Prostate-Specific Antigen 'Velocity' as a Diagnostic Test for Prostate Cancer

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Background: Prostate-specific antigen ''velocity'' (slope) is promoted as a diagnostic test for prostate cancer, but its clinical usefulness is uncertain. Accordingly, we evaluated the sensitivity of prostate-specific antigen (PSA) velocity among men who are diagnosed subsequently with prostate cancer.

Methods: Among 64,545 men receiving primary care at any of nine Veterans Affairs Medical Centers during 1989–1990, 1,313 men at least 50 years old had an incident diagnosis of prostate cancer during 1991–1995. PSA velocity values obtained prior to diagnosis (''test'') were compared with results from prostate biopsies (''truth'').

Results: Among men ($n = 493$) with at least two tests before diagnosis, the sensitivity of PSA velocity ≥ 0.75 ng/mL/yr was 75.5% (95% confidence interval [CI] 71.7–79.3) overall and 48.1% (95% CI 34.8–61.5) among men with normal values of PSA (< 4.0 ng/mL). Based on published data for specificity and prevalence, the estimated positive predictive value of PSA velocity ≥ 0.75 ng/mL/yr is as low as 5%.

Conclusion: PSA velocity may have limited usefulness as a diagnostic test for prostate cancer.

Key words: prostatic neoplasms, prostate-specific antigen, mass screening

Although prostate-specific antigen (PSA) is endorsed as a screening test for prostate cancer,[1] direct evidence is not available to confirm that PSA testing improves survival.[2] Several strategies have been devised to improve the performance of PSA, including age- and race-specific reference ranges.[3,4] Other approaches modify a single, routine PSA measurement, such as PSA density (the value of PSA divided by the apparent volume of the prostate gland)[5] and the ratio of PSA that is free versus bound (in a chemical complex with α_1-antichymotrypsin).[6] Another method involves calculating the rate of change in PSA, called PSA slope or ''velocity''; a higher rate of change has been associated with a higher risk of developing prostate cancer.[7]

Among options for modifying PSA as a test, PSA velocity can be calculated without the need for additional procedures (ultrasonography) or special assays (free vs bound PSA). In an initial study of the rate of change in PSA before diagnosis of prostate cancer, an increase of 0.75 ng/mL/yr was reported to be a sensitive test for prostate cancer.[7] The performance of this ''rule of thumb'' for PSA has not been well studied in clinical practice, however, and the clinical usefulness of the strategy is therefore uncertain.[8] This brief report assesses the operating (test) characteristics of PSA velocity as a marker for the development of prostate cancer, using data from clinical practice settings.

Methods

Based on a previous study,[9] the source population was 64,545 men, at least 50 years of age, receiving care in outpatient primary care clinics at any of nine Department of Veterans Affairs (VA) Medical Centers in New England during 1989–1990. After men with a diagnosis of prostate cancer as of December 31, 1990, were excluded, 1,313 men had a new (incident)

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diagnosis of prostate cancer during 1991–1995, as identified by electronic databases and pathology registries at each institution. The medical records for these men were obtained and photocopied for subsequent review. PSA values during 1990–1995 from the laboratory database at each facility were also retrieved, and data from both sources were merged at the West Haven VA Clinical Epidemiology Research Center.

Measurements of PSA (ng/mL) up to the date of diagnosis were included in calculating the rate of change (velocity). If any two successive PSA values were associated with a rate of change of at least 0.75 ng/mL/yr, that patient was considered to have a positive test. The sensitivity of PSA velocity (proportion with a positive test among those with cancer) and a corresponding 95% confidence interval (CI) were then calculated. This calculation of "serial" slopes recreates clinical practice and is conservative, that is, it enhances the sensitivity of PSA velocity by providing the greatest number of positive tests (and the "best" sensitivity) compared with calculations based on three or more PSA values. In an alternative analysis, PSA velocity was also calculated using a regression model of all values before diagnosis, as well as for the group of men with at least three PSA tests over a 24-month period.

Results

Among all men ($N = 1,313$) with prostate cancer, 980 (75%) had at least one PSA test done prior to diagnosis. Men with two or more PSA tests ($n = 493$) before diagnosis compared with men with a single test ($n = 487$) had similar median values of age (72 years) and Gleason score (6) but were less likely, as expected, to have nonlocalized disease (4% vs 11%, respectively) and had a 1.4 ng/mL lower median PSA. Among men with more than one PSA, the median interval between the first and last tests was 9.8 months (interquartile range 3.8–19.3 months).

Among the 493 men with at least two PSA values, the rate of change in PSA prior to diagnosis was first determined based on two successive values. As shown in Table 1, 372 men had PSA velocity ≥ 0.75 ng/mL/yr, for a sensitivity of 75.5% (95% CI 71.7–79.3). Table 1 also shows the results for PSA velocity ≥ 0.75 ng/mL/yr among clinically relevant subsets of men, including a sensitivity of 72.6% (95% CI 66.2–79.0) for men 70 years or younger ($n = 186$) and a sensitivity of 48.1% (95% CI 34.8–61.5) for men ($n = 54$) with normal values of PSA (< 4.0 ng/mL).

In an alternative analysis, also shown in Table 1, a regression model of all prediagnosis PSA values ($n = 493$) provided a calculated sensitivity of 61.5% (95% CI 57.2–65.8). Among the group of men ($n = 84$) with at least three values over 24 months, the sensitivity was 58.3% (95% CI 47.8–68.9). Exploratory analyses of our results (data not shown) did not find improved sensitivity of PSA velocity among men with nonlocalized prostate cancer or among men who subsequently died during follow-up.

Table 1 Sensitivity of Prostate-Specific Antigen Velocity Based on Specific Calculation (See Text) and among Defined Groups of Patients

Calculation of Velocity: Group	*Sensitivity (%)** (n/N)	95% CI
"Best" two successive PSA tests		
All men	75.5 (372/493)	71.7–79.3
Men age 70 yr or younger	72.6 (135/186)	66.2–79.0
Men with PSA < 4.0 ng/mL	48.1 (26/54)	34.8–61.5
Regression model of all PSA tests		
All men	61.5 (303/493)	57.2–65.8
Men with ≥ 3 tests in 24 mo	58.3 (49/84)	47.8–68.9

CI = confidence interval; PSA = prostate-specific antigen.
*For PSA velocity threshold of ≥ 0.75 mg/mL/yr.

To characterize the clinical usefulness of PSA velocity as a diagnostic test, Figure 1 shows predictive values calculated using actual results for sensitivity from the current study patients, combined with estimated data for hypothetical patients receiving annual screening. A yearly prevalence for prostate cancer of 0.1723% was based on clinical data collected for the Surveillance, Epidemiology, and End Results Program.[10] When these values are combined with a "very favorable" specificity of 97.5% from a published study,[11] the positive predictive value of PSA velocity is 5.0%. Accordingly, despite a positive likelihood ratio of (0.755/[1 − 0.975] =) 30.2, only 1 of 20 positive tests would indicate cancer. If the yearly prevalence of prostate cancer is increased by a factor of 10 (to 1.723%), "favoring" PSA velocity, the positive predictive value (data not shown) increases to 34.6%.

Discussion

This study represents a contemporary example of how a diagnostic test (PSA velocity), in the context of low prevalence of disease (prostate cancer) in the general population will generate many more false-positive than true-positive tests. For every 20 tests done, as few as 1 test would detect cancer, whereas the other 19 would generate anxiety and subsequent

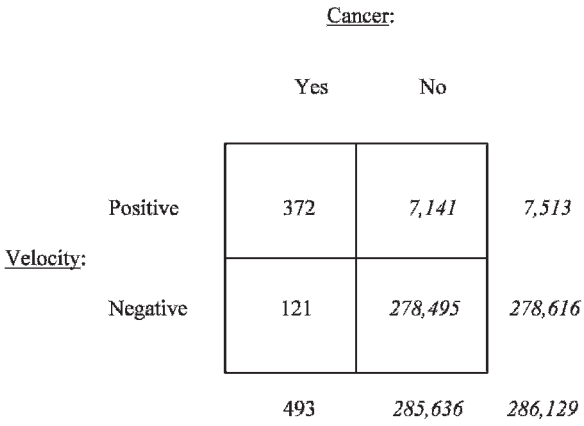

Figure 1 Predictive values of prostate-specific antigen velocity based on observed sensitivity and reported specificity in a hypothetical population. Prevalence = 0.1723% (from Ries and colleagues[10]) = 493 (observed of /286,129 (calculated); sensitivity = 372 of 493 = 75.5% (from current analysis); specificity = 97.5% (from Ciato and colleagues[11]) = 278,495 of 285,636; positive predictive value = 372 of 7,513 = 5.0%; negative predictive value = 278,495 of 278,616 = 99.96% (hypothetical values in italic font).

testing, with additional cost and potential morbidity. Importantly, the sensitivity of the PSA slope was lower among clinically relevant groups of men, including those 70 years or younger, those with initially normal PSA values, and those with three or more PSA values over 2 years. Although clinical practice algorithms often use a PSA velocity of 0.75 ng/mL/yr to help identify prostate cancer, the results suggest that the utility of the test is limited.

The sensitivity of 75.5% for PSA velocity in the current investigation, using the most "favorable" approach, is similar to the value of 72% from a frequently cited study,[7] but that initial report did not comment on how prevalence affects the predictive accuracy of a diagnostic test. Additional studies on this topic include an American Cancer Society report examining the 0.75 ng/mL/yr threshold among 171 men with prostate cancer, with a sensitivity of 54.8%.[12] A more recent analysis[11] of the same PSA velocity threshold found a sensitivity of 55.5% during 4 years of follow-up among 18 men diagnosed with prostate cancer. Thus, the sensitivity of PSA velocity may vary in different situations, a finding consistent with spectrum bias[13] that further limits the usefulness of a test.

Another study[14] compared patients with and without cancer and found a statistically significant difference in PSA velocity, but using such an approach does not provide pertinent information (ie, predictive values) for clinicians measuring PSA velocity prospectively. Other studies have been done in selected subgroups of patients, such as among men with localized disease treated with prostatectomy[15] or radiation therapy.[16] These reports address a different research topic, however, assessing PSA velocity as a prognostic factor for patients receiving selected treatment modalities.

A multidisciplinary panel convened by the American Urological Association reported that "no consensus [exists] on the optimal strategies for using the different modifications of PSA testing," including PSA velocity.[8] Subsequently, data from the European Randomised Study of Screening for Prostate Cancer found the mean PSA velocity of men later diagnosed with prostate cancer to be significantly higher (0.62 ng/mL/yr) than among men with a negative biopsy (0.46 ng/mL/yr), but the overlap in values was considerable, and the authors concluded that "PSA dynamics were of limited value."[17] In addition, a multivariable analysis of data from the same European trial found that PSA velocity "did not appear to be a useful screening tool for the identification of these cancers."[18] Our study's findings, among US veterans, confirm the conclusions of these recent reports.

The distribution of PSA values has "shifted to the left" (ie, toward lower values) since the time period of our study,[19] so we examined the performance of PSA velocity among men with normal PSA values (< 4.0 ng/mL) at baseline. The sensitivity of PSA velocity was less than 50% for these men, representing the group most likely to receive a biopsy for a "positive" PSA velocity (because abnormal PSA values would likely lead to a biopsy, regardless of velocity). The corresponding positive predictive value would be worse than the calculated 5% for the overall study population, suggesting a very limited usefulness for PSA velocity in contemporary clinical practice. In this context, a recent report[20] of men with baseline PSA values from 2.6 to 4.0 ng/mL found that a PSA velocity of 0 ng/mL/yr or greater was predictive of prostate cancer, casting more doubt on the validity of a single threshold for PSA velocity.

The limitations of the current study include a lack of men without prostate cancer, a group needed to determine the specificity of PSA velocity directly in this population. The data were collected early in the PSA era, so many men did not have two PSA values obtained prior to diagnosis, especially in 1991–1992, when the digital rectal examination was the most common method of diagnosis. In addition, PSA velocity may perform better in a controlled (research) setting, with intensive follow-up and a strict protocol.

Nonetheless, the current study has many more men with prostate cancer than the original report[7] and includes data from actual clinical practice.

Our multicenter study of men receiving primary care did not find PSA velocity to be a sensitive marker of incident prostate cancer. Annual PSA testing among asymptomatic men is promoted,[8] but questions have been raised regarding the overall impact of such screening programs.[9,21] As a modification intended to improve the usefulness of PSA, the rate of change in PSA may have limited clinical effectiveness.

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