

AGE-SPECIFIC REFERENCE RANGES FOR SERUM PROSTATE-SPECIFIC ANTIGEN IN BLACK MEN

TED O. MORGAN, M.D., STEVEN J. JACOBSEN, M.D., PH.D., WILLIAM F. MCCARTHY, PH.D., DEBRA J. JACOBSON, M.S., DAVID G. MCLEOD, M.D., AND JUDD W. MOUL, M.D.

ABSTRACT

Background The detection of prostate cancer by screening for prostate-specific antigen (PSA) in serum is improved when age-specific reference ranges are used, but these ranges have been derived from white populations. We determined the distribution of PSA and age-specific reference ranges in black men both with and without prostate cancer.

Methods From January 1991 through May 1995, we measured serum PSA in 3475 men with no clinical evidence of prostate cancer (1802 white and 1673 black) and 1783 men with prostate cancer (1372 white and 411 black). We studied the data as a function of age and race to determine the usefulness of measuring PSA in diagnosing prostate cancer.

Results Serum PSA concentrations in black men (geometric mean in controls, 1.48 ng per milliliter; in patients, 7.46) were significantly higher than those in white men (geometric mean in controls, 1.33 ng per milliliter; in patients, 6.28). The values in the controls correlated directly with age. The area under the receiver-operating-characteristic curve was 0.91 for blacks and 0.94 for whites. If traditional age-specific reference ranges were used in screening black men, with the test specificity kept at 95 percent, 41 percent of cases of prostate cancer would be missed. For the test to have 95 percent sensitivity among black men, the following normal reference ranges should be used: for men in their 40s, 0 to 2.0 ng of PSA per milliliter (test specificity, 93 percent); for men in their 50s, 0 to 4.0 ng per milliliter (specificity, 88 percent); for men in their 60s, 0 to 4.5 ng per milliliter (specificity, 81 percent); and for men in their 70s, 0 to 5.5 ng per milliliter (specificity, 78 percent).

Conclusions Serum PSA concentrations can be used to discriminate between men with prostate cancer and those without it among both blacks and whites. Over 40 percent of cases of prostate cancer in black men would not be detected by tests using traditional age-specific reference ranges, which maintain specificity at 95 percent. In this high-risk population, the alternative approach — maintaining sensitivity at 95 percent — may be used with acceptable decrements in specificity. (N Engl J Med 1996; 335:304-10.)

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WITH 317,000 new cases and 41,000 deaths predicted for 1996, prostate cancer is now the most common cancer and the second leading cause of death from cancer among men in the United States.¹ In blacks the statistics are even more sobering, with a higher incidence of disease, a higher likelihood of diagnosis at a more advanced stage of disease, and a lower rate of survival after adjustment for disease stage than among whites.² The American Cancer Society, the American Urological Association, and the American College of Radiology have made the controversial recommendation that all men over the age of 50 have an annual blood test for prostate-specific antigen (PSA) and a digital rectal examination to screen for prostate cancer. In black men and men with a family history of prostate cancer, it is recommended that testing begin at the age of 40.^{3,4} Little is known, however, about the use of PSA tests in the screening of black men for prostate cancer.

PSA is a serine protease produced by the epithelial cells of normal, hyperplastic, and cancerous prostatic tissue.⁵ Because the enzyme is not specific for prostate cancer, the PSA test has a high false positive rate when used as a screening tool.⁶ Only 26 percent of men with serum PSA levels between 4.1 and 9.9 ng per milliliter have prostate cancer on biopsy.⁷

In men without prostate cancer, PSA levels increase with age, mainly because of increases in prostate volume due to benign prostatic hyperplasia. This fact led Oesterling et al. to develop age-specific reference ranges for white men from Olmsted County, Minnesota.⁸ Other groups have reported normal reference ranges similar to theirs, all based on predominantly white populations of men without prostate cancer, and all designed so that the test would have 95 percent specificity.⁹⁻¹¹ Using these ranges can reduce the number of prostate biopsies by 22 percent in men over the age of 70, while potentially increas-

From the Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, D.C. (T.O.M., D.G.M., J.W.M.); the Sections of Clinical Epidemiology (S.J.J.) and Biostatistics (D.J.J.), Department of Health Sciences Research, Mayo Clinic and Mayo Foundation, Rochester, Minn.; and the Department of Surgery and Center for Prostate Disease Research, Uniformed Services University of the Health Sciences, Bethesda, Md. (W.F.M., D.G.M., J.W.M.). Address reprint requests to Dr. Moul at the Department of Surgery, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd., Bethesda, MD 20814-4799.

ing the sensitivity of the PSA test in younger men, who are most likely to benefit from treatment.¹²

Race may also be an important factor in setting a reference range. A recent study found that a population of healthy Japanese men had lower PSA values than a group of white men of similar age.¹³ We found that blacks with newly diagnosed prostate cancer have higher PSA levels than whites, even after adjustment for the stage, volume, and grade of the tumor and the patient's age.¹⁴ For the PSA test to have a similar sensitivity in blacks the normal reference range might be higher than for whites.

In this study, we sought to determine the distribution of serum PSA levels in a large population of blacks and whites both with and without prostate cancer. All the men studied were in the U.S. military system, where there is equal access to health care. All the PSA tests were performed in the same laboratory by the same method. We evaluated the sensitivity and specificity of various reference ranges: the range currently used (0 to 4.0 ng per milliliter); age-specific ranges based on the specificity of the test in whites⁸; a similar set of ranges based on data from blacks; and a set of age-specific ranges based on data from blacks with prostate cancer in which sensitivity was kept at 95 percent to maximize the detection of cancer.

METHODS

Controls

From January 1991 through May 1995, 14,826 men 40 to 79 years of age had a total of 53,789 serum PSA tests performed at Walter Reed Army Medical Center as part of their general health examinations. All the PSA determinations were performed in a central laboratory with the same assay (IMx, Abbott; normal range, 0 to 4.0 ng of PSA per milliliter). The men included 2129 blacks, 312 Asians, 84 men of Hispanic origin, 12,193 whites, and 108 men of unknown race or ethnic group. Data on the men's PSA values, ages, and race or ethnic group were maintained in a central computer, and all the analyses were based on the results of the first test in each man. Patients with prostatitis were excluded, but those with prostatic hyperplasia were not.

A computer-generated random sample of 2100 white men was combined with the entire group of blacks to form the study sample of 4229 men. This cohort was cross-referenced with the data bases of the hospital pathology department and tumor registry, and 465 men with known prostate cancer were excluded from the study. Among the remaining 3764 men, 576 who had abnormal digital rectal examinations (61 men; 37 whites and 24 blacks), PSA values higher than 4.0 ng per milliliter (538 men; 259 whites and 279 blacks), or both but no known prostate cancer were studied. In this subgroup a total of 684 prostate biopsies were performed; in 127 of these patients (48 whites and 79 blacks) the biopsy revealed prostate cancer. There were 162 additional men who were not evaluated further and were excluded from the analysis. The 287 remaining men with PSA values above 4.0 ng per milliliter, an abnormal digital rectal examination, or both were assumed to be free of prostate cancer because transrectal ultrasonography of the prostate, prostate biopsy, or both were negative for cancer. The final study cohort included 3475 men (1802 whites and 1673 blacks) who had no evidence of prostate cancer. Of these men, 8 blacks (0.5 percent) and 12 whites (0.7 percent) were receiving finasteride at the time of their PSA determinations.

Patients

From January 1991 through August 1995, at the same medical center, a total of 1783 men, 411 black and 1372 white, had PSA tests performed during the six months before a subsequent diagnosis of prostate cancer by biopsy. The reason for the prostate biopsy was known in 79 percent of the patients (345 blacks and 1057 whites). In 7 percent of blacks and 15 percent of whites, the only abnormality was on the digital rectal examination, whereas in 38 percent and 40 percent, respectively, the only abnormality was an elevated PSA level (more than 4.0 ng per milliliter); 55 percent and 45 percent, respectively, had both abnormal digital examinations and elevated PSA levels. Less than 0.5 percent of each racial group had symptoms of metastatic prostate cancer as the only reason for biopsy. Twelve blacks (2.9 percent) and 33 whites (2.4 percent) were receiving finasteride at the time of their PSA determinations.

Statistical Analysis

Because of the log-normal distribution of the PSA concentrations, they were log-transformed in the analyses. The observed 5th, 25th, 50th (median), 75th, and 95th percentiles were calculated on the basis of the empirical distribution of the data in each 10-year age group. A multivariate regression model in which the log-transformed PSA concentration was plotted against age and race was used to determine whether the PSA concentrations differed significantly according to race when we controlled for age. Receiver-operating-characteristic (ROC) curves in which the value for sensitivity was plotted against the false positive rate (1 minus the value for specificity) were generated for the white and black cohorts, both overall and within each 10-year age group. The area under the ROC curve was estimated according to the method of Hanley and McNeil.¹⁵ Population-based ROC curves for white men from Olmsted County, Minnesota, are included in the figures for comparison. In all the analyses, P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Table 1 shows the distribution of serum PSA levels according to race, age, and status as a patient or control for each 10-year age group. In both racial groups the median serum PSA level among the controls was 1.3 ng per milliliter. The mean values differed significantly, however, and the difference persisted after adjustment for age (mean PSA level in blacks, 2.6 ng per milliliter; in whites, 1.9 ng per milliliter; $P < 0.001$). There was more variation with increasing age among blacks than among whites, as shown by the differences in the interquartile range (the range between the 25th and 75th percentiles). Over the entire range of ages, the serum PSA concentrations correlated directly with age among the controls in each racial group ($r = 0.40$ for blacks and 0.34 for whites; $P < 0.001$ for both). The distribution of serum PSA concentrations was shifted to a higher level in the black men than in the whites; the distribution in the whites was nearly identical to that reported by Oesterling et al.⁸ (Fig. 1).

Table 2 shows the sensitivity and specificity of the serum PSA test in diagnosing prostate cancer according to race, age, and PSA level. When the 95th percentile in the black controls (Table 1) was used as a cutoff (with specificity maintained at 95 percent), sensitivity was markedly reduced to 67, 52, and 28 per-

TABLE 1. DISTRIBUTION OF SERUM PSA LEVELS ACCORDING TO RACE AND AGE GROUP AMONG THE CONTROLS AND PATIENTS WITH PROSTATE CANCER STUDIED AT WALTER REED ARMY MEDICAL CENTER, 1991–1995.

RACE AND AGE (YR)	No. STUDIED	SERUM PSA LEVEL			
		5TH PERCENTILE	MEDIAN	25TH, 75TH PERCENTILE	95TH PERCENTILE
ng/ml					
Black controls					
40–49	292	—	0.7	0.4, 1.1	2.4
50–59	398	—	1.1	0.6, 2.3	6.5
60–69	604	—	1.6	0.9, 3.5	11.3
70–79	379	—	2.2	1.1, 4.9	12.5
Black patients					
40–49	70	2.0	4.0	3.7, 6.3	—
50–59	114	3.9	6.2	5.4, 7.7	—
60–69	156	4.4	8.3	7.0, 9.7	—
70–79	71	5.5	10.4	8.7, 12.9	—
White controls					
40–49	196	—	0.7	0.4, 1.0	2.1
50–59	235	—	1.0	0.6, 1.6	3.6
60–69	515	—	1.4	0.8, 2.5	4.3
70–79	856	—	1.8	0.9, 3.5	5.8
White patients					
40–49	287	2.6	4.5	3.5, 6.3	—
50–59	322	3.5	4.9	4.0, 6.2	—
60–69	372	3.3	6.3	4.9, 7.3	—
70–79	391	3.3	7.8	6.6, 9.9	—

cent for men in their 50s, 60s, and 70s, respectively (data not shown). The traditional cutoff of 4.0 ng per milliliter had a sensitivity of 48 percent for men in their 40s and nearly 99 percent for men in their 70s.

The trade-offs in sensitivity and specificity in the study populations are shown in the ROC curves in Figure 2. The area under the curve shows the probability that the PSA level will be higher in a randomly selected patient in this population than in a randomly selected control. The more the area under the curve approaches 1.0 (i.e., the more the ROC curve approaches the upper left-hand corner), the greater the predictive power of the screening test. Overall, serum PSA levels are valuable in discriminating between the absence and presence of prostate cancer; the areas under the ROC curves for blacks are 0.98 for men in their 40s, 0.94 for men in their 50s, 0.91 for men in their 60s, and 0.92 for men in their 70s. Among whites, the corresponding areas under the ROC curves are 0.99, 0.98, 0.97, and 0.96 — very similar to the areas under the population-based ROC curves for the men from Olmsted County (unpublished data).

DISCUSSION

We found that serum PSA levels in black men without prostate cancer increase with age, as they do in whites. The black men we studied had higher PSA

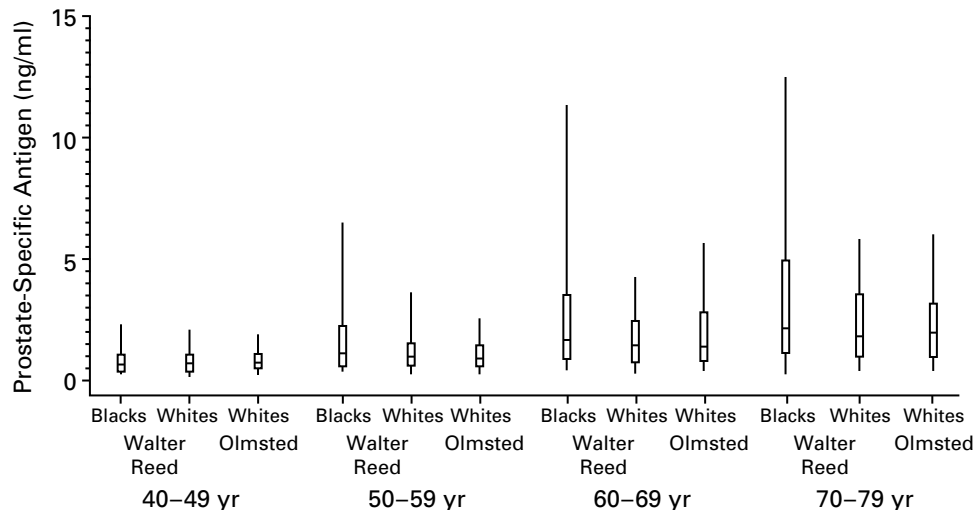


Figure 1. Serum Concentrations of Prostate-Specific Antigen as a Function of Age and Race in Men with No Clinical Evidence of Prostate Cancer.

Values shown were obtained in blacks and whites at Walter Reed Army Medical Center and in whites from Olmsted County, Minnesota, studied at the Mayo Clinic.⁸ In each box plot, the lower and upper ends of the “whiskers” represent the 5th and 95th percentiles, respectively; the lower and upper ends of the boxes, the 25th and 75th percentiles; and the line inside the box, the median.

TABLE 2. SENSITIVITY AND SPECIFICITY OF THE SERUM PSA TEST ACCORDING TO RACE, AGE GROUP, AND SERUM PSA LEVEL IN THE ENTIRE STUDY POPULATION.

PSA LEVEL (ng/ml)	AGE							
	40-49 YR		50-59 YR		60-69 YR		70-79 YR	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
	percent							
Blacks								
1.0	100.0	74.3	100.0	45.7	100.0	32.6	100.0	20.6
2.0	94.3	93.2	100.0	72.6	100.0	58.6	100.0	48.3
3.0	81.4	96.6	98.2	81.9	98.7	71.5	100.0	60.4
4.0	48.6	98.6	94.7	88.4	98.1	79.0	98.6	73.1
5.0	40.0	98.6	80.7	92.0	93.6	82.5	95.8	75.5
6.0	26.2	98.6	54.4	94.7	92.9	86.6	94.4	79.4
7.0	17.1	99.3	35.1	96.2	69.9	89.4	90.1	83.4
8.0	8.7	99.3	21.9	97.2	57.5	91.4	90.1	88.1
9.0	7.1	99.3	13.2	97.5	34.0	92.7	67.6	90.2
10.0	3.7	99.3	8.8	97.7	19.9	93.7	53.5	92.6
11.0	2.9	99.3	6.1	98.2	16.0	94.5	46.5	93.7
12.0	0.0	99.7	2.5	98.5	9.6	95.5	29.6	94.7
13.0	0.0	99.7	0.9	98.7	7.7	96.0	22.5	95.5
14.0	0.0	99.7	0.9	99.0	7.1	96.6	16.9	96.6
15.0	0.0	99.8	0.9	99.1	4.7	97.2	10.6	97.4
Whites								
1.0	99.3	76.0	99.7	52.8	99.7	36.1	99.2	31.3
2.0	98.4	94.6	99.4	83.4	98.4	66.0	98.0	55.4
3.0	84.7	100.0	97.8	93.2	96.5	81.2	97.4	70.0
4.0	62.0	100.0	74.8	97.4	91.1	93.0	92.1	81.2
5.0	38.7	100.0	46.6	98.7	71.0	97.1	90.0	90.8
6.0	25.4	100.0	26.1	99.1	52.2	98.8	88.7	96.3
7.0	20.7	100.0	11.8	99.1	28.0	100.0	65.2	98.8
8.0	16.4	100.0	9.3	100.0	11.3	100.0	46.5	99.8
9.0	12.5	100.0	7.8	100.0	6.7	100.0	31.2	99.9
10.0	10.8	100.0	7.5	100.0	3.1	100.0	22.8	100.0
11.0	9.3	100.0	5.3	100.0	2.5	100.0	15.9	100.0
12.0	8.4	100.0	4.3	100.0	1.3	100.0	11.5	100.0
13.0	7.3	100.0	4.0	100.0	1.1	100.0	7.7	100.0
14.0	6.3	100.0	3.1	100.0	0.8	100.0	7.2	100.0
15.0	5.2	100.0	2.5	100.0	0.5	100.0	6.6	100.0

values, however, and their PSA levels were more widely distributed, particularly among older men. As a result, the 95th percentiles for black men were significantly higher than those for whites. Therefore, if the usual 95th percentiles were used in a black population, more than 40 percent of cases of prostate cancer would go unidentified. This poor sensitivity is especially disturbing because black men are at higher risk for prostate cancer than white men.^{2,16}

The reason for the higher PSA values in black men is unknown. In our prior investigation of PSA levels in men with newly diagnosed prostate cancer, black patients with prostate cancer had higher PSA values even when we adjusted for age, tumor grade, and the clinical stage of disease. Tumor volume, which was greater in black men, accounted for some, but not all, of the racial difference in PSA levels.¹⁴ In the population without clinical evidence of prostate cancer described here, we also found racial differences in PSA levels. Even though we excluded patients

with known prostate cancer and those with elevated levels of PSA (>4.0 ng per milliliter) who did not undergo transrectal ultrasonography or prostate biopsy, it is possible that an excess of high-grade prostatic intraepithelial neoplasia among the black men may have contributed to the difference in serum PSA levels. A study of black and white men at autopsy showed a significantly higher prevalence of high-grade prostatic intraepithelial neoplasia, but not frank carcinoma, among the black men 30 to 59 years of age.^{17,18} Nevertheless, the effect of high-grade prostatic intraepithelial neoplasia alone on serum PSA values is unknown. Higher levels of testosterone in young black men as compared with a similar group of whites¹⁹ suggest that higher levels of stimulation by androgens may also account for racial differences in PSA levels.

A number of issues deserve comment. First, we included as case patients all the men with prostate cancer who had elevated levels of PSA before biopsy,

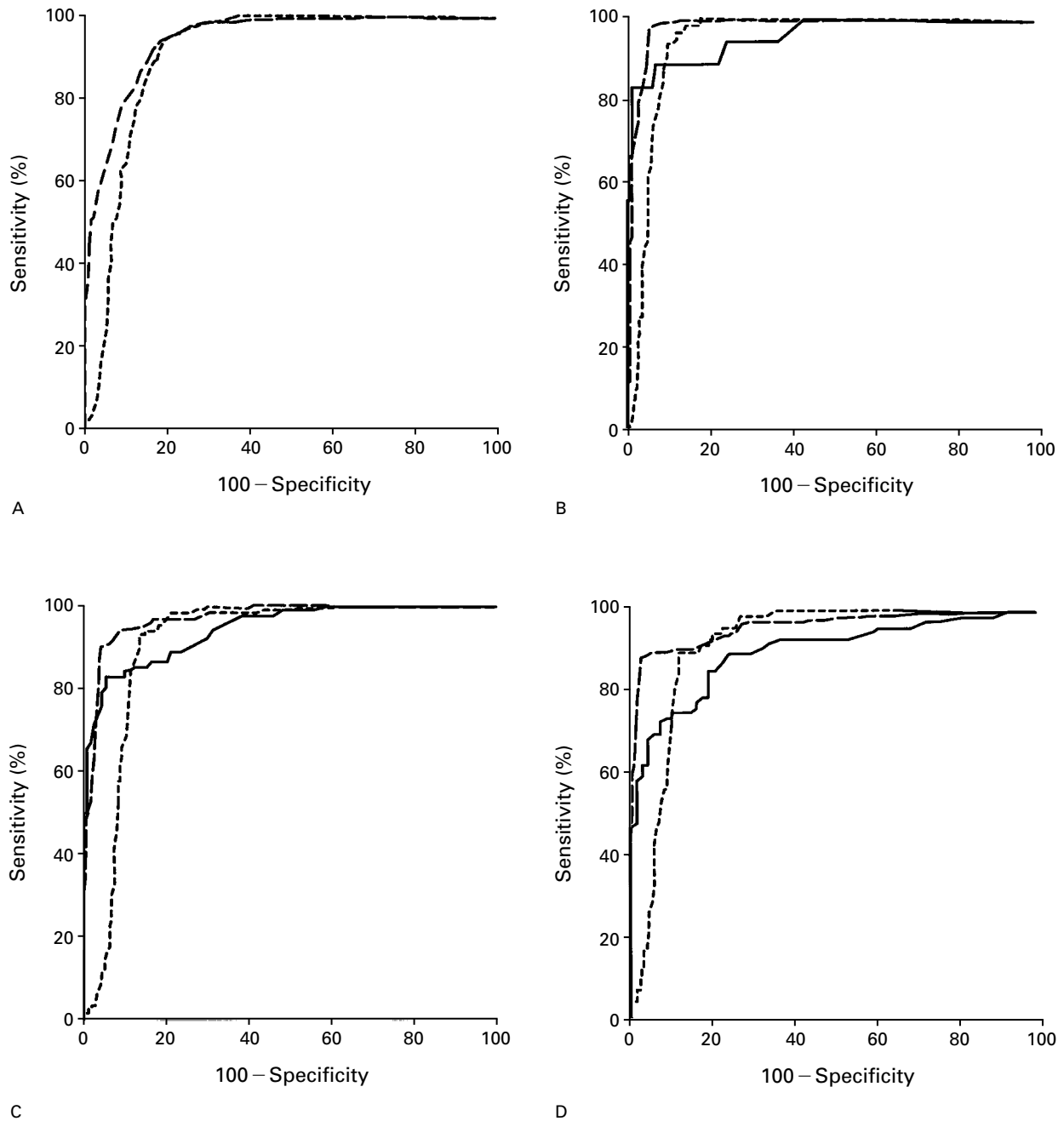


Figure 2. Receiver-Operating-Characteristic Curves of Sensitivity Plotted against 100 minus Specificity for Men 40 to 79 Years of Age. The curve for men in their 40s is shown in Panel A, for men in their 50s in Panel B, for men in their 60s in Panel C, and for men in their 70s in Panel D. Dashed lines denote whites studied at Walter Reed Army Medical Center, dotted lines blacks studied at Walter Reed, and solid lines the white men from Olmsted County, Minnesota, studied at the Mayo Clinic.⁸ No data for Minnesota men appear in Panel A because men in their 40s were not studied by Oesterling et al.

TABLE 3. AGE-SPECIFIC REFERENCE RANGES FOR THE PSA TEST, BASED ON THE 5TH PERCENTILE OF THE DISTRIBUTION OF PSA LEVELS IN THE PATIENTS, ACCORDING TO RACE.

AGE (YR)	WHITES	BLACKS
	ng of PSA/ml	
40–49	0.0–2.5	0.0–2.0
50–59	0.0–3.5	0.0–4.0
60–69	0.0–3.5	0.0–4.5
70–79	0.0–3.5	0.0–5.5

instead of selecting only those in whom such levels were indications for biopsy. This decision did not materially affect the results, since only 7 percent of blacks with prostate cancer had an abnormal digital rectal examination as the only indicator for prostate biopsy. Furthermore, less than 0.5 percent of each racial group underwent biopsy solely because of symptoms. In our control group, we assumed that two separate biopsies could rule out more than 95 percent of cases of prostate cancer²⁰ and that a PSA concentration below 4.0 ng per milliliter combined with a normal digital rectal examination indicated a minimal likelihood of prostate cancer, obviating the need for further evaluation. The latter assumption may have increased the “normal” reference ranges for PSA in men under the age of 50, whereas the former assumption could have increased the values in the older control group. Resolving these uncertainties would require prostate biopsies of all the study patients, coupled with long-term follow-up to rule out the future development of prostate cancer. Our study had no known selection bias, because in the military all eligible patients have access to care without regard to health insurance. PSA levels in our white population (tested with the IMx assay) were similar to those in the Olmsted County population (tested with the Tandem-R assay [Hybritech]),⁸ suggesting that serum PSA levels were not influenced by the choice of assay technique.

With areas under the ROC curve of 0.91 for black men and 0.94 for white men — as compared with 0.70 for Papanicolaou smears for cervical cancer,²¹ for example — the PSA assay is clearly valuable as a screening test. A caveat in this type of analysis, however, is that sensitivity and specificity may not be weighted equally when the test is applied clinically. In a given patient it is important to take into account associated risk factors and coexisting conditions and the patient’s determination and desire to undergo further evaluation. The cutoff levels used with younger men and men at increased risk for prostate

cancer should emphasize sensitivity, whereas the levels used in men more than 70 years old, men with a limited life expectancy, or both should emphasize specificity. Because these judgments vary from person to person, applying reference ranges blindly in clinical practice is inappropriate. With this in mind, we propose that ranges be used only as guides, with the decision to evaluate a patient’s condition further being based on his desires and medical history.

On the basis of our data, reference ranges for black men that give sensitivity priority over specificity by maintaining a sensitivity of 95 percent are as follows: 0 to 2.0 ng of PSA per milliliter for men in their 40s, 0 to 4.0 ng per milliliter for men in their 50s, 0 to 4.5 ng per milliliter for men in their 60s, and 0 to 5.5 ng per milliliter for men in their 70s (Table 3). These reference ranges give superior sensitivity with an acceptable trade-off in specificity as compared with the standard range (0.0 to 4.0 ng of PSA per milliliter), with age-specific reference ranges based on values obtained in whites,⁸ and with the 95th percentiles of the distribution of PSA levels in black men without prostate cancer. Sensitivity is improved the most among men in their 40s (from 49 percent for the standard range and 87 percent for the age-specific reference ranges previously reported⁸). Using a similar approach in white men would produce reference ranges of 0 to 2.5 ng per milliliter for men in their 40s and 0 to 3.5 ng per milliliter for men in their 50s, 60s, and 70s (Table 3).

In conclusion, serum PSA concentrations in black men both with and without clinical evidence of prostate cancer are significantly higher than those in similar white men. The age-specific reference ranges derived from the 95th percentiles of the distribution of PSA levels in a large black population without prostate cancer are much higher than those derived from similar whites and are of limited clinical value. Nonetheless, serum PSA screening is a powerful tool for the detection of prostate cancer in both blacks and whites, and when properly applied on an individual basis, the use of age-specific reference ranges can improve the clinical value of such screening. Our age-specific reference ranges (Table 3) indicate values for clinicians that maximize the detection of cancer in each 10-year period between the ages of 40 and 79 years.

Supported by a Clinical Research Grant from the Diagnostics Division, Abbott Laboratories; by a grant from the Center for Prostate Disease Research, U.S. Army Medical Research and Development Command; and by the Henry M. Jackson Foundation for the Advancement of Military Medicine.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the U.S. Army or the Department of Defense.

We are indebted to Ms. Sondra Buehler and Ms. Renee D. Moon-eyhan for their assistance in the preparation of the manuscript and to Mr. Hugh A. Schmidt for his assistance with the data collection.

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