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Prostate-Specific Antigen Velocity Risk Count Assessment: A New Concept for Detection of Life-Threatening Prostate Cancer During Window of Curability

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Abstract

Objectives—To determine whether the number of times the prostate-specific antigen (PSA) velocity (PSAV) exceeds a threshold (PSAV risk count) is predictive of high-risk prostate cancer.

Methods—The PSAV was determined in 717 men (606 without prostate cancer; 32 with high-risk prostate cancer defined as death from cancer, PSA level of 20 ng/mL or more, or a Gleason score of 8 or more; and 79 with prostate cancer who were alive or dead of another cause). Multiple PSAVs determined from three repeated measures from each subject during 10 to 20 years were used to determine the risk count by summing the number of times a subject exceeded a PSAV threshold. Cox proportional hazards regression analysis was used to evaluate the associations between the risk count and the probability of high-risk disease. The statistical tests were two-sided.

Results—The probability of high-risk disease increased directly with the risk count. After adjusting for age, PSA level, PSAV, and date of diagnosis, the PSAV risk count was significantly associated with the development of high-risk prostate cancer (relative risk 1.41, 95% confidence interval 1.25 to 1.59 for a PSAV cutpoint 0.2 ng/mL/yr; relative risk 1.49, 95% confidence interval 1.29 to 1.71 for a PSAV cutpoint of 0.4 ng/mL/yr; $P < 0.001$).

Conclusions—The PSAV risk count could be a useful method of interpreting a PSA history to help identify those men who will benefit from a diagnosis of prostate cancer at PSA levels associated with curable disease.

Prostate-specific antigen (PSA) is not specific for prostate cancer. The use of lower total PSA thresholds for prostate biopsy increases the likelihood of detecting prostate cancer that would have otherwise remained undetectable during life (ie, overdiagnosis).¹ Thus, clinicians need criteria for prostate biopsy that are predictive of life-threatening disease.

The PSA velocity (PSAV) has been shown to be predictive of lethal prostate cancer in the year before diagnosis at a time when cure is less likely² and 10 to 15 years before diagnosis when local treatment might be curative.³ Thus, PSAV appears to be an important predictor of tumor biology.

The variability in PSA levels has been considered to limit the usefulness of PSAV. However, this variability could be informative if men with life-threatening disease are more likely to have consistent increases in PSA (less variability) compared with those without life-threatening

disease. Because many patients present with long PSA histories, it is possible to assess multiple PSAVs over time and account for PSA variability. To determine whether the number of times a man exceeds a PSAV threshold is predictive of high-risk prostate cancer, we studied the PSA histories of men from the Baltimore Longitudinal Study of Aging.

Material and Methods

Cohort Selection

The study subjects were participants in the Baltimore Longitudinal Study of Aging (National Institute on Aging, Bethesda, MD).⁴ The institutional review boards of Med Star and Johns Hopkins Medical Institutions (Baltimore, MD) approved this study.

The PSA levels were measured using frozen (-70°C) sera before 1991 and at each visit after 1991 using the Tandem-R assay (Hybritech, San Diego, Calif).

PSA measurements were available for 1201 of 1806 male subjects in the Baltimore Longitudinal Study of Aging since 1958. We evaluated men aged 40 years or older, with the following exclusions: diagnosis of prostate cancer with no PSA data before diagnosis ($n = 38$), simple prostatectomy and no PSA data before surgery ($n = 80$), finasteride (Proscar) use ($n = 47$), unknown cause of death ($n = 54$), incomplete diagnostic information ($n = 2$), and a single PSA value suspected to be a laboratory error ($n = 1$). Also, 130 men were excluded who lacked PSA measurements after age 40 years and 132 men who had only one PSA measurement. After the exclusions, the study population consisted of 717 men (111 with and 606 without a known diagnosis of prostate cancer). Of the 717 men, 79% were white, 17% were African American, and 4% were Asian or from other ethnic groups.

Outcome Determination and Study Groups

The cause of death was determined by a consensus of three physicians reviewing correspondence from relatives, medical records, and the National Death Index.

The cohort was divided into three mutually exclusive groups: subjects without a clinical diagnosis of prostate cancer (no cancer group), subjects with a diagnosis of prostate cancer at high risk of prostate cancer death (high-risk group), and subjects with a diagnosis of prostate cancer who were alive or died of another cause and not considered at high risk (cancer group).

The 32 patients in the high-risk group had been diagnosed with prostate cancer and with one of the following: PSA level of 20 ng/mL or greater at any time ($n = 11$), Gleason score of 8 or greater at diagnosis ($n = 11$), or confirmed death from prostate cancer ($n = 17$). Of the 32 high-risk patients, 6 were alive and 26 had died. We also used a more restricted definition of high-risk prostate cancer that included only those men who had died of prostate cancer ($n = 17$).

Of the 606 men without a clinical diagnosis of prostate cancer, 432 were alive and 174 had died. Of the latter, 23 had prostate cancer found at autopsy.

Of the 79 men with a clinical diagnosis of prostate cancer not considered high risk, 28 had died of a cause other than prostate cancer and 51 were alive.

The cancer stage and grade were not consistently available and were not included in the analyses.

Statistical Analysis

The 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. All statistical tests were two-

sided. $P < 0.05$ was considered statistically significant. Subjects at high risk of dying of prostate cancer were considered to be events in all analyses.

PSA Measurements—The PSA measures were censored at the diagnosis of prostate cancer, simple prostatectomy for benign disease, or as of August 2006 for those without prostate cancer. The PSAV was calculated at each visit for which previous PSA measures were available (ie, starting with the second visit). The visit at which the PSAV was determined was referred to as the index visit. The PSAV for the index visit was the average rate of change over three consecutive visits (the index visit and the two preceding visits)⁵ or the simple rate of change if only two measures total.

PSAV Risk Count Determination—Multiple PSAVs using repeated measures from each subject for 10 to 20 years were used to determine a risk count. This was done by counting the number of times a subject reached a PSAV cutoff for all visits up to, and including, the index visit, and we termed this the “PSAV risk count” for the index visit. To illustrate the relationship between the risk count and the probability of high-risk prostate cancer, we chose five PSAV cutoffs (0, 0.2, 0.4, 0.75, and 1.0 ng/mL/yr) that were less than 2 ng/mL/yr because a previous report had suggested that this threshold is a marker for an increased risk of noncurable cancer,² and because the regression of PSAV on PSA in our data set suggested that at these PSAV cutoffs the average PSA level would be less than 6 ng/mL—PSA levels at which most men have curable disease.

Data Set Imputation—Because the time between PSA measurements was not constant, we imputed the annual PSA levels for each man by boot strapping the data set 100 times. These data were entered into a mixed effects model⁶ that regressed $\log\text{[PSA + 1]}$ on initial age, initial age squared, time, and time squared with random effects for intercept, time, and time squared to predict the PSA level annually. The resulting PSA values were then subjected to random sampling from a normal distribution with the PSA value as the mean of the distribution and the average within subject standard deviation as the standard deviation for the distribution. This added “noise” to the estimated PSA to reflect the variability observed in PSA measurements. This imputed data set was used only for the one analysis that included the risk count taking into consideration the years of follow-up. All other analyses used raw data.

Assessment of Risk—The probability of high risk cancer—an event—was the ratio of the number of subjects with high-risk disease to the total number of men at risk. The Cox proportional hazards regression model was used to evaluate associations between the covariates of PSAV risk count, PSA level, PSA velocity, age at diagnosis, diagnosis date, and the outcome high-risk prostate cancer. Likelihood ratio tests were used to assess the fit of the models with different covariates. The follow-up period was defined as the time to death for those who died of prostate cancer and the time to August 2006 for those who had not died during the follow-up period.

Time was divided into the intervals between evaluations, and the value for each variable was determined from the evaluation at the start of the interval. This time-dependent approach used the Anderson-Gill formulation as a counting process using functions developed by Therneau and Grambsch.⁷ Hazard proportionality was tested by plotting the Schoenfeld residuals against a log function of time. No evidence was found for nonproportionality for the variables examined in this study.

Results

The demographic data are shown in Table 1. The probability of high-risk disease increases with PSAV risk count (Fig. 1A), regardless of whether our definition of high-risk disease

included death from prostate cancer and Gleason score and PSA criteria (Fig. 1A) or whether we restricted our definition of high-risk disease to death from prostate cancer only (data not shown). Additionally, the probability of high-risk disease was dependent on the PSAV threshold chosen for the risk count determination. For example, a subject that exceeded a PSAV of 0.75 ng/mL/yr twice (ie, risk count of 2) would have a greater probability of high-risk disease than would a subject who exceeded a PSAV threshold of 0.2 ng/mL/yr twice (ie, risk count of 2). The PSAV cutpoints of 0.75 and 1.0 ng/mL/yr resulted in similar risks, differing from the PSAV cutpoints of 0.2 and 0.4 ng/mL/yr, which were similar, and were all different from 0.0 ng/mL/yr. We stratified the risk counts by PSA level less than 4.0 ng/mL and between 4.1 and 10.0 ng/mL (Fig. 1B,C), which suggested that the risk count provided different information regarding high-risk cancer compared with the absolute PSA level and that the risk count provided information regarding high-risk disease at PSA levels of less than 4.0 ng/mL.

To address whether the PSAV risk count added to the prediction of high-risk prostate cancer over and above the PSA level, a model that included PSA level, age, and date of diagnosis was compared with a similar model that included the risk count. The PSA level, age, and date of diagnosis were all significant variables associated with high-risk prostate cancer. The addition of the risk count to a model that included PSA level, age, and date of diagnosis significantly improved the fit of the model based on the likelihood ratio test ($P < 0.001$).

The relative risk of high-risk prostate cancer, per unit change in PSAV risk count, is shown in Figure 2 according to the PSAV cutpoint chosen for the counting process. The graph demonstrates that after adjusting for age, PSA level, PSAV, and date of diagnosis, the risk count was significantly associated with high-risk prostate cancer. For example, the risk of high-risk prostate cancer increased approximately 50% (relative risk 1.49) each time an individual's PSAV exceeded 0.4 ng/mL/yr.

To address whether the PSAV risk count added to the prediction of high-risk prostate cancer over and above a simple PSAV based on all PSA measurements, a model that included PSAV, risk count, PSA level, age, and date of diagnosis was compared with a model excluding PSAV and a model excluding the risk count. The addition of PSAV to a model that included the risk count did not significantly improve the fit of the model using the likelihood ratio test ($P = 0.18$). In contrast, the addition of risk count (using a PSAV cutpoint of 0.2 ng/mL/yr) to a model that included PSAV significantly improved the fit of the model ($P < 0.001$).

Because the time between PSA measurements was not constant, we used a simulation to predict what the PSA level would have been had annual PSA measurements been performed. Figure 3 shows the probability of high-risk prostate cancer as the PSAV risk count increased. The probability of high-risk cancer appeared to increase with the risk count and also with the risk count as a proportion of the total number of PSAV determinations. For example, a man who had 4 years of PSAV estimations and had exceeded a PSAV of 0.2 ng/mL/yr four times (risk count of 4) would have a 20% risk of high-risk prostate cancer. In contrast, a man with 6 years of PSAV determinations but a risk count of 4 would have less than a 10% risk of high-risk prostate cancer.

Comment

We demonstrated that the number of times a man exceeded a PSAV cutpoint (PSAV risk count) provides additional information regarding the presence of life-threatening prostate cancer compared with a single PSA determination or single PSAV determination. The PSAV risk count takes into consideration the short-term variability in PSA level. In contrast, an assessment of a single PSAV over time does not. Virtually any rise in PSA that occurred consistently was associated with an increased risk of life-threatening prostate cancer (Fig. 1), and this risk was

dependent on the PSAV cutpoint chosen for the counting process (Fig. 2) and the length of follow-up over which the risk count was determined (Fig. 3).

We chose PSAV cutpoints for risk count assessment that could be considered low given the PSA variability over time. However, we have previously demonstrated that when the PSA levels are in a range in which most men have curable disease (eg, 2 to 4 ng/mL), a PSAV greater than 0.35 ng/mL/yr (10 to 15 years before diagnosis) was associated with an almost fivefold risk of death from prostate cancer 15 or more years later³ compared with a PSAV of 0.35 ng/mL/yr or less. Greater PSAV cutpoints (eg, 0.75 ng/mL/yr) might be more appropriate for risk count assessment in those men with PSA levels greater than 4 ng/mL.

The concept of a PSAV risk count has not previously been reported. However, D'Amico *et al.*^{2,8} reported that the PSAV in the year before diagnosis could be used to assess the risk of death after surgical intervention and radiotherapy. In addition, Eggener *et al.*⁹ demonstrated that among men with a PSA level of 2.6 to 4.0 ng/mL and negative biopsy findings, a PSAV of 0.0 ng/mL/yr or greater was associated with an increased risk of a subsequent diagnosis of prostate cancer.

Our study has important clinical implications. The PSAV risk count could provide a more rational approach to determine the need for biopsy compared with performing a biopsy of all men who exceed an absolute PSA threshold. This approach could help identify those men who are more likely to develop life-threatening prostate cancer and benefit the most from curative intervention, as well as reducing the overdiagnosis and overtreatment of prostate cancer. Second, our findings suggest that compared with evaluating the PSAV, an assessment of the entire PSA history to evaluate PSA variability (PSAV risk count) will provide additional information for the prediction of life-threatening prostate cancer at a point at which the PSA levels are associated with curable disease (Fig. 1B).

One strength of our study was the cohort design in which the lifetime risk of death from prostate cancer was similar to that of the U.S. population.³ The limitations included the relatively long interval between PSA measurements, assays of PSA on frozen sera, an inability to assess the stage and grade of prostate cancer in all cases, and the affect of treatment on prostate cancer mortality.

Conclusions

Our data suggest that an assessment of PSA variability by counting the times a PSAV threshold is exceeded (PSAV risk count) could provide valuable information regarding high-risk prostate cancer. This assessment could help clinicians identify those men who will benefit the most from a diagnosis of prostate cancer at a time at which the disease is curable. However, larger studies are needed to confirm the findings in this preliminary study.

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Figure 1.

(A) Probability of diagnosis of high-risk prostate cancer by PSAV risk count (number of times a man exceeded given PSAV cutpoint) according to actual data. Each line represents use of different PSAV cutpoint for counting process (see Material and Methods section for description of risk count). (B,C) Probability of high-risk cancer stratified by PSA level. Triangle in each graph represents probability of high-risk prostate cancer for men whose PSA level was less than 4.0 ng/mL at any point, with censoring of subjects if PSA level was greater than 4.0 ng/mL (B) or PSA 4.1 to 10.0 ng/mL at any point with censoring of men if PSA level was greater than 10.0 ng/mL (C). Probability defined as proportion of men with high-risk disease who had PSA level less than 4.0 ng/mL divided by total number of men with PSA level less than 4.0 ng/mL and proportion of men with high-risk disease who had PSA level of 4.1 to 10 ng/mL divided by total number of men with PSA level of 4.1 to 10 ng/mL. Lines represent probability of high-risk prostate cancer according to PSAV risk count using PSAV cutpoint of 0.2 ng/mL/yr (black squares) and 0.4 ng/mL/yr (white circles) when PSA level less than 4.0 ng/mL (B); and 0.4 ng/mL/yr (black squares) and 0.75 ng/mL/yr (black circles) when PSA level 4.1 to 10 ng/mL (C). Each subject could have had more than one count.

Figure 2.

Relative risk of diagnosis of high-risk prostate cancer (per unit change in risk count) by PSAV cutpoint chosen for counting process using actual data. Solid line represents unadjusted relative risk; dashed line represents relative risk adjusted for age, PSA level, PSAV, and date of diagnosis of prostate cancer. Vertical lines with bars represent 95% confidence limits around relative risk estimates from Cox regression model. Relative risk, with 95% confidence intervals in parentheses and *P* values shown on graph for adjusted model (dashed line) when risk count was determined by PSAV cutpoints of 0, 0.2, 0.4, 0.75, and 1.0 ng/mL/yr.

Figure 3.

Probability of diagnosis of high-risk prostate cancer by PSAV risk count (number of times PSAV cutpoint was exceeded) according to PSAV cutpoint of 0.2 ng/mL/yr using simulated data set. Each line represents number of years that PSAV could be calculated using simulated data.

Table 1

Description of diagnostic groups*

Variable	Total	High Risk	Cancer	No Cancer	Comparison [†] (P Value)		
					High Risk vs. Cancer	High Risk vs. No Cancer	Cancer vs. No Cancer
Subjects (n)	717	32	79	606			
Age at first PSA test (yr)							
Median	53.3	56.5	54.1	53.12			0.166
Range	40 to 92	43.2 to 86	40.1 to 84.8	40 to 92			
Mean (SD)	55.3 (12)	58.4 (11)	55.1 (11.3)	55.2 (12.1)			
Age at last PSA (yr)							
Median	69	75.5	68.7	68.9	0.007	0.001	0.583
Range	42.3 to 95.3	56.8 to 88.1	47.9 to 88.2	42.3 to 95.3			
Mean (SD)	68.2 (11.8)	73.6 (8.6)	68.5 (8.8)	67.9 (12.2)			
Follow-up (first to last PSA test) (yr)							
Median	12.7	20.8	16.7	12.2			
Range	1 to 38.8	2.1 to 29.5	2.1 to 30.6	1 to 38.8			
Mean (SD)	13.3 (8.2)	18.4 (7.5)	15.6 (8.6)	12.7 (8)	0.105	<0.001	0.003
Time from last PSA test or cancer diagnosis to death or censoring [‡]							
Median	5.9	8.5	9.6	5.6			
Range	0 to 34.6	0 to 24.6	1.1 to 20.9	0.05 to 34.6			
Mean (SD)	7.1 (5.1)	7.9 (4.9)	9.5 (4.7)	6.8 (5.1)			
PSA testing							
PSA values repeated (n)					0.030	0.002	0.684
Median	5	6	5	5			
Range	2 to 15	2 to 14	2 to 15	2 to 14			
Mean (SD)	5.4 (2.7)	6.8 (3.3)	5.4 (2.9)	5.3 (2.7)			
Interval between PSA tests (yr)							
Median	2.1	2	2.1	2.1	0.027	0.023	0.598
Range	0.1 to 21.5	0.2 to 11.5	0.1 to 12.7	0.1 to 21.5			
Mean (SD)	2.9 (2.1)	2.6 (1.9)	3 (2.3)	2.9 (2)			

Variable	Comparison [‡] (P Value)				
	Total	High Risk	Cancer	No Cancer	High Risk vs. No Cancer
PSA (ng/mL)					
At first visit					
Median	0.7	1.2	1.2	0.7	0.276
Range	0.05 to 17.1	0.1 to 17.1	0.2 to 8.4	0.05 to 10.93	
Mean (SD)	1.3 (1.67)	2.65 (3.9)	1.86 (1.66)	1.15 (1.41)	
At last visit					
Median	1.60	13.75	4.74	1.3	0.032
Range	0.05 to 351.9	0.5 to 351.9	0.6 to 18.6	0.05 to 16.6	
Mean (SD)	3.89 (15.6)	32.82 (67.37)	6.04 (4.27)	2.08 (2.23)	0.015
First PSAV (ng/mL/yr)					
Median	0.03	0.14	0.09	0.03	0.15
Range	-6.07 to 11.95	-0.2 to 11.95	-2.4 to 3.1	-6.07 to 3.49	0.05
Mean (SD)	0.08 (0.67)	0.83 (2.19)	0.2 (0.71)	0.03 (0.45)	0.013

PSA = prostate-specific antigen; SD = standard deviation; PSAV = PSA velocity.

* Subjects were 717 participants in the Baltimore Longitudinal Study of Aging with high-risk prostate cancer, prostate cancer not high risk, and without prostate cancer (see Material and Methods section for description of diagnostic groups).

[‡] Comparisons by pooled *t* tests for equal variances and Cochran *τ* tests for unequal variances; all statistical tests were two-sided.

[‡] Time from last PSA test to censoring for those without prostate cancer or time from diagnosis of prostate cancer to death or censoring for those with prostate cancer.