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ORIGINAL ARTICLE

PSA velocity and PSA slope

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The aim of this study is to compare different tools for evaluating prostate-specific antigen (PSA) increase or decrease, such as PSA velocity and PSA slope. This study was conducted on 312 male patients evaluated with transrectal ultrasound-guided biopsy of prostate with six or more cores. Patients with at least three consecutive PSA measurements in at least 18 months entered the study. Prostate-specific antigen slope was estimated by the slope of the least-square regression line fit to PSA versus time in years; PSA velocity was calculated with 3 or more PSA arrays. Median age was 66 years (range 45–86). Overall 67 patients were affected by primary prostate cancer, 245 were controls without prostate cancer. Prostate-specific antigen slope and PSA velocity were significantly higher in patients with prostate cancer than in controls. At the ROC analysis, PSA slope evidenced better results than PSA velocity (area under the curve (AUC) 0.743 for PSA slope; AUC 0.663 for PSA velocity; $P = 0.037$). At PSA slope (calculated with the least-square fit) equal to zero, the sensitivity resulted as being 94% with a specificity of 38.8%. In conclusion prostate-specific antigen slope calculated with three or more PSA assays permits longitudinal evaluation of PSA for prostate diagnosis. Prostate-specific antigen slope improves both sensitivity and specificity in prostate cancer diagnosis, compared with PSA velocity.
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Introduction

Prostate cancer will become a social emergency in the near future in Western countries because it is one of the leading causes of cancer death, and because it tends to increase with age more rapidly than many other malignancies. However, the conventional strategy for prostate-specific antigen (PSA) screening, which calls for biopsies in all men with total PSA (tPSA) greater than 4 ng/ml, leads to many false-positive results and is thus associated with a high cost in terms of unnecessary biopsies.[1]

The cost is not only economic but also psychological and emotional as anxiety on the part of the patient and his family can be of considerable detriment to his well being. Considerable efforts are currently under way to improve biopsy performance, and emphasis has been directed primarily at enhancing specificity by reducing false-positive results. The slow-growing and indolent nature of prostate cancer, coupled with the fact that a man will probably be tested more than once in his lifetime, makes a false-negative test of less importance.[2]

In general, whenever efforts are made to enhance the specificity of a diagnostic test, the sensitivity (the identification of patients with the disease in the population) is reduced.[3,4] This inverse relationship of sensitivity and specificity assesses that increasing the PSA threshold enhances specificity, but does so only with a reduction in sensitivity.[5] A lot of methods have been used to enhance the specificity of PSA: PSA velocity, PSA density, PSA transition-zone density, age-specific PSA level, ratio of free PSA (fPSA) to tPSA, level of alfa1-antichymotrypsin complex PSA [5] and artificial neural network.[6]

Carter defined the method for PSA velocity calculation.[7] Despite early enthusiasm for PSA velocity, the enhanced performances suggested by the initial investigators may not be reproducible.[2,8] D'Amico utilised linear regression analysis for PSA evaluation during the year before prostate cancer diagnosis, and he found that it correlated with the risk of death from prostate cancer.[9] The PSA slope of the regression line expresses the change in PSA level per year. Prostate-specific antigen slope has the same unit as that of PSA velocity, but the computation method is completely different, because PSA slope is estimated using linear regression analysis. To our knowledge, no study tested PSA slope for prostate cancer diagnosis. The aim of our study was to compare different tools for evaluating PSA increase or decrease, such as PSA velocity and PSA slope.

Materials and methods

Between January 2001 and June 2005, all men who underwent transrectal ultrasound-guided prostate biopsy

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with six or more cores and with at least three consecutive PSA measurements (carried out in our centralised laboratory) in 547 or more days before biopsy entered the study. Men with PSA interference such as 5-alfa reductase therapy (finasteride or dutasteride) or acute prostatitis were excluded.

All patients were scheduled for transrectal sonography with biopsy because of abnormal digital examination findings and/or PSA levels of 4 μg/l or greater. Three hundred and twelve men entered the study.

All patients provided written informed consent. Antibiotic prophylaxis was orally administered on the day before biopsy and continued for some days after. The patients were examined in the left lateral decubitus position. All examinations were performed using the diagnostic Ultrasound System Leopard 2001 (B&K Medical, Denmark). Grey-scale ultrasonography was carried out with a 7.5 MHz endosonic multiplane transducer (type 8551, B&K Medical).

Serum was obtained before any diagnostic procedure. Both total immunoreactive PSA and fPSA were assayed using the chemiluminescent immunoassay Immulite (Diagnostic Products Corp., Los Angeles, CA, USA), in accordance with the manufacturer's instructions. The assays are solid-phase, two-site, sequential chemiluminescent immunometric tests that are automatically performed on an automated analyser with detection limits of 0.02 and 0.03 μg/l for fPSA and tPSA, respectively. We included PSA measurements carried out before 2001 if they were assayed in our centralised laboratory with the Immulite technique.

Percentage of fPSA was calculated as the ratio of fPSA to tPSA multiplied by 100. Prostate-specific antigen density was calculated as the PSA value divided by the transrectal ultrasound estimated prostate volume. The PSA slope was obtained fitting the line of least squares (PSA versus time) for each patient.

Specifically, we fit the equation: $y = a + bx$ to the data of each patient. Here y symbolises PSA and parameter a is the intercept. Parameter b is the slope and reflects the increase of PSA in 1 year.[9]

The PSA velocity was calculated according to the indication of Khan and Carter; for instance, with three PSA, the equation is 0.5 {[(PSA_2−PSA1)/(elapsed time in years)] + [(PSA3−PSA2)/(elapsed time in years)]}, where PSA1 is the first of the three measurements, PSA2 the second and PSA3 the third; elapsed time refers to time between the two measurements.[10,11] Only PSA measurements with a time interval, from the previous, more than 6 months were considered for PSA velocity elaboration.

Mann–Wintney *U*-test was used to assess the differences between groups (Statistica 6.0). Total PSA and percent fPSA were evaluated. The receiver operating characteristic (ROC) curve was generated by plotting sensitivity versus 1-specificity (MedCalc 7.0). We compared results by comparing the area under the curves (AUCs) according to Hanley and McNeil.[12,13]

Results

The median PSA before biopsy was 7.1 (range 0.74–47.2 μg/l). Median PSA was 6.8 in controls and 8.01 in patients with prostate cancer. Table 1 shows the clinical characteristics of the 312 men. Briefly, median age was 66.3 years (range 45–86). We elaborated 1726 PSA measurements, from 3 to 28 in each men. The median interval of time between the first and last PSA assay was 959 days (range 547–3723).

Median PSA slope was 0.403 ng/ml/year (range −8.7 to 18.07). For PSA velocity calculation, only PSA measurements with a time interval from the previous more than 6 months were considered. This explain why in 13 cases the PSA velocity could not be evaluated, because interval between PSA assays was <6 months (e.g. case C.A., three PSAs assayed at day 0, 84, 720). The median PSA velocity was 0.27 ng/ml/year (range −12.84 to 15.31).

One hundred and thirty seven (43%) men with a first negative biopsy were re-biopsied. A total of 67 cancers were found at the ultrasound-guided prostate biopsies.

In Figure 1 we report the case of a man with elevated PSA slope (0.559 ng/ml/year), but a low PSA velocity (−1.438 ng/ml/year); he underwent sextant biopsy with finding prostate cancer T1cN0M0G6 (3 + 3). We report this case to illustrate the linear regression fit.

Prostate-specific antigen slope and PSA velocity were significantly higher in patients with prostate cancer than in controls.

Table 1 Descriptive statistics of 312 men

	All		*Prostate cancers*		*Controls*		P-*value*
	No.	*Median (range)*	*No.*	*Median (range)*	*No.*	*Median (range)*	
Age (years)	312	66.3 (45.2–86.8)	67	66.6 (50.1–82.4)	245	66.2 (45.2–86.8)	0.83
PSA (ng/ml)	312	7.17 (0.74–47.2)	67	8.01 (3.2–47.2)	245	6.86 (0.74–35.2)	0.035*
free-to-total PSA (%)	266	16.6 (4.05–41.8)	58	11.9 (4.17–35.76)	208	18.3 (4.05–41.8)	0.000000001*
Days between first and last assays	312	959 (547–3723)	67	804 (547–3723)	245	982 (547–3476)	0.40
Numbers of PSA assays for patient	312	5 (3–28)	67	5 (3–12)	245	5 (3–28)	0.29
PSA velocity (ng/ml/year)	299	0.27 (−12.84–15.31)	59	0.73 (−12.84–15.29)	240	0.09 (−8.5–15.3)	0.0001*
PSA slope (least-squares fit) (ng/ml/year)	312	0.403 (−8.7–18.07)	67	0.87 (−0.53–18.07)	245	0.20 (−8.7–6.67)	0.000000002*
PSA intercept	312	6.12 (−294.2–169.67)	67	5.56 (−58.3–19.05)	245	6.2 (−294–169)	0.12
Prostate volume (cm^3)	225	50 (10–151)	47	40 (10–130)	178	52.9 (22–151)	0.0000013*
PSA density	225	0.153 (0.021–1.01)	47	0.236 (0.062–1.01)	178	0.14 (0.02–0.70)	0.0000017*
Transition zone volume (cm^3)	143	32.3 (4–110)	34	15.6 (7.4–60)	109	35.2 (4–110)	0.0000010*
PSA trasition zone density	143	0.265 (0.037–1.3)	34	0.481 (0.076–1.3)	109	0.23 (0.037–1.3)	0.000054*

Abbreviation: PSA: prostate-specific antigen.
The last column reports *P*-value of differences between controls and prostate cancers (Mann–Wintney *U*-test), *P<0,05.

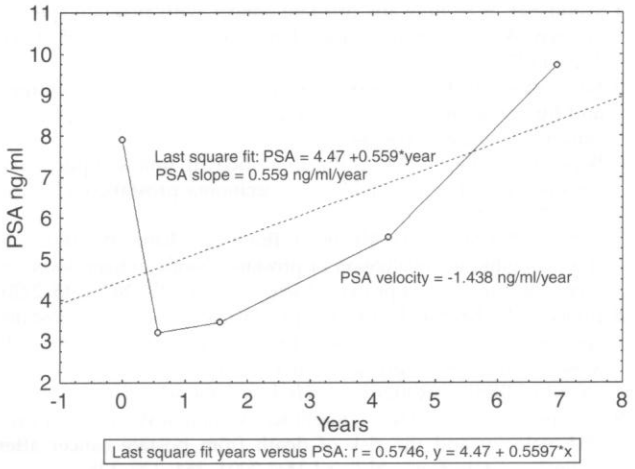

Figure 1 An example of prostate-specific antigen (PSA) velocity and PSA slope. The point is the PSA values, the line is the least-squares fit of these 5 point (PSA = 13.45–3.36 × *t*) and the broken line is the PSA velocity = −1.438 ng/ml/year. Patient G.C. 66 years, prostate cancer T1cN0M0G6(3 + 3).

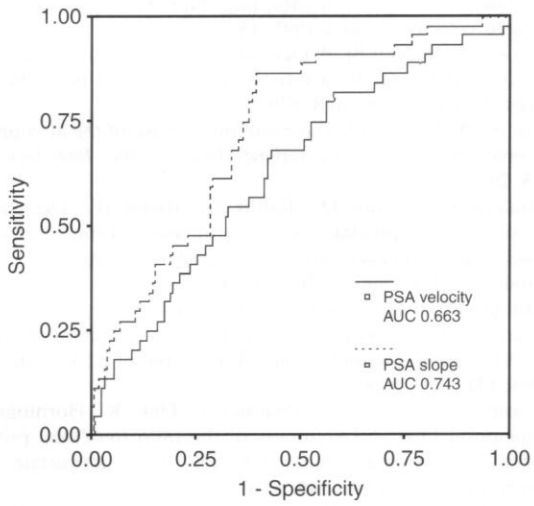

Figure 2 ROC analysis for prostate-specific antigen (PSA) slope and PSA velocity ($P = 0.037$).

No significant differences were found for PSA intercept, number of PSA assays and the time interval between the first and last PSA.

At the ROC analysis, PSA slope evidenced better results than PSA velocity (AUC 0.743 for PSA slope; 95% confidence interval 0.689–0.791; AUC 0.663 for PSA velocity, 95% confidence interval 0.607–0.717; $P = 0.037$) (Figure 2).

To confirm the validity of our data, the significant difference for PSA density and PSA transition zone density are also reported in the table.

At PSA slope (calculated with the least-square fit) equal to zero, the sensitivity was 94% with a specificity of 38.8%, a positive likelihood ratio of 1.54 and a negative likelihood ratio of 0.15. At PSA slope equal to 0.75, the sensitivity was 58.2% and the specificity was 69.8%.

Discussion

Prostate-specific antigen slope is significantly higher in men subsequently diagnosed with prostate cancer than in controls. In this study, PSA slope discriminates patients with prostate cancer from controls better than PSA velocity. Today there is a need for tools that help prostate cancer diagnosis.

The diagnostic tests currently used for early prostate carcinoma detection are fraught with a considerable number of false-positive and false-negative results.[3,9,14] To enhance the specificity of tPSA the determination of fPSA,[15] the concepts of PSA density [5] and of PSA transition zone density[16] have been included in the diagnostic setup for carcinoma of the prostate.

Another approach to assay specificity enhancement has been the so-called PSA velocity. This is the change in PSA over time, and this certainly makes intrinsic sense.[1] A person who develops prostatic carcinoma may eventually have a PSA level in the hundreds or indeed thousands. Certainly the rate of change in his PSA would be expected to be far greater than that in a man who never develops a significant malignancy.[1] This concept was first reported by Carter *et al.*[17] in their evaluation of a cohort of men in which serum had been banked as part of an ageing study. These investigators demonstrated that when the PSA increased more than 0.75 ng/ml per year, it helped to predict those men who had carcinoma. The Seattle group has been unable to reproduce the results of Carter.[18,19] The biggest difference certainly was the fact that in the Baltimore longitudinally ageing study, the subjects had to be enrolled for at least 7 years or were not included. Prostate-specific antigen measurements were performed generally every 2 years.[1,7] In the Seattle group studies could not see stratification of men with and without carcinoma with PSA measurements between 1 and 2 years apart.[18,19] Similarly, Catalona and associates, using relatively short intervals, were unable to support the observation of Carter and associates.[20] In a subsequent analysis, Carter and associates reported that PSA velocity was only useful when a minimum of three consecutive measurements were taken over at least a 2-year time interval with a PSA sampling interval of more than 6 months, but this was supported only on the basis of the number of cases with a PSA velocity more than 0.75 ng/ml/year, not with statistical differences between PSA velocity calculated with 3 or 6 months or 2 years sampling intervals.[11]

There are several concerns for PSA velocity (calculated as the average of at least three measurements) in clinical use, first of all for mathematical reasons. Prostate-specific antigen velocity calculated with three measurements as previously described[10] is contestable, as it is an average of two or more mean velocities. In 13 cases, PSA velocity could not be calculated because elapsed time was too short, instead PSA slope could be calculated in all patients.

D'Amico evaluated PSA velocity within one year before prostate cancer diagnosis in 1095 men who underwent radical prostatectomy.[9] D'Amico used linear regression analysis to calculate the PSA velocity, so the term PSA velocity in his work should be considered as PSA slope. Raaijmakers *et al.* reported that PSA dynamics were of limited value, but the restriction of this study was that they were unable to calculate the PSA dynamics for more than two measurements. In this paper, the term PSA slope is not appropriate; it indicates only the reciprocal value of PSA doubling time.[21]

In our study, we evaluated, for each patient, PSA velocity and PSA slope by the least-square fit; the best result is for the PSA slope by the least-square fit. The least-square fit can easily be calculated with an electronic sheet.[22] Today, patients sometimes come to urological examination with a high number of PSA measurements. The patient expects that the urologist evaluates his PSA list for an answer. The least-squares fit could be the answer, as the PSA slope so obtained discriminates prostate cancer patients from controls. This is accounted for by the interesting results from ROC analysis. In longitudinal evaluation of PSA it is meaningless to divide patients for PSA range (e.g.: <4 ng/ml, 4–10 ng/ml or >10 ng/ml) because every patient has more PSA measurements.

The major limitation of PSA calculated with the least-squares fit is the availability of three or more PSA values made with the same laboratory technique. In the presence of only two PSA values, the longitudinal evaluation of PSA is possible with 'simple arithmetic' PSA velocity that is calculated as the simple rate of change of PSA between two measurements. A problem of PSA velocity is the significant degree of biological variation observed in PSA levels in normal men.[23] A physiological fluctuation in PSA from 10 to 20% was observed in a screening population.[23] The least-squares fit used to elaborate PSA slope reduced this intraindividual fluctuation.

Longitudinal evaluation of PSA (PSA velocity and PSA slope) cannot be evaluated in cases with PSA interference such as 5-alfa reductase therapy (finasteride or dutasteride) or acute prostatitis.

To our knowledge, this is the first study comparing PSA velocity and PSA slope in prostate cancer diagnosis

Conclusion

Prostate-specific antigen slope calculated with three or more PSA assays permits longitudinal evaluation of PSA for prostate diagnosis.

Prostate-specific antigen slope improves both sensitivity and specificity in prostate cancer diagnosis, compared with PSA velocity. At zero, PSA slope corresponds 94% sensitivity and 38.8% specificity in prostate cancer diagnosis.

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