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PSA Doubling Time Versus PSA Velocity to Predict High-Risk Prostate Cancer: Data from the Baltimore Longitudinal Study of Aging

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Abstract

Background—Our group has previously shown that prostate-specific antigen (PSA) velocity (PSAV) is associated with the presence of life-threatening prostate cancer. Less is known about the relative utility of pretreatment PSA doubling time (PSA DT) to predict tumor aggressiveness.

Objective—To compare the utility of PSAV and PSA DT for the prediction of life-threatening prostate cancer.

Design, setting, and participants—From the Baltimore Longitudinal Study of Aging, we identified 681 men with serial PSA measurements.

Measurements—Receiver operating characteristic analysis was used to evaluate the relationship between PSAV, PSA DT, and the presence of high-risk disease.

Results and limitations—Within the period of 5 yr prior to diagnosis, PSAV was significantly higher among men with high-risk or fatal prostate cancer than men without it. By contrast, PSA DT was not significantly associated with high-risk or fatal disease. On multivariate analysis, including

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age, date of diagnosis, and PSA, the addition of PSAV significantly improved the concordance index from 0.85 to 0.88 ($p < 0.001$), whereas PSA DT did not.

Conclusions—These data suggest that PSAV is more useful than PSA DT in the pretreatment setting to help identify those men with life-threatening disease.

Keywords

PSA kinetics; PSA doubling time; PSA velocity; Prostate cancer; Prognosis

1. Introduction

Changes in prostate-specific antigen (PSA) can be described mathematically in various ways, including PSA velocity (PSAV) and PSA doubling time (PSA DT). PSAV has primarily been used to help predict the risk and aggressiveness of prostate cancer (pCA) [1–3].

PSA DT has been primarily used in the post-treatment setting and is considered a surrogate endpoint for pCA-specific survival in men with biochemical recurrence [4,5]. However, the role of PSA DT in predicting tumor biology prior to treatment is unclear, especially among men with an early disease state. Sengupta et al found that preoperative PSA DT predicted clinical outcomes after radical prostatectomy [6], whereas others have reported conflicting results [7].

Furthermore, some have suggested the use of PSA DT to select candidates for active surveillance [8] and to determine the need for intervention in men who have chosen surveillance [8,9]. This assumes that PSA DT would signal the presence of life-threatening pCA and allow for treatment during a window of curability. If so, PSA DT should be associated with the presence of harmful pCA at an early disease state. Thus, our objective was to evaluate the ability of PSA DT to predict aggressive pCA and to compare its performance characteristics with PSAV among men enrolled in a longitudinal aging study.

2. Methods

2.1. Selection of study cohort

Study subjects were participants in the Baltimore Longitudinal Study of Aging (BLSA), a prospective cohort study of the National Institute on Aging (Bethesda, MD, USA) as described previously [3]. Since inception in 1958, this study has included 1806 male participants who receive a comprehensive medical, physical, and neuropsychological examination at regular intervals. The Med Star Institutional Review Boards and the Institutional Review Boards of the Johns Hopkins Medical Institutions (Baltimore, MD, USA) approved this study, and all subjects gave written informed consent.

Since 1991, PSA measurements and digital rectal examination (DRE) were performed at each evaluation. Prostate biopsy was recommended for a PSA >4.0 ng/ml and/or DRE abnormality. PSA levels were measured using frozen sera samples stored at -70°C for visits before 1991. All PSA measurements were performed using a standard monoclonal immunoradiometric assay (Tandem-R, Hybritech Inc., San Diego, CA, USA).

Fig. 1 shows the selection criteria for the study population. Of 1806 male participants, 1071 had PSA measurements after age 40. Within this group, we made the following exclusions:

- Men with no PSA data prior to pCA diagnosis ($n = 38$)
- Men with no PSA data prior to prostate surgery for benign enlargement ($n = 80$)

- Men who took finasteride (Proscar; $n = 47$)
- Men with an unknown cause of death ($n = 54$)
- Men with incomplete diagnostic information ($n = 2$)
- One man with a PSA value suspected to be a laboratory error (ie, an outlier value inconsistent with other values).

For men excluded because of lack of PSA data prior to diagnosis, age and date of diagnosis were similar to the included study cohort, whereas the date of death was significantly earlier (data not shown). We also excluded 24 men diagnosed with pCA at autopsy because not all participants underwent autopsy and therefore did not have the same opportunity for cancer detection. Finally, we excluded 131 men with only one PSA measurement prior to diagnosis and 13 men with no PSA data in the 0–5 yr prior to diagnosis. After these exclusions, the final study population consisted of 681 men, including 98 (14%) with pCA and 583 (86%) with no known diagnosis of pCA.

2.2. Outcome determination and study groups

Cause of death was determined by intermittent telephone follow-up of inactive participants, correspondence from relatives, medical records, and searches of the National Death Index. For deceased BLSA subjects, cause of death was determined by a consensus of BLSA physicians reviewing all available information, including death certificates, letters from physicians and families, medical records, and autopsy reports.

The study cohort was divided into two mutually exclusive groups for comparisons: (1) men with pCA at high risk of dying of their disease (the “high-risk” group) and (2) men (the “other” group) with pCA who were alive or died of another cause and not thought to be at high risk of death from their disease as well as subjects without a clinical diagnosis of pCA. The high-risk group ($n = 27$) included men with pCA who met one of the following criteria:

- PSA ≥ 20 ng/ml at any time ($n = 5$)
- Gleason score ≥ 8 ($n = 7$)
- Confirmed pCA death ($n = 15$)

Among the men who died from pCA, six had a PSA level ≥ 20 ng/ml, and three had a Gleason score ≥ 8 .

Conversely, the “other” group included men with pCA who were not considered high risk based upon the above definition ($n = 71$). Of these men, 25 (35%) died of a cause other than pCA, and 46 (65%) were alive. In addition, the non-high-risk group included male participants without a clinical diagnosis of pCA ($n = 583$). Of these men, 432 (74%) were alive, and 151 (26%) were deceased.

2.3. PSA kinetics

The PSA data in this study were collected until August 2006. All PSA measures were censored at the time of pCA diagnosis, prostate surgery, or death. All subjects were required to have at least two PSA measurements, wherein at least one was within the 5 yr prior to diagnosis. We defined the index visit as the final visit at which PSA was measured prior to diagnosis, within 5 yr before diagnosis. PSAV and PSA DT were calculated using the PSA level at this index visit and prior visits. One hundred twenty-five (18.4%) men had two PSA measurements, and the remaining 556 (81.6%) had more than two PSA measurements for PSA kinetics calculations. For men with only two measurements, PSAV was calculated as the simple rate of change between the index and preceding visit divided by the elapsed time. When ≥ 3 PSA

measurements were available, PSAV was calculated as the running average of the rate of change over three consecutive visits (the index visit and the two preceding visits), as previously described [1]. Subgroup analysis was performed including only men with ≥ 3 PSA measurements.

PSA DT was calculated using the ratio of $\ln(2)$ and the rate of change in $\log(\text{PSA} + 1)$. Because a slope of $\log(\text{PSA} + 1)$ of 0 results in an infinite PSA DT, this was assigned a value of 100 for the purposes of analysis. For PSA DT, subgroup analysis was also performed excluding men ($n = 171$) with a negative PSA slope.

2.4. Statistical analyses

Study group characteristics were compared using pooled t tests in the case of equal variances and Cochran t tests in the case of unequal variances. The t test was also used to compare the distribution of PSAV and PSA DT between groups. Receiver operating characteristic (ROC) analysis was used to evaluate the area under the curve (AUC) for PSAV and PSA DT to discriminate high-risk pCA versus absence of high-risk pCA.

In addition, we used multivariate analysis to evaluate associations between high-risk pCA (event) with the following covariates:

- PSA
- PSAV
- PSA DT
- Age
- Date of diagnosis.

Specifically, the base model included age, date of diagnosis, and PSA to predict the presence of high-risk pCA, to which PSA kinetics parameters were then added one at a time. In these models, all covariates were treated as continuous variables, and the resultant concordance indices were determined. A bootstrap approach was then used, and the results were compared using the t test. We also compared the concordance indices using the method of Hanley et al [10].

Finally, we performed three separate subgroup analyses. First, we examined the association between PSAV and PSA DT with “fatal” pCA in addition to the separate analyses to predict high-risk disease. For these analyses, the 15 men with confirmed pCA death were considered as a separate subgroup. As described above, we also performed subgroup analysis including only men with three or more PSA measurements and a separate subgroup analysis excluding 171 men with a negative PSA slope from the PSA DT calculation. All statistical tests were two sided, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Description of diagnostic groups

The mean age was 68 yr. Of study participants, 84% were white, 12% were black, and 4% were of other ethnic groups. Overall, study participants had a median of five PSA measurements (range: 2–15) separated by a median interval of 2.1 yr and spanning a median follow-up of 12.4 yr. Although follow-up was similar between the groups, the high-risk cancer patients were significantly older (Table 1).

3.2. Distribution of PSA, PSAV, and PSA DT

The median PSA at the index visit was 16.5 ng/ml for men with high-risk PCa versus 1.5 ng/ml in those without high-risk cancer. The median PSAV in the overall study population was 0.07 ng/ml per year (mean: 0.54 ± 5.6 ; range: -7.8 to 138.7). High-risk and “other” patients had a median PSAV of 2.1 and 0.07 ng/ml per year, respectively. The median PSA DT for men with and without high-risk cancer was 3.1 yr and 9.7 yr, respectively.

3.3. PSA kinetics and high-risk prostate cancer

Table 2a compares the distribution of PSAV and PSA DT between men with and without high-risk pCA. As shown, the PSAV distribution 0–5 yr prior to diagnosis was significantly higher among men with high-risk pCA than other men ($p < 0.0001$). However, the PSA DT distribution within 5 yr prior to diagnosis was similar between high-risk and other men ($p = 0.303$). Of note, inclusion of the 24 men with autopsy-detected pCA in the non-high-risk group did not change the results (data not shown).

3.4. PSA kinetics and fatal prostate cancer

Table 2b shows the results of subgroup comparisons for the distribution of PSAV and PSA DT in men with fatal pCA. As shown, PSAV was significantly higher among men with fatal pCA than men without fatal disease ($p < 0.0001$). In contrast, the PSA DT distribution was similar between men with and without fatal pCA ($p = 0.408$).

3.5. Receiver operating characteristic analysis

The AUC for the prediction of high-risk pCA was 0.936 (0.871–1) using PSA and 0.913 (0.845–0.982) using PSAV (Fig. 2). Conversely, PSA DT predicted the absence of high-risk pCA, with an AUC of 0.636 (0.557–0.715).

3.6. Multivariate comparisons using concordance indices

First, we created a base model using age, date of diagnosis, and PSA to predict high-risk pCA, with a concordance index of 0.85. PSA DT did not improve the concordance index ($c = 0.85$). However, the addition of PSAV increased the concordance index to 0.88, representing a significant improvement in the ability to predict high-risk pCA (t test bootstrap, $p < 0.001$). Using the Hanley method [10], we were unable to demonstrate a statistical difference between the concordance indices (data not shown).

In 556 participants with three or more serial PSA measurements, the concordance index was 0.83 for the base model. The addition of PSA DT did not change the concordance index, while PSAV increased the concordance index to 0.86.

After the exclusion of 171 men with a negative PSA slope (approximately 25% of the sample), the concordance index was 0.84 for the base model. The addition of either PSA DT or PSAV increased the concordance index to 0.854 (t test bootstrap, $p = 0.0001$) and 0.866 (t test bootstrap, $p = 0.051$), respectively.

4. Discussion

An increasing body of evidence suggests that PSAV is a useful predictor for pCA aggressiveness. D’Amico et al showed that men with a PSAV >2 ng/ml per year in the year prior to diagnosis had a 9.8-fold increased risk of PCa-specific mortality after radical prostatectomy compared to men with a lower PSAV [2]. Our research group subsequently confirmed that in men from the BLSA, a PSAV >2 ng/ml per year within 2 yr of diagnosis was associated with a 20.4-fold increased relative risk of pCA death—similar to the unadjusted rate

of D'Amico et al [3]. Similar results have been reported in men undergoing radiation therapy for clinically localized disease [11].

In addition, our group recently showed that even the PSAV measured 10–15 yr before diagnosis (when most men had PSA levels <4.0 ng/ml) was associated with cancer-specific survival 25 yr later [3]. Specifically, men with a PSAV ≤ 0.35 ng/ml per year had a cancer-specific survival of 92% compared to 54% in men with a PSAV >0.35 ng/ml per year.

PSA DT has been shown to predict cancer-specific survival after treatment but not in all studies [6,7]. In general, less is known about the performance of PSA DT in the pretreatment setting. Thus, our objective was to expand upon our prior work in defining the performance characteristics of PSAV for the prediction of high-risk disease and to determine whether PSA DT provides similar prognostic value.

Similar to our prior findings within 10–15 yr prior to diagnosis, in this study, we found that PSAV within 5 yr prior to diagnosis was associated with the presence of high-risk and fatal pCA. In contrast, PSA DT was not associated with high-risk or fatal pCA and instead was a marginal predictor for the presence of good-risk disease (AUC = 0.636).

Several possible explanations exist for the differences between our findings with respect to PSA DT and those of others [8,9,12–14]. First, our population was derived from an unselected cohort of men in an aging study, whereas others have studied highly selected patient populations, such as men enrolled in surveillance programs or those undergoing radical prostatectomy [6,9]. That notwithstanding, studies discussing the PSA kinetics among men involved in surveillance programs must be interpreted with caution, because such protocols often differentially remove from surveillance those with faster rises in PSA (shorter PSA DTs). Meanwhile, men with stable or declining PSA values are more likely to remain on surveillance without further evaluation [8,9,13,14]. This creates a “self-fulfilling prophesy,” wherein physicians are more likely to recommend treatment for men on surveillance with a rising PSA, creating the appearance that PSA DT is associated with a greater likelihood of “failing” surveillance. Indeed, when we excluded men with a negative PSA slope from analysis, we likewise found an improvement in the performance characteristics of pretreatment PSA DT. However, in a clinical setting, it would be difficult to select only patients with a rising PSA, because those with a negative slope at one point may still harbor life-threatening disease.

Another difference between our study and others was that the development of high-risk or fatal pCA was our outcome of interest rather than the length of time from diagnosis to treatment [8,9], clinical progression of disease without treatment [12], or treatment outcomes following radical prostatectomy [8,9]. Nevertheless, it is not surprising that others have found a relationship between a short PSA DT and surrogates of pCA aggressiveness, given the known relationship between a rapidly rising pretreatment PSA and worse treatment outcomes [2]. That notwithstanding, showing a relationship between PSA DT and surrogates for poor outcome (cancer grade and stage) is not equivalent to demonstrating that PSA DT can be used to select appropriate candidates for active surveillance or to trigger intervention during a window of curability. On the contrary, our findings would argue that PSA DT does not accurately distinguish between those with and without life-threatening disease. Further, if PSA DT (eg, ≤ 3 yr) were used to trigger intervention in a surveillance program, it is possible that cure would be less likely by the time intervention occurred because men with PSA DTs in this range have a higher PSAV that has been associated with an increased risk of pCA death [2,3].

Several limitations should be considered when interpreting our data. First, detailed biopsy core data was not available, so its impact on cancer detection is unknown. Second, biopsy was recommended for a PSA >4 ng/ml or abnormal DRE, raising the possibility of detection bias. Furthermore, these results may not apply to men with a PSA <4 ng/ml and normal DRE.

Another limitation is that although we used all available clinical information to retrospectively categorize our cohort into groups, the potential for misclassification bias exists. For example, it is possible that some men were misclassified with regard to cause of death. Also, it is unknown whether all “high-risk” men would have had adverse outcomes because only 56% died of their disease. To address this issue, we performed separate analyses including the subset of 15 men with confirmed pCA death and found similar results. However, the sample size was small, limiting the study power.

Another limitation common to studies on PSA kinetics is the exclusion of men without repeated PSA measurements ($n = 131$ men in our population). Conversely, a strength of our study is that 82% of the men had three or more serial PSA values. Correspondingly, in clinical practice, it is not always possible to apply PSA kinetics measurements for patients diagnosed with pCA at the initial screening visit. However, the results of ROC analysis suggest that total PSA may provide a useful prognostic indicator for such patients. Indeed, the PSA at diagnosis is such a powerful predictor of outcomes and is so closely correlated with PSAV that it can be difficult to statistically separate their effects [15]. This does not mean that PSAV does not provide useful information; rather, it suggests that both parameters may offer more information in specific populations, and PSAV may be particularly useful years before diagnosis at a time when PSA is low. In contrast, PSA DT was only useful if negative values were excluded (approximately 25% of the study population), highlighting the difficulty in applying this parameter in daily clinical practice. It is noteworthy that the addition of PSAV to the base model led to a statistical improvement in the concordance index using a bootstrapping approach but not with the method of Hanley et al [10]. Nevertheless, numerous methods are available for comparing concordance indices, and some believe that the Hanley [10] approach may be inappropriate for testing diagnostic accuracies [16].

Other limitations of our study were that the same assay was used for all PSA measurements, and the average interval between PSA measurements was approximately 2 yr. If PSA were measured using different assays and/or more frequent PSA determinations were available, our results might have been different. For example, studies calculating PSAV based upon two PSA measurements separated by ≥ 4 yr have found divergent results [17], suggesting the importance of time interval and method of calculation [18]. A final limitation of our study was that pCA treatment information was not available and could have influenced the outcome.

5. Conclusion

In summary, these data suggest that pretreatment PSAV is a useful marker for the presence of life-threatening pCA. In our cohort, PSA DT was not significantly associated with life-threatening disease unless cases were selected with a rising PSA.

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Fig. 1.

Selection criteria for the study population.

Abbreviations: PSA, prostate-specific antigen; pCA, prostate cancer; BPH, benign prostatic hyperplasia.

Fig. 2.

Receiver operating characteristic analysis for the prediction of high-risk disease using (a) PSA and (b) PSAV and (c) for predicting the absence of high-risk disease using PSA DT.

Abbreviations: PSA, prostate-specific antigen; PSAV, prostate-specific antigen velocity; PSA DT, prostate-specific antigen doubling time; ROC, receiver operating characteristic.

Table 1**Description of diagnostic groups***

	Total	High risk	Other	Comparisons high risk vs other
No. of subjects	681	27	654	
Age at PSA, years				
Median (range)	68.8 (42.3, 95.3)	77.1 (56.8, 88.1)	68.4 (42.3, 95.3)	$p < 0.001$
Mean (SD)	67.8 (11.7)	75.6 (7.8)	67.5 (11.7)	
Time from PSA test or cancer diagnosis to death or censoring [†]				
Median (range)	5.9 (0, 34.6)	7.4 (2, 24.6)	5.9 (0, 34.6)	$p = 0.447$
Mean (SD)	7.1 (5.01)	7.8 (5)	7.1 (5)	
PSA (ng/ml) at index visit				
Median (range)	1.6 (0.1, 351.9)	16.5 (0.5, 351.9)	1.5 (0.1, 18.6)	$p = 0.015$
Mean (SD)	3.9 (16)	38.5 (72.1)	2.5 (2.8)	

Abbreviations: PSA, prostate-specific antigen; SD, standard deviation; pCA, prostate cancer.

* Subjects consisted of 681 participants in the Baltimore Longitudinal Study of Aging with or without high-risk pCA (see "Methods" for description of diagnostic groups). Comparisons were by pooled *t* tests in the case of equal variances and Cochran *t* tests in the case of unequal variances; all statistical tests were two-sided.

[†] Time from last PSA test to censoring for those without pCA or time from diagnosis of pCA to death or censoring for those with pCA.

Table 2
Comparison of PSAV and PSA DT (a) between patients with and without high-risk pCA and (b) between men with and without fatal pCA

	High risk	Other	<i>p</i> value
(a)			
PSAV (ng/ml per year)			
Median	2.1	0.07	
Mean (SD)	10.2 (26.9)	0.15 (0.62)	<0.0001
PSA DT (years)			
Median	3.1	9.7	
Mean (SD)	5.7 (13.3)	-7.9 (330.6)	0.303
	Fatal	Other	<i>p</i> value
(b)			
PSAV (ng/ml per year)			
Median	1.72	0.07	
Mean (SD)	14.98 (35.7)	0.15 (0.62)	<0.0001
PSA DT (years)			
Median	2.3	9.7	
Mean (SD)	3.1 (12.2)	-7.9 (330.6)	0.408

Abbreviations: pCA, prostate cancer; SD, standard deviation; PSAV, prostate-specific antigen velocity; PSA DT, prostate-specific antigen doubling time.