Correction of prostate-specific antigen velocity for variation may improve prediction of cancer following prostate repeat biopsy

Angelish Kumar, MD, Guilherme Godoy, MD, Samir S. Taneja, MD
Division of Urologic Oncology, Department of Urology, New York University School of Medicine, New York, New York, USA

KUMAR A, GODOY G, TANEJA SS. Correction of PSAV for variation may improve prediction of cancer following prostate repeat biopsy. The Canadian Journal of Urology. 2009;16(3):4655-4659.

Objective: *To determine if adjustment of prostate-specific antigen velocity (PSAV) for variation improves prediction of cancer in men with previous negative prostate biopsy.*
Patients and methods: *Records of men undergoing prostate biopsy between 1999 and 2004 by a single urologist were reviewed to identify men with at least three follow up PSA measurements. Patients with atypia, high grade prostatic intraepithelial neoplasia or cancer on baseline biopsy were excluded. Men were rebiopsied if perceived to have rising PSA. Men with cancer, no cancer, or no repeat biopsy were compared for PSAV and a new parameter, PSAV%/Variation. PSAV was calculated by linear regression, and adjusted to percent change (PSAV%). Diagnostic accuracy was assessed by receiver operating characteristic curve.*
Results: *Of 118 men who met inclusion criteria, 32 had repeat biopsies. Nine biopsies were positive (group 1) and 22 were negative (group 2). The PSAV%, PSAV, and PSAV%/Variation for groups 1 versus 2 was 22.9% and 1.7% ($p = 0.004$), 1.12 versus 0.4 ng/ml/year ($p = 0.007$), and 1.07 verus 0.03 ($p < 0.001$), respectively. PSAV%/Variation had the largest area under the curve (0.881), compared with PSAV (0.744) and PSAV% (0.784). At cut off of 0.77, specificity was 86.4% and sensitivity was 87.5% for PSAV%/Variation. At the same sensitivity level, the specificities of PSAV% and PSAV were 77.3% and 63.6%, respectively.*
Conclusion: *Correction for variation could potentially make PSAV a more reliable parameter in patients with prior negative biopsy. The results of our preliminary study warrant further analysis in a larger prospective cohort.*

Key Words: prostate, prostatic neoplasms, tumor markers, prostate-specific antigen

Accepted for publication January 2009

Acknowledgement
Dr. Guilherme Godoy received support from Bruce and Cynthia Sherman Fellowship in Urologic Oncology.

Address correspondence to Dr. Samir S. Taneja, Department of Urology, New York University Medical Center, NYU Urology Associates, 150 East 32nd street, 2nd floor, New York, NY 10016 USA

Introduction

The wide use of prostate-specific antigen (PSA) testing has resulted in an increasing number of prostate biopsies performed annually over the past decade. However, more than 60% of extended core biopsies performed for serum PSA elevation are negative.[1] The management of patients following negative biopsy remains a challenge for the practicing urologist.

There are few guidelines dictating when repeat biopsy is warranted in the setting of a negative initial extended core biopsy. The urologist's index of suspicion is typically defined by the negative predictive value of the initial biopsy and the relative risk of prostate cancer in the patient. The negative predictive value of prostate biopsy is determined by both the number and location of biopsy cores.[2] The use of serum PSA to guide management in longitudinal follow up has historically been limited by physiologic and interassay variability.[3]

We have previously observed that PSA velocity (PSAV) is increased among men found to have cancer on repeat biopsy relative to those not found to have cancer.[4] Because variation confounds accurate measurement of PSAV, we undertook this study to modify the PSAV calculation to minimize the effect of variation. After calculating PSAV, we introduced a new parameter to further correct for variation and improve the prediction of prostate cancer among men with previously negative prostate biopsy.

Patients and methods

The records of patients who underwent prostate biopsy between 1999 and 2004 in a single surgeon practice were reviewed after approval by the Institutional Review Board. This time period was chosen to ensure that a minimum of 12 cores were sampled on initial biopsy, and to allow adequate follow up time for serial PSA measurements and repeat biopsies. Patients with atypia, high grade prostatic intraepithelial neoplasia (HGPIN), or prostate cancer on baseline biopsy were excluded from the analysis. Additionally, a minimum of three PSA measurements (including the baseline PSA drawn prior to initial biopsy) were required, leaving 118 men for inclusion.

All baseline biopsies had a minimum of 12 cores using the previously reported strategy.[2] Repeat biopsy was performed at the discretion of the managing surgeon on the impression of a rising PSA. On repeat biopsy, hypoechoic lesions and transition zone were taken when deemed clinically appropriate.

Patients were divided into three groups: group 1- positive repeat biopsy (biopsy proven cancer); group 2 – negative repeat biopsy (no cancer) and group 3 – no repeat biopsy (stable PSA in follow up).

PSA measurements were performed by a number of assays dependent upon the laboratory selected by the patient in follow up. Several patients underwent measurement by more than one assay. After baseline (prebiopsy) measurement, PSA was measured at months 4, 8, and 12, and then every 6 months up to 3 years. The maximal available number of PSA measurements was used to calculate PSAV.

PSAV was determined by using linear regression to calculate the slope of the line of best fit. Because baseline PSA varies among individuals based on age and other demographic and pathologic parameters, we calculated PSAV by a relative percentage change (PSAV%) using the equation [PSAV (ng/ml/year) / median PSA] * 100%, rather than absolute change in PSA in ng/ml/year, as others have utilized. The absolute value of coefficient of variation expressed as percent change (relative standard deviation) was calculated using the equation [100 x (standard deviation/mean)], with the same PSA values utilized in the PSAV calculation.

Upon modeling of PSAV using a variety of calculations, it was consistently observed that PSA value drawn 4 months after the initial biopsy tended to be an outlier, likely due biopsy related inflammation; therefore, this value was excluded from the PSAV and variation calculation.

Based on the observation that patients with cancer tended to have higher PSAV and less variation over time, we hypothesized that PSAV% divided by the variation may improve the prediction of cancer by PSAV, and applied this parameter to our patient population. PSAV%/Variation was applied as an independent parameter for prediction of cancer and its predictive accuracy was compared to that of PSAV and PSAV% using sensitivity analysis and receiver operating characteristic (ROC) curve.

Because we were primarily interested in using PSAV to select men for repeat biopsy, comparisons were made between men with positive and negative repeat biopsies (groups 1 and 2). Student's t-test and one-way ANOVA were used to analyze the parametric data, and the Mann-Whitney U test was used to compare the means of PSAV, PSAV%, variation and PSAV%/Variation. All statistical procedures were performed with SPSS v.13.0 (SPSS Inc., Chicago, IL).

Results

One hundred eighteen men men with a mean age of 62 years met inclusion criteria. Thirty-one patients had a repeat biopsy at a mean follow up of 27.4 months. The baseline characteristics are described in Table 1. Nine out of 31 patients (29%) had prostate cancer on repeat biopsy. In eight of those men, cancer was detected on the first repeat biopsy. In one man, cancer was detected on a second repeat biopsy.

In the 109 patients without cancer (groups 2 and 3), 66 had a negative PSAV over the first year, and 29/65

TABLE 1. **Patient characteristics**

	Group 1	Group 2	Group 3	All	p
n	9	22	87	118	
Age mean (± SD)	57 (6.4)	62 (10.2)	63 (9.0)	62 (9.1)	0.276
Baseline PSA mean (± SD)	8.85 (7.5)	7.7 (3.4)	6.5 (4.0)	6.9 (4.2)	0.217
PSA at repeat bx mean (± SD)	11.2 (7.8)	8.3 (4.8)	NA	9.1(5.8)	0.217

had negative PSA in long term follow up. Among men with cancer (group 1), two had an initial decline in PSA after baseline biopsy followed by a rise. For these men, PSAV was calculated using only the timeframe during which PSA was rising.

There were nine patients in group 1, but one patient was diagnosed with cancer within the first year of follow up. Since the 4 month follow up PSA values were excluded, this patient only had an insufficient number of PSA measurements for regression analysis according to our methods. Therefore only eight of the nine cancer patients were included in the PSA parameter analysis.

In comparing group 1 and 2, Table 2, both PSAV and PSAV% were significantly different ($p = 0.004$ and $p = 0.007$, respectively). Variation was also significantly different ($p < 0.001$) when comparing group 1 to group 2 or to all men without cancer (group 2 and 3).

The mean PSA%/Variation for group 1 was 1.07 compared to 0.03 for men in group 2, suggesting that among men with negative biopsy correction by variation completely eliminated the clinically observed rise in PSA, which prompted biopsy.

Upon ROC analysis, PSAV%/Variation had the best overall diagnostic accuracy of all tested parameters with an area under the curve (AUC) of 0.881. Using a PSAV%/Variation cut off of 0.77, 86.4% specificity was observed at a sensitivity of 87.5%. At the same sensitivity, the specificity of PSAV% and PSAV were 77.3% and 63.6%, respectively. Relative to PSAV%/Variation, AUC for both PSAV% and PSAV was also reduced to 0.784 and 0.744, respectively, Figure 1.

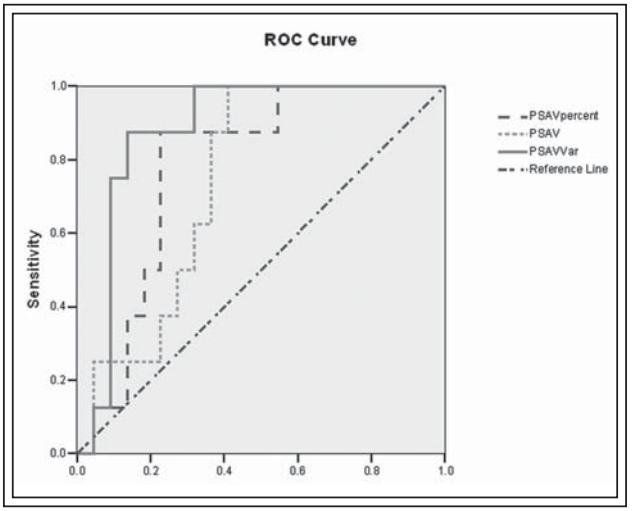

Figure 1. Receiver operating characteristic (ROC) curve.

TABLE 2. **PSA parameters and variation**

Parameters	Group 1	Group 2	p (1 versus 2)	Group 3
n	9	22		87
Median PSAV% (range)	18.13 (4.05 - 39.11)	5.66 (-201.39 - 61.56)	0.004	5.65 (-385.18 - 62.92)
Median PSAV (range)	1.11 (0.72 - 3.77)	0.30 (-12.69 - 4.57)	0.007	0.06 (-3.75 - 1.33)
Median variation (range)	0.15 (-0.93 - 1.91)	21.75 (12.47 - 79.64)	< 0.001	20.48 (0.52 - 85.24)
Median PSAV%/Var (range)	1.09 (0.47 - 1.63)	0.24 (-2.54 - 1.91)	< 0.001	-0.08 (-2.95 - 1.54)

Note: Median PSAV given in ng/ml/year; Median variation given in %; Var = variation

Discussion

Various PSA derivatives have been evaluated to improve the specificity of PSA, and numerous studies have demonstrated that PSAV is elevated in men with prostate cancer compared to those who are never diagnosed with cancer.[5-8] Traditionally, PSAV has been calculated as the slope of the linear regression in ng/ml/year. Carter et al observed that when PSA was measured over 18 months, less than 5% of men without prostate cancer had a PSAV greater than 0.75 ng/ml/year and approximately 70% of men with prostate cancer had a PSAV greater than 0.75 ng/ml/year.[5] A large prospective screening study by Smith and Catalona showed cancer in 47% of men with PSAV greater than 0.75 ng/ml/year and in 11% of men with PSAV less than 0.75 ng/ml/year.[8]

Smith et al also demonstrated that the PSAV cut off point was different in men whose initial PSA levels were normal compared to those whose were elevated. In men whose initial PSA levels were normal, the PSAV was more predictive of cancer in younger men than in older men.[8] A follow up study on 6844 men revealed that 48% of cancers would have been missed using the 0.75 ng/ml/year cut off and proposed using a threshold of 0.4 ng/ml/year in men younger than 60 years old.[9]

In fact, the relative risk of cancer in any cohort would likely be greatly affected by the patient composition. In our patient population, we would have achieved a maximum sensitivity of 87.5% and specificity of 63.6% using a PSAV cut off of 0.84 ng/ml/year. For this reason we hypothesized that calculating PSAV as a percent change instead of an absolute value may obviate the need to stratify velocity cut offs based upon the patients' baseline characteristics.

To additionally minimize the effect of variation on the percent change, we used median PSA in the denominator of our PSAV calculation instead of baseline (prebiopsy) PSA. While baseline PSA in the denominator would compute PSAV as an annualized percent change from the time we began measuring PSA, we believe the PSAV already accounts for all the PSA measurements and the time course over which these were drawn. Once the slope is obtained, the baseline PSA is no longer useful as a temporal reference point. While PSAV has traditionally been calculated as the slope of the linear regression in ng/ml/year, the AUC in this patient population was maximized by incorporating adjustments for variation. When we adjusted PSAV% for observed variation, our specificity improved to 86.4%.

We required patients have at least three PSA values measured 4 to 6 months apart. The major factors that influenced the PSAV were sampling interval between measurements, and to a lesser extent, the number of repeat measurements. Carter et al derived the PSAV cut off of 0.75 ng/ml/year based on three measurements and on PSA that were sampled long term (2 years) but not short term (3-6 months).[10] While some suggest that two PSA measurements is sufficient to calculate PSAV, this applies to two measurements 6 months apart in the same year, and is particularly useful if it is the year before cancer is diagnosed.[11] There was only one patient in our study in whom cancer was diagnosed within 1 year of the initial biopsy.

We observed that variation was significantly lower in men with cancer than those without. Even those men who had a declining PSAV and were not biopsied tended to have a greater variation than men with cancer. Variation, therefore, may be used independently to gauge the clinician's suspicion of malignancy in follow up.

We believe it is a powerful observation that men with perceived rise in PSAV are demonstrated to have no rise upon making adjustments for variation. In our study, dividing the PSAV by the median PSA reduced the velocity, and correction of the PSAV% by variation completely cancelled out the rise in PSA in men without cancer. This suggests that incorporation of variation may allow more accurate decision making regarding PSA rise in prospective clinical follow up.

This study focuses on men with negative extended core biopsy in whom it is unclear whether to perform a repeat biopsy. Our calculation of PSAV may have been optimal in these men because they all had an elevated PSA warranting the first biopsy. It is unclear whether this parameter, or PSAV%/Variation, would be equally as successful if applied to a population of men with normal PSA levels who never had an initial biopsy.

This study is significantly limited by the small number of subjects who met inclusion criteria and the small numbers of follow up cancers. The number of men with a previous negative biopsy, at least three follow up PSA values, and no findings of HGPIN or atypia was a small percentage of our total prostate biopsy population. Many studies which focus on negative biopsy populations include patients with HGPIN or atypia. We felt it was important to exclude these patients because in our center (as in most) they are empirically rebiopsied and we wanted to focus on PSAV as a sole indication for repeat biopsy.

Additionally, our patients visited various laboratories to have PSA drawn, and even in those who visited the same laboratory, different assays may have been used at different points in time. Variation ranged between 20%

to 30%, which was compatible with known rates of up to 20%-46% due to biological and analytical variation alone.[12] Although this is a limitation of the study cohort, we would assert that it is truly representative of clinical practice, and that our observations may suggest that PSAV%/Variation may overcome assay variability.

Repeat biopsy was not performed in all men. This may have resulted in an inaccurate assessment of total numbers of missed cancers, thereby falsely elevating the sensitivity and overall predictive accuracy of our velocity based PSA parameters. Once again, we would assert that this is truly more representative of clinical practice, and that we were most interested in evaluating the performance of PSAV as a sole predictive factor for missed significant cancer. Whether cancers missed in men with stable or declining PSAV are clinically significant must be assessed through additional study and long term clinical follow up. Undoubtedly, the performance of PSAV and PSA doubling time in the urologic literature has been improved by the fact that it is PSA rise that most often prompts repeat biopsy. Although we accept small sample size as a fundamental limitation of this study, we do not believe it makes our preliminary observation invalid. We stress this by only concluding that our initial observation is provocative and deserves attention in a larger cohort, prospectively evaluated. For this reason, we feel it deserves mention in the urologic literature.

Conclusions

Despite the recognized limitations of our study, we believe several important observations are made. First, the use of PSAV% calculated as a percentage change rather than PSAV could avoid the need to stratify cut offs based upon baseline patient characteristics. Introduction of methods to correct for variation would render PSAV a more reliable parameter and could overcome the physiologic and interassay variability of PSA previously observed. PSAV%/Variation is a provocative parameter which greatly improves the specificity of PSAV. Our preliminary observations deserve prospective validation in a larger cohort. □

References

1. Singh H, Canto EI, Shariat SF, Kadmon D, Miles BJ, Wheeler TM et al. Predictors of prostate cancer after initial negative systematic 12 core biopsy. *J Urol* 2004;171(5):1850-1854.
2. Taneja SS. Optimizing prostate biopsy strategies for the diagnosis of prostate cancer. *Rev Urol* 2003;5(3):149-155.
3. Eastham JA, Riedel E, Scardino PT, Shike M, Fleisher M, Schatzkin A et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA* 2003;289(20):2695-2700.
4. Wedmid A, Taneja SS. The role of PSA velocity in the management of men with negative prostate biopsy. *J Urol* 2005;174:A1467.
5. Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267(16):2215-2220.
6. Karazanashvili G, Abrahamsson PA. Prostate specific antigen and human glandular kallikrein 2 in early detection of prostate cancer. *J Urol* 2003;169(2):445-457.
7. Park SJ, Miyake H, Hara I, Eto H. Predictors of prostate cancer on repeat transrectal ultrasound-guided systematic prostate biopsy. *Int J Urol* 2003;10(2):68-71.
8. Smith DS, Catalona WJ. Rate of change in serum prostate specific antigen levels as a method for prostate cancer detection. *J Urol* 1994;152(4):1163-1167.
9. Loeb S, Roehl KA, Catalona WJ, Nadler RB. Prostate specific antigen velocity threshold for predicting prostate cancer in young men. *J Urol* 2007;177(3):899-902.
10. Carter HB, Pearson JD, Waclawiw Z, Metter EJ, Chan DW, Guess HA *et al*. Prostate-specific antigen variability in men without prostate cancer: effect of sampling interval on prostate-specific antigen velocity. *Urology* 1995;45(4):591-596.
11. Yu X, Han M, Loeb S, Gashti SN, Yeh JT, Roehl KA et al. Comparison of methods for calculating prostate specific antigen velocity. *J Urol* 2006;176(6 Pt 1):2427-2431;discussion 2431.
12. Nixon RG, Wener MH, Smith KM, Parson RE, Strobel SA, Brawer MK. Biological variation of prostate specific antigen levels in serum: an evaluation of day-to-day physiological fluctuations in a well-defined cohort of 24 patients. *J Urol* 1997;157(6):2183-2190.

EDITORIAL COMMENT

The authors of this study have made a very interesting observation that the use of percent variation in PSAV for repeat prostate biopsies yields a higher positive rate when compared to the PSA or PSAV by itself. Calculation of % variation in PSAV takes into account the median PSA and thus adjusts for factors (inflammation, large gland size, age) that may increase the absolute PSAV or absolute PSA secondary to nonmalignant causes. Free PSA, PSA velocity, PSA density, age adjusted PSA, and more recently lowering the threshold for initial biopsy in younger men are all tools available in clinical practice to increase positive yield on initial and repeat prostate biopsies. Although the design of this study and its findings are suggestive, its biggest limitation is a very small sample size (only 8 positive cancer cases analyzed). A larger cohort with a longer prospective follow up may help further validate the authors hypothesis. Use of %PSAV may provide clinicians with another factor to consider when deciding on a treatment course for patients with persistently elevated PSA with a prior negative prostate biopsy.

Amar Singh, MD
Chief, Minimally Invasive Surgery
Urological Oncology
Erlanger Medical Center
Chattanooga, TN