Racial Variation in Insulin-Like Growth Factor-1 and Binding Protein-3 Concentrations in Middle-Aged Men[1]

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Abstract

African-American men have the highest and Asian-American men have the lowest prostate cancer incidence rates in the United States; internationally, rates for the Asian continent are among the lowest. Higher insulin-like growth factor (IGF)-1, which participates in the control of cellular growth and differentiation and is modulated by IGF-binding protein-3 (IGFBP-3), was associated with an increased prostate cancer risk in three recent studies. We, therefore, investigated whether plasma levels of IGF-1 and IGFBP-3 vary by race in United States men selected from among members of the Health Professionals Follow-up Study who were 47–78 years old in 1993–1995 when they provided blood ($n = 18{,}000$). All of the men who described their major ancestry as African American ($n = 63$) and a random sample of 75 Asians and 75 Caucasians were invited to provide a second blood sample in 1997, of whom 42, 52, and 55, respectively, did so. IGF-1 and IGFBP-3 concentrations were determined by ELISA. We used nonparametric methods to assess racial variation in age-adjusted levels. Caucasians had the highest median IGF-1 level (224 ng/ml), followed by Asians (208 ng/ml) and African Americans (205 ng/ml). Median IGFBP-3 concentration was similar between Caucasians and Asians but was more than 13% lower in African Americans. Median molar IGF-1:IGFBP-3 ratio was greatest in Caucasians and lowest in Asians. The lower IGF-1 blood levels relative to IGFBP-3 levels among Asian men are consistent with their lower prostate cancer incidence. Although differences in circulating IGF-1 do not seem to account for the greater prostate cancer risk among African-American men, their absolute lower levels of IGFBP-3 may be contributory.

Introduction

African-American men have the highest and Asian-American men have the lowest prostate cancer incidence rates in the United States (1) and, internationally, prostate cancer rates for countries comprising the Asian continent are among the lowest (2). Three recent studies (3–5) observed that men with higher plasma IGF-1[3] levels are at greater risk for prostate cancer. Whether racial variation in components of the IGF pathway is a possible explanation for the prostate-cancer risk gradient by race is unknown.

IGF-1 is involved in the regulation of cellular growth and differentiation *in vivo* and is mitogenic in normal prostate and tumor cells *in vitro* (6, 7). IGFBP-3 is a carrier protein that modulates the effect of IGF-1 by preventing binding of the hormone to IGF or insulin receptors through high-affinity coupling (8). Independent of IGF-1 and IGF-1 receptors, IGFBP-3 has been shown to induce apoptosis (9). Given the two regulatory roles attributed to IGFBP-3, a lower molar ratio of IGF-1:IGFBP-3 as well as a higher absolute level of IGFBP-3 are measurable possible indicators of cellular growth control.

Using an approach similar to that of Ross *et al.* (10) to explore androgen variation by race, we examined heterogeneity in plasma levels of IGF-1 and IGFBP-3 by racial group in a sample of male health professionals ages 47–78 years old who described their major ancestry as African American, Asian, or Caucasian.

Materials and Methods

Participants for this analysis were selected from among members of the Health Professionals Follow-up Study, an on-going prospective cohort study among 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists, 40–75 years old at enrollment in 1986. At baseline, the men completed a semiquantitative food frequency questionnaire and provided information on demographics, life-style factors, and medical history. In 1993–95, approximately 18,000 of the men provided a blood specimen. After receipt by overnight courier, the blood, which was collected in tubes containing sodium EDTA and chilled during transport, was centrifuged, aliquoted into plasma, erythrocytes, and buffy coat, and stored in liquid nitrogen freezers.

On the baseline questionnaire, participants reported their major ancestry as southern European, Scandinavian, other Caucasian, Afro-American, Asian/Oriental, or other origin. Surnames for men who indicated Asian/Oriental ancestry included those from the Indian subcontinent and the Middle East, as well

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[3] The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF-binding protein.

Table 1 Median age-adjusted[a] participant characteristics and plasma IGF-1 and IGFBP-3 concentrations and ratio by self-described race, Health Professionals Follow-up Study

Characteristic	Race			P^b
	African American	Asian	Caucasian	
No.	42	52	55	
Age (yr)	65.7	58.9	62.2	0.07
Body mass index (kg/m^2)	25.5	23.7	24.5	0.01
Height (inches)	69.4	66.8	70.4	<0.0001
Waist circumference (inches)	37.2	34.6	36.9	0.0009
IGF-1 (ng/ml)				
Median	205[c]	208	224[c]	0.08
Mean ± SD	205 ± 74	213 ± 70	239 ± 74	
Range	86–382	83–372	53–440	
IGFBP-3 (ng/ml)				
Median	3373[d,e]	3926[d]	3868[e]	0.01
Mean ± SD	3457 ± 1005	3891 ± 857	3879 ± 881	
Range	1494–7099	1570–5964	1506–6497	
Molar ratio IGF-1:IGFBP-3				
Median	0.23	0.21[f]	0.24[f]	0.13
Mean ± SD	0.23 ± 0.06	0.22 ± 0.06	0.24 ± 0.05	
Range	0.11–0.35	0.09–0.41	0.13–0.37	

[a] Age-adjustment by residual analysis.
[b] Nonparametric Kruskal-Wallis hypothesis test of no difference in the distributions of factor by race.
[c] For the comparison of IGF-1 level between African Americans and Caucasians using the Wilcoxon rank sum test: $P = 0.037$.
[d] For the comparison of IGFBP-3 level between African Americans and Asians using the Wilcoxon rank sum test: $P = 0.009$.
[e] For the comparison of IGF-1 level between African Americans and Caucasians using the Wilcoxon rank sum test: $P = 0.012$.
[f] For the comparison of the molar ratio of IGF-1:IGFBP-3 between Asians and Caucasians using the Wilcoxon rank sum test: $P = 0.046$.

as China, Japan, and Korea. From among the men who: (*a*) provided blood; (*b*) responded to the question on race and indicated only one major ancestry; (*c*) did not report a diagnosis of cancer (except nonmelanoma skin cancer); and (*d*) lived in the continental United States (for rapid return of blood samples), all of those who considered themselves to be African American ($n = 63$) were identified, and a random sample of 75 Asian ($n = 108$) and 75 Caucasian ($n = 14{,}665$) men were chosen.

Because blood levels measured once may not be representative of typical levels over time, we measured IGF-1 and IGFBP-3 at two time points. In December 1996, the 213 men were mailed a letter requesting a second blood specimen. Nonresponses were sent a second letter. Those who agreed to participate (80%), were sent a kit with the materials needed to have their blood drawn and returned by overnight courier. Of these, 150 men returned a blood kit between January and September 1997. The samples were processed as described for the original collection. Blood specimens for both time periods were usable for 149 of the men.

IGF-1 and IGFBP-3 concentrations were determined by ELISA (Diagnostic Systems Laboratory Inc., Webster, TX) with samples for the racial groups randomly interspersed to avoid systematic differences due to laboratory variation. Mean intrapair coefficients of variation for blinded quality control samples were 13.2% for IGF-1 and 11.6% for IGFBP-3. IGF-1 (interclass correlation coefficient, 0.98) and IGFBP-3 (0.96) concentrations have been shown to be stable in chilled whole blood for 24–36 h, the approximate time between blood draw and arrival by overnight courier, compared with immediate processing and freezing (3). The Spearman partial correlation coefficients (adjusting for race) for time 1 *versus* 2 (mean, 3.0 ± 0.5 years apart) was 0.70 for IGF-1, 0.68 for IGFBP-3, and 0.59 for their ratio. For all of the analyses, the mean of time 1 and time 2 concentrations were used.

Because the mean age differed among the three racial groups, and IGF-1 and IGFBP-3 diminish with increasing age, we adjusted for age by regressing IGF-1 or IGFBP-3 level on age and recentering the residuals at the predicted plasma level for the mean age among the 149 men. To evaluate differences in the age-adjusted IGF-1 and IGFBP-3 concentrations or the age-adjusted molar ratio of IGF-1:IGFBP-3 among the three and between any two racial groups, the Kruskal-Wallis test and Wilcoxon rank-sum test were used. All of the analyses were conducted using SAS software version 6.12 (SAS Institute, Cary, NC).

Results

A total of 42 African-American, 52 Asian, and 55 Caucasian men ranging in age from 47 to 78 years were included in the analysis. Demographic characteristics of the participants are shown in Table 1. Caucasians had the highest median age-adjusted IGF-1 level followed by Asians and African Americans (Table 1). Median age-adjusted IGFBP-3 concentration was similar between Caucasians and Asians, but was 13% lower in African-American men. The median age-adjusted molar ratio of IGF-1:IGFBP-3 was highest in Caucasians and lowest in Asians. Excluding seven men for whom either the time 1 or time 2 age-adjusted molar ratio of IGF-1:IGFBP-3 was lower or greater than 2.5 times the SD from the overall mean, did not change the relative ranking of medians by race for age-adjusted IGF-1, IGFBP-3, or their molar ratio.

Discussion

Asian men had the lowest ratio of IGF-1:IGFBP-3, possibly reflecting the circulating free proportion of IGF-1, which is consistent with their lower incidence of prostate cancer nationally and internationally. The ratio for African-American men

was intermediate between Caucasians and Asians, an observation that is not compatible with the hypothesis that the excess prostate cancer incidence and mortality rates among African Americans result from having higher levels of available IGF-1 compared with other racial groups. Possible explanations for the inconsistency between the patterns of the IGF-1:IGFBP-3 ratio and prostate cancer incidence for African Americans compared with other racial groups are that the IGF-1:IGFBP-3 ratio might not be important for racial variation in prostate cancer incidence or that the ratios we observed in these middle-aged and elderly participants might pertain only to older ages, a point in life possibly not relevant for racial differences in prostate carcinogenesis.

The African-American men in this study had a 13% lower median IGFBP-3 level compared with either Asians or Caucasians. A lower mean circulating IGFBP-3 level, also on the order of 13%, among African-Americans compared with Caucasians was observed previously in a preliminary study of 105 middle-aged men at increased risk of prostate cancer (11) and in a study of 12 black and 12 white premenopausal women (12), although the difference in the latter study was not statistically significant. Despite the lack of a clear difference between African Americans and other racial groups in the ratio of IGF-1:IGFBP-3, because IGFBP-3 seems to exert growth control via a second mechanism that is independent of IGF-1 and IGF-1 receptors (9), the lower absolute IGFBP-3 levels in African-American men could have biological consequence for tumor promotion or progression.

Our finding for IGFBP-3 level in Asian men compared with Caucasian men differs from a study of 26 Asian and 27 Caucasian healthy young adults, in which IGFBP-3 levels were statistically significantly lower in the Asian participants (13). Any differences among these studies in the findings for IGF-1 and IGFBP-3 in comparing racial groups may be equally plausibly due to heterogeneity in the underlying ethnic composition of participants within a given racial group, as well as dissimilar age and gender composition, and chance variation.

Because of the relatively small sample sizes and the possible influence of values at the extremes of each of the plasma distributions, we conservatively estimated the differences in median age-adjusted plasma levels of IGF-1 and IGFBP-3 using nonparametric methods. However, we used a parametric method to adjust plasma levels for age. Because age differed notably by race and IGF-1 levels are known to decline with age, we believed it was important to adjust for age before comparing the medians and means of IGF-1 and IGFBP-3 levels by race. Nevertheless, without adjustment for age, the racial variation patterns were similar and the *P*s for the test of no difference among the three races were comparable with the age-adjusted results (0.11, 0.006, 0.14 for IGF-1, IGFBP-3, and their ratio, respectively). We did not adjust for differences in the distribution of anthropometric factors (*e.g.*, body mass index, height, waist circumference) by race because the magnitude of these factors may be a manifestation of IGF-1 and IGFBP-3 levels. Alcohol intake, which may be correlated with IGF-1 levels (14), varied by race, but the predicted IGF-1 and IGFBP-3 levels for each group showed the same ordering by race before and after controlling for alcohol by linear regression.

Racial heterogeneity in circulating IGF-1 and IGFBP-3 levels and their ratio was evident in this sample of men drawn from the Health Professionals Follow-up Study. The lower IGF-1 plasma levels relative to IGFBP-3 levels among Asian men are consistent with their lower prostate cancer incidence. Although differences in circulating IGF-1 level do not seem to account for the greater prostate cancer risk among African-American men, their absolute lower levels of IGFBP-3 may be contributory. In addition to prostate cancer, components of the IGF axis may also be important in lung (15), breast (16), and colorectal (17) cancers. Although differences in smoking patterns, timing of maturation and reproduction, and access to and seeking screening and treatment are major contributors to the variation in rates of these cancers among Caucasians, African Americans, and Asians, the racial variation in IGF-1 and IGFBP-3 that we observed in this group of older men is also largely consistent with the racial patterns of higher incidence and mortality of lung and colorectal cancers and mortality from breast cancer among African Americans compared with Caucasians and Asians (18). Given the heterogeneity of individuals within racial groups and that IGF-1 levels are known to decline with age, whether the variation by race in these components of the IGF pathway that we observed in older men may be generalized to men and women of all ages who would describe their ancestry similarly is unknown.

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