6
+	+	84	64.1
Total		131	100
DRE	**PSA >4**	**Number**	**%**
–	+	41	31.3
+	–	10	7.6
+	+	80	61.1
Total		131	100
DRE	**PSA >10**	**Number**	**%**
–	+	28	23.7
+	–	22	18.6
+	+	68	57.6
Total		118	100

Table 5. Results obtained in cancer diagnosis for different markers

	Number of cancers	Negative biopsies	PPV	Prob. cancer rate
PSA >3	125	428	23	6.09
PSA >4	121	383	24	5.89
PSA >10	96	112	46	4.67
DRE +	90	116	44	4.38
DRE + and PSA >4	82	76	52	3.99
DRE + and PSA >10	68	29	70	3.31
DRE + or PSA >3	131	456	22	6.37
DRE + or PSA >4	129	423	23	6.28
DRE + or PSA >10	118	199	37	5.74

PPV, Positive predictive value.

Table 6. PSAD in patients undergoing biopsy

	Positive biopsy		Negative biopsy	
PSA	Number	%	Number	%
≤0.15	13	14.0	214	54.2
>0.15	80	86.0	181	45.8
Total	93	100	395	100

Table 7. PSAD in patients with negative DRE and PSA levels between 3 and 10 μg/l

	Positive biopsy		Negative biopsy	
PSA	Number	%	Number	%
≤0.15	6	66.7	141	63.5
>0.15	3	33.3	81	36.5
Total	9	100	222	100

DISCUSSION

In recent years, several groups have proposed the use of PSA in the diagnosis of prostate cancer and have reported its value as a screening test [6–9]. We performed a multicentre prospective study to assess the diagnostic efficacy of PSA in patients attending a urology outpatient clinic. The characteristics of the study population should, therefore, be noted, and most patients included in our study showed urinary clinical signs.

PSA permits a population at high risk of prostate cancer to be defined. Therefore, using the cut-off value of 3 μg/l established for PSA in our protocol, we selected a population of 553 patients, of which 125 were diagnosed with prostate cancer; PPV was therefore 23%. This result is consistent with that reported by Labrie and colleagues [7] who found a PPV of 24% using the same cut-off value.

PSA is an antigen produced mainly by the prostate gland, and is particularly increased in the presence of prostate cancer. However, it is not a cancer-specific antigen, and levels above the normal limits of 4 μg/l may be seen in benign prostate hyperplasia (BPH). 25–50% of patients with BPH show abnormal PSA values. For this reason, some authors have agreed to using a cut-off value of 10 μg/l to increase the specificity of the test [11–14].

False positives caused by BPH were also seen in our study, since 73% of the total patients and 85% of the patients who underwent biopsy showed urinary clinical signs. This translates into both the number of negative biopsies and in the PPV of PSA. Thus, the number of negative biopsies for cut-off values of 3, 4 and 10 μg/l were 428, 383 and 112, respectively, and the corresponding PPVs were 23, 24 and 46% respectively. However, the possibility that some patients with high PSA levels and a negative biopsy have prostate cancer cannot be ruled out, as recently pointed out by Gann and colleagues [15]. Therefore, following the recommendations of Carter and coworkers [16], we plan to perform a half-yearly follow-up by PSA measurement in patients with a negative biopsy, and to perform a biopsy in patients in which PSA increases by more than 0.75 μg/l every year.

The second objective of our study was to compare the diagnostic sensitivity of PSA and DRE. DRE allowed us to diagnose a remarkably lower number of cancers than PSA. Thus, DRE was suspicious for cancer in only 90 of the patients in whom biopsy was positive, 35 less than with the use of PSA, and therefore, sensitivity was 69%. Similarly, our data suggest that PSA is more sensitive than DRE even when cut-off values of 4 and 10 μg/l are used, levels for which we obtained a sensitivity of 92 and 73%, respectively. At the same time, the results obtained in our study showed that PSA and DRE were complementary in the diagnosis of prostate cancer, even when the 3 μg/l level was considered as the diagnostic cut-off value for PSA. Thus, DRE permitted us to diagnose cancer in 6 patients in which PSA was lower than 3 μg/l.

The study of the number of cancers diagnosed and PPV is particularly interesting when comparing the diagnostic value of the different cancer markers. According to the data

obtained in our study, the risk for prostate cancer was 6.37% in the study population. However, when PSA was above 3 μg/l, the PPV increased to 23%, and reached 46% when PSA exceed 10 μg/l. PSA and DRE in combination allow us to increase the PPV, although a parallel decrease was seen in the number of diagnosed cancers. Thus, when PSA was higher than 10 μg/l and DRE was suspicious, PPV was 70%.

The results support the use of biopsy in patients with PSA levels above 10 μg/l or with a suspect DRE. With these cancer markers, we diagnosed 118 tumours; the number of negative biopsies was 199, and PPV was 37%. In addition, we think that biopsy is not warranted in patients with PSA levels ranging from 3 to 10 μg/l and non-suspect DRE, since the diagnostic efficacy does not increase remarkably. Thus, of the 270 biopsies performed in patients with PSA levels of 3–10 μg/l and a negative DRE, only 13 (5%) were positive. Again, we must emphasise that our results were obtained in patients attending a urology clinic and, therefore, the conclusions drawn from our study canot be extrapolated to recommend or discourage a screening programme, in which the percentage of negative biopsies in patients with PSA under 10 μg/l would obviously be lower. Thus, Brawer and coworkers [8] diagnosed prostate cancer in 14% of patients with negative DRE and PSA ranging from 4 to 10 μg/l.

Most patients with prostate cancer limited to the gland show PSA levels under 10 μg/l. In order to increase PSA specificity, Benson and colleagues [17–18] have suggested adjusting the serum PSA concentration to the prostate volume, establishing the concept of PSAD. The PPV of PSAD obtained in our series was 31%, lower than that obtained for the cut-off value of 10 μg/l for PSA. This is also reflected in the scant information it provides for the group of patients with PSA levels ranging from 3 to 10 μg/l and a negative DRE. PSAD was calculated in 231 of these patients, and 84 of them had levels above 0.15; the biopsy was positive in only 3 cases and PPV was 3.57%.

The PSAD results reported in this study are different from those given by the group of Benson and coworkers [17–18], who reported a high specificity for this parameter. In our series, 45.8% of the patients with a negative biopsy showed PSAD levels above 0.15. The differences between both studies may be due to a different composition of the series studied. The PSAD value is related both to the prostate volume and the presence of complications (acute urinary retention or urinary infection) associated with BPH. One of the groups participating in this study [19] has recently reported a different PSAD specificity, depending on whether there were BPH complications or not (60 versus 97%). This stresses the importance of excluding patients with complicated BPH to increased PSAD specificity, so that it can be considered as a useful parameter for the diagnosis of prostate cancer in patients with PSA lower than 10 μg/l. The recent description of free PSA, which can supplement the diagnostic efficacy of PSA according to preliminary results [20], points in the same direction.

The results obtained in this study support the combined performance of DRE and PSA as diagnostic tests in prostate cancer. These procedures allow a group of patients with a high risk of cancer to be defined. We think that, based on the results obtained, we must recommend the use of a cut-off value of 10 μg/l of PSA as the diagnostic threshold for prostate cancer in urological patients. This does not rule out the use of other lower levels of PSA when screening studies are performed in a healthy population. In the group of patients with PSA levels lower than 10 μg/l and a negative DRE, we have no method available to select a group of patients with a high risk of prostate cancer. The results for PSAD obtained in this study are disappointing, and only a prior selection of patients with uncomplicated BPH could, perhaps, increase its diagnostic efficacy. However, the preliminary results obtained with the free PSA/total PSA ratio are pending confirmation. This would be an important advance in the diagnosis of prostate cancer, in general, and particularly for the group of patients with PSA levels lower than 10 μg/l and negative DRE.

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