

## RELATIONSHIP OF DEMOGRAPHIC AND CLINICAL FACTORS TO FREE AND TOTAL PROSTATE-SPECIFIC ANTIGEN

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### ABSTRACT

**Objectives.** To characterize the role of demographic and clinical parameters in the measurements of prostate-specific antigen (PSA), free PSA (fPSA), and percent free PSA (%fPSA).

**Methods.** This was a cohort study of volunteers to a randomized screening trial. A central laboratory determined PSA and fPSA for the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. A baseline evaluation of free and total PSA was done for 7183 white, black, Asian, Hispanic, and other male volunteers, aged 55 to 74 years. Comparisons were made across racial and ethnic groups and across a set of clinical parameters from a baseline questionnaire.

**Results.** The median levels of serum PSA were less than 2.1 ng/mL in each age-race grouping of the study participants. The levels of free and total PSA were higher in black ( $n = 868$ , 12%) participants than in white ( $n = 4995$ , 70%) and Asian ( $n = 849$ , 11.8%) participants. Individuals who identified themselves as ethnically Hispanic ( $n = 339$ , 4.7%) had median PSA levels higher than whites who were not Hispanic. The free and total PSA levels increased with age, particularly among men 70 to 74 years old. However, the %fPSA levels showed less variation among the four racial groups or by age. The free and total PSA levels were higher among those who had a history of benign prostatic disease.

**Conclusions.** Demographic (age and race/ethnicity) and clinical (history of benign prostatic disease) variables had a moderate effect on the measures of PSA and fPSA and very little effect on %fPSA. UROLOGY 58: 561-566, 2001. © 2001, Elsevier Science Inc.

The measurement of serum prostate-specific antigen (PSA) is a widely used test for the screening and management of prostate cancer. The use of PSA levels to screen for prostate cancer has not yet been shown to affect cause-specific mortality in a randomized trial.<sup>1</sup> During the past decade, a down-

ward shift has occurred in the stage predominance of newly diagnosed prostate cancers, and there has been a suggestion of improved mortality that may be due to the use of PSA screening.<sup>2</sup> The sensitivity and specificity of PSA screening depends to some degree on the upper limit used for a threshold PSA

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**TABLE I. Distribution of study population by age and race/ethnicity**

Age (yr)	White* (n)	Black* (n)	Hispanic <sup>†</sup> (n)	Asian (n)	Other/Unknown (n)	Total (n)
55–59	11 (0.2)	195 (2.7)	77 (1.1)	155 (2.2)	36 (0.5)	474 (6.6)
60–64	2300 (32.0)	323 (4.5)	156 (2.2)	282 (3.9)	54 (0.8)	3115 (43.4)
65–69	1756 (24.4)	224 (3.1)	74 (1.0)	255 (3.6)	29 (0.4)	2338 (32.5)
70–74	928 (12.9)	126 (1.8)	32 (0.4)	157 (2.2)	13 (0.2)	1256 (17.5)
Total	4995 (69.5)	868 (12.1)	339 (4.7)	849 (11.8)	132 (1.8)	7183 (100.0)

Numbers in parentheses are percentages.

\* Non-Hispanic.

<sup>†</sup> White and black.

**TABLE II. Prevalence of selected conditions based on responses to PLCO baseline questionnaire**

	White (%)	Black (%)	Hispanic (%)	Asian (%)	Total (%)
History of benign prostatic disease	22.7	21.0	21.1	16.1	21.6
History of vasectomy	23.2	4.0	17.5	12.8	19.4
Regular aspirin use	48.7	38.3	46.8	37.8	46.1
Regular ibuprofen use	18.4	19.8	23.8	13.4	18.2
Current cigarette smoker	9.3	20.1	11.0	7.1	10.3
Former cigarette smoker	52.7	47.4	52.4	48.8	51.5
Frequency of nightly urination (n)					
0	15.3	13.7	16.7	14.0	15.0
1	52.8	40.1	43.9	46.8	49.9
2	22.6	25.8	24.6	25.3	23.4
3	7.2	13.1	8.8	9.5	8.3
4+	2.1	7.3	6.0	4.4	3.4

value, currently 4.0 ng/mL. This was originally established using a range of 2 standard deviations of the mean PSA value in asymptomatic men and was confirmed in a large cohort study.<sup>3</sup> The use of lower limits for threshold PSA values may yield more cancer detection, but also may result in a greater false-positive rate.<sup>4</sup> Approximately 20% to 25% of circulating PSA is not bound to serum proteins; this fraction is termed free PSA (fPSA). Determining the proportion of free to total PSA (%fPSA) may improve the specificity of prostate cancer diagnosis, because the amount of PSA bound to serum proteins is increased in men with prostate cancer.<sup>4–12</sup> However, it has been difficult to reach a consensus on the precise cutoff for a threshold level for %fPSA.<sup>4,13,14</sup>

One problem with the establishment of a single maximal level for PSA is that serum PSA levels in men without cancer vary with age and race. Serum PSA levels in asymptomatic men increase with age.<sup>15–17</sup> Race also influences PSA values. Blacks have higher PSA values than whites in every age group.<sup>8,12,13,18,19</sup> Compared with published studies of PSA in blacks and whites, fewer studies have examined the PSA levels for ethnic groups such as Hispanic Americans.<sup>17,20–22</sup> We analyzed the baseline free and total serum PSA levels in a cohort of men from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.<sup>23</sup>

## MATERIAL AND METHODS

### RACIAL/ETHNIC CLASSIFICATION

The PLCO is a long-term randomized study that began in October 1992 to recruit 148,000 men and women, aged 55 to 74 years at entry, to be randomized to a screening arm or a control arm.<sup>23</sup> The objectives of the PLCO trial are to determine in screened participants whether screening can reduce cause-specific mortality from the four PLCO cancers. During the trial, 37,000 men will be screened annually for 5 years for prostate cancer using serum PSA and digital rectal examination. Men were excluded from the study if they had had more than one prior determination of serum PSA within 3 years of study entry. The PLCO collects data on ethnicity by asking participants to identify their racial group.

### STUDY COHORT

Of the approximately 10,000 male subjects randomized to the screened arm of the PLCO by February 1996, 5303 were randomly selected initially for inclusion in this ancillary study. At that time, the PLCO trial only included subjects aged 60 to 74. Participants aged 55 to 59 were added to the PLCO trial at the beginning of 1996. To maximize the minority participation in our study, a second, subsequent selection was made in which all nonwhite and Hispanic men randomized by July 1997 were included; this added 1993 men to give a total of 7296. Because the 55 to 59-year age group was only eligible for this additional selection, the selection process resulted in a skewed distribution of age by race/ethnicity in which non-Hispanic whites were underrepresented in the 55 to 59-year age group. Finally, 113 subjects who had their blood drawn subsequent to their initial screening visit when the baseline questionnaire was completed were eliminated from our analysis, leaving a total of 7183 participants in our data set (see

Table I). A single serum sample drawn from each participant at the initial screening visit was used to determine both the PSA and fPSA levels. All participants completed a baseline questionnaire for family, social, and medical history and an informed consent form.

### PSA AND fPSA DETERMINATIONS

The ImmunoRadioMetric Hybritech PSA and Hybritech free PSA assays from Beckman Coulter (Fullerton, Calif) were used to determine the value of PSA and fPSA in accordance with the procedures specified by the manufacturer. The %fPSA was calculated by dividing the value for fPSA by the value for PSA from the same serum sample. The Hybritech assay for PSA is not accurate at less than 0.1 ng/mL; %fPSA values were considered unreliable if the accompanying total PSA value was 0.2 ng/mL or less. All analyses involving %fPSA were limited to those subjects (n = 6992) with PSA values greater than 0.2 ng/mL.

### STATISTICAL ANALYSIS

We used linear models to estimate the effect of the demographic and baseline questionnaire variables on PSA, fPSA, and %fPSA. Because the PLCO baseline questionnaire was designed to gather information relevant to any of the four PLCO cancers (prostate, lung, colon, ovarian), we chose to consider for the model only those variables thought to have possible relevance to prostate cancer or PSA. These included a history of benign prostatic disease (mostly benign prostatic hyperplasia, also including prostatitis or other benign conditions), history of vasectomy, nighttime urination frequency, smoking history, regular aspirin use, regular ibuprofen use, and body weight. Also considered for the model were age (in 5-year intervals) and race/ethnicity. All of the above variables were included in the initial model; a backward selection procedure with an exit *P* value of 0.01 was then used to create a final model. Separate models were developed for each of the three PSA variables. Whites were the referent group, because they were the largest group and thus had the most stable estimates for comparisons. The model results for total PSA and fPSA were based on a sample of 6984, representing 97% of the total of 7183; the rest were excluded from the model because of missing data on one or more of the variables. For %fPSA, the model was based on 6800 of the 6992 with %fPSA values, again 97% of the total. Baseline questionnaire data were available for all the participants analyzed in the model. To make the distributions approximately normal, all PSA variables were log transformed before entering them in the model.

## RESULTS

The distribution of participants by age and race/ethnicity is shown in Table I. The small number of white participants in the 55 to 59-year age group was a result of the way this particular cohort was selected. Table II shows the prevalence of various conditions among the different racial/ethnic groups as determined from responses to the PLCO baseline questionnaire.

Figure 1 shows the distribution of PSA, fPSA, and %fPSA values by age and race/ethnicity. The most prominent tendency seen was the increase in PSA and fPSA in the older age groups and in blacks. This finding is confirmed by Table III, which displays the results of the linear model with respect to the demographic variables. As seen in Table III, the

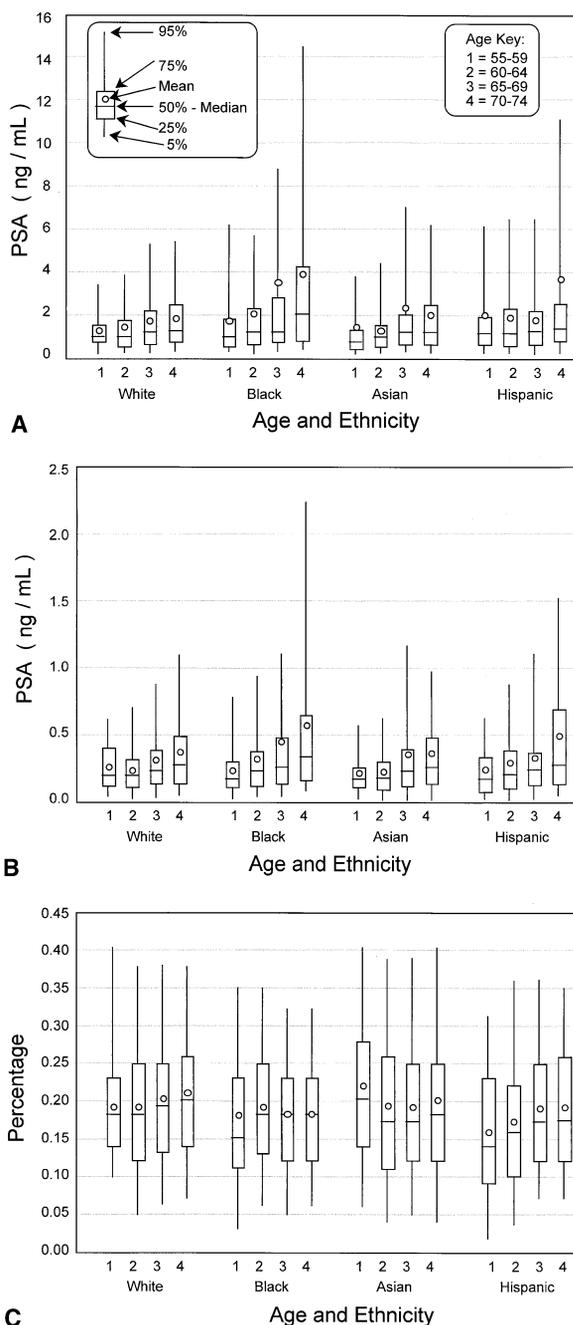


FIGURE 1. Values for each racial/ethnic group and for the age subgroups within each race. Horizontal bar represents the median, circle denotes the mean, box includes the 25th to 75th percentiles, and the top of the vertical bar reaches to the 95th percentile and the bottom to the 5th percentile. (A) Total PSA values, (B) fPSA values, and (C) %fPSA values.

(geometric) mean PSA and fPSA levels in the 70 to 74-year age group were increased 50.4% and 58.1%, respectively, relative to the levels in the 55 to 59-year age group. Blacks had similar increases, in the range of 20% to 30%, in both PSA and fPSA relative to whites. Hispanics showed moderate increases in PSA but no increase in fPSA, relative to

**TABLE III. Model results**

	% Difference* in PSA (P Value)	% Difference in fPSA (P Value)	% Difference in %fPSA (P Value)
Age group (yr)			
55–59	Referent	Referent	Referent
60–64	16.8 (0.002)	13.8 (0.03)	–1.8 (0.6)
65–69	35.7 (0.0001)	38.8 (0.0001)	3.2 (0.4)
70–74	50.4 (0.0001)	58.1 (0.0001)	6.6 (0.09)
Race/ethnicity <sup>†</sup>			
White	Referent	Referent	Referent
Black	29.3 (0.0001)	21.0 (0.0001)	–5.7 (0.02)
Hispanic	20.4 (0.0003)	0.4 (0.95)	–16.0 (0.0001)
Asian	–8.9 (0.02)	–15.2 (0.0002)	–6.0 (0.03)
Benign prostatic disease			
No	Referent	Referent	NA <sup>‡</sup>
Yes	25.8 (0.0001)	27.6 (0.0001)	NA
Frequency of nightly urination (n)			
0	Referent	Referent	NA
1	5.6 (0.065)	5.2 (0.17)	NA
2	11.3 (0.003)	12.5 (0.006)	NA
3	19.8 (0.0001)	21.4 (0.0005)	NA
4+	21.4 (0.003)	22.4 (0.01)	NA
Cigarette smoking			
Never	Referent	Referent	Referent
Former	–8.1 (0.0005)	–12.0 (0.0001)	–4.0 (0.01)
Current	–10.8 (0.002)	–17.6 (0.0001)	–8.1 (0.002)
Weight (continuous) <sup>§</sup>			
150 lb	Referent	Referent	Referent
200 lb	–9.9 (0.0001)	–12.6 (0.0001)	–3.3 (0.009)

KEY: PSA = prostate-specific antigen; fPSA = free PSA; %fPSA = proportion of free to total PSA.

\* % Difference refers to the percentage of increase or decrease in the (geometric) mean PSA (or fPSA, %fPSA) level relative to the mean in the referent group; the P value gives the corresponding statistical significance level.

<sup>†</sup> Among races, whites were chosen as the referent group because they represented the largest group and thus had the most stable estimates for comparisons.

<sup>‡</sup> NA indicates that the given variable was not included in the final model for a given PSA variable because of a lack of statistical significance (see Material and Methods section); vasectomy, aspirin use, and ibuprofen use are not included because none were included in final models for any PSA variable.

<sup>§</sup> Weight modeled as a continuous (i.e., not a categorical) variable; thus, the values for “200 lb” indicate the reduced PSA levels related to any 50-lb weight increase.

whites. In contrast to the results for PSA and fPSA, the effect of the demographic variables on %fPSA was considerably muted. Only a minimal (although still statistically significant) effect of age and race/ethnicity was found.

Table III also displays the model results for the baseline questionnaire variables. As with the demographic variables, the trends were similar for PSA and fPSA, and the effects were muted for %fPSA. Nighttime urination frequency and a history of benign prostatic disease were associated with increased PSA and fPSA levels, and cigarette smoking and increased weight were associated with decreased PSA and fPSA values. Vasectomy, aspirin use, and ibuprofen use were not included in the final models for any of the PSA variables, because they were not statistically significant at the  $P = 0.01$  level.

Although a number of variables were found to have a statistically significant effect on PSA and fPSA, these variables taken together still accounted for only about 5% of the total variability in PSA and fPSA, and explain only 1% of the variability in

%fPSA. PSA and fPSA values correlated highly in this cohort, with a correlation coefficient of about 0.8. In contrast, the correlation between PSA and %fPSA was of a small magnitude and slightly negative (about  $-0.15$ ). Because the data capture was thorough and the percentage excluded for absence of data was small, exclusion was unlikely to have introduced bias in this analysis.

### COMMENT

The data presented show that in a population of healthy volunteers to a randomized screening study, race and age-dependent variations in free and total PSA exist. The data regarding the differences in PSA levels between black and white men are consistent with the results of a large cohort of black men.<sup>24</sup> The reasons for these racial differences in PSA levels are not clear and may be related to the increased incidence of prostate cancer among blacks. However, differences in the incidence of prostate cancer in racial groups are not necessarily reflected in the mean PSA values. For

example, no substantial differences in PSA levels between native Japanese men and Japanese-American men have been found, even though substantial differences in the prostate cancer incidence exist between these two groups.<sup>25</sup> Racial identity may be a surrogate for the complex interaction of a number of complex factors that affect prostate cancer risk. It is important to note that all median PSA values in our cohort were well below the reference value of 4.0 ng/mL, and the differences between the racial and ethnic groups were of little clinical significance.

Morgan *et al.*<sup>24</sup> analyzed samples from 3475 healthy white and black men in different age groups. Our data nearly coincide with the results reported for their cohort with a somewhat different age distribution. Our Hispanic population comprised 30 men who described themselves also as black and 309 men who described themselves also as white. Therefore, we do not believe that the higher PSA levels among the Hispanic group were because a substantial number of them were also black. The finding that the median PSA values for all Hispanics (white and black combined) was higher than whites not of Hispanic origin and lower than blacks is consistent with two other studies that reported similar data.<sup>20,21</sup> The consistency of the relationship between race, ethnicity, and PSA across several studies underscores the complex interaction of lifestyle and genetics on the physiology and pathology of the prostate.

As might have been predicted, men with a history of prostatic "problems" or enlargement or men with frequent nocturia had elevated PSA levels compared with those without a positive history or without symptoms. The fraction of men reporting a history of benign prostatic disease far exceeded the number of prostate cancers that we would expect to find in this large cohort of men. Heavier men and men who smoked (or formerly smoked) had lower PSA levels. We speculate that both the increased weight and cigarette smoking may affect the circulating hormone levels and thereby influence the PSA level. It is likely that obesity affects PSA levels by affecting the steroid hormone metabolism.<sup>26</sup> This may also be true for men who are current or recent smokers, since smoking has been shown to reduce serum testosterone levels in dogs.<sup>27</sup>

Using a cohort of men from the PLCO study, we found racial and ethnic differences in free and total PSA levels, but not for %fPSA. The differences found were small and of limited clinical significance, since all levels were below widely accepted clinical thresholds for prostate biopsy. The finding that racial/ethnic differences did not extend to %fPSA provides support for the use of this param-

eter in comparisons across diverse groups of individuals.

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