Evaluation of Prostate Specific Antigen Acceleration for Prostate Cancer Diagnosis

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Purpose: Prostate specific antigen acceleration can be calculated as the slope of log prostate specific antigen vs time, where log is the natural logarithm. We determined the best interval in which prostate specific antigen acceleration can be calculated with the best result in terms of specificity and sensitivity for prostate cancer diagnosis.

Materials and Methods: Entered in the study were 741 men who underwent transrectal ultrasound guided prostate biopsy with 12 or more cores and at least 3 prior consecutive prostate specific antigen measurements in at least 365 days. Prostate specific antigen acceleration was calculated as the slope of log prostate specific antigen vs time using a minimum of 3 prostate specific antigen measurements. Acceleration was evaluated at different intervals, including within 1 year (365 days), 2 years (730 days), 3 years (1,095 days), 4 years (1,460 days), 5 years (1,825 days) and 6 years (2,190 days) before the last measurement.

Results: A total of 255 cancers (34.4%) were found. On ROC analysis the AUC of prostate specific antigen acceleration (0.728, 95% CI 0.694-0.760) was better than that of prostate specific antigen, prostate specific antigen velocity and prostate specific antigen doubling time. The highest AUC of prostate specific antigen kinetics was for prostate specific antigen acceleration calculated within 3 to 4 years (731 to 1,460 days) before the last measurement.

Conclusions: Three or more prostate specific antigen measurements within 3 to 4 years (731 to 1,460 days) before the last measurement enabled more accurate calculation of prostate specific antigen acceleration than measurement within 1 to 2 years (0 to 730 days).

Key Words: prostate, prostate-specific antigen, prostatic neoplasms, diagnosis, mass screening

Abbreviations and Acronyms

DRE = digital rectal examination

FL = calculated using first and last values only

LR = calculated using linear regression

PSA = prostate specific antigen

PSADT = PSA doubling time

PSAV = PSA velocity

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Investigation of PSA kinetics has a long tradition in urology. Unfortunately the method of calculating PSAV has changed several times so that attention on PSA kinetics decreased. However, new interest in prostate cancer screening has changed this neglect.

In a recent report of a randomized European study of prostate cancer Schroder et al noted that PSA screening was associated with a 20% relative decrease in the rate of death from prostate cancer at a median 9-year followup.[1] Currently we have had to increase our efforts to find the best diagnostic method for prostate cancer with the best balance between sensitivity and specificity to decrease false-positive cases. PSA kinetics offer great opportunities, particularly PSA acceleration.[2] In a previous study we reported an original way to calculate

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PSA acceleration, that is the slope of the natural logarithm of PSA (logPSA slope).[3] Now it is imperative to define the application range of this kinetic marker. Thus, in the current study we determined the best interval in which to calculate PSA acceleration with the best specificity and sensitivity.

PATIENTS AND METHODS

We searched a prospective, institutional review board approved database of 2,208, 12-core prostate biopsies performed at our institution from January 2001 to January 2009 to identify men 45 to 90 years old with at least 3 consecutive PSA measurements made at our centralized laboratory in more than 365 days. Excluded from analysis were men with PSA interference reported in the database, such as 5α-reductase therapy with finasteride or dutasteride, or acute prostatitis.

All patients were scheduled for prostate biopsy due to abnormal digital examination, and/or PSA greater than 4 ng/ml and percent free PSA less than 22% until August 2003, or PSA greater than 3 ng/ml and percent free PSA less than 22% starting September 2003. All prostate biopsies were taken with the patient in the left lateral decubitus position using a 12-core lateral plus parasagittal transrectal ultrasound guided prostate biopsy protocol. Additional biopsies were taken from hypoechoic areas not covered by the standard procedure.

Serum was obtained before any diagnostic procedure. Total immunoreactive and free PSA was assayed using the Immulite® chemiluminescence immunoassay with detection limits of 0.02 and 0.03 ng/ml for free and total PSA, respectively. We included PSA measurements done before 2001 if they were assayed at our centralized laboratory with the Immulite technique.

We calculated PSAV by 2 methods, including FL only and LR, the latter based on the slope obtained by fitting a linear regression of PSA on time using all PSA values. All logPSA (natural logarithm of PSA) values were used to create the best fit line by least squares regression. PSA acceleration (logPSA slope) was the slope of this line. PSA acceleration was calculated using a minimum of 3 PSA measurements. Each PSA measurement and its precise date of blood sampling were inserted in an electronic sheet. The slope was calculated after natural logarithmic transformation of PSA. This daily slope was multiplied by 365.25 to determine the yearly slope. In mathematical terminology from regressing the natural logarithm of PSA with time, it follows that logPSA = a + bt, where a represents the intercept, t represents time and b represents the slope, that is PSA acceleration.

Figure 1 shows an example of the evaluation of PSA acceleration in a patient with prostate cancer. The exponential curve became a line in the logarithmic scale and the slope of this line is PSA acceleration.

To better explain the new concept of PSA acceleration table 1 shows a scheme of different PSADT values and the corresponding PSA acceleration values. We used the PSADT monthly value and the PSA acceleration yearly value. PSA acceleration was evaluated in each man at different intervals, including within 1 year (0 to 365 days), 2 years (366 to 730 days), 3 years (731 to 1,095 days), 4 years (1,096 to 1,460 days), 5 years (1,461 to 1,825 days) and 6 years (1826 to 2,190 days) before the last PSA measurement. Evaluation was repeated at a biannual interval, including within 1 to 2 years (0 to 730 days), 2 to 3 years (731 to 1,460 days) and 5 to 6 years (1,461 to 2,190 days) before the last PSA measurement. PSADT was calculated using the formula, PSADT = ln2/(logPSA slope).

We used the Mann-Whitney U test to assess differences between different groups with Statistica 6.0 (StatSoft®). All variables were assessed as continuous variables. The ROC curve was generated by plotting sensitivity vs 1 − specificity using MedCalc 7.0 (MedCalc Software, Mariakerke, Belgium). We compared results by comparing AUCs according to the method of Hanley and McNeil.[4]

Univariate logistic regression models to predict prostate cancer at biopsy were fitted using DRE, PSA, percent free PSA, PSA density and PSA acceleration. All statistics were considered significant at $\alpha = 0.05$.

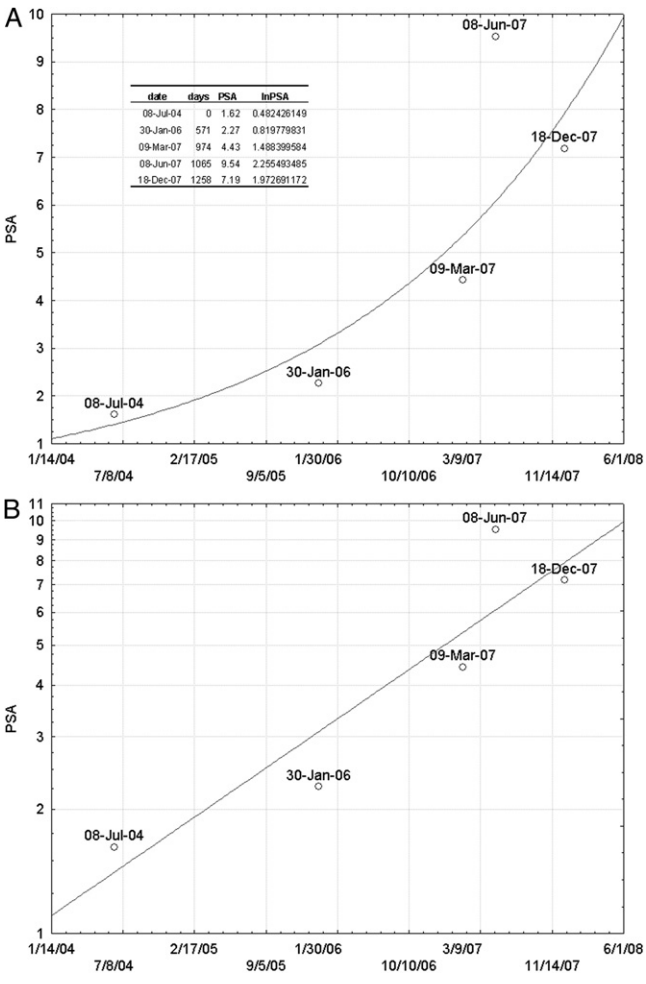

Figure 1. Prostate cancer diagnosis in 65-year-old patient S. G. *A*, exponential curve shows PSA acceleration. *B*, on logarithmic scale exponential curve becomes line with slope y = 0.3417 + 0.5014x, indicating that PSA acceleration is 0.5014 ng/ml per year.[2]

Table 1. *Explication table of logPSA slope and PSADT*

PSA	PSA Acceleration (ng/ml/yr^2)	PSADT (yrs/mos)
Halved (yrs):		
Every 5	−0.138	−5/−60
Every 10	−0.069	−10/−120
Stationary	0	Not evaluable
Duplicated:		
Every 10 yrs	0.069	10/120
Every 5 yrs	0.138	5/60
Every 4 yrs	0.173	4/48
Every 3 yrs	0.231	3/36
Every 2 yrs	0.346	2/24
Yearly	0.693	1/12
Every 6 mos	1.386	0.5/6
Every 3 mos	2.772	0.25/3

RESULTS

Of the 2,208, 12-core prostate biopsies in our database 741 men satisfied study inclusion criteria. Excluded from study were 4 men due to age, 1,230 due to the availability of only 1 or 2 PSA measurements, 191 due to too brief an interval (less than 365 days) from the first to the last PSA measurement and 42 due to therapy with finasteride/dutasteride or to acute prostatitis.

Table 2 shows the clinical characteristics of the 741 men. Briefly, median age was 63 years (range 46 to 86). All men were white. DRE was abnormal in 34% of cases. Of the men 53.4% underwent repeat prostate biopsy. Median PSA before biopsy was 6.81 ng/ml (range 0.74 to 93.4). Median PSA was 6.73 ng/ml in controls and 6.9 ng/ml in patients with prostate cancer. We made a total of 4,184 PSA measurements, including 3 to 28 per man. Median time between the first and last PSA measurements was 1,172 days (range 368 to 5,749).

PSA was not regularly tested in all men. PSA was measured 3 or more times per year in only 361 men within 1 year (0 to 365 days), in 435 within 2 years (366 to 730 days), in 363 within 3 years (731 to 1,095 days), in 271 within 4 years (1,096 to 1,460 days), in 143 within 5 years (1,461 to 1,825 days) and in 52 within 6 years (1,826 to 2,190 days) before the last measurement.

Median PSAV FL was 0.499 ng/ml per year (range −8.08 to 19.17). Median PSAV LR was 0.518 ng/ml per year (range −3.28 to 18.07). Median logPSA slope was 0.087 ng/ml per year^2 (range −0.96 to 0.99).

A total of 255 cancers (34.4%) were found at ultrasound guided prostate biopsy. Gleason score was available in 232 patients, of whom 139 (60%) had a Gleason sum of 6 or less. Of 93 patients 96.7% with a Gleason score of 7 to 10 had positive PSA acceleration.

PSA, PSAV FL and LR, logPSA slope and logPSA slope within 1 year (365 days), 2 years (366 to 730 days), 3 years (731 to 1,095 days), 4 years (1,096 to 1,460 days), 5 years (1,461 to 1,825 days) and 6 years (1,826 to 2,190 days) were significantly higher in patients with prostate cancer than in controls ($p < 0.05$).

PSADT did not differ between controls and men with prostate cancer ($p = 0.32$). Figure 2 shows the complex relation between PSA acceleration and PSADT.

To confirm the validity of our data we noted a significant difference between controls and men with prostate cancer in percent free PSA, PSA density and PSA transition zone density ($p < 0.05$, table 2). No significant differences were found for the number of PSA measurements and the interval between the first and last PSA measurements.

On ROC analysis the AUC of PSA acceleration (0.728, 95% CI 0.694 to 0.760) was the best of all PSA kinetics, including PSAV FL, PSAV LR and PSADT. For well balanced sensitivity and specificity the best PSA acceleration value corresponded to a cutoff of 0.42 ng/ml per year.[2] That cutoff showed

Table 2. *Descriptive statistics in 741 men*

	Overall		Prostate Ca		Control		p Value (Mann Whitney U test)
	No. Pts	Median (range)	No. Pts	Median (range)	No. Pts	Median (range)	
Age (yr)	741	63 (46–86)	255	63 (46–82)	486	64 (46–86)	0.83
PSA (ng/ml)	741	6.81 (0.74–93.4)	255	6.94 (2.12–93.4)	486	6.73 (0.74–43.4)	0.03
% Free-to-total PSA	680	15.99 (1.48–65)	236	11.87 (1.48–40.95)	444	18.3 (3.23–65)	<0.01
FL (days)	741	1,172 (368–5,749)	255	1,030 (368–3,723)	486	1,227 (381–5,749)	<0.01
No. PSA measurements/pt	741	5 (3–28)	255	5 (3–20)	486	5 (3–28)	<0.01
PSAV (ng/ml/yr):							
FL	741	0.5 (−8.093–19.17)	255	0.8 (−3.08–19.17)	486	0.29 (−8.09–13.5)	<0.01
LR	741	0.404 (−3.28–18.07)	255	0.82 (−10.9–18.07)	486	0.35 (−7.47–2.27)	<0.01
PSA acceleration (ng/ml/yr^2)	741	0.087 (−0.96–0.99)	255	0.16 (−0.61–0.99)	486	0.058 (−0.96–0.83)	<0.01
PSADT (ng/ml/mo)	741	3.86 (−2,101–1,076)	255	3.86 (−90–679)	486	3.88 (−2,101–1,076)	0.32
PSA density (ng/ml/cc)	656	0.148 (0.02–1.62)	221	0.19 (0.036–1.62)	435	0.12 (0.02–0.87)	<0.01
Prostate vol (cm^3)	656	50 (9–330)	221	40 (9–150)	435	55 (15–330)	<0.01
Transition zone :							
Vol (cm^3)	460	32 (3–200)	149	23 (3–109)	311	35 (4–200)	<0.01
PSA density (ng/ml/cc)	460	0.23 (0.04–2.51)	149	0.33 (0.04–2.51)	311	0.21 (0.04–1.5)	<0.01

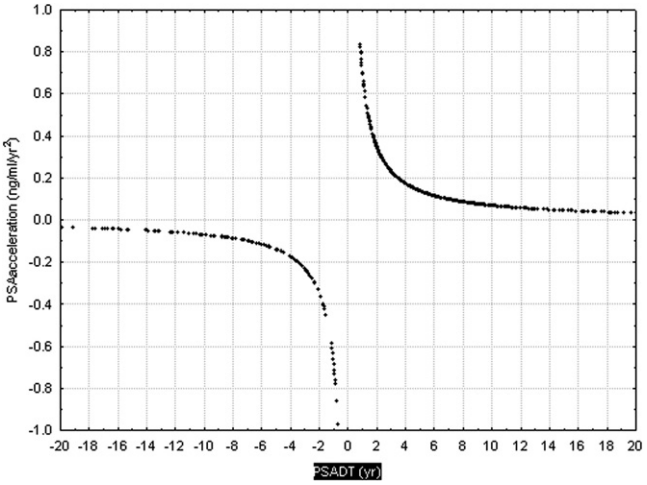

Figure 2. PSA acceleration and PSADT

45.3% specificity (95% CI 40.8 to 49.9), 85.73% sensitivity (95% CI 80.7 to 89.7), 1.57 positive predictive value and 0.32 negative predictive value. A zero cutoff for PSA acceleration corresponded to higher 92.4% sensitivity (95% CI 88.4 to 95.4) with 32.8% specificity (95% CI 28.6 to 37.2), 1.37 positive predictive value and 0.23 negative predictive value.

Table 3 shows the absolute value of the AUC of logPSA slope at different periods. The AUC of PSA acceleration calculated with PSA measurements within 3 to 4 years (731 to 1,460 days) before the last PSA measurement was higher than that calculated with measurements made within 1 to 2 years (0 to 730 days, p = 0.003, fig. 3). We found no statistical difference when comparing the AUC of PSA acceleration calculated with measurements made within 5 to 6 years (1,461 to 2,190 days) with the other 2 groups (0 to 730 and 731 to 1,460 days) but the relatively small sample size of this group (43 men with prostate cancer and 123 controls) led to further investigation. Table 4 shows that PSA acceleration was a statistically significant predictor of prostate cancer at biopsy (p <0.001).

Table 3. *ROC analysis*

	No. Pts	AUC (95% C.I.)
PSA	741	0.547 (0.511–0.584)
Free PSA	680	0.659 (0.622–0.694)
% Free PSA	680	0.757 (0.723–0.789)
Prostate vol	656	0.701 (0.664–0.735)
PSA density	656	0.691 (0.654–0.726)
PSAV:		
FL	741	0.690 (0.656–0.724)
LR	741	0.700 (0.665–0.733)
PSADT	741	0.522 (0.485–0.559)
LogPSA slope within yrs (days):	741	0.728 (0.694–0.760)
1 (0–365)	361	0.632 (0.580–0.682)
2 (366–730)	435	0.683 (0.637–0.727)
3 (731–1,095)	363	0.735 (0.687–0.780)
4 (1,096–1,460)	271	0.734 (0.672–0.789)
5 (1,461–1,825)	143	0.678 (0.595–0.753)
6 (1,826–2,190)	52	0.659 (0.515–0.785)
1–2 (0–730)	501	0.662 (0.619–0.703)
3–4 (731–1,460)	448	0.734 (0.691–0.774)
5–6 (1,461–2,190)	166	0.676 (0.599–0.747)

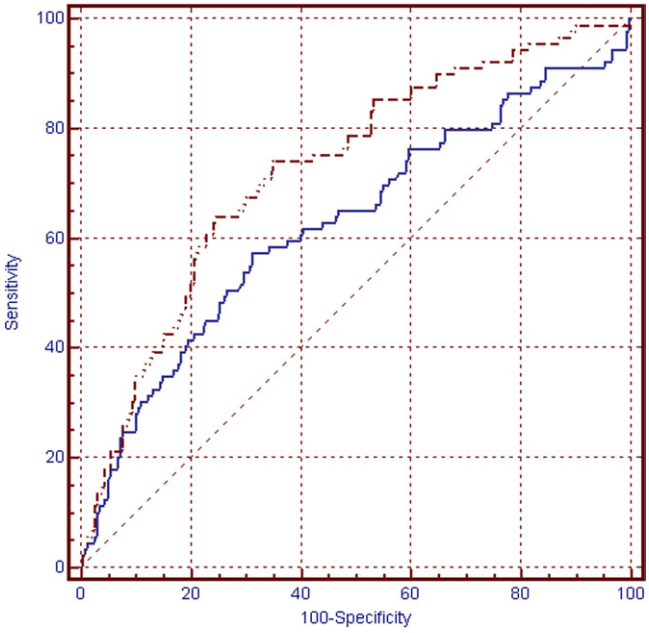

Figure 3. ROC curves show that AUC of PSA acceleration calculated within 3 to 4 years (731 to 1,460 days) (red curve) before last PSA measurement was higher than that calculated within 1 to 2 years (0 to 730 days) (blue curve) (p <0.05).

DISCUSSION

Patients with prostate cancer have a significantly greater rate of change in PSA with time than men with known benign prostatic disease or with normal glands. Such an accelerated PSA increase could precede the diagnosis of prostate cancer by several years. After initial observation in a longitudinal case-control study in the United States[5] these findings were confirmed by independent studies in Europe.[6] Also, PSA increases appeared to be indepen-

Table 4. *Univariate regression analysis*

	OR (95% CI)		p Value
DRE	2.6417	(1.9095–3.6546)	<0.0001
PSA	1.0330	(1.0088–1.0577)	0.0072
% Free PSA	0.8684	(0.8431–0.8944)	<0.0001
PSA density	215.7636	(45.4401–1024.5118)	<0.0001
PSAV:			
FL	1.4548	(0.0581–1.6304)	<0.0001
LR	1.5476	(1.37–1.7483)	<0.0001
PSADT	1.0014	(0.001–0.1842)	0.1842
PSA acceleration	70.1696	(24.7009–199.3358)	<0.0001

dent of age. This is one of the most important confounding factors since androgen levels are known to modulate PSA secretion and evolve with age[5,7]

In the current series we determined the optimal interval for calculating PSA acceleration. Using too short a time only PSA variability could be evaluated and with a too long time the first flat part of the exponential curve crushed acceleration. A practical implication of our study is the suggestion to repeat yearly PSA measurements at the same laboratory and evaluate PSA acceleration after 3 measurements. In the current series, which had a larger cohort than in our previous study,[3] we found that acceleration is best calculated using 3 or more PSA measurements within 3 to 4 years.

A critical point in PSA kinetics is the relation between PSADT and PSA acceleration. Their mathematical relation could suggest a statistical likeness. PSADT has been studied more intensively than acceleration. Initial studies evaluating patients placed on watchful waiting identified PSADT as the strongest predictor of clinical progression.[8] PSADT has been primarily used in the posttreatment setting and it is considered a surrogate marker for prostate cancer specific survival in men with biochemical recurrence.[9,10]

However, the role of PSADT in predicting tumor biology before treatment is unclear, especially in men with an early disease state.[11] Sengupta et al found that preoperative PSADT predicted clinical outcomes after radical prostatectomy[12] while others reported conflicting results.[13] Recently Loeb et al found an association of preoperative PSADT with nonorgan confined disease but not with biochemical progression after radical prostatectomy.[14]

The literature on PSADT before diagnosis also is conflicted.[15] Raaijmakers et al examined 1,689 men undergoing biopsy in the screening arm of the European Randomized Study of Screening for Prostate Cancer.[16] PSADT was significantly different between those with and without prostate cancer. However, further analysis revealed that PSA kinetics conveyed little additional data to predict biopsy results. PSADT was marginally superior to PSAV with an AUC of 0.573 vs 0.549 but neither was significant on multivariate analysis.

In a study of 1,699 men undergoing biopsy with PSA less than 10 ng/ml Spurgeon et al evaluated PSAV FL and PSADT.[17] PSADT 2 to 5 years was weakly associated with positive biopsy and high grade prostate cancer (Gleason 7 or more) but it was not significant when considering other variables. They concluded that PSADT had limited usefulness when selecting patients for prostate biopsy.

On the other hand, PSADT may have a more useful role after an initial negative biopsy. Garzotto et al retrospectively examined a cohort of patients undergoing repeat biopsy and found that PSADT was the best independent predictor of positive results among other well characterized predictors.[18] Others theoretically supposed advantages for a screening program[19,20] but in our study PSADT showed no difference between men with prostate cancer and controls.

Vollmer studied the problem of prediagnostic PSA acceleration and reported an interesting exponential model using PSA data on patients with prostate cancer after undergoing radical prostatectomy.[2] The exponential model was derived from the assumption that serum PSA is due to a sum of 2 PSA components released from benign and malignant tissue, respectively, and each PSA component followed approximately an exponential function with respect to time.

In the simpler exponential model in the current study we hypothesized a more rapid PSA increase in men with malignant prostatic tissue than in men with a benign prostate. This increase was a first order kinetic. The slope obtained from fitting a linear regression of the natural logarithm of PSA on time best describes this concept.[21]

A problem of PSA kinetics is the significant degree of biological variation in PSA in normal men.[22,23] A 10% to 20% physiological fluctuation in PSA was observed in a screening population.[23] The least square fit used to elaborate logPSA slope and the large number of PSA measurements (3 to 28 in our study) decreased this intra-individual fluctuation.[24,25]

The potential limitation of our study must be considered. Time from first to last PSA measurement, and the number of PSA measurements were different in controls than in patients ($p < 0.05$). This was because longitudinal evaluation ends with the prostate cancer diagnosis but in controls it continues without interruption.

Another important consideration for PSA acceleration is that it can be invalidated when PSA values are not homogenous, for example if PSA was assayed at different laboratories with different methods or there was a lack of control in laboratory procedures.[24] Otherwise the optimization of PSA kinetics before diagnosis suggest that serial PSA screening is important to develop a PSA history that can be used in this assessment.

CONCLUSIONS

To our knowledge this is the first study to define the best interval for PSA acceleration. The results of PSA acceleration were better than those of PSA, PSAV FL, PSAV LR and PSADT for prostate cancer diagnosis in men who underwent prostate biopsies with 12 or more cores. Three or more PSA measurements within 3 to 4 years (731 to 1,460 days) before the last measurement permitted more accurate calculation of PSA acceleration than those within 1 to 2 years (0 to 730 days).

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EDITORIAL COMMENT

These authors report rediagnostic PSA kinetics in 741 men undergoing initial or repeat 12-core or greater prostate biopsy. Results show that, regardless of the PSAV calculation or interval used to calculate PSA slope, greater increases in PSA with time were significantly associated with prostate cancer detection on biopsy. The only PSA kinetic measurement that was not associated with biopsy results was PSADT, consistent with prior studies suggesting that this calculation may be less useful in the pretreatment setting (reference 11 in article). On ROC analysis PSA acceleration calculated using at least 3 PSA values within 3 to 4 years was associated with the greatest discrimination in this population.

An important limitation of the study is that 1,320 of the 2,208 men (59.8%) in their biopsy database were excluded from analysis due to a PSA history insufficient to calculate PSA acceleration (2 or fewer measurements). Similar issues were reported in other studies of PSA kinetics.[1] Correspondingly in daily clinical practice these calculations are only possible in men with a more extensive PSA history. In light of recent randomized evidence demonstrating that PSA screening is associated with improved prostate cancer specific survival (reference 1 in article),[2] serial screening may become more acceptable in the future, enabling greater use of PSA kinetics.

Conversely problems with the over diagnosis of low risk prostate cancer through increased screening could possibly be decreased by screening protocols with greater specificity for clinically significant disease. In this regard these authors report that 96.7% of patients with a Gleason score of 7 or greater on biopsy had positive PSA acceleration, although multivariate models and ROC analysis to predict high grade disease are not presented.

An alternate way to capture the concept of PSA acceleration is a calculation of the PSAV risk count or the number of serial occasions on which PSAV exceeds a specific threshold value.[3] Our research group reported that after adjusting for age and PSA multiple PSAVs greater than 0.4 ng/ml per year (a PSAV risk count of 2) were associated with an 8-fold increased risk of overall prostate cancer detection and a 5-fold increased risk of high grade disease on biopsy compared with 0 to 1 PSAV measurements greater than 0.4 ng/ml per year (a risk count of 0 to 1).[4]

Together these findings suggest that sustained PSA increases, whether quantified as PSA acceleration or a PSAV risk count, indicate a higher risk of clinically significant prostate cancer. Future prospective studies are warranted to examine the clinical outcomes of a screening protocol based on PSA kinetics.

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