Large-Scale Study of Clinical Impact of PSA Velocity: Long-Term PSA Kinetics as Method of Differentiating Men with from Those without Prostate Cancer

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OBJECTIVES To assess the longitudinal prostate-specific antigen (PSA) changes in a screening population with or without prostate cancer during a 10-year period.

METHODS Serial PSA measurements performed during a 10-year period were evaluated in 4272 participants of a screening program who had no evidence of prostate malignancy and 528 men who eventually developed prostate cancer.

RESULTS Of the 4272 men with no evidence of prostate cancer, the mean total PSA level increased from 1.16 to 1.49 ng/mL during the 10 years, corresponding to a PSA velocity (PSAV) of 0.03 ng/mL/yr. Younger men had lower total PSA values throughout the 10-year period. Of the 528 patients with prostate cancer, the total PSA level increased from 2.19 at 10 years before diagnosis to 6.09 ng/mL at the time of positive biopsy findings, corresponding to a PSAV of 0.39 ng/mL/yr. The PSAV increased in the years before diagnosis (0.225 ng/mL/yr in the 8 to 10 years before diagnosis compared with 0.98 ng/mL/yr in the 2 years before diagnosis). The PSAV was greater in patients with Stage pT3-T4 cancer than in men with organ-confined tumors (median 0.53 versus 0.32 ng/mL/yr; $P < 0.001$).

CONCLUSIONS In men with prostate cancer, the PSAV was significantly greater than in those without prostate cancer and correlated with pathologic stage and Gleason score but not with prostate volume. In the patients with prostate cancer, the PSAV increased in the years before the diagnosis. In contrast, men without prostate cancer had only slight PSA changes over time. Hence, PSA kinetics may help identify men with potentially curable prostate cancer. UROLOGY 69: 134–138, 2007. © 2007 Elsevier Inc.

Prostate-specific antigen (PSA) has been widely used to screen for prostate cancer. As a result, the number of prostate cancer cases detected at an advanced stage has decreased.[1] Thus, metastatic prostate cancer has practically been eliminated by annual PSA screening.[2] However, the PSA threshold that warrants additional evaluation is still a matter of discussion. The use of percent-free PSA has been shown to help avoid 20% of unnecessary biopsies in men with elevated PSA levels.[3] Nevertheless, more than one half of the men with PSA levels exceeding the threshold—whether 4.0 ng/mL or less—will be subjected to unnecessary biopsy. The use of age-related PSA cutoff values has resulted in a dramatic increase in the number of men undergoing prostate biopsy, and the costs for cancer detection have risen correspondingly.

It has been shown that single PSA values lack sensitivity and specificity for prostate cancer detection. The PSA velocity (PSAV) has been reported to constitute a potential clinical marker for prostate cancer.[4–6]

A high preoperative PSAV has been shown to be associated with a greater risk of death from prostate cancer and is of great prognostic relevance if it increases in the years before diagnosis.[7] A major goal of the present study was to use the PSAV to identify men whose cancer was likely to be localized and thus curable by radical prostatectomy.

To date, only a few, long-term studies have compared the PSAV in men with no evidence of prostate cancer with that in men who eventually develop prostate cancer. The present study is the largest to date to evaluate

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Submitted: April 13, 2006, accepted (with revisions): September 7, 2006

0090-4295/07/$32.00
doi:10.1016/j.urology.2006.09.018

Table 1. Longitudinal changes in tPSA

Prostate Cancer	Year 0	Year 2	Year 4	Year 6	Year 8	Year 10
No (n)	4.272	4.272	4.272	4.272	4.272	4.272
tPSA (ng/mL)						
Mean	1.16	1.27	1.34	1.38	1.47	1.49
Median	0.9	0.9	0.9	1	1.04	1.09
SD	0.97	1.13	1.23	1.32	1.35	1.31
25th percentile	0.6	0.6	0.6	0.6	0.62	0.64
75th percentile	1.4	1.5	1.7	1.7	1.8	1.9
Yes (n)	48	228	528	528	528	528
tPSA (ng/mL)						
Mean	2.19	2.33	2.62	3.26	4.14	6.09
Median	1.85	1.7	2	2.55	3.4	4.68
SD	1.63	1.97	2.04	2.37	2.9	5.02
25th percentile	1	1.2	1.3	1.7	2.2	3.07
75th percentile	3	3	3.3	4.2	5.2	7.32

tPSA = total prostate-specific antigen.

PSA changes during a 10-year period in men who were eventually diagnosed with prostate cancer. In addition, the differences in PSA kinetics between those with and without cancer were assessed.

MATERIAL AND METHODS

The present retrospective study included 4272 subjects without malignancies undergoing PSA testing at least every second year over a total period of 10 years and 528 men who underwent PSA testing over 6 to 10 years (minimum: 6) and were eventually diagnosed with prostate cancers.

In 1993 a mass screening project using PSA as the only screening test was launched in the Federal State of Tyrol, Austria. From 1988 to 1992 both PSA and digital rectal examination (DRE) had been used in the diagnostic workup of patients with suspected prostate cancer and occasionally of asymptomatic men as well. Age-referenced PSA levels,[8] combined with a percent-free PSA of less than 22%, were used as biopsy criteria. Since October 1995, bisected PSA levels have been used, together with a percent-free PSA of 18%.[9] In addition, patients with PSA levels greater than 10 ng/mL or suspicious findings on digital rectal examination were advised to undergo biopsy.

The serum total (tPSA) and percent-free PSA levels were assessed using the Abbott IMx Immunoassay (Abbott Laboratories, Abbott Park, Ill).

Patients with a history of prostate surgery, men taking 5-alpha-reductase inhibitors, and those undergoing chemotherapy were excluded from the study.

The data are expressed as the mean ± standard deviation, median, and 25th and 75th percentiles. $P < 0.05$ was considered statistically significant. We compared the PSAV and tPSA between two groups using the Mann-Whitney *U* test and between more than two groups using the Kruskal-Wallis test. The Statistical Package for Social Sciences for Windows, version 11.5, software (SSPS, Chicago, Ill) was used for all analyses.

RESULTS

The study group included 4272 men with no evidence of prostate cancer (median age at most recent visit 65.9 years, range 40 to 94) and 528 patients with cancer (median age at cancer diagnosis 61.4 years, range 41 to 94). Of the 528 men eventually diagnosed with prostate cancer, the tPSA values were available for the 10 years before diagnosis for 46, for 8 years for 228, and for 6 years for 252 patients.

In men with no evidence of prostate cancer, the mean tPSA increased from 1.16 ± 0.97 ng/mL (25th percentile 0.60, 75th percentile 1.40) to 1.49 ± 1.31 ng/mL (25th percentile 0.64, 75th percentile 1.90) during the 10-year period (Table 1), corresponding to a PSAV of 0.03 ng/mL/yr (Fig. 1A). Younger men had significantly lower tPSA values throughout the 10-year period: mean 0.89 in year 1 and 1.22 in year 10 for the 674 men 45 to 50 years old at the initial PSA measurement (PSAV 0.033 ng/mL/yr), 1.06 to 1.45 ng/mL/yr for the 1954 men 50 to 60 years old (PSAV 0.039 ng/mL/yr), and 1.48 to 1.77 ng/mL/yr for the 1160 men aged 60 to 70 years (PSAV 0.029 ng/mL/yr). However, the PSAV was equal in the different age groups (Fig. 1B). No difference was found in the PSAV in those men without evidence of malignancy and initial tPSA values of 4 to 10 ng/mL compared with those with initial tPSA values of less than 4 ng/mL. In men without prostate cancer, no differences were found for percent-free PSA, although a trend was noted for increased levels with advancing age.

After 10 years, of the 4272 men, 2910 (68.1%) had greater tPSA values than at baseline, 58 (1.4%) had unchanged tPSA levels, and 1304 (30.5%) had lower tPSA values. In 216 men (5.1%), a single value was found during the 10-year period that was at least twice as high as the second greatest value.

In men with prostate cancer, the mean tPSA increased from 2.19 ± 1.63 ng/mL (25th percentile 1.0, 75th percentile 3.0) at 10 years before the diagnosis to 6.09 ± 5.02 ng/mL (25th percentile 3.07, 75th percentile 7.32) at positive biopsy (Table 1), corresponding to a PSAV of 0.39 ng/mL/yr (Fig. 1A). The median tPSA increased from 1.8 ng/mL at 10 years before the diagnosis to 4.7 ng/mL at positive biopsy.

Of the 528 patients with biopsy-proven prostate cancer, 366 underwent radical prostatectomy (RRP) and 162

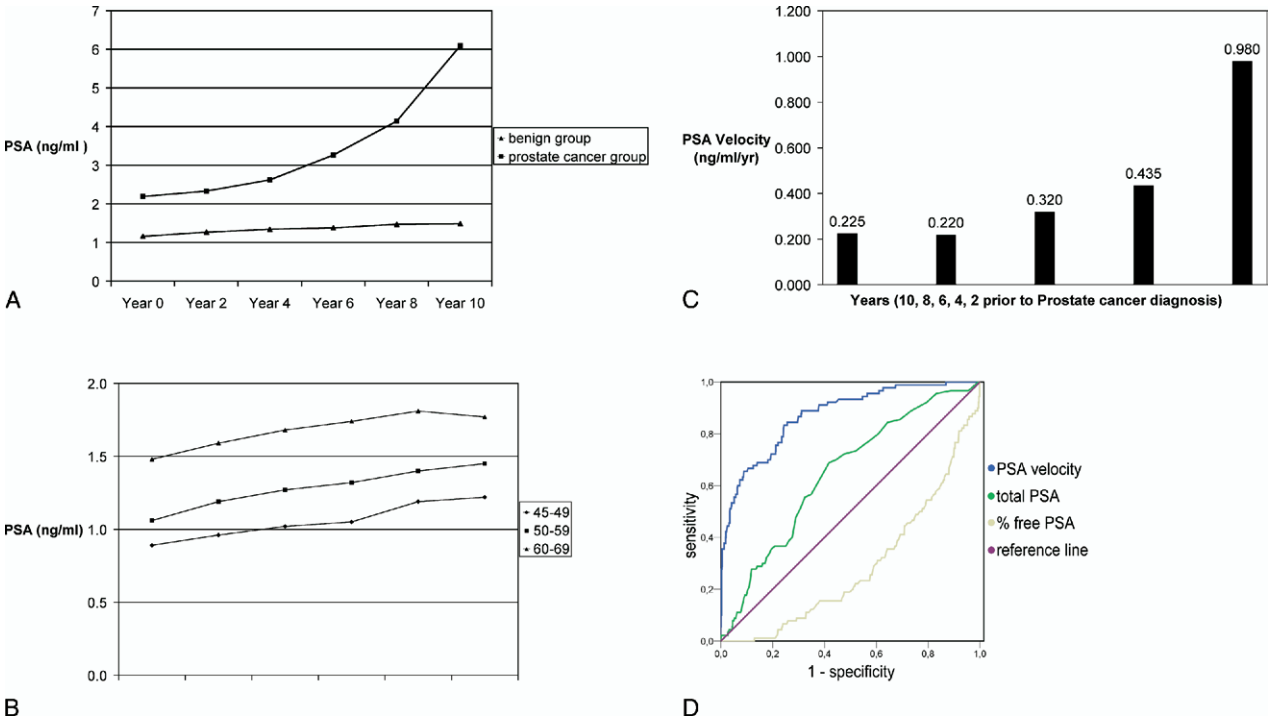

Figure 1. **(A)** PSAV increased significantly in patients with prostate cancer compared with those without prostate cancer. Mean tPSA values were greater in patients with prostate cancer than in those with benign glands at any time in the study. **(B)** In men with benign prostates, tPSA values increased with age (45 to 49 years, n = 674; 50 to 59 years, n = 1954; 60 to 69 years, n = 1160). However, PSAV remained constant (45 to 49 years, PSAV 0.033 ng/mL/yr; 50 to 59 years, PSAV 0.039 ng/mL/yr; 60 to 69 years, PSAV 0.029 ng/mL/yr). **(C)** In patients with prostate cancer, PSAV increased in years before prostate cancer diagnosis. **(D)** Receiver operating characteristic curve analysis for PSAV compared with tPSA and percent-free PSA (area under the curve [AUC] for PSAV 0.872; AUC for tPSA 0.646; AUC for percent-free PSA 0.287).

underwent other treatment modalities (external beam radiotherapy, brachytherapy, androgen deprivation, no active treatment). Of the 528 patients undergoing RRP, 420 (79.5%) presented with organ-confined disease and 108 (20.5%) had Stage pT3 or pT4. Of the 173 men with a tPSA value of 4 ng/mL or less at surgery, 152 (87.9%) had organ-confined disease. Of the 30 men with a tPSA value of 2 ng/mL or less, 28 (93.3%) had organ-confined disease and 2 had Stage pT3.

Also, 73.2% of patients undergoing RRP had organ-confined disease and a mean PSAV of 0.4 ng/mL/yr or more for 6 years before diagnosis compared with 69.6% with a mean PSAV of 0.5 ng/mL/yr or more for 6 years.

An increase in PSAV was observed in the years before diagnosis. The PSAV was 0.225 ± 1.26 ng/mL/yr (25th percentile 0.0, 75th percentile 0.65) 8 to 10 years before diagnosis; 0.220 ± 1.18 ng/mL/yr (25th percentile 0.0, 75th percentile 0.80) 6 to 8 years before positive biopsy; and had increased to 0.320 ± 1.14 ng/mL/yr (25th percentile 0.1, 75th percentile 1.1) 4 to 6 years before cancer diagnosis. At 2 to 4 years before diagnosis, the PSAV was 0.435 ± 1.49 ng/mL/yr (25th percentile 0.2, 75th percentile 1.5). However, in the 2 years before diagnosis, the PSAV was 0.98 ± 3.29 ng/mL/yr (25th percentile 0.5, 75th percentile 2.32; Fig. 1C).

In patients with organ-confined disease, the median tPSA was significantly lower than in those with non-organ-confined disease (median 4.83 versus 6.68 ng/mL, respectively, $P < 0.05$), not only at surgery, but also 6 years earlier (2.25 versus 2.93 ng/mL, respectively, $P < 0.05$).

The PSAV measured during the 6-year period was significantly greater in patients with Stage pT3-pT4 disease than in those with organ-confined disease (median 0.53 versus 0.32 ng/mL/yr, respectively, $P < 0.001$).

In patients with cancer, the PSAV was significantly associated with tPSA. In men with a tPSA level of 0 to 2 ng/mL at 6 years before the diagnosis, the PSAV was 0.44 ng/mL/yr versus 0.57 ng/mL/yr in men with a tPSA level of 2 to 4 ng/mL. In men with a tPSA level of more than 4 ng/mL, the PSAV increased to 0.97 ng/mL/yr ($P < 0.01$). The likelihood of presenting with a PSAV of more than 2 ng/mL/yr was 9.1% in men with an initial tPSA level of more than 4 ng/mL compared with 1.8% in men with an initial tPSA level lower than 4 ng/mL.

Of the patients with cancer, 58.9% had a Gleason score of 6 or less at biopsy, 29.2% had a Gleason score of 7, and 11.9% had a Gleason score of 8 or more. The tPSA level was lowest in patients with a Gleason score of 6 or less and greatest in those with a Gleason score of 8 or worse (at diagnosis, median 5.13 versus 6.77 versus 9.36, respectively, $P < 0.05$). A similar trend was also observed 6 years before positive biopsy (median 2.43 versus 2.80 versus 2.99, $P = 0.85$). In the 6 years before

Table 2. Performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value for different PSAV thresholds)

PSAV Cutoff (ng/mL/yr)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.03	0.998	0.856	0.691	0.995
0.3	0.642	0.946	0.691	0.934
0.4	0.53	0.978	0.82	0.912
0.5	0.437	0.986	0.849	0.904
0.75	0.264	0.998	0.964	0.879

PSAV = prostate-specific antigen velocity; PPV = positive predictive value; NPV = negative predictive value.

diagnosis, the PSAV was significantly different among the three groups (median 0.34 versus 0.46 versus 0.74 ng/mL/yr, respectively, $P < 0.001$).

The patients undergoing RRP were stratified into three groups according to their prostate volume (less than 30, 30 to 60, and more than 60 cm^3). The PSAV for the 6 years before cancer diagnosis did not significantly correlate with the prostate volume, although a trend was noted for an increased PSAV in patients with large prostates (corresponding PSAV 0.33 versus 0.38 versus 0.48 ng/mL/yr, respectively, $P = 0.06$).

The sensitivitiy, specificity, and positive and negative predicive values for the selected PSAV thresholds are given in Table 2. The area under the curve for PSAV was significantly greater than for the total PSAV or percent-free PSA (Fig. 1D).

COMMENT

The present study is the largest analysis to date of longitudinal PSA changes in men with or without prostate cancer. It has been demonstrated that in men with prostate cancer, the PSAV is clearly greater than in those without cancer.

In men with no evidence of prostate cancer, the annual PSAV was 0.03 ng/mL/yr, slightly lower than that reported by investigators of smaller studies.[10] In fact, 30.5% of all subjects in the benign group had lower PSA values 10 years after the initial PSA measurement. This implies that patients with significant increases in PSA over time should be followed up closely. In contrast, in 216 men (5.1%), a single value was found during the 10-year period that was at least twice as high as the second highest value, indicating that elevated PSA levels may also result from infection, instrumentation, digital rectal examination, or recent ejaculation. Obviously, several PSA measurements for a longer period allow for more accurate determination of PSA kinetics than two or three tPSA values obtained within a short period.

Of note is the increase in PSAV observed in the years before the diagnosis of prostate cancer. This parameter seems to have significant clinical implications, as was shown by D'Amico and coworkers,[7] who demonstrated that men whose PSA levels increased by more than 2.0 ng/mL in the year before the diagnosis of prostate cancer might have a relatively high risk of death from prostate cancer despite RRP. This implies that a high PSAV before diagnosis may be associated with an increased likelihood of incurable prostate cancer. Consequently, it seems important to detect prostate cancer at a stage at which the PSAV is still low.

The PSAV correlated significantly with the tPSA levels. Men with a high initial tPSA value were significantly more likely to have a greater PSAV than those who had a low level. In the group with an initial tPSA level of more than 4 ng/mL, the likelihood of a PSAV of more than 2 ng/mL/yr was five times greater than in the group with an initial level of less than 4 ng/mL. This suggests that PSAV should be related to the initial tPSA levels.

In the present study, a significant difference in PSAV was found between patients with organ-confined disease and those with non-organ-confined disease (0.32 versus 0.53 ng/mL/yr during the 6-year period before diagnosis). Of all men undergoing RRP, 79.5% had pT2 disease, indicating that a significant number of patients have non-organ-confined prostate cancer. Even in the 173 patients with a tPSA value of 4 ng/mL or less at surgery, 21 (12.1%) had pT3 or pT4 disease. If a lower PSAV had been used, these cancers might have been detected at a stage at which they were still surgically curable. The present data have demonstrated that in our screening population, the PSAV starts to increase at about 6 years before the cancer diagnosis. The question is whether the 20.5% of non-organ-confined cancers could have been detected at a potentially curable time if the PSAV of 0.435 ng/mL/yr at 2 to 4 years before positive biopsy had been used. Only 73.2% of patient undergoing RRP had organ-confined disease when the mean PSAV was 0.4 ng/mL/yr or less in the 6 years before the diagnosis of prostate cancer. We, therefore, have concluded that a mean PSAV of 0.4 ng/mL/yr or more during a 3-year period or longer may indicate the presence of tumor and thus warrants biopsy. However, not only the pathologic stage, but also the Gleason score, seems to have a significant impact on PSAV. An increased PSAV was associated with worse Gleason scores. In the present study, patients with a Gleason score of less than 7 had lower PSAV (0.34 ng/mL/yr) than those with Gleason score 7 (PSAV 0.46 ng/mL/yr) and those with a Gleason score of 8 or more (PSAV 0.74 ng/mL/yr).

In contrast, the prostate volume was not significantly associated with the PSAV. The main factor contributing to the PSAV in patients with prostate cancer seems to be cancer load. The PSAV may help identify patients with small tumors and thus increase the detection rate of potentially curable prostate cancer.

A potential limitation of the present study was that the biopsy criteria at our institution were changed in 1995. This could have resulted in delayed cancer detection in some patients and thus a greater tumor volume at diagnosis. Moreover, the present data were assessed in a

screening population, and the findings may not be valid in patients from referral populations. The results of the present study may not be representative of other ethnic groups, because all participants were whites. Some evidence has shown that the prevalence of prostate cancer and the propensity for more advanced stages at diagnosis are greater in black men.[11] With regard to cancer curability, a striking difference was found between black and white men with tPSA levels greater than 5.0 ng/mL, although the cure rates were comparable for both groups if the tPSA level was 4.0 ng/mL or less.[12]

CONCLUSIONS

In a screening population, the PSAV was significantly greater in the patients with prostate cancer than in the men without prostate cancer and correlated with the pathologic stage and Gleason score, but not the prostate volume. In patients with prostate cancer, the PSAV increased in the years before diagnosis. Although men without prostate cancer had only slight PSA changes, younger men had significantly lower tPSA values than did older subjects. Hence, PSA kinetics may help identify men with potentially curable prostate cancer.

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