Correlation Between Serum Prostate Specific Antigen Level and Prostate Volume in a Community-based Cohort: Large-scale Screening of 35,223 Korean Men

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OBJECTIVE To investigate the relationship between prostate specific antigen (PSA) level and prostate volume (PV) according to age in a community-based population of Korean men enrolled in a large-scale screening program.

METHODS A total of 35,223 men who enrolled in the Korean Prostate Health Council Screening Program from January 2001 to December 2011 were included in this study. Patients with a serum PSA level of >10 ng/mL or younger than 40 years were excluded. We analyzed PSA level and PV as measured through transrectal ultrasonography according to stratified age cohorts. We used Pearson correlation and linear regression analysis according to age to describe the correlation between PSA level and PV.

RESULTS Mean PSA level and mean PV increased significantly with age (all P values <.001). Based on data from 5 age cohorts, mean PSA level increased about 0.3 ng/mL every 10 years and mean PV increased about 3 mL every 10 years. The slope of the linear regression between PSA level and PV was 4.582, and the slope of the linear regression increased with age. We derived equations relating PSA level and PV for the various age cohorts.

CONCLUSION Based on a large-scale health screening program, we derived equations relating PSA level to PV according to age group. These data provide a baseline for the normal population by avoiding the interventional bias of urinary symptoms, in contrast to previous data derived from patients who visited hospitals because of prostate-related health concerns. UROLOGY 82: 1394–1399, 2013.

Clinical benign prostatic hyperplasia (BPH), diagnosed by the presence of benign prostate enlargement and lower urinary tract symptoms (LUTS), is considered to be a chronic and progressive disease.[1] Because baseline prostate volume (PV) has been linked to the progression of BPH (eg, acute urinary retention and surgery for BPH), PV has therefore been included as a useful tool to help guide treatment.[2,3] Prostate specific antigen (PSA) is a marker for prostate cancer and BPH.[4] The relationship between PSA level and PV has frequently been examined in men with BPH, in part to determine how PSA level can be used to predict PV. These studies have consistently shown a positive correlation between PSA level and PV.[5-11] The Proscar Long-Term Efficacy and Safety Study demonstrated that the strongest predictor of future prostate growth was baseline serum PSA level, which was more predictive than baseline PV and age.[10] In the Krimpen study, PSA level was used to detect prostate enlargement; these authors suggested that the clinical advantage of the formula over PSA level alone was only modest, as shown by their analysis of men without prostate cancer.[11] However, most studies of the relationship between PSA level and PV have been performed in Western countries; few studies have been conducted in Asia. One Asian study that evaluated the relationship between PSA level and PV reported Asian-specific criteria for detecting PV according to PSA level stratified by age.[12] Although this study was a multicenter study, the subjects were patients who had visited the hospital because of health concerns.

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Table 1. Baseline characteristics according to age groups

Variables	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age ≥80	Total	*P* Value
No. of patients	486	3856	10,853	16,041	3987	35,223	
Mean age (y) ± SD	46.2 ± 2.5	55.6 ± 2.7	65.4 ± 2.8	73.9 ± 2.7	83.0 ± 3.6	70.0 ± 8.4	<.001
Median PSA (ng/mL)	0.65	0.72	0.89	1.09	1.38	0.98	
Mean PSA (ng/mL) ± SD	0.85 ± 0.69	0.98 ± 0.86	1.27 ± 1.23	1.63 ± 1.60	2.01 ± 1.89	1.48 ± 1.49	<.001
Range of PSA (ng/mL)	0.15-6.67	0.02-8.79	0.00-9.78	0.00-10.00	0.00-9.96	0.0-10.0	
Mean BMI (kg/m^2) ± SD	24.9 ± 3.2	24.7 ± 2.9	23.9 ± 3.1	23.2 ± 3.1	22.4 ± 3.1	23.6 ± 9.7	<.001
Mean PV (mL) ± SD	21.9 ± 6.4	25.2 ± 8.6	28.0 ± 11.0	31.4 ± 15.2	34.7 ± 19.4	29.9 ± 14.2	<.001
Range of PV (mL)	8.2-57.1	8.2-175.0	9.4-150.0	12.1-217.0	4.3-234.0	4.3-234.0	
Mean IPSS ± SD	8.3 ± 7.4	9.6 ± 7.3	12.6 ± 8.0	14.2 ± 8.4	16.1 ± 8.7	13.4 ± 8.4	<.001

BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PV, prostate volume; SD, standard deviation.

Furthermore, correlation studies between PSA level and PV have been conducted in patients who attended the hospital because of troublesome LUTS, limiting the application of their results to community-based populations.[13] Thus, we investigated the relationship between PSA level and PV according to age group in 35,223 men who had enrolled in a large-scale prostate health screening program in Korea.

MATERIAL AND METHODS

After obtaining institutional review board approval, a total of 35,223 men who first enrolled in the Korean Prostate Health Council Screening Program between January 2001 and December 2011 were included in this study. This program provides a free medical examination to the general community-based population of men. After advertising the program through public health centers in Korea, all men who participated in the program underwent a urologic examination, including serum PSA measurement, and their PV was determined using transrectal ultrasonography (TRUS). Questionnaires, including the International Prostate Symptom Score (IPSS), were also administered. Serum PSA level was assayed using a chemiluminescence method and commercially available kits. TRUS was conducted using a 7.5 MHz rectal probe. PV was calculated by substituting the formula for an ellipsoid (ie, $\pi/6 \times$ [height] $\times$ [length] $\times$ [width]) with the height, length, and width of the prostate as measured by TRUS. Patients with a serum PSA level of >10 ng/mL were excluded from the study to reduce the likelihood of including those with occult prostate cancer. Patients who had undergone prior biopsies or surgical treatment of prostate disease were excluded from the study. We also excluded those who were younger than 40 years. Accordingly, a total of 35,223 patients were included in our study. Total subjects were stratified into 5 groups according to age: 40-49, 50-59, 60-69, 70-79, and above 80 years. Baseline factors—age, PSA, body mass index (BMI), prostate volume, and IPSS—were compared according to age group via one-way analysis of variance. After log transformation of PSA values, PSA level and PV showed a linear relationship. The relationship between PSA level and PV was evaluated in each age group using linear regression models, and equations, including the slope of the line, were calculated for each age group. Pearson correlation coefficients were used to evaluate correlations among serum PSA level and PV according to age group. Aforementioned analyses according to age groups were repeated in a subgroup divided by PSA level (PSA level <4.0 ng/mL vs 4.0∼10.0 ng/mL) and IPSS level (IPSS 0∼19 vs 20∼35). The SPSS software package, version 15.0 (Statistical Package for Social Sciences, Chicago, IL), was used for all statistical analyses. A 2-tailed $P < .05$ was considered significant for all analyses.

RESULTS

The mean age of the 35,223 patients was 70.0 ± 8.4 years (range 40-98 years), and the mean serum PSA level was 1.48 ± 1.49 ng/mL (range 0.0-10.0 ng/mL). Mean PV was 29.9 ± 14.2 mL (range 4.3-234.0 mL) and mean IPSS was 13.4 ± 8.4 (range 0-35). As shown in Table 1, mean PSA level and mean PV increased significantly according to age group (all *P* values <.001). Based on data for 5 age groups, the mean PSA level increased about 0.3 ng/mL every 10 years, whereas the mean PV increased by about 3 mL every 10 years. Mean BMI decreased significantly according to age ($P < .001$).

After log transformation, serum PSA level demonstrated a significant correlation with PV in all subjects (Table 2). The same trend was evident in all age cohorts. Among all cohorts, Pearson's *r* value between PSA level and PV was 0.514. Pearson's *r* value was 0.240 for men aged 40-49 years, 0.330 for men aged 50-59 years, 0.454 for men aged 60-69 years, 0.523 for men aged 70-79 years, and 0.555 for men 80 years and older. After linear regression analysis, the equation relating PSA level to PV for the total cohort of subjects was calculated as PV = 23.118 + 4.582 × PSA. The slope of the linear regression model increased significantly according to age: PV = 20.055 + 2.247 × PSA (age 40-49 years), PV = 22.027 + 3.214 × PSA (age 50-59 years), PV = 23.107 + 3.863 × PSA (age 60-69 years), PV = 24.189 + 4.419 × PSA (age 70-79 years), and PV = 24.275 + 5.142 × PSA (age ≥80 years). PV increased by 5.142 mL per 1 ng/mL increase in PSA level in men aged ≥80 years, whereas PV increased 2.247 mL per 1 ng/mL increase in PSA level in men aged 40-49 years.

Figure 1 shows that the PV increase per unit PSA increased with age in all subgroups. The r^2 values (power of explanation of the correlation degree between 2 variables) of the slopes were 0.083 for men aged 40-49 years, 0.104 for men aged 50-59 years, 0.189 for men aged 60-69 years, 0.228 for men aged 70-79 years, and 0.260 for men 80 years or older.

Table 2. Relationships between serum prostate-specific antigen level and prostate volume according to age groups

Variables	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age ≥80	Total
No. of patients	486	3856	10,853	16,041	3987	35,223
R value by Pearson's correlation test	0.240	0.330	0.454	0.523	0.555	0.514
P value by Pearson's correlation test	<.001	<.001	<.001	<.001	<.001	<.001
B value by linear regression model	2.247	3.214	3.863	4.419	5.142	4.582
R^2 value by linear regression model	0.083	0.104	0.189	0.228	0.260	0.239
P value by linear regression model	<.001	<.001	<.001	<.001	<.001	<.001

Total cohort: PV = 23.118 + 4.582 × PSA; age 40-49: PV = 20.055 + 2.247 × PSA; age 50-59: PV = 22.027 + 3.214 × PSA; age 60-69: PV = 23.107 + 3.863 × PSA; age 70-79: PV = 24.189 + 4.419 × PSA; age ≥80: PV = 24.275 + 5.142 × PSA.

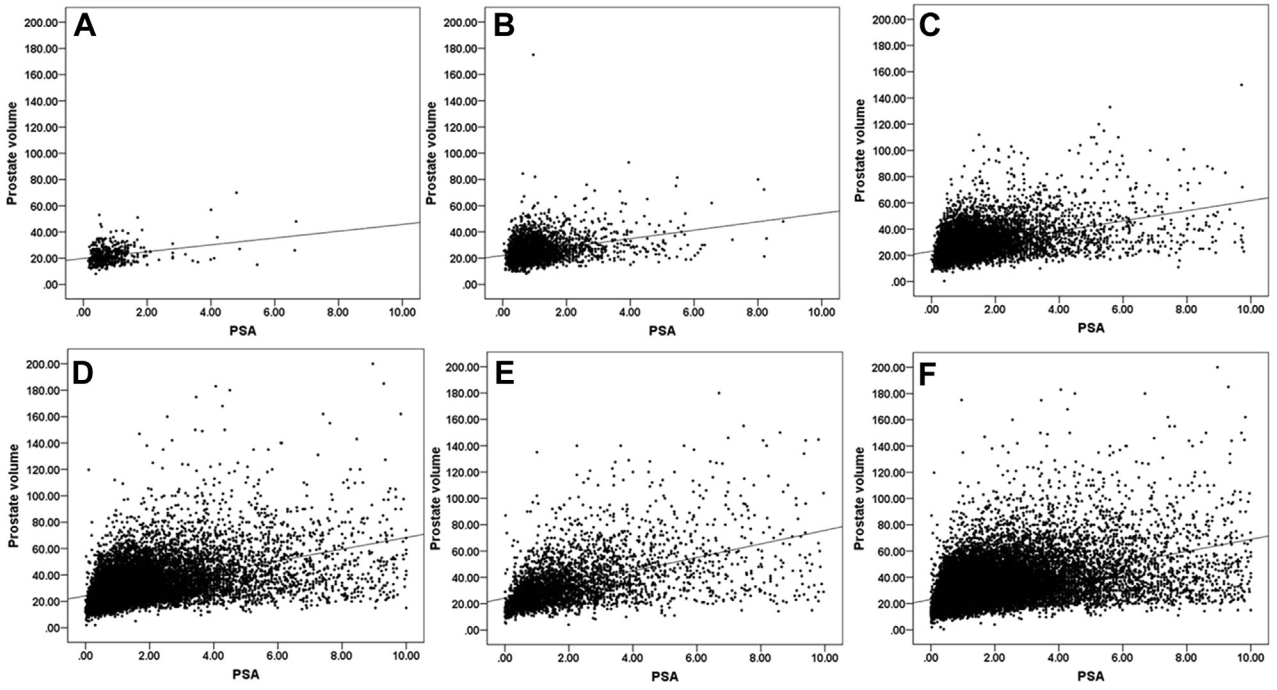

Figure 1. The scatter plots show the relationships between prostate-specific antigen and prostate volume according to each age groups. **(A)** Age 40-49 years, **(B)** age 50-59 years, **(C)** age 60-69 years, **(D)** age 70-79 years, **(E)** age ≥80 years, and **(F)** total cohorts.

As shown in Table 3, the patients who had severe symptoms with IPSS above 20 were 10,555 (30.0%) and the patients whose PSA level was above 4.0 ng/mL were 2395 (6.8%). All analyses were re-evaluated according to PSA level and IPSS. In subgroup analysis, PSA had more higher correlation with PV among 22,733 patients who had low PSA level (<4.0 ng/mL) and low IPSS (<20 points) than 9632 patients whose PSA <4.0 ng/mL and high IPSS (≥20 points). These trends were also verified in patients whose PSA level was above 4.0 ng/mL. Correlation coefficients was relatively lower in 1463 patients whose PSA ≥4.0 ng/mL and low IPSS (<20 points) than 22,733 patients whose PSA <4.0 ng/mL and IPSS <20. Higher correlation was found in patients whose PSA and IPSS were lower.

COMMENT

We found a strong correlation between PSA level and PV in our community-based cohort of Korean men. PV increased 5.142 mL per 1 ng/mL increase in PSA level in men aged 80 years and older, whereas PV increased 2.247 mL per 1 ng/mL increase in PSA level in men aged 40-49 years. In this study, the correlation between PSA level and PV grew stronger with age, and the slope of the linear regression between PSA level and PV also increased with age. The crude Pearson correlation coefficient was 0.514, and the crude slope of linear regression of PSA level and PV in this study was 4.582; both these values are higher than those reported in previous series.[13-16] Several studies have confirmed a correlation between PSA level and PV; Hochberg et al[7] reported such a correlation in patients with biopsy-confirmed BPH, with correlation coefficients of 0.33-0.41. Other studies from Western countries have reported correlation coefficients ranging between 0.37 and 0.6.[8,14,17] The studies performed in Asian countries reported somewhat higher coefficient values between PSA level and PV than those performed in Western countries. Basawaraj et al[15] reported a significant correlation between PV and serum PSA level ($r = 0.415$, $P < .0001$). Chang et al[16] reported

Table 3. Subgroup analyses via prostate-specific antigen level and International Prostate Symptom Score: relationships between serum prostate-specific antigen level and prostate volume according to age groups

Variables	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age ≥80	Total
Subgroup analysis in 22,733 patients with PSA level <4.0 ng/mL and IPSS <20						
No. of patients	419	3214	7682	9862	2028	23,205
R value by Pearson's correlation test	0.291	0.345	0.486	0.529	0.568	0.531
P value by Pearson's correlation test	<.001	<.001	<.001	<.001	<.001	<.001
B value by linear regression model	2.220	3.852	4.885	5.894	7.953	5.813
R^2 value by linear regression model	0.081	0.118	0.196	0.251	0.279	0.267
P value by linear regression model	<.001	<.001	<.001	<.001	<.001	<.001
Subgroup analysis in 9623 patients with PSA level <4.0 ng/mL and IPSS ≥20						
No. of patients	61	575	2712	4821	1454	9623
R value by Pearson's correlation test	0.151	0.296	0.376	0.435	0.501	0.454
P value by Pearson's correlation test	.006	<.001	<.001	<.001	<.001	<.001
B value by linear regression model	1.243	3.668	4.668	5.360	7.009	5.478
R^2 value by linear regression model	0.011	0.088	0.148	0.189	0.251	0.206
P value by linear regression model	.006	<.001	<.001	<.001	<.001	<.001
Subgroup analysis in 1463 patients with 4.0 ng/mL ≤ PSA level <10.0 ng/mL and IPSS <20						
No. of patients	6	52	305	832	268	1463
R value by Pearson's correlation test	0.040	0.374	0.112	0.102	0.130	0.129
P value by Pearson's correlation test	.940	.007	.053	.004	.034	<.001
B value by linear regression model	0.636	4.895	1.546	1.489	2.242	1.957
R^2 value by linear regression model	0.002	0.140	0.013	0.010	0.017	0.017
P value by linear regression model	.940	.007	.053	.004	.034	<.001
Subgroup analysis in 932 patients with 4.0 ng/mL ≤ PSA level <10.0 ng/mL and IPSS ≥20						
No. of patients	0	15	154	526	237	932
R value by Pearson's correlation test	NA	0.166	0.044	0.121	0.160	0.133
P value by Pearson's correlation test	NA	.554	.589	.006	.015	<.001
B value by linear regression model	NA	2.440	0.655	1.992	1.292	1.599
R^2 value by linear regression model	NA	0.028	0.002	0.015	0.026	0.018
P value by linear regression model	NA	.554	.589	.006	.015	<.001

Abbreviations as in Table 1.

a Pearson correlation value of 0.369 for the correlation between PV and PSA level in patients with biopsy-proven BPH. Lee et al[13] also reported a relationship between PSA level and PV in Korean men with biopsy-proven BPH ($r = 0.41$, $P < .001$). However, the aforementioned studies were performed in patients who visited the hospital because of BPH or LUTS. In our community-based study, we found a higher correlation between PSA level and PV than reported in these previous studies of hospital patients. For this reason, our r^2 values (0.239) between PSA and PV was relatively higher than results (0.137∼0.185) from previously reported studies.[13,16] Oesterling et al[18] reported that serum PSA concentration was correlated with prostate volume with a Pearson correlation coefficient of 0.55 ($P < .001$) in a community-based population of healthy Japanese men, consistent with the value reported in our study (0.514, $P < .001$). Actually, in our subgroup analysis of patients with IPSS ≥20, relatively low correlation results than counterparts who had lower IPSS were obtained. These results might have a reason from the prostatic inflammation, which elevated the PSA level by itself. If the PSA level was elevated by prostatic inflammation, it had lower explanation power for predicting PV and this was inferred by equation between PSA and PV. No confirmation of the presence of prostatic inflammation among included patients could be another limitation of this study.

Similar to the study by Oesterling et al,[18] we examined a community of men regardless of their urologic symptoms. The lower correlation between PSA level and PV in men who visited the hospital with LUTS may be because of the relationship between PSA level and LUTS. Although the predictive value of PSA level for LUTS above a cutoff level was not excellent, men with high IPSS tended to have a much higher PSA level than those with low IPSS.[19] Furthermore, Masumori et al[20] suggested that Americans have a larger average PV measured by TRUS than Asian men, even after adjusting for differences in age, height, and weight. Osterling et al[18] also reported that Japanese men have a higher PSA level per unit volume than white men, based on a comparative analysis of their data on Japanese men with the data of Roehrborn et al.[21]

We analyzed a large cohort of men who were enrolled in a large-scale, well-protocolized free health screening program. The number of men analyzed in this study − 35,223 men—is the largest number of men screened in a single study to determine the relationship between PSA level and PV. Our equations are therefore applicable to real-world settings. In fact, most primary clinics in Korea do not have a TRUS instrument, and can therefore not accurately estimate PV, so we anticipate that the equations derived in this study will help determine whether patients require treatment for BPH or not. The equations for each age group are presented below:

$PV = 20.055 + 2.247 \times PSA$ (age 40-49 years),
$PV = 22.027 + 3.214 \times PSA$ (age 50-59 years),
$PV = 23.107 + 3.863 \times PSA$ (age 60-69 years),

PV = 24.189 + 4.419 × PSA (age 70-79 years), and
PV = 24.275 + 5.142 × PSA (age ≥80 years).

One limit of our study was its retrospective nature. Furthermore, a history of medication use, which can affect PSA levels, was not assessed. Although we excluded men with a PSA level >10 ng/mL, we could not exclude all cases with potentially occult prostate cancer. Actually, the correlation results in our subgroup analysis were relatively lower among patients who had higher PSA than lower PSA, it might be resulted from a hidden malignancy that independently elevated PSA level. Further study should be necessary for accurate correlation between PSA and PV, as well as histological confirmation in patients whose PSA was ≥4.0 ng/mL. The growth of the prostate is known to be highly dependent on testosterone.[22] Moreover racial variations in serum levels of hormones, including testosterone, also affected the prostatic growth disparity.[23] There was another limitation that we could not adjust the testosterone level among enrolled men. In general, the difference between PSA levels in white and Asian men is because of factors such as obesity and prostate size; our results differ slightly from those reported for men in Western countries.[7,12,24] The PSA level and PV distributions we measured in our cohort of Korean men was narrower than that reported for white men, probably because Korean men are ethnically homogenous, whereas white men are far more ethnically heterogeneous.

CONCLUSIONS

The serum PSA level was significantly correlated with PV in a community-based population regardless of LUTS symptoms, and we derived equations of the relationship between PSA level and PV according to age group. By avoiding the interventional bias of urinary symptoms, these data reflect the real relationship between PSA level and PV. Efforts should be made to establish separate cutoff values or nomograms for Asian men to assess the risks of BPH-related morbidity and the efficacies of various BPH treatments.

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EDITORIAL COMMENT

Serum prostate-specific antigen (PSA) measurements often represent a real problem for both urologists and general practitioners. As a matter of fact, PSA testing for prostate cancer screening is still a very controversial issue, having improved diagnosis but not specific survival, and, in any case, representing a great source of emotional distress to patients heavily affecting their quality of life. It is also true that underestimation of total PSA rise or of altered surrogate measures like PSA velocity may lead to the risk of missing a curable prostate cancer, which may cost life in case of delayed diagnosis.

The present article demonstrates that, in a general Asian male population, PSA increases by 0.3 ng/mL and prostatic gland volume by about 3 mL every 10 years, regardless of the presence or absence of lower urinary tract symptoms. Prostatic volume and its derivative PSA density may well be not particularly relevant to prostate cancer diagnosis, as already widely demonstrated in the recent literature. On the other hand, PSA velocity in individuals with normal total PSA values may be a valid aid to an absolutely early detection of prostate cancer in order to plan an effective therapeutic treatment of a biochemical, really initial, and totally asymptomatic disease.

The knowledge of the average total PSA concentrations and of the behavior of a biological marker such as PSA in a definite ethnic/racial group is a further relevant aspect of this study, becoming even more important if we take into account the current huge migratory flows and the consequent environmental changes, depending upon dietary factors, drinking water features, air pollution, and lifestyle.

With their results, the authors confirm that the published data obtained in Western countries are similar in Asia as well, providing additional parameters depending not only upon environment, as previously mentioned, but also upon human biotypes (without forgetting the correlation between weight and mean PSA concentrations).

In the present work, PSA levels and prostatic gland volume maintain a good correlation when International Prostate Symptom Score is <20 and total PSA is <4 ng/mL. Such correlation is lost in case International Prostate Symptom Score score >20 and PSA >4 ng/mL. The main responsibility for this discrepancy is probably prostatic inflammation, an emerging relevant variable able to affect both normal PSA levels and PSA kinetics (and possibly playing a role in prostatic carcinogenesis in the long run). The role of prostatic inflammation and of its features has been interestingly highlighted in a pre-PSA article,[1] demonstrating the existence of prostatic inflammation in benign prostatic hyperplasia, the definition of its extent, and the characteristics of its cellular composition. Because all the patients of the series underwent operations for benign prostatic hyperplasia associated with lower urinary tract symptoms, it is likely that a percentage of the voiding symptoms were due to or worsened by phlogosis. The epidemiological data from this Korean work may help to start to clarify the role of prostatic inflammation in an otherwise healthy population, not stratified upon lower urinary tract symptoms.

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