Lifestyle Determinants of 5α-Reductase Metabolites in Older African-American, White, and Asian-American Men[1]

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Abstract

Men with higher endogenous 5α-reductase activity may have higher prostate cancer risk. This hypothesis raises two questions: (*a*) Could racial differences in 5α-reductase activity explain the observed racial differences in prostate cancer risk? and (*b*) Could a man reduce his activity level by modifying his lifestyle? To address these questions, we measured two hormonal indices of 5α-reductase activity [serum levels of androstane-3α-17β-diol glucuronide (3α-diol G) and androsterone glucuronide (AG)] in healthy, older African-American, white, and Asian-American men, who are at high, intermediate, and low prostate cancer risk, respectively. We also examined associations between these metabolite levels and such lifestyle characteristics as body size and physical activity as well as select aspects of medical history and family history of prostate cancer. Men included in this cross-sectional analysis ($n = 1054$) had served as control subjects in a population-based case-control study of prostate cancer we conducted in California, Hawaii, and Vancouver, Canada and provided information on certain personal attributes and donated blood between March 1990 and March 1992. In this study, concentrations of 3α-diol G declined significantly with age and increased significantly with body mass index. Mean levels of 3α-diol G, adjusted for age and body mass index, were 6.1 ng/ml in African-Americans, 6.9 ng/ml in whites and 4.8 ng/ml in Asian-Americans. These differences were statistically significant (African-Americans *versus* whites: $P < 0.01$; whites *versus* Asian-Americans: $P < 0.001$). Concentrations of AG decreased significantly with age, but only in whites, and were unrelated to any of the reported personal attributes. Mean levels of AG, adjusted for age, were 44.1 ng/ml in African-Americans, 44.9 ng/ml in whites, and 37.5 ng/ml in Asian-Americans (Asian-Americans *versus* whites, $P < 0.001$). In conclusion, older African-American and white men have similar levels of these two indices of 5α-reductase activity, and these levels are higher than those of older Asian-American men. This difference may be related to the lower prostate cancer risk in Asian-Americans.

Introduction

T[3] and its metabolite, DHT, are necessary for the normal growth and maintenance of the prostate gland. These hormones have been investigated as potential risk factors for prostate cancer in many epidemiological studies. However, blood levels of T and DHT have been disappointing markers of prostate cancer risk. In a recent meta-analysis of prospective studies on prostate cancer and endogenous sex hormones (1), neither SHBG nor any of the sex steroid hormones (including total T, non-SHBG bound T, DHT, androstenedione, dehydroepiandrosterone sulfate, estrogens, luteinizing hormone, and prolactin) were associated with prostate cancer risk. The only exception was 3α-diol G; the mean serum levels were 5% (ratio, 1.05; 95% confidence interval, 1.00–1.11) higher among 644 men who developed prostate cancer compared with 1048 men who did not (1). This pooled analysis included prospective studies conducted among Japanese men in Hawaii (2) and Caucasian men in the United States (3, 4), Finland (5), and Norway (6). The modest increase in serum 3α-diol G levels in men with prostate cancer may reflect increased intracellular conversion of T to DHT and hence cell division in the prostate tissue.

However, the relationship between serum 3α-diol G levels and prostate cancer risk remains controversial. Conversion of T to DHT is catalyzed by the enzyme 5α-reductase, which exists in two forms, types I and type II. Both types are found in the liver, but type I predominates in the skin, whereas type II predominates in the prostate and other male accessory sex glands (7, 8). Serum levels of 3α-diol G are likely to reflect the activities of both types of enzymes. At present, there are no data to correlate blood levels of 3α-diol G with tissue levels of either DHT or 3α-diol G or with the conversion of T to DHT within the prostate. Moreover, we are aware of only a small cross-sectional study that has compared serum 3α-diol G levels in healthy men of different racial background who have different risks of prostate cancer (9). In this study, 3α-diol G levels among young men (mean age, 20.9 years) in Japan were 25–

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[3] The abbreviations used are: T, testosterone; DHT, dihydrotestosterone; SHBG, sex hormone binding globulin; 3α-diol G, 5α-androstane-3α,17β-diol glucuronide; AG, androsterone glucuronide; BMI, body mass index.

35% lower than those of young adult white and African-American men, consistent with the lower incidence rates of clinical prostate cancer among Asians (9). However, the 3α-diol G levels were slightly higher (5%) in young white men than young African-American men (9). It is not known whether 3α-diol G levels in older African-American, white, and Asian-American men are consistent with their respectively high, intermediate, and low risks of prostate cancer. There are also few known determinants of circulating levels of 3α-diol G (10). If blood 3α-diol G levels are a marker of prostate cancer risk, then identification of modifiable factors that influence circulating 3α-diol G levels is important because this could lead to preventive measures to reduce the risk of prostate cancer.

We conducted a cross-sectional study on some 1050 older (mean age, 70 years) healthy men to further investigate differences in blood levels of 3α-diol G among African-American, white, and Asian-American men at differing risks of prostate cancer. We also measured blood AG levels. This metabolite is interconvertible with 3α-diol G and in combination with 3α-diol G has been suggested to characterize 5α-reductase activity (11). However, the data on AG levels are sparse, and AG levels were not associated with prostate cancer risk in the two studies that have investigated this question (2, 4). We investigated the influence of age on these two DHT metabolites because only circulating T, but not DHT, levels appeared to decrease with increasing age (10, 12–14). Using detailed questionnaire data that are already available in this group of men, we also investigated the relationships between levels of these metabolites and various personal (*e.g.*, body weight, height, and history of prostate condition) and lifestyle characteristics (*e.g.*, physical activity and use of tobacco and alcohol).

Materials and Methods

Study subjects in this analysis included African-Americans, whites, Chinese, and Japanese, who served as population controls in a multicenter population-based case-control study of prostate cancer that we conducted in California (Los Angeles County, San Francisco Bay Area), Hawaii, and Vancouver, Canada (15). Hereafter, Chinese and Japanese Americans are referred to as Asian-Americans. As described in our analysis of serum androgen (T and DHT) and SHBG determinants in the control men (12), these participants were interviewed between March 1990 and March 1992 and donated an early morning (typically before 10:00 a.m.) fasting sample of venous blood within several months of the initial interview. In each respective study center, after the specimens were collected, they were returned to the laboratory on ice and processed within 2 h of the blood draw. The samples were then stored at −70°C at the respective study center until they were shipped in sealed containers on dry ice to one of us (A. H. W.) at the University of Southern California for this specific study. The frozen aliquots (*i.e.*, 1-ml aliquot of serum from each subject for 5α-reductase metabolite assays) were then delivered to the laboratory of one of us (F. Z. S.) for analysis. To minimize bias in racial comparisons attributable to any temporal changes in laboratory results, each analytic batch of 30–35 specimens included approximately equal numbers of samples from the three centers and three race groups. The laboratory measurements were conducted blinded to the subjects' race and study center.

The two 5α-reductase metabolites were measured using published methods. Serum 3α-diol G levels were quantified using direct RIA with an ^{125}I-Androstanediol Glucuronide kit (Diagnostic Systems Laboratories, Inc., Webster, TX) as described previously (16). The intraassay and interassay coefficients of variation at three different 3α-diol G concentrations ranged from 4 to 14% (10 samples at each concentration). The methods described by Matteri *et al.* (17) were used to measure serum AG levels. After removal of unconjugated steroids from serum by extraction with diethyl ether, glucuronide conjugates were hydrolyzed at 37°C by addition of β-glucuronidase to the extracted serum, which was first adjusted to pH 6.8. After 16 h of hydrolysis, unconjugated hormones were extracted with diethyl ether, and androstanediol was separated by Celite column chromatography and quantified by RIA; [^{3}H]A-G was added to serum sample prior to hydrolysis to allow for monitoring of procedural losses. Also, AG levels were corrected for molecular weight differences before and after hydrolysis. Intraassay and interassay laboratory coefficients of variation ranged between 5 and 10% at three different AG concentrations. However, there are much fewer data regarding the within-person variation of these 5α-reductase metabolites. An intraclass correlation coefficient of 0.90 was found for 3α-diol G in a small group of men in Hawaii who provided multiple blood samples over a 1-month period (three samples each from 9 men and two samples each from 2 men).[4]

Information on height (1 year before interview), weight at three ages (ages 20 and 40 and 1 year before interview), physical activity (1 year before interview), history of benign prostate disease and vasectomy, and family history of prostate cancer were collected at interview. In addition, at the time of specimen collection, we also asked about smoking habits and alcohol consumption during the year preceding the blood draw. Thus, in this analysis, "current" lifestyle habits refer to patterns defined at 1 year before interview or blood draw. The methods used to estimate physical activity levels have been described elsewhere (12). In brief, total energy expenditure was calculated based on the number of hours spent in sleeping, sitting, light activity, and vigorous activity, weighted by the respective metabolic equivalent score for each of these activities and the subject's body weight.

We used ANOVA and analysis of covariance to assess the influence of age, race, and lifestyle factors on levels of 3α-diol G and AG (18). Statistical analysis was performed on logarithmically transformed values, and geometric mean levels (and SEs) were presented. To evaluate associations with age, race-specific (*i.e.*, for African-Americans, whites, and Asian-Americans) levels of these two 5α-reductase metabolites were calculated for five categories of age in years (<60, 60–64, 65–69, 70–74, and 75+). To determine whether age-adjusted mean levels differ between the three race groups, we used analysis of covariance models including two race groups in every run. Two-sided *P*s for the comparison between African-Americans and whites, African-Americans and Asian-Americans, and whites and Asian-Americans were presented. Analysis of covariance methods with age as a covariate (in single years) were used to compare levels of these two 5α-reductase metabolites between different quartiles of BMI (weight in kilograms divided by the square of height in meters), height, physical activity, and other factors of interest. For variables with three or more levels, we present trends across the categorical levels for the variable of interest. For example, *P*s for trend test were calculated across quartiles of BMI, height, and physical activity. For variables such as height, weight, BMI, and physical activity, the quartile cutpoints were based on the distribution of all subjects combined. All *P*s quoted are two-sided. Calcula-

[4] L. Kolonel, personal communication.

Table 1 Distribution of study subjects and mean[a] levels with SE (in parentheses) of 3α-diol G (ng/ml) and AG (ng/ml), by age and race

Age[b] (yr)	African-Americans			Whites			Asian-Americans		
	n	3α-diol G	AG	*n*	3α-diol G	AG	*n*	3α-diol G	AG
<60	34	8.1 (1.6)	45.6 (1.7)	35	7.8 (1.8)	56.0 (2.1)	23	5.2 (1.5)	37.5 (1.8)
60–64	37	6.2 (1.8)	44.0 (1.7)	64	7.7 (1.6)	52.7 (1.8)	43	5.1 (1.9)	37.9 (1.6)
65–69	89	6.2 (1.8)	44.0 (1.8)	101	7.0 (1.8)	45.6 (1.9)	91	5.3 (1.7)	38.9 (1.6)
70–74	68	6.7 (1.7)	46.9 (1.8)	90	6.9 (1.7)	41.5 (1.9)	98	4.7 (2.0)	37.6 (1.7)
75+	75	5.3 (2.0)	41.2 (1.7)	108	6.4 (2.1)	39.7 (2.5)	98	3.9 (1.9)	36.0 (1.8)
Total	303	6.2 (2.1)[c]	44.1 (1.9)[c]	398	7.0 (1.8)[c]	44.9 (2.1)[c]	353	4.6 (2.1)[c]	37.5 (1.7)[c]
Rate of change (ng/ml/yr)		−0.015	−0.006		−0.010	−0.016		−0.017	−0.003
P[d]		<0.001	0.24		<0.01	0.0006		<0.001	0.51

[a] Geometric mean levels with SEs are shown.
[b] Mean age (SDs) was 69.1 (7.7) in African-Americans, 69.8 (7.8) in whites, and 70.4 (6.8) in Asian-Americans. The range in age was 40–84 in African-Americans, 35–89 in whites, and 47–85 in Asian-Americans.
[c] Adjusted for age (in single years).
[d] Two-sided *P* for trend.

tions were performed using the SAS statistical software system (SAS Institute, Cary, NC).

Results

Analyses of these two 5α-reductase metabolites were conducted on 1054 men: 303 African-Americans, 398 whites, and 353 Asian-Americans [we did not have sufficient blood specimens on another 73 men who were included in our previous study on androgens (12) but excluded in this analysis]. Table 1 shows the effects of age on levels of 3α-diol G, by race. In each of the three race groups, there was a significant reduction in 3α-diol G levels with increasing age. The reduction was 1.0% per year ($P < 0.01$) in whites, 1.5% per year ($P < 0.001$) in African-Americans, and 1.7% per year ($P < 0.001$) in Asian-Americans. Overall, the age-adjusted levels of 3α-diol G were highest in whites (7.0 ± 1.8 ng/ml), intermediate in African-Americans (6.2 ± 2.1 ng/ml), and lowest in Asian-Americans (4.6 ± 1.9 ng/ml). The levels in Asian-Americans were statistically significantly lower than those in white ($P < 0.0001$) and African-American ($P < 0.0001$) men. Levels of 3α-diol G also differed significantly between white and African-American men in this study ($P = 0.006$).

Table 1 also shows levels of AG by age and race. In all three racial groups, levels of AG were lowest in men aged 75+ years or older, but a smooth and statistically significant trend of decreasing AG levels with increasing age ($P = 0.0006$) was observed only among white men in this study. Although Asian-Americans displayed statistically significantly lower AG levels (37.5 ± 1.7 ng/ml) than did whites (44.9 ± 2.1 ng/ml) and African-Americans (44.1 ± 1.9 ng/ml; $P < 0.004$), the levels in white and African-American men were similar.

Table 2 shows levels of 3α-diol G and AG in association with physical activity, smoking, alcohol intake, family history of prostate cancer, history of benign prostate disease, and vasectomy. Levels of the two 5α-reductase metabolites did not differ significantly between men with and without specific history of benign prostate disease, vasectomy, family history of prostate cancer, and smoking habits (Table 2). Physical activity was not associated with levels of 3α-diol G in African-American and white men. Although levels of 3α-diol G increased significantly with increasing physical activity in Asian-American men, this finding was no longer statistically significant after adjustment for current BMI. Levels of AG were not associated with physical activity in any of the three race groups. High daily alcohol intake (>12 g/day) was associated with significantly higher 3α-diol G levels in African-Americans, but a consistent pattern of increasing levels with increasing amounts drank was not observed. In addition, alcohol intake was not associated with 3α-diol G levels in whites and was associated with lower levels in Asian-Americans. Levels of AG were not associated with alcohol intake in African-Americans and whites but were significantly lower in Asian-American men in the high daily alcohol group (Table 2).

Table 3 shows levels of the two 5α-reductase metabolites by BMI and height. In each of the three race groups, levels of 3α-diol G tended to increase with increasing levels of current BMI. In Asian-Americans and whites, the positive associations between BMI and 3α-diol G levels were statistically significant. From the lowest (≤23.14) to the highest (>27.4) quartile of current BMI, 3α-diol G levels increased 15% in African-American ($P = 0.42$), 26% in white ($P = 0.02$), and 31% ($P = 0.0001$) in Asian-American men. This increase in 3α-diol G levels was also observed with increasing BMI at age 40 in Asian-American and white men. In Asian-Americans and whites, levels of 3α-diol increased 12% ($P = 0.06$) and 18% ($P = 0.05$), respectively, from the lowest to the highest quartile of BMI at age 40. In African-American men, levels of 3α-diol differed by <1% by quartiles of BMI at age 40. Levels of 3α-diol G were weakly associated with BMI at age 20 in all three race groups, although none of these findings were statistically significant. From the lowest to the highest quartile of BMI at age 20, 3α-diol G levels increased 8, 9, and 6%, respectively, in African-American, white, and Asian-American men. Levels of AG were not significantly associated with current BMI (Table 3).

In this population, levels of 3α-diol G were positively correlated with levels of T ($r = 0.10$; $P < 0.05$) and DHT ($r = 0.05$, $P = .10$) and negatively correlated with SHBG ($r = -0.18$; $P < 0.05$). Because of the inverse associations between BMI and levels of T, DHT, and SHBG in this population (12), we also investigated the relationship between current BMI and levels of 3α-diol G after adjustment for levels of T, DHT, and SHBG. The positive association between BMI and 3α-diol G levels remained and was strengthened after adjustment for age, race, and levels of T, DHT, and SHBG; the 3α-diol G levels for the quartiles of current BMI were 4.9, 5.9, 6.2, and 6.5 ng/ml, respectively ($P < 0.001$). On the other hand, the inverse associations between T, DHT, and SHBG and current BMI were somewhat weakened after adjustment for 3α-diol G levels (data not shown).

The racial differences in 3α-diol G and AG levels described in Table 1 remained statistically significant after ad-

Table 2 Age-adjusted[a] mean concentrations of 3α-diol G (ng/ml) and AG (ng/ml) by lifestyle characteristics and personal histories (number of subjects in each category given in parentheses)

	African-Americans		Whites		Asian-Americans	
	3α-diol G	AG	3α-diol G	AG	3α-diol G	AG
Physical activity (METS/wk)[b]						
≤27.7	5.9 (46)	49.8 (45)	6.8 (53)	44.4 (52)	4.3 (161)	36.2 (154)
>27.7–32.2	6.1 (64)	41.5 (63)	7.3 (88)	50.0 (89)	4.7 (101)	39.8 (102)
>32.3–37.4	6.9 (67)	47.8 (63)	6.9 (129)	42.6 (125)	5.3 (63)	37.8 (62)
>37.4	6.0 (115)	41.1 (114)	6.9 (122)	44.3 (121)	5.3 (22)	37.4 (22)
Smoke						
No/former[c]	6.1 (196)	44.0 (192)	6.8 (319)	45.0 (315)	4.7 (307)	38.0 (297)
Current, ≤10 cigarettes/day	7.0 (49)	46.1 (47)	8.0 (33)	48.5 (32)	4.0 (25)	38.8 (24)
Current, >10 cigarettes/day	5.8 (47)	43.2 (46)	7.2 (38)	41.3 (38)	4.3 (20)	29.7 (19)
Alcohol						
Never drink[d]	6.3 (112)	47.4 (111)	6.8 (89)	45.6 (88)	4.9 (151)	38.9 (14.9)
Drink, ≤12 g/day	5.4 (100)	41.9 (95)	6.7 (166)	42.4 (162)	4.6 (127)	38.5 (124)
Drink, >12 g/day	7.3 (80)	42.9 (79)	7.4 (135)	47.7 (135)	4.2 (74)	32.9 (67)
Family history of prostate cancer[c]						
No	6.2 (262)	43.5 (255)	7.1 (350)	45.3 (345)	4.6 (331)	37.5 (320)
Yes	5.0 (14)	50.5 (14)	6.6 (29)	43.8 (29)	5.2 (17)	36.7 (16)
Benign prostate condition[c]						
No	6.3 (243)	44.7 (240)	6.9 (332)	44.3 (328)	4.6 (327)	37.4 (317)
Yes	5.8 (41)	43.9 (38)	7.3 (57)	50.7 (56)	4.9 (21)	40.1 (20)
Vasectomy[c]						
No	6.2 (274)	44.4 (268)	7.1 (304)	46.3 (298)	4.6 (330)	37.6 (319)
Yes	5.5 (19)	40.2 (18)	6.6 (88)	40.9 (89)	4.5 (22)	35.4 (21)

[a] Adjusted for age (in single years).
[b] In Asian-Americans, the 3α-diol G levels by quartiles of physical activity after adjustment for current BMI were 4.6, 4.7, 5.1, and 5.1 ($P = 0.24$). *P*s in African-Americans and whites were >0.05 for 3α-diol G. All *P*s for AG were >0.05. METS, metabolic equivalents.
[c] All *P*s were >0.05.
[d] In African-Americans, *P* for trend was <0.05 for 3α-diol G. In Asian-Americans, *P* for trend was <0.05 for AG. All other *P*s were >0.05.

Table 3 Age-adjusted[a] mean concentrations of 3α-diol G (ng/ml) and AG (ng/ml) by current height and BMI (number of subjects in each category given in parentheses)

	African-Americans		Whites		Asian-Americans	
	3α-diol G	AG	3α-diol G	AG	3α-diol G	AG
Height						
≤166	6.7 (17)	44.7 (17)	8.2 (14)	55.5 (14)	4.3 (120)	36.8 (116)
>166–172	6.3 (91)	43.7 (88)	7.2 (124)	44.4 (122)	4.7 (199)	37.5 (191)
>172–177	5.7 (85)	41.7 (82)	6.9 (109)	45.5 (109)	5.6 (34)[b]	40.1 (34)[b]
>177 cm	6.4 (100)	46.6 (99)	6.8 (145)	44.2 (142)		
P for trend	0.54[c]	0.95[c]	0.19[c]	0.85[c]	0.0003	0.09
BMI						
≤23.14	5.4 (48)	44.6 (46)	6.1 (85)	42.8 (84)	3.9 (127)	35.0 (120)
>23.14–25.14	6.3 (61)	46.8 (61)	6.9 (106)	45.7 (105)	5.1 (96)	41.0 (93)
>25.14–27.4	6.7 (66)	43.9 (66)	7.3 (107)	51.6 (106)	5.1 (78)	37.3 (76)
>27.4	6.2 (117)	43.0 (112)	7.7 (94)	39.5 (92)	5.1 (47)	38.9 (47)
P for trend	0.42	0.97	0.02	0.21	0.0001	0.12
Age- and BMI-adjusted means	6.1	44.0	6.9	44.7	4.8	37.8

[a] Adjusted for age (in single years).
[b] Combined for quartiles 3 and 4.
[c] Combining quartiles 1 and 2 in the calculations yielded *P* trends of 0.33, 0.50, 0.57, and 0.94, respectively, for 3α-diol G and AG in African-American and white men.

justment for current BMI, as seen in Table 3. The age- and BMI-adjusted mean levels of 3α-diol G in African-Americans, whites, and Asian-Americans were 6.1, 6.9, and 4.8 ng/ml, respectively; the age- and BMI-adjusted mean levels of AG in African-Americans, whites, and Asian-Americans were 44.0, 44.7, and 37.8 ng/ml, respectively.

Discussion

There are strong suggestions in the literature of an androgenic etiology for prostate cancer, but the specific manner in which androgens influence prostate cancer risk is not well understood (19). A long-standing difficulty in this research is the reliance on circulating levels of the active androgens (T and DHT) as markers of the exposure of prostate tissues to endogenous steroid hormones. The current thinking is that serum 3α-diol G may be a better marker for DHT levels and 5α-reductase activity in the prostate than serum levels of T or DHT (7). However, we are not aware of data correlating serum levels of 3α-diol G with either tissue levels of DHT or 3α-diol G or with the conversion of T to DHT within the prostate. Although most previous studies measured blood 3α-diol G levels only, we also quantified serum AG levels to investigate whether either of the

two metabolites would better characterize 5α-reductase activity and androgen action. The clearer effects of age, race, and BMI on 3α-diol G levels than on AG levels in this study may be attributable partly to the differences in pathways leading to the formation of 3α-diol G and AG from T and DHT levels (7, 8).

The effects of age on these two 5α-reductase metabolites have been investigated mainly among whites and not in non-white populations. In this study, we observed significant and consistent reductions in 3α-diol G levels with increasing age, ~1.4% per year between ages 35 and 89 years of age. In the three race groups under study, 3α-diol G levels were 17–34% lower among men 75 years or older compared with those 60 years or younger. The magnitude of reductions in 3α-diol G levels in our study are compatible with those reported in three previous studies of primarily white men of comparable ages (10, 13, 14). In the study by Belanger *et al.* (14), levels of AG were ~30% lower in 80-year-old men compared with 40-year-old men, similar to our results among whites. Although a few studies (2, 9, 20) have included non-white subjects, we are not aware of published data on the effects of age on levels of 3α-diol G and AG in Asian-Americans and African-Americans.

Results from this study add to the sparse literature that has demonstrated racial differences in levels of 3α-diol G and AG, in particular, lower levels of these metabolites in Asian men (9, 20). In both previous studies, men in their twenties living in Hong Kong (20) or Japan (9) were compared with whites and African-American men of similar ages in the United States. Our study of older men also showed that the levels of 3α-diol G and AG were significantly lower in Asian-American men compared with white and African-American men in each of the age groups investigated. However, levels of 3α-diol G were statistically significantly higher in white men compared with African-American men, whereas levels of AG did not differ between the two groups. Our findings of higher serum 3α-diol G levels in whites than in African-Americans are compatible with those reported by Ross *et al.* (9), but both of these results are unexpected. We have hypothesized that African-American men, at highest risk of prostate cancer, would exhibit greater 5α-reductase activity than other racial groups who are at lower risk of this cancer. One interpretation is that very low levels of 3α-diol G may contribute, in part, to the lower risks of prostate cancer among Asians. The absence of a consistent linear relationship between levels of 3α-diol G and prostate cancer risk does not necessarily argue against the hypothesis. We have little understanding of the tissue concentration of DHT needed to activate androgen receptor binding and to induce the cascade of events in the androgen signaling pathway that will lead to proliferation of prostate cells. More importantly, 3α-diol G is only one component of the very complex hormonal milieu that influences prostate cancer risk.

Reasons for the racial differences, in particular, the lower levels of 3α-diol G and AG levels in Asian-American men, are not known. Environmental influences, genetic control, and an interplay of genetic and environmental factors are likely explanations for these differences. Of the lifestyle factors we investigated, body size emerged as an important determinant of 3α-diol G levels. In the study by Field *et al.* (10), increasing BMI was also associated with increasing levels of 3α-diol G such that the levels were 22% higher among men in the highest compared with the lowest quintile of BMI. As in the study by Field *et al.* (10), levels of AG were not influenced by BMI in our study. The strong positive association between 3α-diol G levels and BMI is somewhat surprising because we and others have observed strong inverse associations between BMI and levels of T, DHT, and SHBG (10, 12, 21).

It is of interest that a specific missense mutation, involving the substitution of valine (V) with leucine (L) at codon 89 in the steroid *5α-reductase type II* (*SRD5A2*) gene has been found to influence circulating levels of 3α-diol G (22). Specifically, among 102 Asian men from Singapore, Hawaii, and Los Angeles, 3α-diol G levels were highest among men who were valine homozygotes (VV), intermediate among valine heterozygotes (VL), and lowest among leucine homozygotes (LL). Moreover, the prevalence of LL homozygotes was highest in Asians (22%), intermediate in Latinos (15%), and substantially lower in African-American (3%) and whites (4%), providing a possible explanation for the lower 3α-diol G levels in Asians (22). Although the relation between tissue androgen levels and this missense mutation is uncertain, investigation of the possible associations between BMI, 3α-diol G levels, and the V89L substitution in the *SRD5A2* gene in healthy men and those with prostate cancer is warranted. Further studies are needed to determine whether the lower rates of prostate cancer among Asian men may be explained in part by their higher prevalence of LL genotype at the V89L substitution of the *SRD5A2* gene and their generally lower BMI. Both of these factors may predispose, in part, to their substantially lower levels of 3α-diol G levels, which reflect 5α-reductase activity and subsequently lower prostate cancer risk.

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