Screening Prostate-specific Antigen Concentration and Prostate Cancer Mortality: The Korean Heart Study

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Abstract

OBJECTIVE—To evaluate the association between serum prostate-specific antigen (PSA) concentration from a screening test and prostate cancer mortality in an Asian population.

METHODS—We included 118,665 men in the Korean Heart Study, a large prospective cohort study of participants who voluntarily underwent private health examinations that included PSA-based prostate cancer screening. The baseline visit occurred between January 1994 and December 2004, and follow-up was through December 2011. Deaths from prostate cancer were ascertained from the underlying cause of death from a computerized search of death certificate data from the National Statistical Office in Korea. We used the Cox proportional hazards regression to estimate the association between serum PSA and risk of prostate cancer death adjusting the baseline age, cigarette smoking status, and body mass index.

RESULTS—During 1,381,901 person-years of follow-up, 6036 men died of any cause, and of these, 56 men died of prostate cancer. The multivariate-adjusted hazard ratio for prostate cancer death statistically significantly increased across PSA concentrations (*P* trend <.0001). The hazard ratio increased 7% per 1-ng/mL increase in PSA. The association between PSA concentration and death from prostate cancer was stronger in younger than in older men and in heavier than leaner men.

CONCLUSION—In conclusion, an increased screening PSA level is associated with an increased risk of prostate cancer death in Korean men. Our findings may have implications for the development of targeted PSA cutpoints for biopsy recommendation.

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APPENDIX

Supplementary Data

Prostate cancer is the second most diagnosed cancer worldwide and is a leading cause of cancer mortality in Western and other developed countries.[1] The number of men diagnosed with prostate cancer is rapidly increasing around the world; the annual percentage increase in Korea was 12.6% from 1999 to 2010.[2]

The measurement of serum prostate-specific antigen (PSA) concentration has been used extensively in the United States since the early 1990s to screen for prostate cancer. The US Preventive Services Task Force does not currently recommend PSA-based prostate cancer screening after an assessment of the risks vs the benefits,[3] whereas the American Urological Association continues to recommend its use in the urologic setting for screening of men aged 55-69 years old.[4] Nevertheless, use of PSA to screen for prostate cancer has been partially credited with the observed decline in prostate cancer mortality in the United States.[5]

Prostate cancer mortality rates have steadily decreased over the past 10 years, including in the United States[6] and Europe,[7] but are increasing in some Asian countries including Korea[2] and Eastern European countries.[8] Aside from the United States, PSA-based prostate cancer screening has not been routinely performed globally, although uptake has occurred to some extent.[8] Thus, it is unknown whether the decline in the prostate cancer mortality rate observed in some countries is due to PSA screening or improved treatment of prostate cancer,[5] or other cause.

Prospective studies using banked blood specimens have reported that the higher the serum PSA concentration the greater the incidence of prostate cancer years to decades later.[9] However, only a few prospective observational studies of men without a diagnosis of prostate cancer at baseline have reported on the association between serum PSA concentration in banked specimens and prostate cancer mortality.[10,11] No prospective studies have been conducted to address this association in Asian countries, where the prostate cancer mortality rate is lower than that in North America and Europe,[8] which, in part, might be attributable to differences in access to PSA testing.[12]

Thus, the objective of this study was to evaluate the association between serum PSA concentration from a screening test and prostate cancer mortality in an Asian population. We analyzed data from the Korean Heart Study, a large prospective cohort study of participants who voluntarily underwent private health examinations that included PSA-based prostate cancer screening.

METHODS

Study Population

The Korean Heart Study is a prospective cohort study formed from data from men and women who have voluntarily undergone private health examinations in 18 health promotion centers located in 1 capital and 6 provinces in South Korea from 1996 to 2004.[13] We conducted this analysis using data from 15 of the 18 centers that provided approval for research on cause-specific mortality. South Korean citizens are assigned a personal identification number at birth. This number was used to link the participants' health

examination records with death registers. The linkage resulted in 521,585 individuals aged 20 years older at their health examination that occurred at the earliest between January 1994 and December 2004. That health examination was considered to be their baseline.

Of this population, 296,771 men were the source population for this prostate cancer study. From these men, we excluded 101,001 men with missing information on PSA level; information was missing because 2 of the centers did not perform PSA-based prostate cancer screening, and in several of the centers, the men had to opt-into an optional examination that included a screening PSA test. Men excluded from the analysis for missing PSA information had a similar age-standardized prostate cancer mortality rate as the men included in the analysis, although their all-cause mortality rate was higher (Supplementary Table 1). We also excluded 612 men who already had a cancer diagnosis of any site by their baseline health assessment and 76,483 participants with missing baseline smoking status, body mass index (BMI), systolic or diastolic blood pressure, total cholesterol, and fasting glucose information. The final analytical study sample included 118,665 men.

Under the January 2005 Bioethics and Safety Act (no. 7159) of the Ministry of Health and Welfare, the Korean Heart study was conducted as a retrospective study was performed using the data collected from individuals who underwent medical examinations before December 2004 (waiver of informed consent). The Institutional Review Board of Human Research of Yonsei University and all the individual health promotion centers participating in the Korean Heart Study approved the investigation.

Data Collection

In this study, we used data, including on PSA concentration that were collected during the voluntary private health examinations. We obtained the following data from the health examination records: smoking status (never, past, or current smoker), history of cancer, cardiovascular disease, diabetes or hypertension, history of use of medications for diabetes or hypertension, weight and height, which were measured during health examination while the examinees were wearing light clothing, and blood pressure, which was measured either by registered nurses or technicians.

We obtained from the health examination record serum total PSA concentration, which was measured immunochemically using the ADVIA Centaur XP Immunoassay (Siemens Diagnostics, Deerfield, IL), which is standardized to the World Health Organization international reference standard for PSA (90:10) 96/670 and has an assay range of 0.01-100 ng/mL. Per the health promotion center protocol, samples with a PSA concentration >100 ng/mL were diluted and remeasured. We also obtained from the health examination record serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, and fasting glucose concentrations, and among other clinical chemistry tests, which were measured at each health promotion center using auto analyzers. Per the health promotion center protocol, each measurement laboratory had internal and external quality control procedures as required by the Korean Association of Laboratory Quality Control.[13]

Follow-up for Mortality

The men were followed up from their baseline health examination occurring between 1994 and 2004 to death or December 30, 2011, whichever was earlier. The primary outcome for this analysis was death from prostate cancer (International Classification of Diseases-10 code C61). Deaths were ascertained from the underlying cause of death on death certificates. Computerized searches of death certificate data were provided by the National Statistical Office in Korea.

Statistical Analysis

In the analysis, we used the PSA test performed at the baseline health examination. For the main analysis, we used the same cutpoints (<1.0, 1.0-1.9, 2.0-2.9, 3.0-3.0, 4.0-9.9, and 10.0 ng/mL) as were used in previous studies,[11] rather than distributional cutpoints. The PSA 3.0-3.9 ng/mL category had few deaths, and thus, we combined PSA 2.0-2.9 and 3.0- 3.9 ng/mL categories. Therefore, we divided the men into 5 PSA concentration categories (<1.0, 1.0-1.9, 2.0-3.9, 4.0-9.9, and 10.0 ng/mL). In an alternative analysis, we divided PSA concentration into quintiles. We calculated age-specific and overall mortality rates for all causes and prostate cancer. To evaluate the association between PSA concentration and risk of prostate cancer death, we used the Cox proportional hazards regression and adjusted for risk factors for death from prostate cancer—age, cigarette smoking status,[14] and BMI[15] at the baseline. To avoid the possible confounding effects of health status on mortality, in a subanalysis, we excluded the person-time at risk and deaths from prostate cancer during the first 2 years of follow-up. We stratified the multivariate-adjusted analysis by the baseline age (cutpoint at the median of 60 years) and BMI (cutpoint at 25 kg/m^2). Statistical interaction between PSA concentration and age or BMI was assessed by likelihood ratio tests. We repeated the main analysis for prostate cancer mortality using a competing risks model.[16] Analyses were performed using Stata, version 12. All statistical tests were 2 sided, and *P* <.05 was considered to be statistically significant.

RESULTS

At the baseline, the average age of the men included in the analysis was 47.1 years, and mean follow-up was 11.6 years. Men who had higher PSA concentrations were older and after adjusting for age were slightly leaner, had lower fasting glucose concentrations, and were less likely to currently smoke (Table 1). The distribution of selected characteristics of the men by age category is shown in Supplementary Table 2. Of the 118,665 men and during 1,381,901 person-years of follow-up, 6036 men died of any cause, and of these, 56 men died of prostate cancer (Table 2). The prostate cancer mortality rates (per 100,000 person-years) by age category were as follows: 0.2 for 40-49 years, 4.6 for 50-59 years, 11.5 for 60-69 years, and 99.3 for 70 years (Table 2). The all-cause mortality rates (per 100,000 person-years) were as follows: 186.9 for 40-49 years, 524.5 for 50-59 years, 1359.2 for 60-69 years, and 3916.9 for 70 years (Table 2).

The age-adjusted and multivariate-adjusted hazard ratios (HRs) for prostate cancer death statistically significantly increased across PSA concentration (*P* trend <.0001; Table 3). Even men with a PSA concentration between 2.5 and <4 ng/mL, which is below the usual

cutpoint for biopsy recommendation, appeared to have more than twice the risk of death from prostate cancer compared with men with a concentration <1 ng/mL. After excluding the first 2 years of follow-up, the association between PSA concentration and prostate cancer death was similar to overall (Table 3). When we considered competing risk analyses, the overall results were not changed (Supplementary Table 3). When we modeled PSA concentration in quintiles, the trends for the age-adjusted analysis, multivariate adjusted analysis, and the analysis excluding the first 2 years of follow-up remained statistically significant (data not shown).

Unlike for prostate cancer death, the age-adjusted and multivariate-adjusted HRs for all-cause mortality did not linearly increase across increasing PSA concentration, although when modeling PSA as a continuous variable, a weak positive association of borderline statistical significance was observed (Supplementary Table 4).

For each 1-ng/mL increase in PSA concentration, the multivariate-adjusted HR of prostate cancer death increased by 7% (Table 3; Fig. 1). The association between PSA concentration and death from prostate cancer was stronger in men who were younger than in those who were older at the baseline (*P* interaction <.0001; Fig. 1) but was similar in men who were heavier and leaner at the baseline (*P* interaction = 0.12; Fig. 1).

COMMENT

In this large prospective Korean cohort study, we found that the risk of death from prostate cancer increased with increasing serum PSA concentration in men screened for the disease, including when considering competing risks of death. The common threshold for biopsy is >4.0 ng/mL,[17] but our results support that any PSA level when compared with 1 ng/mL is associated with an increased risk of death from prostate cancer in this Korean study population.

Our results on prostate cancer mortality support the results from previous studies examining PSA levels and risk of prostate cancer mortality.[10,11,18] Unlike our study, which used PSA levels from prostate cancer screening in a prospective cohort study, most previous studies on prostate cancer mortality were prospective, but measured PSA in banked specimens for research purposes, or were case-control studies.

The association between baseline PSA levels and incidence of prostate cancer is well known.[9] A previous study reported that even low levels of PSA (0.70 ng/mL) reflect a higher risk of prostate cancer.[19] The most important goal of PSA screening is to reduce the risk of death from prostate cancer.[20] Two major randomized trials on PSA screening and prostate cancer mortality have been published. In the US trial, prostate cancer mortality did not differ between the screen and control groups,[21] but PSA screening reduced prostate cancer mortality in the European trial.[22] Reasons for differences in the findings of the 2 trials have been extensively discussed. [23] The detection of prostate cancer is increased by PSA screening, but such screening also increases the rate of detection of cases that may never manifest clinically and may not have the potential to cause death.[21,22] Early detection through PSA screening may lead to unnecessary biopsies, whereas postponing biopsy may lead to a missed opportunity for early treatment of men with prostate cancer.[11] Therefore, it

is important to detect and treat the appropriate men at the appropriate time in the natural history of this cancer.

We found that PSA concentration was more strongly associated with prostate cancer mortality in younger men (aged <60 years); the risk of prostate cancer death increased by 20% per 1 ng/mL in younger men and 7% per 1 ng/mL in older men. As men age, their PSA concentration increases because of increasing prostate volume[24] and increasing prevalence of benign prostatic hyperplasia,[25] and they experience competing causes of death (eg, from cardiovascular disease).[26] Therefore, higher reference serum PSA ranges for use in screening for prostate cancer may be prudent in older men as Oesterling et al have suggested previously.[24]

Asian populations tend to have higher proportion of men diagnosed at an advanced stage of prostate cancer compared with Western population,[12] despite a lower prostate cancer mortality rate.[8] When comparing across countries, however, prostate cancer death rates and HRs by PSA concentration categories are similar (Supplementary Table 5). When compared across studies, age-specific PSA concentrations in Asian countries, the United States, and Europe are generally similar.[12,27,28] A previous review suggested that differences in uptake of PSA screening and access to urology clinics could explain the discrepancy in the diagnosis of advanced stage disease.[12]

In our data, risk of all-cause mortality did not linearly increase across increasing PSA concentration, although when modeling PSA as a continuous variable, a weak positive association was observed. Unlike our study, 1 previous study reporting a significant relationship between continuous PSA concentration and all-cause mortality did not support our study.[29] When we analyzed finer causes of death, risk of cause-specific death other than prostate cancer was lower in men with a PSA level of 1-<4.0 ng/mL compared with men with a PSA level of <1 ng/mL.

Most men in the Korean Heart Study had a PSA level measured automatically as a component of a panel of tests performed during their health examination. Thus, in these men, the likelihood of differential uptake of PSA screening based on the patient's characteristics, which may themselves be risk factors for prostate cancer death, is reduced. However, at some centers, PSA-based prostate cancer screening was part of an opt-in examination. At 2 centers, screening PSA testing was not performed. To assess whether differential uptake of PSA testing may have occurred in the source population, we compared men with (eligible to be included in the analysis) and without (not eligible to be included in the analysis) information on PSA. The 2 groups of men had similar self-rated health status and income status, suggesting lack of major selection bias.

Our study has a number of strengths. This cohort includes a large sample size and a wide age range. Although the number of prostate cancer deaths was not large, the number observed was higher than what was expected (data not shown) based on national data.[30] Also, we investigated the association between PSA level and death from prostate cancer in an Asian population. However, our study has several limitations. First, we did not have information on previous PSA screening tests, prostate biopsies, digital rectal examination,

incidence of prostate cancer, stage at diagnosis, and treatment for prostate cancer. As a consequence, we could not determine the association between PSA level and prostate cancer incidence in the cohort, or prostate cancer death in men in the cohort who were diagnosed with prostate cancer. Furthermore, we cannot determine whether the increased risk of prostate cancer death in men with higher PSA was due to greater inherent disease aggressiveness (ie, irrespective of early detection and appropriate treatment, the cancer would still have caused death) or poorer ability to treat disease diagnosed at a later phase in its natural history. Second, we used only the PSA level measured at the baseline. Finally, because all men included in the analysis were screened, we cannot comment on the effectiveness of prostate cancer screening vs no screening for the reduction in prostate cancer mortality.

CONCLUSION

In conclusion, an increased screening of the PSA level is associated with an increased risk of prostate cancer death in Korean men. Our findings may have implications for the development of targeted PSA cutpoints for biopsy recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Appendix

Korean Heart Study (mortality study) participating institutes and principal collaborators: Hyon-Suk Kim (Shinchon Severance Hospital), Duk Chul Lee (Gangnam Severance Hospital), Moon Jong Kim (CHA Bundang Medical Center), Gyu Jang Lee (Korea Medical Institute), Jidong Sung (Samsung Medical Center), BeLong Cho (Seoul National University), Eung Soo Kim (Daejeon Sun General Hospital), Byung-Yeon Yu (Konyang University Hospital), Tae-Yong Lee (Chungnam National University), Jong Sung Kim (Chungnam National University), Sung Hi Kim (Daegu Catholic University Hospital), Jong-Ku Park (Yonsei University Wonju College of Medicine), Sang Baek Koh (Yonsei University Wonju College of Medicine), Sat Byul Park (Ajou University School of Medicine), Soon Young Lee (Ajou University School of Medicine), Cheol-In Yoo (University of Ulsan College of Medicine), Moon Chan Kim (University of Ulsan College of Medicine), and Joo-sung Park (Dong-A University Medical Center).

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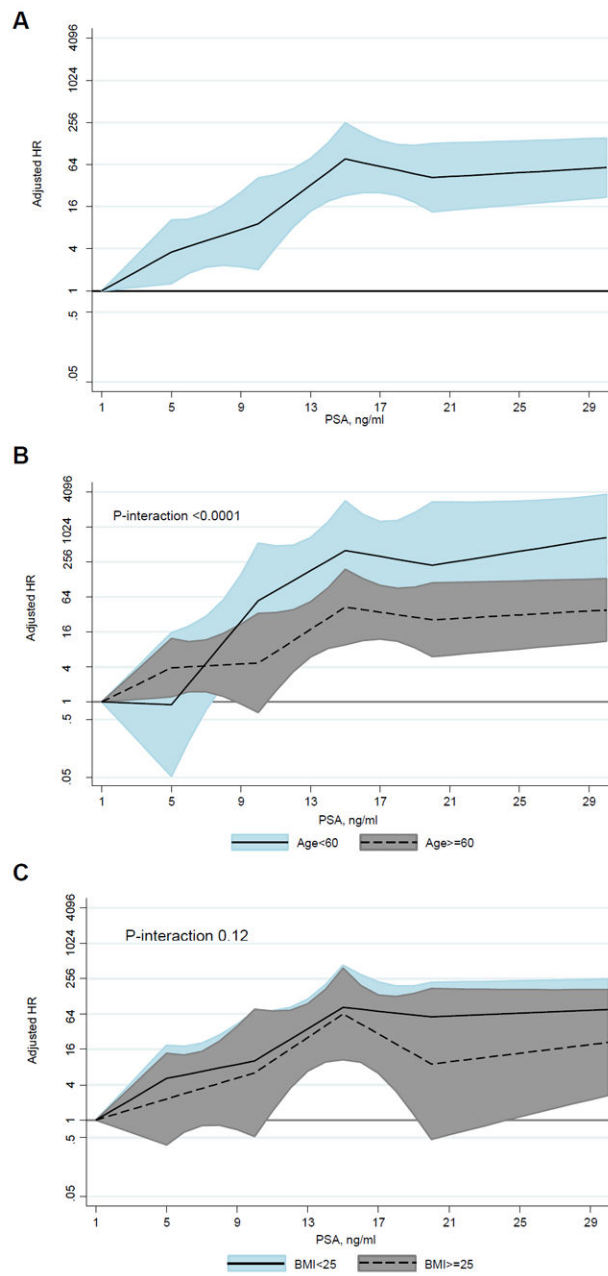
Figure 1.
Multivariate-adjusted hazard ratio of prostate cancer mortality for screening prostate-specific antigen concentration overall **(A)**, by baseline age **(B)**, and body mass index **(C)**. BMI, body mass index; HR, hazard ratio; PSA, prostate-specific antigen.

Table 1

Baseline characteristics by serum PSA concentration at baseline, Korean Heart Study, 1994-2011[*]

	Serum PSA Concentration, ng/mL					P Trend
	<1.0	1.0-1.9	2.0-3.9	4.0-9.9	10.0	
N	71,524	36,809	8313	1747	272	
Mean (SE) age, y	45.6 (0.0)	48.1 (0.1)	52.6 (0.1)	56.4 (0.2)	60.3 (0.6)	<.0001
Mean (SE) body mass index, kg/m²	23.9 (0.0)	23.8 (0.0)	23.7 (0.0)	23.8 (0.1)	23.6 (0.2)	<.0001
Mean (SE) systolic blood pressure, mm Hg	124.0 (0.1)	123.8 (0.1)	124.6 (0.2)	125.1 (0.4)	123.8 (1.0)	.033
Mean (SE) diastolic blood pressure, mm Hg	77.9 (0.0)	78.1 (0.1)	78.2 (0.1)	77.3 (0.3)	75.0 (0.7)	.65
Mean (SE) total cholesterol, mg/dL	195.1 (0.1)	195.6 (0.2)	195.1 (0.4)	194.2 (0.8)	193.1 (2.1)	.65
Mean (SE) fasting glucose, mg/dL	101.2 (0.1)	99.1 (0.1)	98.6 (0.3)	97.1 (0.6)	96.0 (1.5)	<.0001
Mean (SE) PSA, ng/mL	0.6 (0.0)	1.3 (0.0)	2.5 (0.0)	5.5 (0.0)	19.3 (0.0)	<.0001
Smoking status (%)						
Never	22.2	21.8	23.3	25.3	26.5	<.0001
Past	23.8	27.2	30.9	33.0	34.9	
Current	54.1	51.0	45.8	41.7	38.6	

PSA, prostate-specific antigen; SE, standard error of the mean.

[*] Adjusted for age.

Table 2

Number of deaths and age-specific mortality rates for deaths from all causes and prostate cancer, Korean Heart Study, 1994-2011

| Age (y) | Number of Men (%) | Person-years at Risk | Number of Deaths (Mortality Rate Per 100,000 Person-years) | |
			All Causes	Prostate Cancer
20-29	3637 (3.1)	40,765	31 (76.1)	0 (0.0)
30-39	25,697 (21.7)	296,668	291 (98.1)	0 (0.0)
40-49	43,018 (36.3)	507,842	949 (186.9)	1 (0.2)
50-59	30,816 (26.0)	367,753	1929 (524.5)	17 (4.6)
60-69	13,330 (11.2)	147,734	2008 (1359.2)	17 (11.5)
70	2167 (1.8)	21,139	828 (3916.9)	21 (99.3)
Total	118,665 (100.0)	1,381,901	6036 (436.8[*])	56 (4.1[*])

[*] The rate in the study population; not standardized to an external age distribution.

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Table 3

Hazard ratio and 95% confidence interval of prostate cancer death by serum PSA concentration at baseline, Korean Heart Study, 1994-2011

Serum PSA Concentration at Baseline, ng/mL	Deaths	Person-years	HR (95% CI)		
			Age Adjusted	Adjusted for Age, BMI, and Smoking Status	Excluding the First 2 years of Follow-up*
<1.0	11	818,989.3	1.00	1.00	1.00
1-<2.0	14	441,292.5	1.57 (0.71-3.47)	1.57 (0.71-3.47)	1.88 (0.81-4.38)
2-<4.0	9	98,878.0	2.40 (0.97-5.93)	2.41 (0.97-5.95)	2.85 (1.10-7.36)
4-<10.0	5	19,707.7	4.31 (1.44-12.91)	4.32 (1.44-13.0)	4.09 (1.21-13.8)
10.0	17	3033.4	64.4 (27.9-148.6)	65.0 (28.2-150.0)	72.4 (29.7-176.8)
Per 1-ng/mL increase in PSA			1.07 (1.06-1.09)	1.07 (1.06-1.09)	1.08 (1.07-1.09)
P trend			<.0001	<.0001	<.0001

BMI, body mass index; CI, con3dence interval; HR, hazard ratio; other abbreviation as in Table 1.

*
Excluded 4 prostate cancer deaths and 236,698.3 person-years.