

## Optimal Measure of PSA Kinetics to Identify Prostate Cancer

Luigi Benecchi, Anna Maria Pieri, Carmelo Destro Pastizzaro, and Michele Potenzoni

<b>OBJECTIVES</b>	To compare different tools for evaluate prostate-specific antigen (PSA) kinetics before prostate biopsy, such as PSA velocity, PSA slope, natural logarithm PSA slope (lnPSA slope), and PSA doubling time (PSADT).
<b>METHODS</b>	This study was conducted involving 325 male patients evaluated with transrectal ultrasound-guided biopsy of prostate. Patients with at least three consecutive PSA measurements taken in at least 24 months entered in the study. We estimated PSA slope from the slope of the least squares regression line fit to PSA versus time in years; PSA velocity was calculated as the running average of the rate of change during at least three consecutive assays. The acceleration of PSA (lnPSA slope) was calculated as the slope of lnPSA versus time, where ln is the natural logarithm. PSADT was calculated using the formula: $PSADT = \ln 2 / (\ln PSA \text{ slope})$ .
<b>RESULTS</b>	We found a total of 74 cancers at the ultrasound guided prostate biopsies. At the receiver operating characteristic (ROC) analysis, lnPSA slope (area under the curve [AUC], 0.793) evidenced better results than PSA (AUC, 0.585; $P < 0.001$ ), PSA velocity (AUC, 0.734; $P < 0.009$ ), PSA slope (AUC, 0.752; $P < 0.043$ ), and PSADT (AUC, 0.516; $P < 0.001$ ).
<b>CONCLUSIONS</b>	The results for PSA, PSA velocity, PSA slope, and lnPSA slope were significantly higher in patients with prostate cancer than in controls. The results of the present study suggest that lnPSA slope may be useful for prostate cancer diagnosis. At the ROC analyses, the lnPSA slope AUC was better than that of PSA, PSA velocity, PSA slope, and PSADT. UROLOGY 71: 390–394, 2008. © 2008 Elsevier Inc.

For more than a decade, the prostate-specific antigen (PSA) test has been a way for doctors to gauge prostate cancer risk. Men whose PSA levels, measured by a simple blood test, rose above a specific level were considered likely to harbor cancer cells within their prostate gland.

However, the conventional strategy for PSA screening, which calls for biopsies in all men with a total PSA above a certain absolute threshold (such as 2.5 or 4.0 ng/mL), leads to many false positive results and is thus associated with a high cost in terms of unnecessary biopsies.<sup>1,2</sup>

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 to total PSA, level of  $\alpha 1$ -antichymotrypsin complex PSA,<sup>3</sup> and artificial neural network.<sup>4</sup>

The PSA velocity is the rate of change in PSA over time. The original description, by Carter *et al.*, differentiated between men subsequently diagnosed with prostate cancer who had a PSA velocity of 0.75 ng/mL per year or greater and those who had benign prostatic hyperplasia

(BPH) or no appreciable prostatic disease.<sup>5</sup> Despite early enthusiasm for PSA velocity, the enhanced performance suggested by the initial investigators may not be reproducible.<sup>1,6</sup>

The difficulty with this approach is the confounding effect or the biologic variability of PSA.<sup>7</sup> An answer could be identification of the kinetic pattern that results in identification of men with a rapid rise of PSA compatible with the biological behavior of tumor.

In men with relapse, increases in serum PSA after radical prostatectomy or radiation therapy follow an exponential growth curve and the relationship between lnPSA and time is linear.<sup>8,9</sup> D'Amico *et al.* found that a PSA doubling time (PSADT) of less than 3 months before potentially curative treatment predicts death from prostate cancer.<sup>10</sup>

The aim of our study was to compare different tools for evaluate PSA kinetics before prostate biopsy, such as PSA velocity, PSA slope, natural logarithm PSA slope (lnPSA slope), and PSA doubling time.

### MATERIAL AND METHODS

Between January 2001 and June 2006, all men who underwent transrectal ultrasound-guided prostate biopsy with six or more cores and with at least three consecutive PSA measurements (done in our centralized laboratory) 731 or more days before

From the Department of Urology, Fidenza Hospital, Parma, Italy  
Reprint requests: Dr. Luigi Benecchi, Via Comazzano 154, 43010 Parma, Italy.  
E-mail: benecchi.luigi@libero.it  
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biopsy entered the study. Men with PSA interference such as 5 $\alpha$ -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  $\mu$ g/L or greater. A total of 325 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.

We obtained serum before any diagnostic procedure. Both total immunoreactive and free PSA were assayed using the chemiluminescent immunoassay Immulite (Immulite Diagnostic Products Corp., Los Angeles, CA), 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 analyzer with detection limits of 0.02 and 0.03  $\mu$ g/L for fPSA and tPSA. For PSA velocity calculation were considered only PSA measurements with a time interval from the previous one more than 6 months. All PSA measurements assayed in our centralized laboratory with this technique were included in our study.

We calculated the percentage of free PSA as the ratio of free PSA to total PSA multiplied by 100. PSA density was calculated as the PSA value divided by the TRUS-estimated prostate volume. We calculated PSA velocity as the increase of PSA per year from the first to the last PSA assay before prostate biopsy. We calculated the PSA slope with the least square fit (PSA versus time) using an electronic sheet, so the line slope value and the intercept value were obtained for each patient. Specifically, we fit the equation:  $y = a + bx$  to the data of each patient, where  $y$  represents PSA and  $a$  the intercept. Parameter  $b$  is the slope and reflects the increase of PSA in 1 year.<sup>11</sup> The acceleration of PSA (lnPSA slope) was the slope of lnPSA versus time, where ln is the natural logarithm. We calculated PSADT using the formula:  $PSADT = \ln 2 / \mu(\ln PSA \text{ slope})$ .<sup>12</sup> We used the Mann-Whitney  $U$  test to assess the differences in PSA between groups (Statistica 6.0, StatSoft, Inc., Tulsa, OK). The receiver operating characteristic (ROC) curve was generated by plotting sensitivity versus 1 – specificity (MedCalc 7.0, MedCalc software, Mariakerke, Belgium). We compared results by comparing the areas under the receiver operating characteristics curve (AUC) according to Hanley and McNeil.<sup>13</sup> Stepwise logistic regression analysis was used to assess continuous variables (age, PSA, percent free PSA, PSA density, PSA velocity, lnPSA slope, and PSA doubling time).

## RESULTS

The median PSA before biopsy was 7.11  $\mu$ g/L (range, 0.8 to 52.7  $\mu$ g/L). Median PSA was 6.8 in controls and 8.1 in patients with prostate cancer. The median age was 65.6 years (range, 45 to 83 years). Table 1 shows the clinical characteristics of the 325 men. All men were white. We elaborated 1982 PSA measurements, from 3 to 28 in each man. The median interval of time between the first and last PSA assay was 1321 days (range, 739 to 4581 days).

Median PSA slope was 0.404 ng/mL per year (range, –3.28 to 18.07 ng/mL per year). The median PSA velocity

**Table 1.** Descriptive statistics of 325 men

	All			Prostate Cancer Patients			Controls			P Value
	No.	Median (Range)	No.	Median (Range)	No.	Median (Range)	No.	Median (Range)		
Age (yr)	325	65.6 (45.2–83)	74	64.34 (50.6–82.4)	251	65.8 (45.2–83)	251	65.8 (45.2–83)	0.49	
PSA (ng/mL)	325	7.11 (0.8–52.7)	74	8.1 (2.12–52.7)	251	6.81 (0.8–35.2)	251	6.81 (0.8–35.2)	0.025*	
Free-to-total PSA (%)	287	17.41 (3.23–65)	64	11.96 (4.26–35.76)	223	18.4 (3.23–65)	223	18.4 (3.23–65)	0.0000000012*	
Days between first and last assays	325	1321 (739–4581)	74	1245 (739–3723)	251	1343 (740–4581)	251	1343 (740–4581)	0.038	
No. PSA assays for patient	325	5 (3–28)	74	5 (3–12)	251	6 (3–28)	251	6 (3–28)	0.0014	
PSA velocity (ng/mL/yr)	325	0.392 (–3.72–19.17)	74	0.776 (–0.61–19.17)	251	0.189 (–3.7–5.9)	251	0.189 (–3.7–5.9)	0.0000000008*	
PSA slope (last square fit) (ng/mL/yr)	325	0.404 (–3.28–18.07)	74	0.849 (–0.53–18.07)	251	0.24 (–3.2–5.8)	251	0.24 (–3.2–5.8)	0.0000000004*	
PSA intercept	325	5.58 (–294.2–209.9)	74	4.096 (–279–12.86)	251	5.9 (–294–209)	251	5.9 (–294–209)	0.00000000022	
lnPSA slope	325	0.068 (–0.61–0.996)	74	0.162 (–0.074–0.99)	251	0.04 (–0.6–0.74)	251	0.04 (–0.6–0.74)	0.00000000000002	
lnPSA intercept	325	639 (–149–1758)	74	541 (–149–1018)	251	658 (–109–1758)	251	658 (–109–1758)	0.0000853	
PSADT (yr)	325	4.1 (–367–1758)	74	3.9 (–59–549)	251	4.1 (–367–1076)	251	4.1 (–367–1076)	0.678	
Prostate volume (cm <sup>3</sup> )	265	50.8 (10–151)	57	35 (10–130)	208	53.2 (15–151)	208	53.2 (15–151)	0.000000046*	
PSA density (ng/mL/mL)	265	0.148 (0.03–1.01)	57	0.208 (0.055–1.01)	208	0.137 (0.03–0.62)	208	0.137 (0.03–0.62)	0.0000002401*	
Transition zone volume (cm <sup>3</sup> )	179	33 (4–120)	41	15.6 (5–74)	138	35.2 (4–120)	138	35.2 (4–120)	0.000000595*	
PSA transition zone density (ng/mL/mL)	179	0.243 (0.052–2)	41	0.466 (0.085–2)	138	0.22 (0.052–1.3)	138	0.22 (0.052–1.3)	0.00000049*	

lnPSA = natural logarithm prostate-specific antigen; PSA = prostate-specific antigen. The last column reports the  $P$  value of differences between controls and prostate cancers (Mann-Whitney  $U$  test), \*  $P < 0.05$ .

**Table 2.** Receiver operating characteristic analyses

	Area Under Curve	Standard Deviation	95% Confidence Interval
PSA	0.585	0.039	0.530–0.639
Free to total PSA	0.749	0.031	0.695–0.798
PSA density	0.723	0.041	0.665–0.776
PSA transition zone density	0.735	0.048	0.664–0.798
PSA velocity	0.734	0.036	0.683–0.782
PSA slope	0.752	0.035	0.701–0.798
lnPSA slope	0.793	0.033	0.745–0.836
PSADT	0.516	0.038	0.460–0.571

PSADT = PSA doubling time; other abbreviations as in Table 1.

was 0.392 ng/mL per year (range, –3.72 to 19.17 ng/mL per year).

We rebiopsied 170 men (52.3%) with a first negative biopsy. A total of 74 cancers were found at the ultrasound-guided prostate biopsies.

The PSA, PSA velocity, PSA slope, and lnPSA slope were significantly higher in patients with prostate cancer than in controls. To confirm the validity of our data, Table 1 also shows the significant difference for free to total PSA, PSA density, and PSA transition zone density. We found no significant differences for PSA intercept, number of PSA assays, and time interval between the first and last PSA. At ROC analysis, lnPSA slope (AUC, 0.793; 95% confidence interval [CI], 0.745 to 0.836) evidenced better results than PSA (AUC, 0.585; 95% CI, 0.530 to 0.639;  $P < 0.001$ ), PSA velocity (AUC, 0.734; 95% CI, 0.683 to 0.782;  $P < 0.009$ ), PSA slope (AUC, 0.752; 95% CI, 0.701 to 0.798;  $P < 0.043$ ), and PSADT (AUC, 0.516; 95% CI, 0.460 to 0.571;  $P < 0.001$ ) (Table 2).

At an lnPSA slope equal to 0, the sensitivity was 95.9% with a specificity of 35.1%, a positive likelihood ratio of 1.48, and a negative likelihood ratio of 0.12. At an lnPSA slope of 0.41, the sensitivity was 90.3% with a specificity of 50.2%.

Of the 325 patients reviewed, 275 presented all clinical data (age, PSA, percent free PSA, PSA density, and lnPSA slope) for multivariate logistic regression. For the multivariate logistic regression, only percent free PSA (odds ratio, 0.905) and lnPSA slope (odds ratio, 173.48) showed statistical significance.

## COMMENT

Serum PSA concentrations increase with age at a rate of 0.04  $\mu\text{g/L}$  per year in healthy men.<sup>5</sup> The rate at which PSA increased annually is between 0.07 and 0.27  $\mu\text{g/L}$  in patients with BPH, between 0.47 and 3.08  $\mu\text{g/L}$  for patients with localized cancers, and between 1.02 and 26.49  $\mu\text{g/L}$  for patients with metastatic disease.<sup>14</sup> A linear relationship has been reported between serum PSA and size of prostate cancer.<sup>14,15</sup>

In the previous study the PSADT apparently exceeded 48 months in stages T1 and T2, and was less than 24

months for stages T3 and T4.<sup>15</sup> PSADT values vary from 73.9 to 98.9 years in controls and from 12.4 and 16.9 years in BPH patients.<sup>14</sup> In patients with prostate cancer, the pattern is biphasic. The first phase is linear, with an identical doubling time for localized and metastatic disease (13.6 to 18.6 years) and the second phase is exponential, with a PSADT of 2.4 years for localized cancers and 1.8 years for metastasis.<sup>16</sup>

In the current study we compared different methods for evaluate PSA kinetics before prostate biopsy. Specifically, PSA velocity, PSA slope, and lnPSA slope were higher in patients with prostate cancer than in controls. PSADT did not show a difference between prostate cancer patients and controls. PSADT as PSA velocity, PSA slope, and lnPSA slope were analyzed as continuous variables (i.e., they could have negative or positive values). In fact, in our analysis, even in men with decreasing PSA, the PSADT was easily calculated with the logarithm transformation of PSA. In a previous study it was reported that PSA doubling time and log slope PSA were equivalent<sup>17</sup>; instead, we think that PSA doubling time is related to lnPSA slope (PSADT =  $\ln 2 / \ln \text{PSA slope}$ ) but they are mathematically different. PSADT correlates with tumor progression, therapeutic outcome, and cancer specific mortality,<sup>17,18</sup> but in our patients it showed no value as a diagnostic tool for prostate cancer, in contrast to theoretic advantages for screening.<sup>19,20</sup> PSADT depend on the baseline PSA measurement such that it works only when men start out at the same baseline (such as an undetectable PSA after surgery) and does not work well for comparing subsequent PSA rise among men starting at different PSA levels. Stephen *et al.* reported that PSADT was of limited utility in selecting patients for a prostate biopsy.<sup>21</sup>

Raaijmakers *et al.* reported that PSA dynamics were of limited value in predicting the biopsy outcome, but the restriction of this study was that they were unable to calculate PSA dynamics for more than two measurements.<sup>22</sup> In this report, the term “PSA slope” is not appropriate because it indicates only the reciprocal value of PSA doubling time<sup>22</sup> and corresponds with limitations to lnPSA slope in the current study.

A great problem in PSA kinetics is the semantic confusion in terminology: For example, PSA slope is not PSA velocity<sup>11</sup> and PSA doubling time is not equal to the logarithm PSA slope as reported by Patel *et al.*<sup>17</sup> We promote a “mathematical” terminology for PSA kinetics so the correct term for logarithm PSA is lnPSA, which is the natural logarithm of PSA.

For clinical use of the lnPSA slope, it is better to use 3 or more PSA values over a period of 2 or more years. If the time interval is less than 2 years, it is better to use the PSA slope.<sup>11</sup> The lnPSA slope permits evaluation of the acceleration of PSA in men with prostate cancer. In fact, it indicates the value of its exponential growth.<sup>23</sup> D’Amico *et al.* evaluated PSA velocity within 1 year before prostate cancer diagnosis in 1095 men who underwent radical pros-

tatectomy.<sup>9</sup> The authors used linear regression analysis to calculate the PSA velocity, so the term “PSA velocity” in their work should be considered the PSA slope. Instead, lnPSA slope needs more time than PSA velocity or PSA slope to evidence pathological variation.

Today, patients sometimes come to urological examination with a high number of PSA measurements. The patient expects that the urologist can evaluate his PSA list for a diagnosis. The lnPSA slope can provide the answer because it can discriminate prostate cancer patients from controls. This is evidenced by the interesting results from ROC analysis. In our study it was difficult to divide patients for PSA range (for example, less than 4 ng/mL, 4 to 10 ng/mL, and greater than 10 ng/mL) because every patient had 3 to 28 PSA measurements.

The major limitation of lnPSA slope is the availability of 3 or more PSA values made with the same laboratory technique over 2 or more years.

A problem of PSA kinetics is the significant degree of biological variation observed in PSA levels in normal men.<sup>7,23</sup> A physiological fluctuation in PSA from 10% to 20% was observed in a screening population.<sup>7</sup> The least square fit used to elaborate PSA slope and lnPSA slope reduced this intraindividual fluctuation.

The longitudinal evaluation of PSA (PSA velocity, PSA slope, lnPSA slope, and PSA doubling time) cannot be evaluated in cases with PSA interference such as prostatitis. Therapy with 5 $\alpha$ -reductase inhibitors affects PSA kinetics, making it impossible to apply the same threshold values in patients with this therapy. The ideal threshold for a cancer marker is at 95% of sensitivity. That for lnPSA slope corresponds to 0, but the slow-growing and indolent nature of prostate cancer, coupled with the fact that a man will be tested again and again in his lifetime, makes a false negative test less important. Therefore, we suggest limiting the sensitivity to 90%, which corresponds to a specificity of 50%. In another words, above 0.041 lnPSA slope, for every 2 prostate biopsies, 1 will result in a positive outcome.

The potential limitations of this study must be considered. The time from first to last PSA and the number of PSA assays are different in controls than in patients ( $P = 0.038$ ) because with prostate cancer diagnosis the longitudinal evaluation ends, but in controls this continues without interruption. Another limitation of our report is the cutoff of 4.0 ng/mL of PSA used as the threshold for biopsy according to our strategy at that time. We are aware that the current conventional strategy for biopsy is to reduce PSA threshold,<sup>2</sup> so we recommend a prospective study to confirm our analysis.

## CONCLUSIONS

To our knowledge, this is the first report on the use of a natural logarithm PSA slope in prostate cancer diagnosis. PSA, PSA velocity, PSA slope, and lnPSA slope were significantly higher in patients with prostate cancer than in controls. The results of the present study suggest that

the lnPSA slope may be useful for prostate cancer diagnosis, whereas the PSA doubling time showed no diagnostic use. At the ROC analyses, the lnPSA slope AUC is better than that of the PSA, PSA velocity, PSA slope, and PSA doubling time.

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