Total and Percent Free Prostate-Specific Antigen Levels among U.S. Men, 2001-2002

Mona Saraiya,[1] Benny J. Kottiri,[2] Steven Leadbetter,[1] Don Blackman,[1] Trevor Thompson,[1] Matthew T. McKenna,[3] and Fred L. Stallings[1]

[1]Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Division of Health and Nutrition Examination Survey, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland; and [3]Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion

Abstract

Background: Because total prostate-specific antigen (PSA) and, more recently, the percent free PSA are used to screen men for prostate cancer, population-based, age- and race-specific distributions are needed of both PSA tests among American men to estimate the effect of lowering the PSA threshold or widespread introduction of the free PSA test as an additional screening test.

Methods: We did PSA assays on serum samples from men of ages 40 years and older (n = 1,320) who participated in the 2001-2002 National Health and Nutrition Examination Survey.

Results: About 6.1% (95% confidence interval, 4.7-7.7%), corresponding to an estimated 3.4 million (range, 2.7-4.3 million) men nationwide, ages 40 years and older, had a total PSA of >4.0 ng/mL. Among men ages 50 to 69 years old, the age group for which PSA testing is most prevalent, 5.4% or an estimated 900,000 to 2 million men had a total PSA of >4.0 ng/mL. An equal number had a total PSA between 2.5 and 4.0 ng/mL and a percent free PSA of <25%. Approximately 27% of men in this age group, corresponding to a range of 5.7 to 8.1 million men, had a total PSA <2.5 ng/mL and a percent free PSA of <25%.

Conclusion: The effect of lowering the total PSA threshold or introducing another screening test is significant. Provision of the number of U.S. men with certain total PSA and percent free PSA values may help guide prostate cancer public health policy and screening practices. (Cancer Epidemiol Biomarkers Prev 2005;14(9):2178–82)

Introduction

Although the prostate-specific antigen (PSA) test was approved by the Food and Drug Administration in 1994 for early detection of prostate cancer, the effectiveness of this test for population-based screening has not been established (1) despite its widespread use (2-4). A cutoff level for total PSA of 4.0 ng/mL has become conventional as a threshold for further diagnostic workup (5, 6). Using a threshold of 4 ng/mL for biopsy, Draisma et al. (7), reporting from a European screening study, found that 27% more prostate cancers would be detected by a screening test at age 55 than if screening were not done. Recent evidence from the Prostate Cancer Prevention Trial in the United States, however, has shown that prostate cancer may not be rare in men with total PSA values of ≤4.0 ng/mL, particularly in those with a total PSA of 2.1 to 4.0 ng/mL (8). In a group of 2,950 men (ages 62-91 years) whose total PSA never exceeded 4.0 ng/mL and who had no abnormal digital rectal examinations, 449 (15%) had developed prostate cancer at the end of 7 years, with rates of 24% and 27% for those whose total PSA was 2.1 to 3.0 ng/mL and 3.1 to 4.0 ng/mL, respectively. In addition, 15% of the cancers detected were of high grade (Gleason score ≥ 7). Not surprisingly, the debate continues about whether lower cutoff values might be needed (6, 9).

To help distinguish benign PSA elevations from elevations more likely to cause prostate cancer, the Food and Drug Administration approved the percent free PSA as an adjunct screening test in 1998. Some researchers have recommended using a percent free PSA cutoff value of 25% or lower (10) to increase specificity when total PSA values are between 4.0 and 10.0 ng/mL (11) or when total PSA values are between 2.5 and 4.0 ng/mL (12-14) and even for lower total PSA values (15, 16). The prevalence and distribution of free PSA tests remain unknown. The present study was designed to estimate the population-based distribution of total PSA and percent free PSA among men in the United States by age and race/ethnicity.

Materials and Methods

Study Population and Sample Design. The National Health and Nutrition Examination Survey (NHANES) 2001-2002 is a nationally representative cross-sectional survey of the civilian noninstitutionalized population of the United States. Details of the procedures involved in sampling and data collection have been published elsewhere (17). Briefly, this survey used a complex, multistage probability sample based on a selection of counties, blocks, households, and persons within households. Mexican Americans, non-Hispanic blacks, and adults of ages ≥60 years were oversampled. Overall response rates were 83.9% for the interview and 79.7% for the exam component. All procedures were approved by the National Center for Health Statistics institutional review board; written, informed consent was obtained from all participants.

Men ages ≥40 years were eligible for PSA testing. After these men received general information about the test from the examining NHANES physician, they were offered the opportunity to be tested. Men were excluded from the test if they refused or reported having any of the following procedures or conditions, as these may have altered the results: current infection or inflammation of the prostate gland, digital rectal exam in the past week, prostate biopsy in the past 30 days, cystoscopy in the past 30 days, or history of prostate cancer. Men with total PSA of >4.0 ng/mL received a letter within 4 weeks of

their PSA test, notifying them that this result was outside the normal reference range and advising them to discuss the findings with their physician. All men (irrespective of the PSA value) were notified of their total PSA and percent free PSA results in a package mailed ~12 weeks after their exam.

The total PSA values were examined as both a continuous and a categorical variable based on published cutoff values for further diagnostic workup (<2.5, 2.5-4.0, and >4.0 ng/mL; refs. 9, 13) and based on strata (whenever numbers permitted such fine detail) from the Prostate Cancer Prevention Trial (0-1.0, 1.1-2.0, 2.1-3, 3.1-4.0, and >4.0 ng/mL; ref. 8). Percent free PSA was examined as both a continuous variable and a dichotomous variable (<25%, ≥25%; ref. 10).

NHANES categorizes race/ethnicity as non-Hispanic white, non-Hispanic black, Mexican American, and other (other Hispanics and all others). Because the number of participants was limited in the ''other'' category, estimates by race/ethnicity were restricted to non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. Age was categorized in four groups: 40 to 49, 50 to 59, 60 to 69, and >70 years. In some instances, age was grouped into categories relevant to some prostate cancer screening recommendations (40-49, 50-69, and >70 years; ref. 18).

Collection of Samples, Storage, and Assays. As part of the exam, blood samples were drawn by venipuncture, centrifuged, and the sera frozen at −20°C within 1 hour of the blood draw. Within 1 week, the frozen specimens were sent on dry ice to the University of Washington Medical Center Department of Laboratory Medicine, Immunology Division Laboratory (Seattle, WA), where they were kept at −70°C until analyzed (19). The PSA values were determined using the Hybritech PSA and Hybritech free PSA monoclonal antibody assays (Hybritech, San Diego, CA) on the Beckman Access analyzer (Fullerton, CA). Both are chemiluminescence-based, ''sandwich type,'' immunometric, solid-phase assays employing murine monoclonal antibodies. The total PSA had a coefficient of variation of <4.6% for quality control pool means with a range of 0.17 to 22.32 µg/L (20). The percent free PSA had a coefficient of variation of <4.1% for quality control pool means with a range of 0.59 to 3.30 µg/L (21). Details about measurement of PSA and quality control procedures are provided elsewhere (17).

Statistical Analysis. Of the 2,263 eligible men ages ≥40 years, 1,601 men (70.7%) participated in the overall NHANES examination. Of these 1,601 men, 48 (3.0%) refused the PSA test, 40 (2.5%) had a missing PSA result, 114 (7.1%) were considered ineligible, and an additional 79 (4.9%) were missing information on exclusion criteria that could significantly affect PSA levels, leaving a final study population of 1,320 men (1,320 of 1,601 or 82.4% of all men ages ≥ 40 years participated in the NHANES examination).

The 79 men with missing information were significantly older ($P = 0.03$) and more likely to be non-Hispanic white ($P = 0.004$) than the study sample as a whole. Of the 79 men, only 60 had a PSA drawn. Missing information status was not associated with mean total PSA or mean percent free PSA in linear regression models adjusting for age and race/ethnicity.

Distributions of total PSA and percent free PSA for this sample were reported as the median and 90th percentile (total PSA) and as the median and 10th percentile (percent free PSA), within age and race/ethnicity groups. The 10th and 90th percentiles, rather than the standard 5th and 95th percentiles, were reported because of limited sample sizes.

National estimates of PSA at different levels (i.e., 0 to <2.5, 2.5-4.0, and >4.0 ng/mL) were calculated. Confidence intervals for percentages were calculated as exact limits based on the binomial distribution (22). National estimates of the number of men in each PSA group were determined by multiplying the percentages and confidence intervals by population estimates from the 2001 and 2002 Current Population Survey. Variance estimates were calculated using Taylor series linearization. No statistical testing was done in the descriptive analysis; testing for significant differences was done using the regression models.

Two linear regression models were fit to determine the relationship between total PSA and age and between percent free PSA and age. Age was transformed in each model using restricted cubic spline functions to allow for nonlinearity (23). In both models, we adjusted for race/ethnicity and examined an interaction between age and race/ethnicity to determine if the relationship between age and each PSA measure was similar across race groups. The dependent variables were log transformed in all models because of nonnormality. Due to the small number of denominator degrees of freedom, the F-statistic with Satterthwaite correction for the degrees of freedom was used to test significance. In all the analyses, $P < 0.05$ was considered statistically significant.

All statistics were generated using SUDAAN version 9.0 (Research Triangle Institute, Research Triangle Park, NC) and SAS version 9.1 (SAS Institute, Inc., Cary, NC). The sample was weighted to represent the total civilian noninstitutionalized U.S. population of men 40 years and older and to account for oversampling and nonresponse to the household interview and medical exam component examination.

Results

Total PSA and Percent Free PSA and Age or Race/ Ethnicity. The median and 90th percentile values for the distribution of total PSA are summarized by age and race/ethnic groups in Table 1. In each of the three race/ethnic groups, the median total PSA increased progressively by age group. The median total PSA among non-Hispanic white men ranged from 0.73 ng/mL [95% confidence interval (95% CI), 0.60-0.84] among men ages 40 to 49 years to 2.02 ng/mL (95% CI, 1.67-2.29) among men 70 years and older.

In contrast to the pattern seen with total PSA and age, the median percent free PSA was fairly constant across the age groups within the three race/ethnicity groups. Among non-Hispanic black men, however, the median percent free PSA for men ages 40 to 49 years was higher than for men 70 years and older: 31.3% (95% CI, 27.3-35.4%) versus 19.8% (95% CI, 16.8-28.4%).

Regression analysis showed that total PSA increased nonlinearly with age. The relationship between age and total PSA varied across the three race/ethnic groups (age by race/ethnicity interaction, $P = 0.031$; Fig. 1). The total PSA increased more steeply after age 65 among non-Hispanic whites and Mexican Americans whereas there was a significant linear increase in total PSA with increasing age among non-Hispanic blacks. There was a significant nonlinear relationship between percent free PSA and age among non-Hispanic blacks ($P = 0.009$). Increased age was associated with decreased percent free PSA for non-Hispanic black men under 60 years of age (Fig. 2).

We estimated that 6.1% (95% CI, 4.7-7.7%) of U.S. men ages 40 years and older, or 3.4 million (range, 2.7-4.3 million), had a total PSA of >4.0 ng/mL (data not shown).

The distribution of percent free PSA by total PSA and age is shown in detail in Table 2. Due to sample size limitations, we could not report the proportion of percent free PSA at all PSA levels, especially for men ages 40 to 49 years with total PSA levels >2.5 ng/mL and for men ages 50 to 69 years with total PSA levels >4.0 ng/mL. Among men ages 40 to 49 years, almost all had a total PSA <2.5 ng/mL. In this age group, 36% of men had both a total PSA <2.5 ng/mL and a percent free PSA <25%. Among men ages 50 to 69 years, the age group for which the PSA test is most prevalent (24), 5.4%, or an

Table 1. Median and other selected percentiles for PSA and free/total PSA among U.S. men ≥40 years, NHANES 2001-2002

Age	n	PSA (ng/mL)* Median	95% CI	90th percentile[†]	95% CI	Free/Total PSA (%)* Median	95% CI	10th percentile[‡]	95% CI
Overall									
Overall[§]	1,320	0.84	(0.78-0.91)	3.04	(2.73-3.53)	27.24	(26.44-29.45)	14.61	(13.50-16.04)
40-49 y	415	0.71	(0.64-0.82)	1.48	(1.29-1.87)	27.84	(25.52-30.53)	15.16	(13.29-18.16)
50-59 y	301	0.84	(0.76-0.95)	2.59	(1.90-3.61)	26.30	(25.79-27.70)	13.75	(12.56-16.92)
60-69 y	261	1.00	(0.91-1.18)	3.30	(2.83-3.50)	27.58	(26.23-29.93)	15.56	(14.30-18.98)
≥70 y	343	1.98	(1.64-2.23)	6.76	(5.83-9.18)	27.05	(25.80-29.84)	13.88	(12.58-16.83)
Non-Hispanic black									
Overall	227	0.83	(0.70-0.94)	2.83	(2.23-5.23)	28.57	(26.44-32.70)	14.02	(12.86-15.85)
40-49 y	97	0.65	(0.52-0.81)	1.51	(1.16-2.15)	31.26	(27.28-35.43)	14.76	(12.69-21.53)
50-59 y	50	0.90	(0.65-1.10)	3.25	(1.94-7.30)	25.99	(21.89-29.15)	15.11	‖
60-69 y	55	1.59	(1.28-2.07)	5.33	(3.41-8.14)	28.05	(21.47-32.98)	12.38	(10.79-15.73)
≥70 y	25	1.84	(1.21-4.11)		‖	19.78	(16.79-28.43)		‖
Non-Hispanic white									
Overall	768	0.85	(0.78-0.95)	3.11	(2.69-3.58)	27.31	(26.54-28.64)	15.23	(13.71-17.66)
40-49 y	195	0.73	(0.60-0.84)	1.53	(1.26-1.77)	27.87	(26.04-31.25)	16.00	(13.33-18.80)
50-59 y	187	0.82	(0.76-0.99)	2.42	(1.92-3.94)	26.49	(25.85-28.57)	13.85	(12.39-18.39)
60-69 y	130	0.99	(0.87-1.25)	3.25	(2.48-4.09)	27.45	(25.82-29.77)	15.85	(13.89-20.71)
≥70 y	256	2.02	(1.67-2.29)	6.30	(5.43-9.23)	27.64	(26.42-30.75)	14.45	(13.06-16.39)
Mexican Americans									
Overall	244	0.86	(0.73-1.01)	2.53	(1.98-4 00)	25.35	(23.06-26.83)	15.20	(13.50-16.83)
40-49 y	98	0.78	(0.65-0.98)	1.55	(1.25-2.55)	26.27	(24.48-28.25)	16.03	(13.82-18.91)
50-59 y	40	0.83	(0.57-1.11)		‖	20.63	(18.87-24.95)		‖
60-69 y	61	1.12	(0.76-1.63)	3.19	(1.88-4.33)	22.82	(20.75-26.82)	14.03	(12.09-18.21)
≥70 y	45	1.40	(1.07-3.16)		‖	25.41	(20.72-27.45)		‖

*Weighted estimates.
[†]90th percentile used for PSA rather than 95th percentile due to small sample size.
[‡]10th percentile presented for free/total PSA rather than 5th percentile due to small sample size.
[§]Overall group includes additional men of other race/ethnicity groups (n = 81).
‖Confidence intervals for percentile could not be calculated due to small sample size.

estimated 900,000 to 2 million men, had a total PSA >4.0 ng/mL. Similarly, an estimated 5.4% of men in this age group had both a total PSA between 2.5 and 4.0 ng/mL and a percent free PSA <25%. An estimated 22.7% or 1.8 to 2.6 million men, ages ≥70 years, had a total PSA >4.0 ng/mL. Another 9% of this age group had a total PSA between 2.5 and 4.0 ng/mL and a percent free PSA <25%.

Distribution of total PSA by age using the finer strata used in the Prostate Cancer Prevention Trial showed that among men ages 40 to 49 years, 73.4% of men had a PSA between 0 and 1 ng/mL; 21.8% between 1.1 and 2 ng/mL; 2.7% between 2.1 and 3 ng/mL; 0.6% between 3.1 and 4 ng/mL; and 1.5% >4 ng/mL. Among men ages 50 to 69 years, the distribution was 56.6%, 26.1%, 6.7%, 5.1%, and 5.4%, respectively. Among men ages 70 years and older, the distribution of total PSA was 30.5%, 19.8%, 15.1%, 12.0%, and 22.7%. Due to small numbers, we were not able to present race-specific information or present percent free PSA values within these smaller strata.

Discussion

Prostate cancer presents a unique set of challenges for the public health community, the internists, family physicians, and urologists who care for men of ages 40 years and above, and the 56 million American men in this age group, as the great majority either bear some risk for the disease or have already been diagnosed with it. The tasks now are to continue to find out about the range of PSA values both in the community and among men diagnosed with prostate cancer, to determine the optimal ways to use the PSA test and its derivatives to guide decisions about screening and the need for a diagnostic workup, and to match the PSA with factors such as age and race/ethnicity and other measurable factors in measuring a man's chances of having a clinically significant cancer.

The present study is the first to provide population-based distributions of both total PSA and percent free PSA by age

for American non-Hispanic white, non-Hispanic black, and Mexican American men ages 40 years and older. As expected, total PSA increased with age, which is consistent with previous studies that attributed the increase to an age-specific growth in the size of the prostate (25-28). However, our finding that the increase in total PSA with age was nonlinear and varied across race/ethnicity has not been reported from other population-based studies (28). Explanations for the higher total PSA among non-Hispanic blacks have included greater prostatic volume, higher circulating testosterone values, and genetic and dietary factors (26, 29, 30) Percent free PSA has not been shown previously to vary by age or by race (28, 31, 32), but data from the present study indicate that percent free PSA decreases with increasing age for non-Hispanic black men under the age of 60 years.
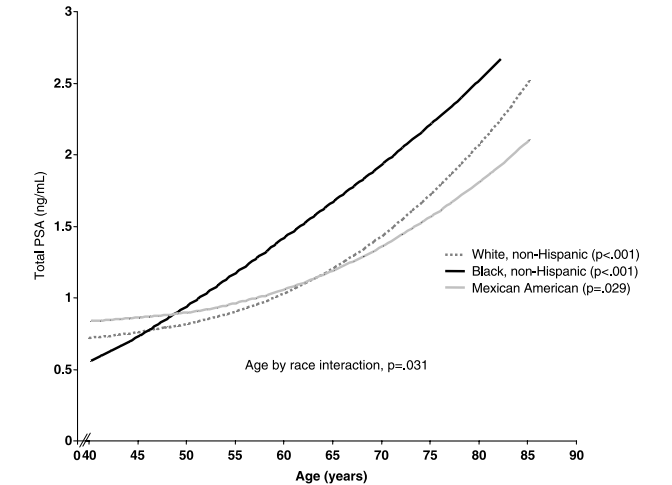

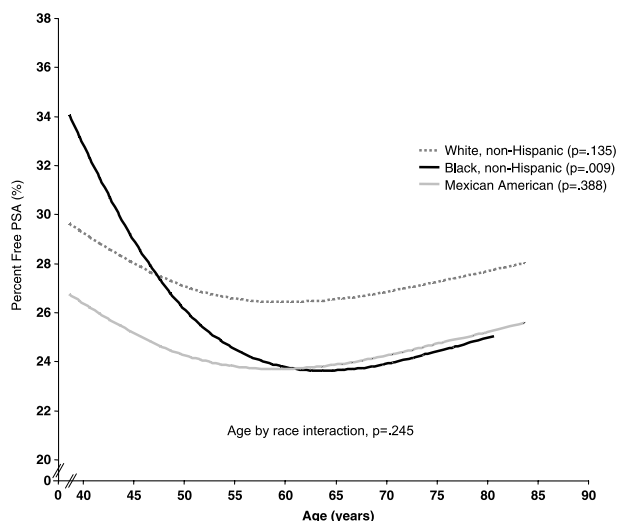**Figure 1.** Total PSA versus age by race, NHANES 2001-2002.

Figure 2. Percent free PSA versus age by race, NHANES 2001-2002.

The distribution of total PSA values from this study is generally consistent with Oesterling's results for non-Hispanic white men, except that our results have narrower confidence intervals, consistent with our larger sample. Oesterling reported median values of 0.7 ng/mL for men ages 40 to 49 years; 1.0 ng/mL, 50 to 59 years; 1.4 ng/mL, 60 to 69 years; and 2.0 ng/mL, 70 to 79 years. The median total PSA values among non-Hispanic black men in our study were also generally consistent with published literature (26, 28, 29, 33) Our prevalence estimate of the number of men with a total PSA >4.0 ng/mL is slightly lower than the 8% estimated in prior years (29), but this is appropriate given that this was not the first PSA for many of the men in the sample, reflecting the popularity of this test during the PSA era. Almost 2 of 5 (38.3%) of the men (95% CI, 34.8-41.5%) reported having a previous PSA test (data not shown). The median PSA was

slightly higher for men reporting a previous PSA (not shown) and, thus, we might expect our estimates to be slightly lower in men for whom this is the first PSA test. Our intention was to provide a population-based distribution of asymptomatic men; we thus excluded men who reported they were diagnosed with prostate cancer and therefore lowered the prevalence estimates of PSA >4.0 ng/mL.

Several factors should be considered in interpreting our results. Unlike in other studies that have described distributions of total PSA, researchers of this study did not have the results of previous PSA tests or digital rectal examinations. Second, the researchers did not have access to any additional prostate-related clinical information (such as PSA density, size of the prostate, or results of transrectal ultrasounds). Third, criteria for exclusion such as a diagnosis of prostate cancer, prostatitis, and prostate-related procedures were based on self-reported data and not validated by medical records. Finally, the relatively small number of elderly non-Hispanic black men represented in the 2001-2002 NHANES data means that generalizations from our findings about this group should be made with caution. Two strengths of the present study were the use of a nationally representative sample and the high response rates in the NHANES. Although the survey was weighted to make the sample nationally representative of all U.S. males ages 40 years and older, the final weights did not take into account nonresponse to phlebotomy and PSA testing once the man arrived at the medical exam component. The PSA estimates may have a bias related to higher nonresponse to PSA testing by black men and elderly men in the examined sample. The present study also included Mexican Americans, a group about whom not a great deal is known in terms of distribution of PSA values. Another strength is that total PSA and percent free PSA were measured using the Hybritech immunoassay in a single laboratory setting using a standardized protocol.

This study does provide age- and race-specific distributions of total PSA and percent free PSA from a source that is nationally representative. The clinical and public health communities can use the estimated number of U.S. men with total PSA and percent free PSA values above and below certain

Table 2. Distribution of free/total PSA by PSA categories among U.S. men, NHANES 2001-2002

	n	Relative SE (%)	Overall %*	95% CI of overall %[†]	Estimated N[‡]	95% CI of estimated N[§]
Age 40-49 y	415					
Total PSA 0 to <2.5 ng/mL						
Free/total<25%	142	9.84	36.1	(28.6-44.2)	7,608,851	(6,020,375-9,311,298)
Free/total PSA≥25%	258	6.20	61.0	(52.4-69.0)	12,850,934	(11,049,905-14,553,280)
Total PSA 2.5-4.0 ng/mL[‖]	10	44.96				
Total PSA >4.0 ng/mL[‖]	5	52.35				
Age 50-69 y	562					
Total PSA 0 to <2.5 ng/mL						
Free/total<25%	163	8.01	26.8	(22.3-31.7)	6,850,260	(5,700,084-8,098,902)
Free/total PSA≥25%	311	3.49	60.3	(55.7-64.8)	15,429,453	(14,242,189-16,582,437)
Total PSA 2.5-4.0 ng/mL						
Free/total <25%	36	23.99	5.4	(3.0-8.9)	1,384,361	(764,089-2,281,645)
Free/total PSA≥25%	16	22.63	2.1	(1.1-3.6)	533,950	(274,648-931,046)
Total PSA >4.0 ng/mL	36	18.79	5.4	(3.4-8.0)	1,380,875	(880,689-2,048,218)
Age ≥ 70 y	343					
Total PSA 0 to <2.5 ng/mL						
Free/total<25%	48	14.92	13.0	(9.1-17.7)	1,251,726	(879,628-1,708,880)
Free/total PSA≥25%	150	6.53	44.2	(37.9-50.5)	4,266,479	(3,664,981-4,881,408)
Total PSA 2.5-4.0 ng/mL						
Free/total<25%	32	19.04	9.1	(5.8-13.5)	880,195	(555,887-1,308,594)
Free/total PSA≥25%	34	16.90	11.1	(7.4-15.7)	1,069,283	(714,060-1,520,943)
Total PSA >4.0 ng/mL						
Free/total<25%	53	10.85	15.3	(11.6-19.5)	1,477,119	(1,125,393-1,888,010)
Free/total PSA≥25%	26	14.10	7.4	(4.9-10.7)	718,157	(472,474-1,037,612)

*Weighted percentages.
[†]Confidence intervals are exact limits based on the binomial distribution.
[‡]Calculated by multiplying % by the estimated U.S. population of the age group, based on the Current Population Survey.
[§]Constructed by multiplying % confidence limits by the estimated U.S. population of that age group, based on the Current Population Survey.
[‖]Relative SE is >30%, indicating that the corresponding estimates are unstable. Consequently, we suppressed detailed information.

thresholds to help provide estimates of the resources required if the threshold PSA values for biopsy were lowered or if adjunct tests such as percent free PSA were used for total PSA values below a certain threshold. If, following the recommendations of the American Cancer Society (18), all men ages 50 to 69 years in the United States were offered a PSA test and all took the test, an estimated 25.6 million PSA tests would be administered. Of those, an estimated 1.4 million would have a PSA value >4.0 ng/mL and would potentially require further diagnostic workup according to current practice (5). The remaining 24.2 million men would have a PSA value <4.0 ng/mL. If the threshold for biopsy was lowered to 2.5 ng/mL in accordance with recent guidelines from the National Comprehensive Cancer Network, an additional 2 million men would be subject to further diagnostic workup. Or if the recommendation of using percent free PSA for men with a total PSA concentration between 2.5 and 4.0 ng/mL to identify men at high risk for prostate cancer was implemented (13), this would entail a diagnostic workup of an additional 1.4 million ages 50 to 69 years. Additionally, a biopsy might be pursued among the 880,000 men who are 70 years and older who have a total PSA between 2.5 and 4 ng/mL and a percent free PSA <25%. In contrast, the number of men who were diagnosed with prostate cancer was 230,000 (of which ~80% of cases were considered confined to the prostate), and the number of men who died from prostate cancer in 2004 was ~30,000 (34). A search for a more specific and accurate screening method seems warranted, and a better understanding of approaches to primary prevention is needed (35).

The present study indicates that values for both the total PSA and percent free PSA differ by age. Additionally, this study shows differences by race/ethnicity in the relationship between age and total PSA. The projections of both total PSA and percent free PSA to the U.S. population of men ages 40 years and older, along with cost data, may help guide public health policy and screening practices for prostate cancer, and the findings of relationships by age and race/ethnicity may help to inform decision making in ways that promote the most efficient use of these technologies with the least resulting morbidity and mortality.

Acknowledgments

References

1. Harris R, Lohr KN. Screening for prostate cancer: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002: 137:917–29.
2. Swan J, Breen N, Coates RJ, Rimer BK, Lee NC. Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey. Cancer 2003;97:1528–40.
3. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? JAMA 2003;289:1414–20.
4. Schwartz LM, Woloshin S, Fowler FJ, Jr., Welch HG. Enthusiasm for cancer screening in the United States. JAMA 2004;291:71–8.
5. Eastham JA, Riedel E, Scardino PT, et al. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003;289:2695–700.
6. Anonymous. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology—v.1.2004: Prostate Cancer Early Detection; 2004.
7. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95: 868–78.
8. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.
9. Carter HB. Prostate cancers in men with low PSA levels—must we find them? N Engl J Med 2004;350:2292–4.
10. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279:1542–7.
11. Catalona WJ, Smith DS, Wolfert RL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA 1995;274:1214–20.
12. Gann PH, Ma J, Catalona WJ, Stampfer MJ. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol 2002;167:2427–34.
13. Catalona WJ, Partin AW, Finlay JA, et al. Use of percentage of free prostate-specific antigen to identify men at high risk of prostate cancer when PSA levels are 2.51 to 4 ng/mL and digital rectal examination is not suspicious for prostate cancer: an alternative model. Urology 1999;54:220–4.
14. Etzioni R, Falcon S, Gann PH, Kooperberg CL, Penson DF, Stampfer MJ. Prostate-specific antigen and free prostate-specific antigen in the early detection of prostate cancer: do combination tests improve detection? Cancer Epidemiol Biomarkers Prev 2004;13:1640–5.
15. Raaijmakers R, Blijenberg BG, Finlay JA, et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/mL: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. J Urol 2004;171:2245–9.
16. Recker F, Kwiatkowski MK, Huber A, Stamm B, Lehmann K, Tscholl R. Prospective detection of clinically relevant prostate cancer in the prostate specific antigen range 1 to 3 ng/mL combined with free-to-total ratio 20% or less: the Aarau experience. J Urol 2001;166:851–5.
17. National Center for Health Statistics. National Health and Nutrition Examination Survey; 2004.
18. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2004. CA Cancer J Clin 2004;54:41–52.
19. Sokoll LJ, Bruzek DJ, Dua R, et al. Short-term stability of the molecular forms of prostate-specific antigen and effect on percent complexed prostate-specific antigen and percent free prostate-specific antigen. Urology 2002; 60:24–30.
20. Total prostate specific antigen in serum—NHANES 2001-2001. 2004.
21. Free prostate specific antigen in serum—NHANES 2001-2001. 2004.
22. Korn EL, Graubard BI. Analysis of health surveys. New York (NY): Wiley; 1999.
23. Smith PL. Splines as a useful and convenient statistical tool. Am Stat 1979;33:57–62.
24. Ross LE, Coates RJ, Breen N, Uhler RJ, Potosky AL, Blackman D. Prostate-specific antigen test use reported in the 2000 National Health Interview Survey. Prev Med 2004;38:732–44.
25. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993;270:860–4.
26. Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med 1996;335:304–10.
27. Weinrich MC, Jacobsen SJ, Weinrich SP, et al. Reference ranges for serum prostate-specific antigen in black and white men without cancer. Urology 1998;52:967–73.
28. Cooney KA, Strawderman MS, Wojno KJ, et al. Age-specific distribution of serum prostate-specific antigen in a community-based study of African-American men. Urology 2001;57:91–6.
29. DeAntoni EP, Crawford ED, Oesterling JE, et al. Age- and race-specific reference ranges for prostate-specific antigen from a large community-based study. Urology 1996;48:234–9.
30. Fowler JE, Jr., Bigler SA, Kilambi NK, Land SA. Relationships between prostate-specific antigen and prostate volume in black and white men with benign prostate biopsies. Urology 1999;53:1175–8.
31. Oesterling JE, Jacobsen SJ, Klee GG, et al. Free, complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. J Urol 1995;154:1090–5.
32. Gelmann EP, Chia D, Pinsky PF, et al. Relationship of demographic and clinical factors to free and total prostate-specific antigen. Urology 2001;58: 561–6.
33. Heeringa SG, Alcser KH, Doerr K, et al. Potential selection bias in a community-based study of PSA levels in African-American men. J Clin Epidemiol 2001;54:142–8.
34. Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics. CA Cancer J Clin 2004; 54:8–29.
35. Hernandez J, Thompson IM. Prostate-specific antigen: a review of the validation of the most commonly used cancer biomarker. Cancer 2004;101: 894–904.

Cancer Epidemiology, Biomarkers & Prevention

Total and Percent Free Prostate-Specific Antigen Levels among U.S. Men, 2001-2002

Mona Saraiya, Benny J. Kottiri, Steven Leadbetter, et al.

Updated version	Access the most recent version of this article at: http://cebp.aacrjournals.org/content/14/9/2178

Cited articles	This article cites 30 articles, 1 of which you can access for free at: http://cebp.aacrjournals.org/content/14/9/2178.full#ref-list-1
Citing articles	This article has been cited by 1 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/14/9/2178.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/14/9/2178. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.