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Serum Estrogen, But Not Testosterone, Levels Differ between Black and White Men in a Nationally Representative Sample of Americans

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Context: Higher testosterone in black compared with white men has been postulated to explain their higher prostate cancer incidence. Previous studies comparing hormone levels by race might have been limited by size, restricted age variation, or lack of representation of the general population.

Objective: Our objective was to compare serum testosterone, estradiol, and SHBG concentrations among non-Hispanic black, non-Hispanic white, and Mexican-American men.

Participants, Design, and Setting: A total of 1413 men aged 20+ yr and who attended the morning examination session of the Third National Health and Nutrition Examination Survey (NHANES III) in 1988–1991 were included in this cross-sectional study.

Measurement: Serum hormone concentrations were measured by electrochemiluminescence immunoassays.

Results: After applying sampling weights and adjusting for age, percent body fat, alcohol, smoking, and activity, testosterone concentrations were not different between non-Hispanic blacks (n = 363; geometric mean, 5.29 ng/ml) and non-Hispanic whites (n = 674; 5.11 ng/ml; $P > 0.05$) but were higher in Mexican-Americans (n = 376; 5.48 ng/ml; $P < 0.05$). Non-Hispanic blacks (40.80 pg/ml) had a higher estradiol concentration than non-Hispanic whites (35.46 pg/ml; $P < 0.01$) and Mexican-Americans (34.11 pg/ml; $P < 0.01$). Non-Hispanic blacks (36.49 nmol/liter) had a higher SHBG concentration than non-Hispanic whites (34.91 nmol/liter; $P < 0.05$) and Mexican-Americans (35.04 nmol/liter; $P < 0.05$).

Conclusions: Contrary to the postulated racial difference, testosterone concentrations did not differ notably between black and white men. However, blacks had higher estradiol levels. Mexican-Americans had higher testosterone than whites but similar estradiol and SHBG concentrations. Given these findings, it may be equally if not more important to investigate estradiol as testosterone in relation to diseases with racial disparity. (***J Clin Endocrinol Metab* 92: 2519–2525, 2007**)

SEX STEROID HORMONES are necessary for pubertal development and sexual function. They are involved in the metabolism, accumulation, and distribution of adipose tissue (1) and in the development and maintenance of the bones (2), and they may influence the development of common diseases such as type 2 diabetes mellitus, cardiovascular disease, and osteoporosis. The incidence of these conditions in the United States varies by race/ethnicity, with Hispanics and blacks having a higher prevalence of diabetes (3), blacks having a higher incidence of prostate cancer (4) and mortality from cardiovascular disease (3), and whites having a higher incidence of osteoporosis (5). Some, but not all, of this variation in disease incidence may be explained by racial/ethnic differences in the prevalence of risk factors for these conditions. Indeed, variation in hormone levels has been hypothesized to contribute to the racial/ethnic disparities in the incidence of these important diseases (6, 7).

Despite long-standing hypotheses that variation in sex steroid hormone levels contributes to racial differences in the development of certain diseases, whether differences between black and white men in circulating levels of sex steroid hormones exist has not been investigated across a wide age range in a large-scale study nationally representative of noninstitutionalized American men. Furthermore, few studies have examined sex steroid hormone concentrations in Hispanic men (8, 9). Hispanics are the fastest growing ethnicity in the United States, and they are disproportionately affected by obesity and diabetes (3). In a cross-sectional analysis, we investigated serum concentrations of total testosterone, free testosterone, androstanediol glucuronide (AAG), estradiol, and SHBG in males of three major U.S. racial/ethnic groups

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Abbreviations: AAG, Androstanediol glucuronide; BMI, body mass index.

from early to late adulthood in the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of non-institutionalized Americans.

Subjects and Methods

Study population

Between 1988 and 1994, the National Center for Health Statistics conducted NHANES III (10). NHANES III was designed as a cross-sectional study using a multistage stratified, clustered probability sample of the U.S. civilian non-institutionalized population at least 2 months old, in which Mexican-Americans, non-Hispanic blacks, and the elderly were oversampled. Subjects participated in an interview and an extensive physical examination. Body height and weight and waist circumference were measured during the medical examination. Cigarette smoking, alcohol consumption, and physical activity were assessed using a questionnaire. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters). We calculated body fat and percent body fat from bioelectrical impedance analysis, height, weight, and age (11).

NHANES III was conducted in two phases (1988–1991 and 1991–1994). Unbiased national estimates of health and nutrition characteristics can be independently produced for each phase. Within each phase, subjects were randomly assigned to participate in either the morning or afternoon/evening examination session. In total, 33,944 subjects were interviewed in NHANES III, of which 30,818 had a physical examination. Of the 14,781 males with an examination, 7772 were at least 20 yr old, of whom 1998 participated in the morning session of phase I. Morning sample participants were chosen for this hormone study to reduce extraneous variation due to diurnal production of hormones. Serum was still available for 1470 of these men: 674 non-Hispanic white, 363 non-Hispanic black, 376 Mexican-American, and 57 other race/ethnicity. In our analysis of the morning examination session of phase I, 97.4% of Mexican-American men were white and 2.6% of other race. The men of other racial/ethnic groups were excluded because of small sample size, leaving 1413 men 20+ yr old for this analysis.

Hormone measurements

Blood was drawn after an overnight fast for participants in the morning sample. After centrifugation, the serum was aliquotted and stored at −70 C until they were pulled from the freezers for this project. The serum samples were shipped on dry ice directly from the National Center for Health Statistics' main repository in Atlanta, GA, to the assay laboratory.

Serum concentrations of total testosterone, AAG, estradiol, and SHBG were measured in the laboratory of Dr. Nader Rifai at Children's Hospital in Boston, MA. Competitive electrochemiluminescence immunoassays on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN) were used to quantify serum testosterone, estradiol, and SHBG. AAG was measured by an enzyme immunoassay (Diagnostic Systems Laboratories, Webster, TX). The participant samples were randomly ordered for testing, and the laboratory technicians were blinded to the identity, age, and race/ethnicity of the participants. The lowest detection limits of the assays were as follows: testosterone, 0.02 ng/ml; estradiol, 5 pg/ml; AAG, 0.33 ng/ml; and SHBG, 3 nmol/liter. The coefficients of variation for quality control specimens included during the analyses of the NHANES III specimens were as follows: testosterone, 5.9 and 5.8% at 2.5 and 5.5 ng/ml; estradiol, 6.5 and 6.7% at 102.7 and 474.1 pg/ml; AAG, 9.5 and 5.0% at 2.9 and 10.1 ng/ml; and SHBG, 5.3 and 5.9% at 5.3 and 16.6 nmol/liter. In addition, we ran quality control samples with a mean estradiol concentration of 39.4 pg/ml, which is in the range of typical male estradiol concentrations; the interassay coefficient of variation was 2.5%. Serum testosterone could not be measured for eight, estradiol for five, AAG for 16, and SHBG for seven men. Serum concentrations of testosterone and estradiol detected in the adult men in NHANES III were generally within what is considered as reference values in adult men in the United States (testosterone, 1.94–8.33 ng/ml; estradiol, ≤50 pg/ml) (12). We estimated free testosterone concentration from measured testosterone, SHBG, and albumin (available in the NHANES III public use database) (13).

We selected these hormones for evaluation for the following reasons: 1) testosterone is the major male androgen and free testosterone is a measure of bioavailable testosterone; 2) AAG is an indicator of the conversion of testosterone to dihydrotestosterone, the major intraprostatic androgen; 3) estradiol is the major estrogen in men; and 4) SHBG is the major carrier of testosterone and estradiol in the peripheral circulation.

Statistical analysis

All statistical analyses were performed using SUDAAN (14) as implemented in SAS version 8.1 (Cary, NC) software. We applied sampling weights to take into account the specific probabilities of selection, nonresponse, and differences between the sample and the total U.S. population (10). We evaluated racial/ethnic differences in the hormones and SHBG 1) overall after adjusting for age and 2) within three age categories reflecting hypothesized hormonal transitions through life: early adulthood (20–44 yr old), mid-adulthood (45–69 yr old), and late adulthood (70+ yr old). Because the serum concentrations were not normally distributed, we compared geometric means among the three racial/ethnic groups using ANOVA. Molar ratios of testosterone to SHBG, estradiol to SHBG, and testosterone to estradiol were calculated and analyzed in the same way.

In linear regression models, we adjusted for age (1-yr increments), cigarette smoking (never smoker, former smoker, current smoker <35 cigarettes/d, current smoker 35+ cigarettes/d), alcohol consumption (never drinker, less than one drink/wk, one or more drinks/wk to less than one drink/d, one or more drinks/d), and physical activity (moderate or vigorous physical activity on 0, 1–2, 3–4, 5–6, or ≥7 d/wk), because these factors may influence hormone concentrations and their prevalence may vary by race/ethnicity. We used two measures to account for adiposity: 1) in one multivariable model we adjusted for BMI (continuous; kg/m^2), and 2) in a second multivariable model we adjusted for percent body fat (continuous; percent) because BMI itself might be an indicator of overall body fat but also of muscle mass, especially in younger men (15). Data on bioelectrical impedance analysis and, thus, percent body fat were not available for 118 men. All tests were two-sided; P values < 0.05 were considered to be statistically significant.

The protocols for the conduct of NHANES III were approved by the Institutional Review Board of the National Center for Health Statistics, U.S. Centers for Disease Control and Prevention. Informed consent was obtained from all participants. The assay of these stored serum specimens for sex steroid hormones was approved by Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health and the National Center for Health Statistics, U.S. Centers for Disease Control and Prevention.

Results

Baseline characteristics of the participants by race/ethnicity and age category are shown in Table 1. Within each age category, median age was comparable between the racial/ethnic groups. Median BMI and percent body fat were lowest in the youngest age group, whereas men in the oldest age group had the highest percent body fat. Mexican-American men had the highest percent body fat. Smoking status tended to differ by age and by race/ethnicity within each age group. Also, the frequency of moderate/vigorous physical activity and alcohol consumption varied by age and by race/ethnicity within each age group.

Differences by race/ethnicity adjusting for age

Circulating total testosterone did not differ significantly between non-Hispanic black and non-Hispanic white men after adjusting for age, BMI or percent body fat, smoking, alcohol consumption, and physical activity (Table 2). However, after adjusting for percent body fat, Mexican-American men had a higher testosterone level than non-Hispanic white and non-Hispanic black men, although only the former was

TABLE 1. Characteristics of 1413 male participants, NHANES III (Phase 1), 1988–1991

	20–44 yr old			45–69 yr old			70+ yr old		
	NHW	NHB	MA	NHW	NHB	MA	NHW	NHB	MA
No. of participants	252	206	239	232	117	112	190	40	25
Median age (yr)	31.8	29.5	28.6	55.9	56.2	52.6	74.4	73.4	72.6
Median BMI (kg/m^2)	26.0	26.1	26.5	27.0	25.9	29.0	26.6	27.7	26.2
25th percentile	23.4	23.1	24.2	24.8	22.6	26.8	24.1	22.5	24.3
75th percentile	28.7	29.9	29.4	30.6	28.7	31.5	29.5	30.9	29.0
Median body fat (%)[a]	23.8	24.9	26.8	26.2	25.4	27.7	26.6	25.6	29.0
25th percentile	20.4	21.9	23.6	23.0	22.6	24.5	22.5	20.7	27.6
75th percentile	27.4	30.3	30.0	28.9	29.2	31.6	30.6	28.9	30.1
Smoking status (%)									
Never	38.6	45.2	53.2	22.0	20.4	25.6	31.1	40.8	37.1
Former	26.1	15.0	14.6	47.3	30.0	54.3	58.1	45.7	53.8
Current, 1–35 cigarettes/d	29.8	38.3	31.5	25.4	45.1	20.1	10.2	13.5	9.1
Current, >35 cigarettes/d	5.5	1.6	0.8	5.4	4.5	0.0	0.6	0.0	0.0
Moderate and vigorous physical activity, times/wk (%)									
0	5.6	3.3	19.3	8.6	19.6	28.8	12.5	25.5	46.8
1–2	19.7	18.5	33.3	24.9	19.8	27.9	22.0	24.2	11.7
3–4	15.6	12.4	11.6	20.4	14.0	9.2	10.0	24.4	3.3
5–6	10.2	11.1	4.3	7.8	6.7	9.3	5.9	1.8	1.3
≥7	48.9	54.8	31.6	38.3	39.9	24.9	49.5	24.1	36.8
Alcohol consumption, no. drinks (%)									
0	24.9	33.3	22.0	36.4	38.1	40.2	52.2	87.4	90.0
> 0 to ≤1/wk	16.7	14.4	34.8	15.4	15.2	19.9	8.9	7.8	3.6
≥1/wk to <1/d	42.6	37.0	28.6	25.7	25.1	22.4	20.7	4.8	4.5
≥1/d	15.8	15.3	14.6	22.5	21.6	17.6	18.3	0.0	1.9

MA, Mexican-American; NHB, non-Hispanic black; NHW, non-Hispanic white.
[a] Percent body fat was not available for 118 men.

significant. Although not different in the age-adjusted model, Mexican-American men had a higher estimated free testosterone concentration than non-Hispanic white men in the multivariable model when adjusting for percent body fat. AAG concentration was higher in non-Hispanic white men than in men of the two other racial/ethnic groups. Circulating estradiol was higher in non-Hispanic black compared with non-Hispanic white and Mexican-American men. SHBG concentration was significantly higher in non-Hispanic black compared with non-Hispanic white men. Mexican-American men had significantly lower SHBG concentration than non-Hispanic black or non-Hispanic white men in the age-adjusted model. In the full model taking into account percent body fat, circulating SHBG concentration in Mexican-American men did not differ significantly from men in the other two racial/ethnic groups.

Mexican-American men had a higher circulating testosterone/SHBG molar ratio than non-Hispanic white and non-Hispanic black men, although only the former was significant in the multivariable models. The estradiol/SHBG ratio was significantly higher in non-Hispanic black than non-Hispanic white or Mexican-American men. Non-Hispanic black men had the highest estradiol/testosterone ratio, followed by non-Hispanic white and Mexican-American men.

Differences by race/ethnicity within age groups

Presented in Table 3 are multivariable-adjusted geometric mean hormone concentrations. We show the results adjusted for percent body fat instead of BMI because it appeared to account better for the known inverse correlation between SHBG concentration and adiposity (16). In young adult men (20–44 yr old), total testosterone concentration was significantly lower in non-Hispanic white than in Mexican-American men (Table 3). In older men (70+ yr old), non-Hispanic black men had the lowest circulating testosterone concentration, which differed significantly from Mexican-American men. No racial/ethnic differences in circulating total testosterone were observed in middle-aged men (45–69 yr old). In young adult men, Mexican-Americans had significantly higher free testosterone concentrations than non-Hispanic white men; in older Mexican-American men, free testosterone concentrations were significantly higher than in the other two racial groups. Young non-Hispanic white men had significantly higher serum AAG concentrations than non-Hispanic black and Mexican-American young men, but no significant differences were seen in other age groups. At all ages, non-Hispanic black men had higher estradiol concentrations than non-Hispanic whites and Mexican-Americans; this difference was significant in the young and middle-aged groups. Circulating SHBG did not differ between racial/ethnic groups with the exception of a higher concentration in older non-Hispanic whites compared with non-Hispanic blacks. Young adult Mexican-Americans had a significantly higher molar testosterone/SHBG ratio than non-Hispanic white or non-Hispanic black men. This was also seen for older but not middle-aged men. Young adult, middle-aged, and older non-Hispanic black men had higher molar estradiol/SHBG ratios than non-Hispanic white and Mexican-American men, although the differences were not always statistically significant. Similarly, we noted the highest estradiol/testosterone ratio in young adult and older non-Hispanic black men compared with non-Hispanic white and Mexican-American men.

TABLE 2. Serum concentrations of sex steroid hormones and SHBG by race/ethnicity, men 20+ yr old, NHANES III (Phase 1), 1988–1991

Hormone and race/ethnicity	Age-adjusted		Multivariable adjustment, model 1		Multivariable adjustment, model 2	
	Geometric mean	95% Confidence interval	Geometric mean	95% Confidence interval	Geometric mean	95% Confidence interval
Testosterone (ng/ml)						
NHW	5.11	4.93–5.31	5.10	4.93–5.27	5.11[a]	4.94–5.28
NHB	5.25	4.90–5.62	5.24	4.90–5.61	5.29	4.93–5.68
MA	4.95	4.81–5.08	5.17	5.00–5.34	5.48	5.29–5.67
Testosterone (nmol/liter)/SHBG (nmol/liter)						
NHW	0.506	0.484–0.528	0.505[a]	0.485–0.526	0.508[a]	0.488–0.530
NHB	0.502	0.474–0.532	0.503	0.476–0.532	0.505	0.476–0.536
MA	0.531	0.511–0.552	0.540	0.522–0.559	0.542	0.527–0.558
Free testosterone (ng/ml)						
NHW	0.101	0.097–0.105	0.101	0.097–0.104	0.101[b]	0.098–0.104
NHB	0.103	0.097–0.111	0.104	0.097–0.111	0.105	0.098–0.112
MA	0.101	0.099–0.104	0.105	0.102–0.108	0.109	0.106–0.112
AAG (ng/ml)						
NHW	12.32[d,a]	11.67–13.01	12.31[d,a]	11.64–13.03	12.43[d,a]	11.77–13.13
NHB	10.41	9.64–11.23	10.44	9.68–11.25	10.42	9.70–11.20
MA	10.92	10.27–11.61	10.98	10.15–11.88	10.85	9.92–11.86
Estradiol (pg/ml)						
NHW	35.31[d]	33.65–37.05	35.28[d]	33.82–36.81	35.46[d]	34.07–36.92
NHB	40.96[f]	39.28–42.70	40.85[f]	39.10–42.68	40.80[f]	39.00–42.69
MA	33.08	31.25–35.00	33.63	31.48–35.93	34.11	32.29–36.02
Estradiol (nmol/liter)/SHBG (nmol/liter)						
NHW	3.69[c]	3.40–4.01	3.69[c]	3.43–3.97	3.73[c]	3.48–3.99
NHB	4.13	3.91–4.36	4.13[e]	3.90–4.38	4.10[e]	3.87–4.35
MA	3.76	3.48–4.06	3.71	3.41–4.05	3.57	3.36–3.79
SHBG (nmol/liter)						
NHW	35.13[a]	33.53–36.80	35.08	33.61–36.60	34.91[c]	33.43–36.45
NHB	36.38[f]	34.92–37.90	36.28[e]	34.60–38.03	36.49	35.08–37.95
MA	32.30	30.88–33.79	33.21	31.76–34.72	35.04	33.58–36.55
Estradiol (nmol/liter)/testosterone (nmol/liter)						
NHW	7.30[c]	6.84–7.79	7.32[c]	6.90–7.76	7.34[a]	6.96–7.75
NHB	8.24[f]	7.64–8.88	8.22[f]	7.62–8.87	8.13[f]	7.51–8.80
MA	7.07	6.66–7.51	6.88	6.46–7.33	6.58	6.26–6.92

Model 1 is adjusted for age, BMI, smoking, alcohol consumption, and physical activity; model 2 is the same as model 1 but adjusted for percent body fat instead of BMI; percent body fat is missing for 118 men. MA, Mexican-American; NHB, non-Hispanic black; NHW, non-Hispanic white.

[a,b] NHW *vs.* MA: [a] $P < 0.05$; [b] $P < 0.01$.

[c,d] NHW *vs.* NHB: [c] $P < 0.05$; [d] $P < 0.01$.

[e,f] NHB *vs.* MA: [e] $P < 0.05$; [f] $P < 0.01$.

Discussion

This is the first cross-sectional study of racial and ethnic variation in circulating sex steroid hormone and SHBG concentrations in a representative sample of adult U.S. men. There was no significant difference in circulating concentrations of testosterone or free testosterone concentrations between non-Hispanic black and white men overall, but Mexican-American men had higher levels than non-Hispanic white men. However, non-Hispanic black men had the highest estradiol level overall and across all ages, which was not explained by racial differences in the prevalence of factors that influence hormone levels.

We cannot confirm observations of a difference in circulating testosterone concentration between African-American and Caucasian men as reported previously in some studies (6, 9, 17, 18), including in young men (6, 9, 17). Differences between our results and the results of previous studies comparing circulating total testosterone concentrations between racial groups might be due to differences in age variation or in sample size or due to lack of representation of the general population. In our analysis, serum testosterone concentration was similar in young non-Hispanic white and non-Hispanic black men, which has also been reported in three U.S. cross-sectional studies (19–21). In a U.S. longitudinal study, testosterone concentration was higher in young black than white men after adjustment for age and BMI (22). However, after further adjustment for waist circumference, there was no difference between non-Hispanic white and non-Hispanic black men. In our study, non-Hispanic black and non-Hispanic white men did not differ notably on their extent of adiposity. Thus, the results did not change after we adjusted for waist circumference in addition to BMI (data not shown) or after we adjusted for percent body fat instead in the regression models. A recent review concluded that high circulating testosterone concentrations are associated with a lower risk of type 2 diabetes in men (23). Although several cross-sectional studies reported that men with low testosterone levels have an increased risk of coronary artery disease, this association is not clearly seen in prospective studies (24). Testosterone is important for prostate development and

TABLE 3. Serum concentrations of sex steroid hormones and SHBG by race/ethnicity within age strata, NHANES III (Phase 1), 1988–1991

Age category and race/ethnicity	n	Geometric mean concentration; 95% confidence interval							
		Testosterone (ng/ml)	Free testosterone (ng/ml)	Testosterone/ SHBG	AAG (ng/ml)	Estradiol (pg/ml)	Estradiol/ SHBG	SHGB (nmol/liter)	Estradiol/ testosterone
Young adult men (20–44 yr old)									
NHW	245	5.17[a];4.95–5.40	0.104[a];0.105–0.110	0.524[a];0.485–0.567	12.65[d,a];11.50–13.91	35.87[c];34.51–37.27	3.85[c];3.60–4.11	34.22;32.03–36.56	7.34[c,a];6.86–7.86
NHB	188	5.35;4.92–5.81	0.107;0.104–0.118	0.519[e];0.471–0.572	10.60;9.32–12.05	42.24[f];40.06–44.54	4.32[f];3.92–4.76	35.88;32.97–39.04	8.33[f];7.70–9.01
MA	219	5.55;5.27–5.86	0.113;0.107–0.119	0.573;0.537–0.610	10.95;9.63–12.45	34.65;32.46–36.99	3.78;3.53–4.05	33.60;31.22–36.15	6.60;6.20–7.02
Middle-aged men (45–69 yr old)									
NHW	221	5.00;4.60–5.44	0.098;0.087–0.112	0.497;0.424–0.582	11.92;10.50–13.52	34.39[c];31.50–37.54	3.61[c];3.14–4.15	34.92;31.44–38.79	7.27;6.41–8.24
NHB	103	5.62;4.93–6.41	0.107;0.093–0.123	0.515;0.441–0.603	10.15;8.18–12.58	37.84[e];35.13–40.77	3.66;3.09–4.34	37.89;33.49–42.87	7.12;6.12–8.28
MA	101	5.25;4.79–5.75	0.101;0.091–0.112	0.480;0.427–0.539	10.19;8.61–12.05	32.50;30.42–34.72	3.13;2.81–3.49	37.99;34.32–42.05	6.54;5.93–7.21
Older men (70+ yr old)									
NHW	166	5.00;4.53–5.52	0.088[a];0.075–0.103	0.420[b];0.333–0.530	12.59;9.73–16.28	36.24;33.53–39.16	3.18[d];2.56–3.95	41.94[d];33.98–51.76	7.65[c,a];6.64–8.81
NHB	34	3.84[e];2.89–5.12	0.075[e];0.054–0.105	0.384;0.273–0.538	9.92;6.68–14.75	38.31;34.17–42.95	4.00;3.27–4.90	34.92;28.71–42.46	10.52[f];7.87–14.06
MA	19	5.96;4.71–7.54	0.113;0.091–0.140	0.537;0.422–0.683	15.10;9.80–23.26	36.13;30.49–42.80	3.43;2.73–4.31	38.63;31.21–47.80	6.40;5.18–7.90

The geometric mean concentration was adjusted for age, percent body fat, cigarette smoking, alcohol consumption, and moderate/vigorous physical activity. MA, Mexican-American; NHB, non-Hispanic black; NHW, non-Hispanic white.

[a,b] NHW *vs.* MA: [a] $P < 0.05$; [b] $P < 0.01$.

[c,d] NHW *vs.* NHB: [c] $P < 0.05$; [d] $P < 0.01$.

[e,f] NHB *vs.* MA: [e] $P < 0.05$; [f] $P < 0.01$.

function and is a target for treatment of metastatic prostate cancer, yet results from epidemiological studies that examined the association between total and bioavailable testosterone and prostate cancer have been inconclusive (25–27). Our study provides little evidence for the hypothesis that racial variation in testosterone and free testosterone accounts, in part, for the higher risk of prostate cancer in African-American men, at least as measured by circulating levels.

AAG concentration is commonly used in epidemiological studies as an indirect measure of 5α-reductase activity and, thus, the conversion of testosterone to dihydrotestosterone. Serum AAG concentration was significantly higher in non-Hispanic whites than in men of the other two racial/ethnic groups. This was observed overall and in the different age groups. Higher AAG in white compared with black men has been seen in other studies in middle-aged (8, 28) and in elderly (29) but not in young adult men (30). A lower AAG concentration in non-Hispanic black than white men is not compatible with the hypothesis that a greater 5α-reductase activity could be associated with the increased risk of prostate cancer in African-American men based on a meta-analysis that reported an increased risk of prostate cancer with higher circulating AAG concentration (31). Lower AAG might result in men who have a lower conversion of dihydrotestosterone to 3α-androstanediol or, alternatively, a higher reconversion of 3α-androstanediol to dihydrotestosterone (32). However, not much is yet known about racial variation in the activity of the enzymes that catalyze these conversions. Second, lower AAG could result in men with a greater efficiency of conversion of testosterone to estradiol via higher aromatase activity. Polymorphisms in the CYP19 gene, which encodes aromatase, have been reported. However, plasma concentration of total testosterone, AAG, and SHBG did not differ by genotype in a Caucasian population (33). Racial variation in CYP19 alleles has been observed in women (34), but to our knowledge, no study has been published with respect to differences in hormone concentrations in men for most of these CYP19 polymorphisms.

We observed higher serum estradiol concentrations and higher estradiol/SHBG ratios in non-Hispanic black than in non-Hispanic white or Mexican-American men, a difference that was pronounced in young and mid-adulthood. Previous studies aside from one small study of young men (35) did not report differences in circulating estradiol concentrations between African-Americans and Caucasians in young (6, 17, 20), middle-aged (28), or older men (18). It has been hypothesized that higher estradiol concentrations in African-American men might contribute to higher bone mass and, thus, lower fracture risk (7) because estradiol inhibits bone resorption (36). The role of estrogens in the development and progression of prostate cancer, which is more common among African-American than Caucasian or Hispanic men (4), is not clear. In the Physicians' Health Study, an inverse association between circulating estradiol concentration and prostate cancer was observed after taking testosterone and SHBG concentrations into account statistically (37), whereas other studies did not report statistically significant positive or inverse associations (25).

SHBG transports sex steroid hormones in the circulation and, along with albumin, is a determinant of bioavailable testosterone and estradiol. It mediates steroid hormone signal transduction at the plasma membrane, which allows steroid hormones to act without entering the cell by interacting with SHBG membrane receptors (38). SHBG concentration was lower in Mexican-American than non-Hispanic white and non-Hispanic black men in the age-adjusted model; however, the differences were attenuated after taking into account all covariates, particularly percent body fat. The attenuation of the racial/ethnic differences in the multivariable model is explained by SHBG concentration being inversely associated with body fat (16) and the higher percentage of body fat in Mexican-Americans compared with either of the other two racial/ethnic groups. SHBG concentrations were similar in non-Hispanic blacks and non-Hispanic whites. Similar to our results, two cross-sectional studies did not observe significant differences in circulating SHBG concentration between young adult black and white men (17, 19), whereas a third study reported a higher SHBG concentration in young African-American than Caucasian men (6).

To date, Hispanic males infrequently have been examined

concerning their sex steroid hormone profile. In a cross-sectional study that included 200 Hispanic men aged 31–44 yr old, Hispanics had a testosterone concentration that was similar to the concentration in non-Hispanic white but lower than in black men (9). Similarly, no differences in total testosterone concentration were observed in the Boston Area Community Health Survey, which included 648 Hispanics, aged 30–79 yr (21). In the Hawaii-Los Angeles Multiethnic Cohort (8), which included 523 U.S. Latinos, aged 47–74 yr, U.S. Latinos had a slight but not significantly lower circulating testosterone concentration than U.S. whites after adjusting for age. AAG concentration was higher than the concentration in African-American men and lower than in U.S. whites, but neither difference was statistically significant (8). In NHANES III, we studied Mexican-American men, which is the largest Hispanic group in the United States. Whether our results for Mexican-American men may be compared with the results in other Hispanic populations may depend on the composition of those Hispanic populations by country of origin.

Several aspects of our study merit further discussion. First, sex steroid hormone and SHBG concentrations in humans are influenced by a number of factors. Our goal was to determine whether there was racial variation in hormones beyond the variation due to differences in prevalence of modifiable factors that influence hormone concentrations. Therefore, we adjusted the regression models for factors that correlate with hormones and that differ by race, *i.e.* percent body fat, cigarette smoking, alcohol consumption, and physical activity. However, it should be noted that these modifiable predictors of hormone concentrations are also risk factors for chronic diseases and that hormones may mediate their influence on disease risk. Thus, assessment of crude (or age-adjusted) differences in hormone concentrations is key to understanding the contributions of hormones to the racial/ethnic variation in the burden of disease. Second, serum testosterone concentration exhibits diurnal variation. In one study, mean testosterone concentrations were 25–30% lower at 2000 h than at 0800 h, which was similar in African-American and Caucasian men (6). Therefore, we selected only men who participated in the morning session of the first phase of NHANES III (0830–1130 h). Additionally adjusting for time when blood was drawn did not appreciably change the results. Third, due to the number of comparisons we evaluated, we cannot exclude chance as an alternative explanation for any given finding. Fourth, NHANES III is a cross-sectional study representative of the civilian non-institutionalized U.S. population, thus aiding in the broad generalizability of these results. Main characteristics, such as age, percent body fat, smoking, alcohol consumption, or physical activity, of the subset of men used in this analysis were comparable to all men 20 yr and older who participated in the morning session of the first phase of NHANES III (data not shown). Also, the over-sampling of minorities and elderly and the large sample size allowed for reasonably stable estimates even after adjusting for possibly confounding variables. Fifth, the analyses were based on a single hormone measurement and may not perfectly reflect serum hormone levels averaged over time (39), although some studies have shown that using only one sample was highly accurate in predicting sex steroid hormone levels for a time frame up to 3 yr (26, 40). Sixth, NHANES III is a cross-sectional study, and thus, we could not assess differences in the hormones trajectories over age by race/ethnicity.

In conclusion, in this large, nationally representative sample, there was no difference in circulating testosterone concentrations between non-Hispanic black and white men overall. However, black men had the highest estradiol level overall across all ages, which was not explained by racial differences in the prevalence of factors that influence hormone levels. Mexican-American men had hormonal profiles similar to non-Hispanic white men, with the exception of higher testosterone. Given these findings, it may be equally if not more important to investigate levels of estradiol than testosterone in relation to diseases that show racial disparity, such as prostate cancer.

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