RESEARCH ARTICLE

Association of Prostate Specific Antigen Concentration with Lifestyle Characteristics in Korean Men

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Abstract

We investigated the relationships between demographics, lifestyle characteristics, and serum total prostate specific antigen (PSA) concentration and examined the population-based distribution of total PSA by age among 2,246 Korean men with a median age of 45 years. We obtained data about demographic and lifestyle characteristics based on self-reporting using a questionnaire. We also performed physical examinations, anthropometric measurements, and biochemical measurements. The PSA concentration increased with age and there was a significant difference in total PSA concentration between the age groups of 21-60 years and >60 years. Age >60 years, height ≥1.8 m, a low frequency of alcohol consumption, and taking nutritional supplements showed a significantly increased odds ratio for increased PSA when 3.0 ng/mL was chosen as the PSA cut-off level. Smoking status, BMI, percent body fat, diabetes mellitus, fatty liver, herbal medicine use, vitamin use, and diet were not significantly associated with total PSA regardless of the cut-off level. When interpreting a single PSA test, height, alcohol consumption, and nutritional supplement use should be considered, in addition to age.

Key words: Demographics - lifestyle - prostate specific antigen - Korean

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Introduction

The prostate specific antigen (PSA) test is widely used for early detection of prostate cancer even though the effectiveness of the test for mass screening has not been established. Serum PSA concentration is correlated with prostate volume and age and can also be elevated by numerous benign conditions that compromise the integrity of prostate tissue structure such as acute prostatitis, and prostatic ischemia or infarct (Glenski et al., 1992). Although high serum PSA concentration does not always mean the presence of prostate cancer, elevation is the primary indication for prostate biopsy to detect cancer. Therefore, it is important to know which factors besides the recognised ones of age and benign prostate diseases could affect serum PSA concentration.

The strongest risk factors for prostate cancer are age, African American race, and family history (Gann, 2002). Other risk factors under investigation include diet, anthropometric factors, physical activity, dietary supplements use, endogenous hormones, and concomitant medical conditions. Considering that migrants from low- to high-risk areas adopt the risk pattern of the host country (Shimizu et al., 1991), risk factors concerning lifestyle characteristics might be closely related to the development of prostate cancer. There have been several studies on the association of serum PSA concentration with a few anthropometric or lifestyle factors such as body mass index (BMI), diet, and physical activity (Ku et al., 2003; Kristal et al., 2006; Parekh et al., 2008). However, no studies have investigated the influence of various demographic or lifestyle factors on the serum PSA concentration in Korean men.

Here, we investigated the association of demographic and lifestyle characteristics with serum total PSA concentration and the population-based distribution of PSA by age among Korean men.

Materials and Methods

Participants

The study population was composed of 2,246 Korean men who visited the Total Health Care Center of Kangbuk Samsung Hospital in Seoul, South Korea, for comprehensive health examinations between January and February 2007. The median age of these men was 45 years (range: 21-79 years). Exclusion characteristics were: any history of prostate malignancies; use of narcotic drugs or hormones; and recent history of surgery, chemotherapy, radiation therapy, and transfusion during

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the preceding 3 months. All participants agreed to the study protocol and the local ethics committee of Kangbuk Samsung Hospital approved this study.

Detailed questionnaire items

Based on self-reporting using a questionnaire, we obtained extensive data about smoking habits; alcohol consumption habits such as frequency, duration, and amount; any medicine being taken; underlying diseases such as hypertension and diabetes mellitus (DM); diet; and exercise and physical activity. To evaluate dietary quality, we used a Mini Dietary Assessment (MDA) index developed in Korea (Kim et al., 2003) based on the Healthy Eating Index (HEI) which is a measure of diet quality provided by the Center for Nutrition Policy and Promotion (CNPP) of the United States Department of Agriculture (USDA) (Basiotis et al., 2002). Diet quality was defined as "good" if the total score was ≥30 out of the total possible score of 50. We also asked about the use of herbal medicine, vitamins, and nutritional supplements within one month. Exercise was assessed with respect to frequency (none, 1-2/week, 3-4/week, 5-6/week, every day), duration, and intensity. The intensity of usual physical activity was categorised into 'sedentary', 'light', 'moderate', 'active', and 'very active' using the coding scheme described by Ainsworth et al. (2000).

Measurements

We performed a physical examination, anthropometric measurements and biochemical measurements. We measured height, body weight, and percent body fat. The body mass index (BMI) was calculated as weight divided by height squared (kilograms/meters^2), and World Health Organization (WHO) recommendations were used to categorize BMI scores (WHO Western Pacific Region IASO and IOTF, 2000).

The serum concentration of total PSA was measured using the Elecsys E170 system (Roche Diagnostics, Mannheim, Germany). We also measured the serum concentrations of cholesterol, LDL-cholesterol, and fasting glucose with the ADVIA 1650 (Bayer HealthCare Ltd., Tarrytown, NY, USA). Plasma insulin concentrations were measured by radioimmunoassay. Insulin resistance was estimated by calculation of homeostasis model assessment-insulin resistance (HOMA-IR) (Bonora et al., 2002); low HOMA-IR concentrations indicate high, whereas high HOMA-IR concentrations indicate low insulin sensitivity (insulin resistance).

Evaluation of total PSA distribution.

We evaluated the mean, median, 90th, 95th, and 97.5th percentiles, and the standard deviation (SD) of total PSA concentrations according to age groups. General distributions of total PSA concentrations and laboratory quality control data were examined initially.

Statistical analysis

All calculations were performed using SPSS (Version 18.0) for Windows. The Kolomogorov-Smirnov (K-S) test was used to assess whether the distribution was Gaussian. Comparison of mean concentrations among more than three groups was performed using Kruskal-Wallis test and comparison between two groups was performed using the Mann-Whitney test. Correlation analysis was performed for PSA concentrations and BMI. Odds ratios (ORs) for association of high serum PSA concentrations with various factors were estimated by multiple logistic regression analyses. Only factors that were statistically significant on the univariate analysis were included in the multivariate logistic regression model. Results were considered statistically significant

Table 1. Demographic, Anthropometric, and Biochemical Characteristics of Subjects (n=2,246)

Characteristics		Number (%)
Age (years, median±SD)		45±10.82 (range: 21-79)
Height (m)	< 1.7	1051 (46.8)
	1.7-1.8	1064 (47.4)
	≥1.8	131 (5.8)
Body mass index (BMI, kg/m^2)	<18.5 (lean)	28 (1.2)
	18.5-22.9 (normal)	593 (26.4)
	23.0-24.9 (overweight)	682 (30.4)
	≥25.0 (obese)	943 (42.0)
Percent body fat (%)	<10.0	9 (0.4)
	10.0-20.0	800 (35.6)
	20.1-24.9	907 (40.4)
	≥25.0	530 (23.6)
Total Cholesterol (mmol/L)	<5.17	1382 (61.7)
	5.17-6.21	680 (30.3)
	≥6.21	183 (8.0)
HOMA-IR	≤0.76	455 (20.5)
	0.77-1.10	439 (19.8)
	1.11-1.49	438 (19.8)
	1.50-2.15	442 (20.0)
	≥2.16	441 (19.9)

*HOMA-IR, homeostasis model assessment-insulin resistance, The HOMA-IR was categorised on the basis of quintile distribution

Table 2. Lifestyle Characteristics of Subjects (n=2,246)

Characteristics		Number (%)
Smoking status	Current smoker (%)	773 (34.4)
	Past smoker (%)	529 (23.5)
	Non-smoker (%)	743 (33.1)
Alcohol drinking (%)		1,623 (79.1)
Hypertension (%)		460 (20.5)
Diabetes mellitus (%)		125 (5.6)
Fatty liver (%)		948 (42.2)
Benign prostate hypertrophy (%)		29 (2.6)
Nutritional supplement taker (%)		323 (14.4)
Herbal medicine taker (%)		189 (8.4)
Vitamin taker (%)		320 (14.2)
MDA score	1st quartile (0-32.0)	467 (20.8)
	2nd quartile (33.0-36.0)	457 (20.3)
	3rd quartile (37.0-40.0)	463 (20.6)
	4th quartile (≥41.0).	311 (13.8)
Exerciser (%)		1,062 (51.9)
Physical activity	Sedentary to Moderate	1,584 (88.1)
	Active to Very active	214 (11.9)

*MDA, Mini Dietary Assessment

when P values were <0.05.

Results

In the 2,246 subjects, median values (SD) of height, percent body fat, and BMI were 1.7 m (0.06), 21.7% (4.67), and 24.46 kg/m^2 (2.75), respectively. Table 1 and Table 2 show the demographic and lifestyle characteristics of the subjects. Among 29 subjects with benign prostate hypertrophy (BPH), four showed PSA >4.0 ng/mL. The distribution of total PSA concentrations was non-Gaussian. Seventy-seven (3.4%) subjects had PSA >3.0 ng/mL and 52 (2.3%) showed PSA above 4.0 ng/mL. Table 3 shows the distribution of total PSA according to age groups. A significant difference in PSA between the age groups of 21-60 years and >60 years remained even after a Bonferroni correction. The mean concentrations (SD) of total cholesterol, LDL-cholesterol, high sensitivity (hs)-C-reactive protein (CRP), and insulin were 4.99 mmol/L (0.87), 2.86 mmol/L (0.73), 1,300 μg/L (2,300), and 41.6 pmol/L (25.2), and all were within reference intervals. The mean MDA score was 36.2 (range; 16-50) of a possible 50.

We analysed the association of mean PSA concentration with demographic and lifestyle characteristics. There was no significant correlation between PSA concentration and BMI. When 3.0 ng/mL was chosen as the PSA cut-off level, old age (≥61 years), height ≥1.8 m, hypertension, long smoking duration (≥20-29 years), less frequent alcohol consumption (≤2-3/month), lower alcohol consumption (<1 bottle/time), and taking nutritional supplements were significantly associated with a PSA level above the cut-off. When 4.0 ng/mL was chosen as the cut-off level, old age (≥61 years), hypertension, long smoking duration (≥20-29 years), lower alcohol consumption (<1 bottle/time), and taking nutritional supplements were significantly associated with PSA concentration above the cut-off. Smoking status, BMI, percent body fat, DM, fatty liver, use of vitamins, taking herbal medicine, and MDA score were not significantly associated with PSA concentration regardless of the cut-off level. There was also no significant relationship between PSA concentration and total cholesterol, LDL-C, hs-CRP, and HOMA-IR. Exercise frequency, duration, intensity, and intensity of physical activity were also not related to PSA concentration.

Table 3. Distribution of Total PSA According to Age

	Age (years)						
	Overall	21-30	31-40	41-50	51-60	61-70	≥71
Number	2246	79	509	946	369	310	33
Total PSA (μg/L)							
Mean	1.17	0.94[a]	1.02[a]	1.03[a]	1.18[a]	1.78[b]	2.34[b]
Median	0.89	0.83	0.86	0.85	0.92	1.03	1.28
SD	2.1	0.47	0.68	0.83	1.47	4.93	4.11
90th percentile	1.84	1.68	1.69	1.61	2.06	2.89	4.84
95th percentile	2.5	1.92	2.12	1.99	2.71	4.18	11.66
97.5th percentile	3.95	2.06	2.99	2.59	4.15	5.77	23.71

*PSA, prostate specific antigen, The same superscript letters indicate non-significant differences among age groups based on Mann-Whitney test after Kruskall-Wallis test, The mean PSA concentrations were significantly (P<0.001) different between the age groups 21-60 and >60 years, This result was significant even after a Bonferroni correction

Table 4. Adjusted Odds Ratios of Characteristics According to Total PSA Cutoff Levels

Characteristics	Adjusted odds ratio (95% Confidence interval, P value)	
	PSA > 3.0 ng/mL	PSA > 4.0 ng/mL
Age (years)		
21-60	1.00	1.00
≥61	3.03 (1.47-6.24, 0.003)	2.33 (1.00-5.44, 0.05)
Height (m)		
< 1.8	1.00	-
≥1.8	3.60 (1.48-8.76, 0.005)	-
Hypertension		
Absent	1.00	1.00
Present	1.32 (0.62-2.79, 0.47)	1.72 (0.74-3.98, 0.21)
Alcohol consumption frequency		
≥1/week	1.00	-
≤2-3/month	2.00 (1.04-3.84, 0.04)	-
Alcohol consumption amount (bottles/drink)		
≥2	1.00	1.00
≤1	2.00 (0.79-5.05, 0.14)	2.16 (0.80-5.82, 0.13)
Smoking duration (years)		
≤10-19	1.00	1.00
≥20-29	1.95 (0.97-3.90, 0.06)	2.15 (0.94-4.93, 0.07)
Nutritional supplements		
No	1.00	1.00
Yes	2.11 (1.06-4.22, 0.03)	3.46 (1.61-7.42, 0.001)

*PSA, prostate specific antigen, Odds ratios (ORs) for association of high serum PSA concentrations with various factors were estimated by multiple logistic regression analyses, Only factors that were statistically significant on the univariate analysis were included in the multivariate logistic regression model, Nutritional supplements include all dietary supplements except herbal medicines and multivitamins

In the logistic regression analysis (Table 4), age ≥61 years, height ≥1.8 m, lower frequency of alcohol consumption, and taking nutritional supplements showed significantly increased odds ratios for an increased PSA concentration when 3.0 ng/mL was chosen as the cut-off level. When 4.0 ng/mL was chosen as the cut-off level, taking nutritional supplements was the only factor showing a significantly increased odds ratio of an increased serum PSA concentration.

Discussion

Serum PSA concentration of 4.0 ng/mL has been widely used as the cut-off value for prostate cancer screening. However, another study suggested that it is relatively safe to use a PSA cut-off value of 3.0 ng/mL in a setting of repeated screening, and lower cut-offs such as 2.5 ng/mL have also been suggested (Schroder et al., 2009). In this study, more demographic and lifestyle characteristics were significantly associated with PSA above the cut-off when 3.0 ng/mL was chosen as the cut-off than when 4.0 ng/mL was used. Therefore, if cut-off

levels less than 4.0 ng/mL were used in clinical settings, more characteristics should be considered when making decisions. As expected, PSA concentration increased with age in our study. In particular, mean PSA concentrations were significantly different between the age groups of 21-60 years and ≥61 years. This result supports many studies showing that an age-specific reference range of PSA is necessary, especially in men older than 60 years.

Among anthropometric factors, only height was significantly associated with PSA. The lack of association of obesity with PSA was consistent with previous studies (Kristal et al., 2006). Indeed, some reports suggested an inverse relationship between PSA and obesity, which is likely due to lower testosterone concentrations that influence PSA production (Gapstur et al., 2007) and/or haemodilution of PSA among obese men (Ohwaki et al. 2010). In this study, height ≥1.8 m was significantly associated with PSA above 3.0 ng/mL, which is similar to a previous report that height independently influences PSA (Fowke et al., 2006). In addition, prior investigations have reported an association between height and clinical BPH (Fowke et al., 2005). Mechanisms linking height to PSA may be related to higher concentrations of insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein (IGFBP) associated with a greater prostate volume (Sarma et al., 2002).

In this study, there was a significant inverse association between alcohol intake and PSA. Although alcohol consumption has been extensively studied in relation to the risk of prostate cancer, findings on the direction of the association are equivocal (Platz et al., 2004), and there have only been a few previous studies on the relationship between PSA concentrations and alcohol consumption. While there are similar studies to ours that report a decrease in PSA associated with an increase in the intensity of alcohol consumption (Ukoli et al., 2003; Pizent et al., 2009), one study that investigated the association of PSA with excessive alcohol drinking gave opposite results (Ahmed et al., 2008). Our results support the theory that alcohol reduces hormonal promotion of prostate growth; that is, men who drink alcohol every day have sustained depression of testosterone relative to oestrogen (Platz et al., 2004) which would lead to decreased PSA.

About one third of our subjects were taking more than one kind of dietary supplements and taking nutritional supplements was related to increased PSA concentrations, while use of vitamins and herbal medicine was not. In our questionnaire, nutritional supplements meant health food products such as ginseng, royal jelly, etc or synthetic nutrients such as fish oil, dehydroepiandrosterone (DHEA), calcium, zinc, etc. There have been some studies investigating the association of dietary supplement use with prostate cancer risk. Multivitamin use (Lawson et al., 2007) and calcium intake (Butler et al., 2010) are known to increase the risk of prostate cancer, while selenium (Lindshield et al., 2010) and zinc (Song et al., 2010) showed in-vitro inhibitory effects on the growth of prostate cancer cells and decreased oxidative DNA damage in the prostate, respectively. Considering that this study showed no association of vitamin intake with increased PSA, vitamin use might increase the risk of prostate cancer without elevation of serum PSA. Although DHEA exerts minimal effects on normal prostate, in cancer-associated tissues a reactive stromal microenvironment can promote prostate proliferation or PSA production in the presence of DHEA (Arnold et al., 2008). Although many kinds of nutritional supplements are increasingly consumed for their anti-aging effects, their effectiveness and long-term safety for prostate tissues are uncertain and rather risky.

In univariate analysis, a long smoking duration was associated with high PSA. Some studies have reported that smoking was not associated with increased PSA although a significant relationship between smoking and the rate of increase of PSA was reported in another study (Kristal et al., 2006). Cadmium (Cd) from cigarette smoke accumulates in the prostate where it interacts with selenium (Se) in a manner suggesting the formation of a 1:1 Cd-Se-protein complex. At higher Cd exposures, Cd may weaken the anticarcinogenic effects of Se and increase prostate cancer risk (Schopfer et al. 2010). Therefore, older subjects with a smoking duration of more than 20 years might have prostate Cd levels in stoichiometric excess over Se, which may explain why they showed high PSA levels even though daily consumption of cigarettes did not show a significant association with high PSA in our study.

A few limitations need to be considered when interpreting the results of our study. We were unable to determine whether specific kinds of nutritional supplements affect PSA as our questionnaire did not ask for the detailed name of nutritional supplements, although we did divide dietary supplements into three categories: herbal medicine, vitamins, and nutritional supplements. In addition, there may be undetected prostate infection and inflammation among the subjects that might cause increased PSA. We also did not exclude the subjects who had a recent digital rectal examination or other maneuvers that may cause artificial PSA elevation.

In summary, we found significant associations of several demographic and lifestyle characteristics with PSA concentrations. PSA concentrations above the cut-off were related to age, height, alcohol consumption, and use of nutritional supplements. Thus, when interpreting a single PSA test, height, alcohol consumption, and nutritional supplement use should be considered as well as age. In particular, obesity and vitamin use, which are known risk factors of prostate cancer, were not related to increased PSA, and thus PSA concentrations within the reference range should be interpreted cautiously for obese people or vitamin takers.

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