Prostatic Diseases and Male Voiding Dysfunction

Prostate-Specific Antigen Velocity in Healthy Korean Men with Initial PSA Levels of 4.0 ng/mL or Less

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OBJECTIVES

To assess the longitudinal changes in serial prostate-specific antigen (PSA) levels in healthy Korean men with initial PSA levels of 4.0 ng/mL.

METHODS

The rate of PSA change or PSA velocity (PSAV) in 24,869 healthy men with an initial PSA level of 4.0 ng/mL or less who were clinically free of genitourinary disease was analyzed at intervals of at least 12 months. The influence of age, initial PSA level, and the interval between measurements was assessed.

RESULTS

The mean age, initial PSA level, interval between measurements, and change in PSA and PSAV was 46.2 years, 0.86 ng/mL, 21.9 months, and 0.03 ng/mL and 0.02 ng/mL/y, respectively. A cumulative frequency plot of PSAV demonstrated that 50%, 95%, and 97% of subjects had a PSAV of 0.01, 0.40, and 0.52 ng/mL/y or less, respectively. The PSAV correlated with age, initial PSA level, and interval between measurements. The percentage of men with a PSAV greater than 0.75 ng/mL/y was 0.61% (151 of 24,869) and was 0.51% (92 of 17,985) for those with an initial PSA level of less than 1.0 ng/mL, 0.86% (50 of 5,807) for those with a PSA level of 1.1-2.0 ng/mL, and 0.84% (9 of 1077) for those with an initial PSA level of 2.1-4.0 ng/mL.

CONCLUSIONS

In healthy Korean men with an initial PSA level of 4.0 ng/mL or less, most will have a PSAV of less than 0.75 ng/mL/y. Thus, traditional PSAV cutoff values are not applicable in this population. We propose that a lower PSAV cutoff value should be used to indicate biopsy. Additional large-scale prospective studies, including biopsy data, are required to assess the cutoff value of PSAV for healthy Korean men with a PSA level of 4.0 ng/mL or less. UROLOGY 72: 99–103, 2008. © 2008 Elsevier Inc.

Prostate-specific antigen (PSA) can be nonspecifically elevated, not only in patients with prostate cancer, but also in those with benign prostatic hyperplasia or urinary tract infections. To overcome this limitation in the use of PSA measurements, various concepts, such as age-specific ranges, percent-free PSA, PSA density, and PSA velocity (PSAV), have been introduced for clinical application.1-4

PSAV means the PSA change divided by the elapsed interval between measurements. It has been reported that the PSAV in patients with prostate cancer is greater than that in patients without prostate cancer. Moreover, although a patient might have a PSA level within the normal range, if the PSAV level is 0.75 ng/mL/y or greater, the possibility of finding prostate cancer would be high.2,5 However, this traditional PSAV threshold of 0.75 ng/mL/y was mainly determined in men with a PSA level of 4-10 ng/mL. In the present era, an increasing proportion of men of all ages is diagnosed with prostate cancer at a PSA level of 4.0 ng/mL or less; thus, it is unclear whether the traditional PSAV threshold can apply to healthy Korean men with a PSA level of 4.0 ng/mL or less.

To use the PSAV as a tool to separate subjects with prostate cancer from those without in healthy Korean men with a lower PSA, we should be able to first predict the variation in PSA values in the healthy Korean male.
population. However, at present, large-scale research on the PSAV frequency distribution in healthy Korean men with an initial PSA level of 4.0 ng/mL or less has not been done. Therefore, this study was designed to analyze the PSAV and related parameters in healthy Korean men with a PSA level of 4.0 ng/mL or less.

MATERIAL AND METHODS

We used the measured PSA values of men who had undergone PSA testing as a part of their routine health checkup in eight domestic hospitals from 1998 to 2005. From the beginning of the data collection, we collected data only for men who had two or more PSA measurements with an interval of at least 12 months, had had an initial PSA level of 4.0 ng/mL or less, and had not had urinary tract infections, voiding difficulty, or a prostate cancer or prostate surgery. Through data collection from eight domestic hospitals, 24,869 men were enrolled in this study.

The serum PSA levels were measured using three different assays in eight hospitals: Abbott AxSYM, Abbott Architect i2000 (Abbott Laboratories, Abbott Park, IL), or Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). We used BD Vacutainer tubes (Becton Dickinson, Oxford, UK) for blood collection. Blood samples were centrifuged at venipuncture and immediately frozen at −70°C, and the PSA levels were assessed within 3 days. Variations in PSA values can occur among the different assays, but Kim et al. showed that the coefficient of variation for the PSA levels in each laboratory was approximately 10%, similar to the coefficient of variation for one vendor. To minimize the variation among PSA assays statistically, the mean and standard deviation of the PSA values according to age category (5-year unit) in each hospital were obtained and converted to the standard normal distribution. These PSA values were incorporated into the new data set. The PSA value was multiplied by the standard deviation of the PSA values according to the age category (5-year unit) across all hospitals, and then added to the corresponding mean to calculate the individually standardized PSA value. The PSAV was defined as the converted values per year after the difference between the first and the second PSA values was divided by the interval between the measurements. In cases in which the PSA level had been measured more than three times, the first and last PSA values were used for the calculation of the PSAV for sufficient interval measurements.

Pearson correlation analysis was used to determine the effect of age, PSA, and interval between measurements on the change in the PSA level and PSAV. Multivariate linear regression analysis was used to analyze the correlation among age, PSA, and interval between measurements in predicting the PSAV. An analysis of variance test was used to compare patient age, PSAV, and interval between measurements, stratified by the initial PSA level.

In cases in which the PSA level varied within the interassay coefficient of variation during the follow-up period, we categorized the PSA level as “unchanged.” In cases in which the PSA level varied outside the range of the interassay coefficient of variation, we categorized it as “changed.” For the 24,869 men in this study, a chi-square test was used to evaluate the PSAV trend according to the initial PSA level.

RESULTS

Of the 24,869 men, 2,568 (10.3%) had three or more PSA measurements. The mean age, initial PSA level, interval between measurements, change in the PSA, and PSAV was 46.2 ± 7.2 years (range 30-79), 0.86 ± 0.54 ng/mL (range 0.4), 21.9 ± 5.5 months (range 12-36), 0.03 ± 0.40 ng/mL (range −3.20 to 3.46), and 0.02 ± 0.24 ng/mL/y (range −2.97 to 3.07).

A cumulative frequency plot of the PSAV demonstrated that 50%, 95%, and 97% of subjects had a PSAV of 0.01, 0.40, and 0.52 ng/mL/y or less, respectively (Fig. 1).

The change in the PSA level correlated with patient age (r = 0.023, P < .001) and the initial PSA level (r = −0.323, P < .001), but not with the interval between measurements (r = 0.005, P = .390). Although PSAV correlated with age (r = 0.028, P < .001), initial PSA (r = −0.309, P < .001), and the interval between measurements (r = −0.015, P = .20), the relationship with age and the interval between measurements showed a negligible correlation, with correlation coefficients of −0.1 to 0.1, and the relationship with the initial PSA level showed a strong negative correlation (Fig. 2).

Multivariate linear regression analysis of the PSAV using age, initial PSA, and the interval between measurements found statistical significance with age, initial PSA, and the interval between measurements. However, patient age and the interval between measurements did not have a large effect on the PSAV, in that the parameter estimate was small (0.002 and −0.001, respectively; Table 1).

Age, PSAV, and the interval between measurements were compared among three groups of the initial PSA level: 1.0 ng/mL or less, 1.1-1.9 ng/mL, and 2.0-4.0 ng/mL. Age significantly increased as the initial PSA level increased, but the PSAV decreased significantly with age (P < .05; Table 2).
Among all target groups, 1650 men (6.63%) had a PSAV of 0.25 ng/mL/y or more and 421 (1.69%) had a PSAV of 0.50 ng/mL/y or more. In each PSA group, stratified by the initial PSA level, the percentage of men with a PSAV of 0.25 ng/mL/y or more increased significantly (\( \text{P} < .007 \)), but the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)). The percentage of men with a PSAV of 0.75 ng/mL/y or more was 0.61% (151 of 24,869). According to the stratified PSA level, the percentage of men with a PSAV of 0.5 ng/mL/y or more did not (\( \text{P} = .736 \)).

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**COMMENT**

For the patients with a PSAV of 0.75 ng/mL/y or greater, the prostate cancer detection rate was 47% and was 11% for those with a PSAV of less than 0.75 ng/mL/y. Although the sensitivity and specificity for predicting prostate cancer was 78% and 60%, respectively, with PSA alone, the sensitivity was 55%–72% and the specificity was more than 90%, with the cutoff PSAV level of 0.75 ng/mL/y. However, in men with a PSA level of 4 ng/mL or less, the specificity decreased to 11%, although the sensitivity remained high. Moreover, the traditional PSAV cutoff value of 0.75 ng/mL/y was determined mainly in men with a PSA level of 4-10 ng/mL. In the present era, with an increasing proportion of men of all ages diagnosed with prostate cancer at a PSA level of 4.0 ng/mL or less, it is unclear whether the traditional PSAV cutoff values can be applied to healthy Korean men with a PSA level of 4.0 ng/mL or less.

Nevertheless, it is clear that the PSAV remains an important tool for risk stratification even when the PSA level is less than 4.0 ng/mL. For example, Carter et al. recently reported that the PSAV could help to identify men with life-threatening prostate cancer during a period when their PSA level was less than 4.0 ng/mL. However, few data are available on the PSAV frequency distribution in men with a low PSA level who do not have prostate cancer, despite evidence that the PSAV is associated with aggressive prostate cancer in men with a PSA level of 4.0 ng/mL or less, and it has been suggested that the cutoff PSAV value should be lowered for the screening of prostate cancer in men with a small prostate and a PSA level of 4.0 ng/mL or less.

Loeb et al. suggested that the traditional PSAV cutoff values are not applicable in this population. Their proposal to use a lower PSAV cutoff value of 0.4 ng/mL/y for biopsy may be useful, in that 95% of our subjects had an increase of PSAV of 0.315 ng/mL/y or less.

The PSAV correlated with patient age, the interval between measurements, and the initial PSA level, but the influence of age and the interval between measurements was not powerful. The PSAV decreased with increases in PSA, in contrast to the results from a previous study. Considering the fluctuations in the PSA values, we would calculate the average PSAV using three measurements rather than the first and last PSA measurements to estimate the PSAV if we had many men with three or more PSA measurements. However, because only 10.3% of our patients had three or more PSA measurements, the average PSAV would be more representative of the PSA levels.
measurements, we used the first and the last PSA values to calculate the PSAV to have sufficient interval measurements.

One limitation of our study was that we used the measured PSA values of men who had undergone PSA measurement with an interval of at least 12 months. The mean interval between measurements was 21.9 ± 5.5 months (range 12.0-36.0). Because of the short-term variability in PSA, longitudinal measurements using a longer period might provide more valuable information. However, it has been suggested that the interval between measurements should be more than 1-1.5 years for PSAV measurement and that using a longer period might provide more valuable information. However, it has been suggested that the interval between measurements should be more than 1-1.5 years for PSAV measurement and that using a longer period might provide more valuable information.

Another limitation was the lack of biopsy data in men who had an PSA level greater than 4 ng/mL during follow-up, because our data were collected from the measured PSA values obtained during routine health checkups at eight domestic hospitals. Additional large-scale prospective studies that have included the biopsy data are required to assess the precise cutoff value of PSAV for healthy Korean men with less than 0.75 ng/mL/y. Therefore, a lower PSAV cutoff value for biopsy in this population is needed.

CONCLUSIONS

The results of our study have shown that the traditional PSAV cutoff value of 0.75 ng/mL/y is not applicable in healthy Korean men with an initial PSA level of 4.0 ng/mL or less because most of our men had a PSAV of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.068</td>
<td>0.012</td>
<td>5.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.002</td>
<td>0.002</td>
<td>8.92</td>
<td>&lt;.001</td>
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<tr>
<td>Initial PSA (ng/mL)</td>
<td>-0.143</td>
<td>0.003</td>
<td>-51.92</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Interval between measurements (mo)</td>
<td>-0.001</td>
<td>0.000</td>
<td>-2.51</td>
<td>.012</td>
</tr>
</tbody>
</table>

PSAV = prostate-specific antigen velocity; PSA = prostate-specific antigen.

Table 2. Age, PSAV, interval between measurements, and percentage of men according to PSAV stratified by initial PSA level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Initial PSA (ng/mL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>17,985</td>
<td>5807</td>
<td>1077</td>
</tr>
<tr>
<td>Age* (yr)</td>
<td>45.86 ± 6.88</td>
<td>46.90 ± 7.47</td>
<td>48.54 ± 8.86</td>
</tr>
<tr>
<td>PSAV* (ng/mL/yr)</td>
<td>0.05 ± 0.18</td>
<td>-0.03 ± 0.29</td>
<td>-0.25 ± 0.52</td>
</tr>
<tr>
<td>Interval between measurements* (mo)</td>
<td>21.98 ± 5.41</td>
<td>21.83 ± 5.55</td>
<td>21.85 ± 5.93</td>
</tr>
<tr>
<td>PSAV (ng/mL/yr)</td>
<td>≥1.0</td>
<td>46.27 (8321)</td>
<td>26.50 (1539)</td>
</tr>
<tr>
<td></td>
<td>1.1–2.0</td>
<td>7.49 (435)</td>
<td>8.08 (87)</td>
</tr>
<tr>
<td></td>
<td>2.1–4.0</td>
<td>2.50 (145)</td>
<td>2.52 (31)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.51 (92)</td>
<td>0.86 (50)</td>
</tr>
<tr>
<td></td>
<td>&gt;0</td>
<td>1.36 (245)</td>
<td>1.26 (15)</td>
</tr>
<tr>
<td></td>
<td>≥0.25</td>
<td>0.43 (77)</td>
<td>0.79 (46)</td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td>0.51 (92)</td>
<td>0.86 (50)</td>
</tr>
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<td></td>
<td>≥0.75</td>
<td>0.43 (77)</td>
<td>0.79 (46)</td>
</tr>
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| Abbreviations as in Table 1. * Data represent the mean ± SD.

References


