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Distribution of PSA Velocity by Total PSA Levels: Data From the Baltimore Longitudinal Study of Aging

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Abstract

OBJECTIVES—To describe the distribution and implications of prostate-specific antigen velocity (PSAV) by prostate-specific antigen (PSA) in an unselected population. A PSAV >0.35 and >2.0 ng/mL/y have been associated with an increased risk of prostate cancer (CaP) death more than 10 years and 1 year before diagnosis, respectively. It is unknown how frequently PSAVs of this magnitude occur in community men.

METHODS—From the Baltimore Longitudinal Study of Aging, we examined the PSAV distribution in 786 men with serial PSA measurements (3474 PSAV observations) at total PSA levels <10 ng/mL. We also determined whether PSAV altered the probability of overall and life-threatening CaP at PSA levels <3 and 3–10 ng/mL.

RESULTS—Overall, the mean PSA and PSAV were 1.3 ng/mL and 0.05 ng/mL/y, respectively. PSAV rose continuously with increasing PSA ($P < .0001$), and was significantly higher in cancers than controls for observations at PSA levels <3 ng/mL ($P = .02$) and 3–10 ng/mL ($P = .0008$). The probability of life-threatening CaP was 3% at a PSA <3 ng/mL, but increased to 13.6% with PSAV >0.4 ng/mL/y. At PSA levels of 3–10 ng/mL, the probability of life-threatening CaP was 9.8% based on PSA alone vs 12% with PSAV >0.4 ng/mL/y.

CONCLUSIONS—PSAV was significantly higher in CaP observations than controls in all PSA ranges studied and altered the risk of overall and life-threatening CaP at a given PSA level. Because the value of PSAV is PSA-dependent, the PSA level should be taken into account when interpreting PSAV.

Prostate-specific antigen (PSA) was initially approved by the U.S. Food and Drug Administration using a threshold of 4 ng/mL as the upper limit of normal. However, approximately 15% of men with a PSA <4 ng/mL and normal digital rectal examination have biopsy-detectable prostate cancer.¹ Moreover, among men with prostate cancer, the probability of organ-confined disease and recurrence-free survival are directly related to the PSA level at diagnosis.² Accordingly, some urologists currently recommend a prostate

biopsy at lower PSA thresholds, such as 2.5 or 3 ng/mL (the threshold used in the European Randomized Study of Screening for Prostate Cancer).³

However, Welch et al estimated that reducing the PSA threshold from 4.0 to 2.5 ng/mL would cause an additional 1.8 million men aged 40–69 years to be labeled as “abnormal.”⁴ In addition, there is concern that the use of lower PSA thresholds could increase the detection of potentially indolent tumors.⁵

In light of these controversies, PSA kinetics have emerged as a variation on the use of PSA, which may have greater specificity for clinically significant prostate cancer. PSA velocity (PSAV) was initially described in a small sample of participants from the Baltimore Longitudinal Study of Aging (BLSA).⁶ Specifically, a PSAV greater than 0.75 ng/mL/y was significantly associated with prostate cancer rather than benign prostatic hyperplasia.

Today, the majority of men undergoing prostate cancer screening have total PSA levels <4. For example, in men aged 40 and older from the National Health and Nutrition Examination Survey (NHANES) 2001–02 sample, the mean PSA level was 1.56 ng/mL (95% CI, 1.3–1.74).⁷ The proportion of men in their 40s, 50s, and 60s with PSA levels >4 ng/mL were 1.5%, 5.3%, and 5.7%, respectively.

Accordingly, recent investigation has focused on the use of PSAV among men with lower total PSA levels.⁸ Indeed, it is possible that PSAV may be most useful for risk stratification many years before diagnosis at a time when the total PSA is low.⁹ Although PSA and PSAV are closely associated,¹⁰ relatively little is known about the joint distribution of these parameters in community-based populations. Thus, the objective of our study was to perform a descriptive analysis of the PSAV at various total PSA levels among men in the BLSA, and to examine whether the implications of PSAV are PSA-dependent.

MATERIAL AND METHODS

The BLSA is a prospective cohort study, beginning in 1958, of the National Institute on Aging designed to evaluate the effects of aging. Study participants undergo medical examinations approximately every 2 years, as previously described.⁶ All subjects provided written informed consent, and the study protocol was approved by the Institutional Review Boards of MedStar and the Johns Hopkins Medical Institutions (Baltimore, MD).

Beginning in 1991, prostate cancer screening was performed at each examination. Men with PSA levels >4 ng/mL and/or suspicious digital rectal examination were notified and recommended to undergo biopsy outside the study protocol. PSAV was not used as a criterion for biopsy. The Tandem R assay (Hybritech, Inc., San Diego, CA) was used for all PSA measurements.

Of the 1806 male BLSA participants, 1201 (66.5%) had PSA measurements, using frozen sera samples stored at –70°C for visits performed before September 9, 1991, or on sera collected prospectively for visits after September 9, 1991. PSA measurements were excluded for men with finasteride use, observations at PSA >10 ng/mL, suspected laboratory error, and <2 PSA measurements before either prostate cancer diagnosis, surgery for benign

prostatic hyperplasia, or the final study visit. The final study population thus included the remaining 786 men with serial PSA measurements, yielding a total of 3474 PSAV observations. Because of the longitudinal nature of the BLSA, it was common for participants to have numerous PSA (and PSAV) measurements at varying time intervals before diagnosis or censorship.

PSAV was calculated as the running average of the rate of change over 3 consecutive visits (the index visit and the 2 preceding visits), when more than 2 PSA measurements were available as in previous studies ($n = 2688$),⁶ or as the simple rate of change for the first 2 PSA measurements ($n = 786$).

First we examined the mean PSAV for observations in men with and without prostate cancer within the following total PSA ranges: <3 and $3\text{--}10$ ng/mL. We selected the PSA threshold of 3 ng/mL, which was used in the European Randomized Study of Screening for Prostate Cancer.³ In addition, we calculated the proportion of observations with a PSAV >0.4 or >2 ng/mL/y (previously associated with prostate cancer mortality^{9, 11}), stratified by the total PSA level. Of note, because PSAV thresholds of 0.35 and 0.4 ng/mL/y have been used in the literature, we used the rounded value (0.4 ng/mL/y) in the current analysis for simplicity of calculation.

We also performed subset analysis in observations at a PSA <3 ng/mL to examine the proportion with a PSAV >0.4 ng/mL (previously suggested as a PSAV threshold for men with lower total PSA levels⁸) at varying time intervals before prostate cancer diagnosis (cases) or censorship (controls). Finally, we calculated the probability of overall and high-risk prostate cancer based on PSA alone (<3 vs $3\text{--}10$ ng/mL), and the shift in this probability with the additional information of a PSAV >0.4 or >0.4 ng/mL/y. For this analysis, high-risk or life-threatening prostate cancer was defined as a PSA ≥ 20 ng/mL, Gleason score of 8–10, or confirmed prostate cancer death, as previously described.¹²

Study group characteristics at baseline were compared using one-way analysis of variance. Mixed effects models, with a random slope for intercept to account for the intraindividual correlation between multiple PSAV measurements were used when examining all observations. R (R. Development CoreTeam, <http://www.R-project.org>, version 2.9.0) was used for all statistical analyses.

RESULTS

Table 1 shows the demographics of the study population. Overall, the mean initial age was 55.4 years (53.5 years in men with PSA <3 and 69.7 years in men with PSA $3\text{--}10$ ng/mL). The racial distribution was 79% Caucasian, 17% African American, and 4% other. The median initial PSA and PSAV in the overall study population were 1.0 ng/mL (range, 0–9.9) and 0.04 ng/mL/y (range, -7.8 to 3.8), respectively.

Overall, PSAV rose continuously with increasing total PSA in both prostate cancer cases and controls ($P < .0001$). However, PSAV was significantly higher in prostate cancer cases than controls for observations at PSA levels <3 ng/mL ($P = .02$) and from $3\text{--}10$ ng/mL ($P = .0008$). Specifically, the mean PSAV was 0.02 (± 0.29) and 0.30 (± 0.59) ng/mL/y in

observations from controls at PSA levels <3 and 3–10 ng/mL, respectively. Among prostate cancer cases (without regard to time before diagnosis), the mean PSAV was 0.08 (± 0.25) ng/mL/y for observations at PSA levels <3 ng/mL and 0.50 (± 0.67) ng/mL/y at PSA levels from 3–10 ng/mL.

The proportion of observations with a PSAV >0.4 or >2 ng/mL/y was also highly dependent on the total PSA level. Figure 1A shows the distribution of PSAV in observations from cancer cases and controls at PSA levels <3 ng/mL. In this PSA range, 1.1% and 5% of observations from controls and prostate cancer cases, respectively, had a PSAV >0.4 ng/mL/y. No observations at a PSA <3 ng/mL had a PSAV >2 ng/mL/y in either group.

At PSA levels of 3–10 ng/mL (Fig. 1B), 34% and 1.6% of observations in controls had a PSAV >0.4 and >2 ng/mL/y, respectively. Among prostate cancer cases in this PSA range, 46% of observations had a PSAV >0.4 ng/mL/y and 3% had a PSAV >2 ng/mL/y.

Figure 2 shows the proportion of observations with a PSAV >0.4 ng/mL/y at varying time intervals before diagnosis or censorship in the subset with PSA levels <3 ng/mL. PSAV was significantly higher in observations from prostate cancer cases than controls even 10–20 years before diagnosis at a time when total PSA was low.

Finally, Figure 3 shows the probability of overall and life-threatening prostate cancer using PSA and PSAV. Among men with a PSA <3 ng/mL, the probability of overall prostate cancer was 10% with PSA alone, which increased to 34% for those with a PSAV >0.4 ng/mL/y (Fig. 3A). At PSA levels of 3–10 ng/mL, the probability of prostate cancer was 34% considering PSA alone and 45% for those with a PSAV >0.4 ng/mL/y (Fig. 3B).

As shown in Figure 3C, the probability of life-threatening prostate cancer was 3% at PSA levels <3 ng/mL, but was 13.6% for those with a PSAV >0.4 ng/mL/y. At PSA levels of 3–10 ng/mL, the probability of life-threatening prostate cancer was 9.8% based on PSA alone, and 12% with the additional information of a PSAV >0.4 ng/mL/y (Fig. 3D).

COMMENT

Several recent studies have demonstrated a relationship between PSA velocity in the year before prostate cancer diagnosis and cancer-specific mortality after treatment. D'Amico et al first examined this issue among 1095 men undergoing radical prostatectomy.¹¹ In multivariable Cox regression analysis with total PSA, clinical stage, and biopsy Gleason score, a preoperative PSAV >2 ng/mL/y was associated with a 9.8-fold increased hazard ratio for prostate cancer death (95% CI, 2.8–34.3, $P < .001$) when compared with a PSAV of 2 ng/mL/y or less. Similar results were reported in a separate population of 358 men with localized prostate cancer undergoing external beam radiation therapy.¹³ Specifically, a pretreatment PSAV >2 ng/mL/y was associated with a 12-fold increased risk of prostate cancer mortality (95% CI, 3.0–54.0, $P = .001$) when compared with a PSAV of 2 ng/mL/y or less.

Other studies have examined the implications of PSAV in community men undergoing PSA testing. For example, our group previously reported that a PSAV >0.35 ng/mL/y was

associated with a five-fold increased risk of prostate cancer death more than a decade later when compared with those with a PSAV >0.35 ng/mL/y.⁹

Although numerous studies have characterized the total PSA distribution in a population-based setting,⁷ less is known about the overall distribution of PSAV in community men. This information would be useful in establishing appropriate clinical cutpoints. For example, if one were to use a PSAV threshold of 0.4 ng/mL/y to recommend a prostate biopsy, how many ambulatory community men would be labeled as having an “abnormal” PSA velocity, and does the prevalence depend upon the total PSA level?

In the current study, we found that only 1.1% of control observations at a PSA <3 ng/mL had a PSAV >0.4 ng/mL/y. Thus, very few men with “normal” PSA levels <3 ng/mL would be considered to have an “abnormal” PSAV through the use of this threshold. Moreover, among men with PSA levels <3 ng/mL whose probability of life-threatening prostate cancer was low (3%), the presence of a PSAV >0.4 ng/mL/y increased the probability of high-risk disease to 13.6%.

By contrast, a much larger proportion (34%) of observations from controls with PSA levels from 3–10 ng/mL had a PSAV >0.4 ng/mL/y. In this PSA range, a PSAV >0.4 ng/mL/y altered the probability of life-threatening prostate cancer to a lesser extent (from 9.8% based on PSA alone to 12% with a PSAV >0.4 ng/mL/y). These combined findings suggest that the 0.4 ng/mL/y threshold may be more clinically relevant for men with lower PSA levels and highlight the importance of the total PSA range for interpreting PSA velocity.

For men with prostate cancer, another issue of clinical importance is the likelihood of presenting with a PSAV >2 ng/mL/y that is associated with a higher risk of fatal prostate cancer after treatment.¹¹ At PSA levels <3 and 3–10 ng/mL, in our study 0% and 3%, respectively, of observations from prostate cancer cases had a PSAV >2 ng/mL/y. These results are encouraging, suggesting that community men with PSA levels <10 ng/mL are unlikely to harbor high-risk disease.

Vickers et al recently performed a systematic review of studies on prediagnostic PSA kinetics and reached the conclusion that there is limited evidence to support incremental predictive information beyond PSA alone.¹⁴ However, it is noteworthy that their study did not stratify the data on PSAV by total PSA levels. As our results show, the PSAV distribution varies directly by PSA, and therefore a given PSAV might have very different implications within different total PSA ranges. Thus, we believe that both PSA and PSAV are most informative when considered together.

Limitations of our study is that the biopsy protocol was not standardized and the population was primarily Caucasian, such that the PSA and PSAV distributions may not be generalizable to other ethnic groups.¹⁵ In addition, despite the use of a previously published formula to calculate PSAV, the results may be different using an alternate method of calculation.¹⁶ Also, PSAV was calculated using only 2 PSA measurements in some cases. Further, few men in our study population had high-risk prostate cancer ($n = 28$) and there are many different published criteria for high-risk disease. Thus, these results should be confirmed in larger populations and using alternate risk classifications. Also, it should be

emphasized that in the primary analysis, observations were grouped together without regard to time before a prostate cancer diagnosis. This was done to simulate a clinical scenario in which patients present at differing points in the natural history of the disease. Nevertheless, PSAV levels among cases are higher within a few years of prostate cancer diagnosis. This might explain why we found a lower proportion of observations in prostate cancer cases with a PSAV >2 ng/mL/y compared with other studies that calculated PSAV exclusively in the year before diagnosis.^{11,17}

Strengths of our study included the use of a community-based population of men from an aging study, rather than a clinical cohort. In addition, the large number of PSAV observations over time (n = 3474) permitted a detailed examination of its expected distribution in unselected U.S. men, stratified by PSA.

CONCLUSIONS

There is a strong association between PSAV and total PSA in men with and without prostate cancer. The PSAV distribution was significantly higher in cancer cases than controls within all PSA ranges studied. At PSA levels <3 ng/mL, only ~1% of observations in controls had a PSAV >0.4 ng/mL/y. The presence of a PSAV >0.4 ng/mL/y among men with PSA levels <3 ng/mL increased the probability of life-threatening prostate cancer from 3% to 13.6%. A PSAV >0.4 ng/mL/y was more prevalent at PSA levels of 3–10 ng/mL and influenced the probability of life-threatening prostate cancer to a lesser degree than in men with PSA levels <3 ng/mL. Finally, fewer than 1% of observations in prostate cancer cases or controls had a PSAV >2 ng/mL/y at PSA levels <10 ng/mL.

Acknowledgments

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Figure 1. PSA velocity distribution in observations from prostate cancer cases (*triangles*) and controls (*circles*), at PSA levels (A) <3 ng/mL and (B) 3–10 ng/mL.

Figure 2.

Proportion of observations with PSA velocity >0.4 ng/mL/y over time before prostate cancer diagnosis or censorship at PSA levels <3 ng/mL.

Figure 3. Probability of (A, B) overall and (C, D) life-threatening prostate cancer for observations at PSA levels <3 (A, C) and 3–10 ng/mL (B, D). The horizontal line shows the probability based on PSA alone (without considering PSAV), and triangles/circles indicate the probability with the additional information of a PSAV ≤ 0.4 vs >0.4 ng/mL/y.

Table 1

Demographics of the study population

	Overall (n = 786)	No Cancer (n = 680)	Cancer (n = 106)	P Value*
Initial age in years, mean (SD)	55.4 (14.6)	54.8 (15.0)	58.8 (11.0)	.008
Initial PSA, ng/mL, mean (SD)	1.3 (1.5)	1.2 (1.4)	2.3 (2.1)	<.0001
Initial PSAV, ng/mL/y, mean (SD)	0.05 (0.45)	0.03 (0.42)	0.18 (0.59)	.001

* Comparison of cancers and noncancers.