Dietary and Lifestyle Correlates of Plasma Insulin-Like Growth Factor-I (IGF-I) and IGF Binding Protein-3 (IGFBP-3): The Multiethnic Cohort

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Abstract

High circulating concentration of insulin-like growth factor-I (IGF-I) and low circulating concentration of IGF binding protein-3 (IGFBP-3) have been associated with increased risk for breast, prostate, and colorectal cancers. Building on previous work in the Multiethnic Cohort (MEC) showing significant differences in IGF-I levels across racial/ethnic groups, we investigated which lifestyle and dietary factors are associated with levels of IGF-I and IGFBP-3 in a random sample of 1,000 MEC participants, which included Native Hawaiian, African American, Japanese, Latino, and White men and women. Crude analyses confirmed the existence of differences in protein levels with race/ethnicity, sex, age, and body size. Reproductive, physical activity, smoking, and diet variables had less consistent effects. In multivariate analyses, IGF-I levels were lower and IGFBP-3 were higher in females versus males. IGF-I and IGFBP-3 declined with increasing age in both genders. Women in the highest quartile of body mass index showed depressed IGF-I and IGFBP-3 levels; in men, height was significantly positively associated with both proteins. In women, alcohol was directly associated with IGFBP-3. Both proteins were lowest among female Latinos. IGF-I was highest among female African Americans. In men, IGFBP-3 was lowest among African Americans. Overall, although these factors were statistically significant determinants of IGF-related protein levels, they did not explain much of the variation in these levels. A positive correlation was found between IGF-I levels (ng/mL) and colon cancer incidence rates (per 100,000) within the MEC by race/ethnicity for both sexes but not for either breast or prostate cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1444–51)

Introduction

The insulin-like growth factor (IGF) system comprises a set of proteins that regulate vital cell processes in myriad tissues, including breast, colon, and prostate. The two growth factors, IGF-I and IGF-II, interact with six known IGF binding proteins (IGFBP), which regulate binding to the two IGF receptors (IGF-IR and IGF-IIR). The binding proteins are in turn regulated by a group of IGFBP proteases and recently identified IGFBP-related proteins (1). The physiology of the IGF system has been reviewed recently (2-4). Biological evidence has shown that IGF signaling plays important roles in several cancer cell lines, such as breast, prostate, and colon (reviewed in refs. 4, 5). The exact mechanisms by which IGF-related proteins play roles in transformation and progression have not been fully elucidated. One hypothesis, which is based on the assumption that circulating IGF-I levels reflect tissue activity, links high bioavailable IGF-I to cancer risk. Because the majority of IGF-I in the circulation is bound to IGFBP-3, several recent epidemiologic studies have targeted high IGF-I and low IGFBP-3 as a potential biomarker of increased cancer risk. IGFBP-3 has also been suggested to play an independent role (reviewed recently in ref. 6). Results from these studies have been mixed, with the strongest evidence for associations between high bioavailable IGF-I and breast, colorectal, and prostate cancers coming from case-control studies nested within the Physicians' and Nurses' Health Studies (7-10). However, several studies have shown no direct association between IGF-I or IGFBP-3 levels and incidence of cancer or have found associations of limited strength (11-14).

Building on previous work on female participants in the Multiethnic Cohort (MEC), which showed that plasma IGF-I levels varied significantly across racial/ethnic groups (15), we did a cross-sectional study on a large, random sample of participants in a population-based cohort study to determine which lifestyle and dietary factors are associated with plasma levels of IGF-I and IGFBP-3 in each sex, whether we could validate an independent racial/ethnic relationship with IGF levels after adjustment for potential confounders, and whether trends in these levels across racial/ethnic groups (African American, Japanese, Native Hawaiian, Latino, and White) lie in parallel with incidence rates of colorectal, breast, and prostate cancers in the underlying cohort.

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Materials and Methods

Study Subjects. Participants included in these analyses were selected from a large population-based cohort study, the Hawaii and Los Angeles MEC. The primary aim of this study was to evaluate the dietary and other environmental contributions to the racial/ethnic variability in cancer risk. The MEC consists of 215,251 volunteers of both sexes, mainly Japanese, Whites, and Native Hawaiians in Hawaii and African Americans and Latinos in Los Angeles. Subjects were recruited between 1993 and 1996 primarily through drivers' license files. All participants were between ages 45 and 75 years at the time of enrollment. Baseline data were collected on cohort participants via a mailed questionnaire that contained five sections: (*1*) background, including medical history and family cancer history; (*2*) diet history; (*3*) medication use; (*4*) physical activity; and, for women, (*5*) female reproductive history, including use of hormones. Blood was collected on a subcohort of ~5,000 randomly selected participants after stratification on sex and race/ethnicity. These participants are being used as controls in nested case-control studies. The draw was completed in the morning, typically at the person's home, after informed consent was obtained. Handling of samples was achieved with attention to minimization of time between draw and processing. Ninety percent of samples were processed within 4 hours of the blood draw, and 98% were processed within 24 hours of draw. Sodium heparin was used as an anticoagulant in the blood collection tubes. The participation rate for providing a blood sample was 66% and did not vary greatly across different racial/ethnic groups. Details of the MEC study have been published previously (16).

Incident cancer diagnoses are identified through annual linkage of the cohort with files of the Hawaii Tumor Registry and the Cancer Surveillance Program in Los Angeles (both are Surveillance, Epidemiology, and End Results registries and include annual death certificate searches within their respective states for possible missed cases). Linkage is also done annually with the California Tumor Registry and the Hawaii and California death certificate files and periodically with the National Death Index.

We measured plasma IGF-I and IGFBP-3 in a random sample of 1,000 MEC blood subcohort participants [100 for each of 10 sex-racial/ethnic groups with equal representation of each 5-year age group at blood draw (>45 years for men and >55 years for women)]. Women who reported that they were taking estrogen replacement therapy at the time of blood draw were excluded. There were 955 subjects who had complete IGF-I and IGFBP-3 measurements, of whom 926 had complete questionnaire data.

IGF-I and IGFBP-3 Measurements in Plasma. Samples were analyzed blind as to race/ethnicity and sex of the participants. To reduce the effect of laboratory variability, each analytic batch included equal numbers of subjects from each sex-racial/ethnic group. IGF-I and IGFBP-3 were measured by ELISAs from Diagnostic System Laboratories (Webster, TX). IGF-I assays included an acid-ethanol precipitation of IGF-I binding proteins to avoid interference of IGFBPs with the IGF-I assay. The average overall intrabatch coefficients of variation were 6.0% and 5.2% for IGF-I and IGFBP-3, respectively. The average overall interbatch coefficients of variation were 13.9% and 10.6% for IGF-I and IGFBP-3, respectively.

Data Analysis. ANOVA and analysis of covariance were used to test for differences in crude and adjusted mean IGF-related protein levels by sex-racial/ethnic group and covariate level. We assumed homogeneity of effects across racial/ethnic groups and did not correct for differences in the sampling proportion used for each group. The hormone measurements were transformed via the natural log to produce the best approximate normal distribution. These values have been transformed back to normal physiologic levels in the tables for the purpose of presentation. Diet intake data were adjusted for total calorie intake by the calculation of nutrient densities. Nutrient densities were calculated by multiplying the daily diet component intake in grams by the inverse of total daily energy intake in calories (17). Means presented are least-squares means (LS means). Multiple linear regressions were done to determine which covariates were associated with IGF-I, IGFBP-3, and IGF-I-IGFBP-3 molar ratio (IGFMR) levels. We used past reports (18-23) and the known biology about the IGF-I pathway (for review, see refs. 24, 25) to guide the selection of variables to be considered in the models. The R^2 selection method was used in conjunction with Mallow's Cp to identify important associated variables. Plots of the Cp statistic, as well as examination of incremental changes in the R^2, assisted in the final determination of variables for inclusion in the models. Although the sampling proportions were not equal for each racial/ethnic group, we adjusted the models for this variable and therefore expect the results to be generalizable to the entire cohort. All analyses were done in SAS version 9 (SAS Institute, Cary, NC).

Results

Table 1 shows the means and 95% confidence limits (95% CL) for the main characteristics and the crude plasma IGF-related protein levels for the 465 healthy women and 490 healthy men with complete IGF-related protein measurements by racial/ethnic group. Body size characteristics such as height, weight, and body mass index (BMI) differed significantly across racial/ethnic groups. African American and Latino women had higher mean BMI scores (29.3 and 29.1 kg/m^2, respectively) than Native Hawaiians (28.7 kg/m^2), Whites (26.2 kg/m^2), and Japanese (24.0 kg/m^2). Comparison of the two extreme groups yielded $P < 0.0001$. In men, the Native Hawaiians had the highest mean BMI (29.1 kg/m^2) followed by the other four racial/ethnic groups in roughly parallel order as seen in women (Native Hawaiians versus Japanese, $P_{diff} < 0.0001$).

In a crude analysis, race/ethnicity, sex, age, and body size were significantly associated with plasma IGF-I levels. To begin, men had higher LS mean plasma IGF-I than women. The mean IGF-I (adjusted for race/ethnicity) for males was 177.6 ng/mL and the mean plasma IGF-I for females was 142.3 ng/mL ($P_{diff} < 0.0001$). Adjustment for BMI did not significantly attenuate this result. The difference in IGFBP-3 across gender was in the opposite direction (women had higher LS

Table 1. Mean (95% CL) for main characteristics and plasma IGF-I, IGFBP-3, and IGFMR levels from 955 MEC participants by sex and racial/ethnic group

	Native Hawaiian	African American	Japanese	Latino	White	*P**
Females						
No. subjects (% women)	77 (17)	96 (21)	100 (22)	99 (21)	93 (20)	
Age, y	66.7 (65.1, 68.3)	67.6 (66.2, 69.1)	69.1 (67.7, 70.6)	67.5 (66.1, 69.0)	68.2 (66.8, 69.7)	0.23
Height, in.	63.8 (63.3, 64.3)	64.3 (63.8, 64.8)	60.6 (60.2, 61.1)	62.7 (62.2, 63.2)	64.5 (64.0, 65.0)	<0.0001
Weight, lb.	166 (159, 173)	172 (166, 179)	125 (119, 132)	162 (155, 168)	155 (148, 161)	<0.0001
BMI, kg/m^2	28.7 (27.5, 29.9)	29.3 (28.3, 30.4)	24.0 (23.0, 25.1)	29.1 (28.0, 30.1)	26.2 (25.1, 27.3)	<0.0001
IGF-I, ng/mL	144 (131, 159)	157 (144, 171)	147 (135, 160)	122 (112, 133)	142 (130, 155)	0.002
IGFBP-3, ng/mL	2,854 (2,641, 3,084)	2,571 (2,399, 2,756)	2,871 (2,682, 3,073)	2,218 (2,072, 2,375)	2,641 (2,641, 3,041)	<0.0001
IGFMR	0.19 (0.17, 0.20)	0.23 (0.21, 0.24)	0.19 (0.18, 0.20)	0.21 (0.19, 0.22)	0.19 (0.17, 0.20)	0.0006
Males						
No. subjects (% men)	98 (20)	98 (20)	98 (20)	99 (20)	97 (20)	
Age, y	64.4 (62.7, 66.2)	65.1 (63.3, 66.9)	65.2 (63.4, 67.0)	65.2 (63.4, 67.0)	65.3 (63.5, 67.1)	0.96
Height, in.	68.9 (68.4, 69.4)	70.0 (69.5, 70.5)	66.2 (65.7, 66.8)	68.0 (67.4, 68.5)	69.3 (68.8, 69.8)	<0.0001
Weight, lb.	197 (190, 203)	195 (189, 202)	156 (150, 163)	178 (172, 185)	188 (181, 194)	<0.0001
BMI, kg/m^2	29.1 (28.2, 30.0)	28.0 (27.1, 28.9)	25.1 (24.2, 26.0)	27.2 (26.3, 28.1)	27.5 (26.6, 28.4)	<0.0001
IGF-I, ng/mL	190 (174, 207)	175 (160, 191)	177 (162, 193)	167 (153, 182)	180 (165, 197)	0.37
IGFBP-3, ng/mL	2,713 (2,531, 2,908)	2,375 (2,216, 2,546)	2,652 (2,474, 2,843)	2,481 (2,316, 2,659)	2,769 (2,582, 2,969)	0.01
IGFMR	0.26 (0.24, 0.28)	0.27 (0.26, 0.29)	0.25 (0.23, 0.27)	0.25 (0.23, 0.27)	0.24 (0.23, 0.26)	0.14

*P for testing homogeneity of means across race/ethnicity derived from ANOVA and analysis of covariance models.

mean IGFBP-3 than men), but this difference was not statistically significant. The race/ethnicity–adjusted and BMI-adjusted mean IGFBP-3 was 2,595 ng/mL for males and 2,671 for females ($P_{diff} = 0.22$; data not shown). Race/ethnicity was a statistically significant predictor of IGF-I in women and IGFBP-3 in both sexes. The age-adjusted LS mean IGF-I levels (ng/mL) by race/ethnicity for females were 154.4 for African Americans, 148.5 for Japanese, 144.8 for Native Hawaiians, 143.8 for Whites, and 122.8 for Latinos ($P_{diff\ African\ Americans\ to\ Latinos} < 0.0001$) and for males were 190.1 for Native Hawaiians, 180.4 for Whites, 180.0 for Japanese, 176.5 for African Americans, and 169.3 for Latinos ($P_{diff\ Native\ Hawaiians\ to\ Latinos} = 0.08$ and $P_{diff\ men\ to\ women} < 0.0001$; Table 2). In a race/ethnicity–adjusted model, both IGF-I and IGFBP-3 declined significantly with increasing age (IGF-I, $P_{linear\ trend\ men} = 0.001$ and $P_{linear\ trend\ women} = 0.001$; IGFBP-3, $P_{linear\ trend\ men} < 0.0001$ and $P_{linear\ trend\ women} < 0.0001$). Table 2 illustrates this finding and shows further that the decline in IGFBP-3 was somewhat stronger than the decline in IGF-I, contributing to a very slight but nonsignificant increase in IGFMR. No statistically significant interactions were found among race/ethnicity, age, BMI, and weight on their effects on IGF-I or IGFBP-3 in sex-stratified models. However, with both sexes combined, suggestions of interactions between race/ethnicity and BMI, race and age, and sex and age were evident and merit further investigation.

We observed that (see Table 2) plasma IGF-I and IGFBP-3 increased with height in men (IGF-I, $P_{linear\ trend\ men} = 0.002$; IGFBP-3, $P_{linear\ trend\ men} = 0.003$). In women, we observed that those with very high body weight and/or BMI (>29 kg/m^2 in women) had depressed IGF-I and IGFBP-3 levels. In women, increasing parity was nonsignificantly associated with declines in both IGF-related protein levels. No clear statistically significant relationship could be seen between these proteins and physical activity or smoking. Of the diet variables, total fat and saturated fat intakes were significantly inversely associated with IGFBP-3 in men but not in women; they were not associated with IGF-I in either sex. We further analyzed total fat by investigating the food sources of fat, including fat from meat, fat from poultry, and fat from dairy. The nonsignificant decrease in IGF-I in men seen with increasing intake of total fat and saturated fat becomes significant when looking at fat intake from meat sources (IGF-I, $P_{linear\ trend\ men} = 0.001$), whereas the trends in women remain nonsignificant. Alcohol intake (measured by quartile of alcohol intake density in g/1,000 kcal/d) was directly associated with IGFBP-3 in women and inversely with IGFMR in men.

The results of a sex-stratified multiple regression of IGF-I, IGFBP-3, and IGFMR on race/ethnicity, age, height, weight, BMI, parity, age at menarche, age at menopause, physical activity, smoking, and dietary variables indicated that age, race/ethnicity, and BMI were statistically significantly associated with IGF-I and IGFBP-3 among women (Table 3). In addition, alcohol was directly associated with IGFBP-3 in this group. The R^2 for the overall model in women was 0.08 for IGF-I and 0.16 for IGFBP-3. Race and BMI only were statistically significantly associated with IGFMR in women.

In men, age, height, fat from meat, and current smoking were significantly associated with IGF-I level; however, race/ethnicity was not (overall $R^2 = 0.08$; Table 3). For consistency, we added race to this model. Male plasma IGFBP-3 levels were significantly associated with race/ethnicity, age, height, fat from meat, and low-fat milk intake ($R^2 = 0.12$). Race/ethnicity, smoking, and alcohol were significantly associated with IGFMR in men.

We saw some evidence of correlation between LS mean IGF-I levels and colon cancer incidence rates within the MEC by race/ethnicity in both sexes (see Table 4). For example, the African American women have the highest LS mean IGF-I level (160 ng/mL) and the highest colon cancer rate (139 cases per 100,000).

Table 2. Age-adjusted and race/ethnicity–adjusted LS mean levels for IGF-I, IGFBP-3, and IGFMR by sex, race/ethnicity, age, height, BMI, parity, and lifestyle variables

		Females					Males			
		Variable	IGF-I	IGFBP-3	IGFMR		Variable	IGF-I	IGFBP-3	IGFMR
Race/ethnicity		Native Hawaiian	144.8	2,847	0.19		Native Hawaiian	190.1	2,709	0.26
		African American	154.4	2,586	0.22		African American	176.5	2,379	0.28
		Japanese	148.5	2,934	0.19		Japanese	180.0	2,678	0.25
		Latino	122.8	2,234	0.20		Latino	169.3	2,520	0.25
		White	143.8	2,836	0.19		White	180.4	2,794	0.24
		*P**	0.003	<0.0001	0.57		*P**	0.48	0.011	0.10
Age, y	Q1	<61	150.4	2,956	0.19	Q1	<57	189.1	2,851	0.25
	Q2	61–67	156.2	2,858	0.20	Q2	57–64	197.7	2,772	0.27
	Q3	68–72	132.9	2,461	0.20	Q3	65–71	166.7	2,538	0.24
	Q4	73+	131.9	2,461	0.20	Q4	72+	165.3	2,319	0.27
		P†	0.001	<0.0001	0.24		*P*†	0.001	<0.0001	0.23
Height, in.	Q1	<61	136.0	2592	0.20	Q1	<66	159.3	2340	0.25
	Q2	61–62	144.2	2747	0.20	Q2	66–67	171.3	2550	0.25
	Q3	63–64	147.6	2693	0.20	Q3	68–69	176.2	2770	0.24
	Q4	65+	141.8	2663	0.20	Q4	70+	195.8	2668	0.27
		P†	0.72	0.93	0.73		*P*†	0.006	0.02	0.24
BMI, kg/m^2	Q1	<23	149.6	2,579	0.22	Q1	<24	192.7	2,711	0.26
	Q2	23–25	155.1	2,928	0.20	Q2	24–26	180.9	2,613	0.26
	Q3	26–29	144.2	2,792	0.19	Q3	27–28	177.9	2,639	0.25
	Q4	30+	126.8	2,477	0.19	Q4	29+	168.9	2,524	0.25
		P†	0.03	0.31	0.06		*P*†	0.10	0.36	0.27
Parity		0–2 Children	146.2	2,731	0.20					
		3–4 Children	142.7	2,671	0.20					
		5+ Children	137.3	2,595	0.20					
		*P**	0.53	0.57	0.95					
Physical activity, h/wk vigorous work		0	145.2	2,702	0.20		0	180.2	2,587	0.26
		>0	134.7	2,596	0.19		>0	178.3	2,632	0.25
		*P**	0.13	0.33	0.49		*P**	0.81	0.61	0.44
Smoking		Never	144.3	2,635	0.20		Never	179.0	2,628	0.25
		Past	135.5	2,689	0.19		Past	186.0	2,606	0.27
		Current	151.1	2,799	0.20		Current	155.8	2,563	0.23
Energy intake, kcal/d		*P**	0.20	0.40	0.18		*P**	0.01	0.88	0.005
	Q1	<1,333	136.2	2,578	0.20	Q1	<1,591	174.2	2,638	0.25
	Q2	1,333–1,812	142.9	2,784	0.19	Q2	1,591–2,257	177.7	2,481	0.27
	Q3	1,813–2,441	142.6	2,685	0.20	Q3	2,258–2,894	175.2	2,602	0.25
	Q4	2,442+	148.2	2,655	0.21	Q4	2895+	189.7	2,729	0.26
		P†	0.22	0.92	0.17		*P*†	0.09	0.11	0.62
Alcohol intake density, g/1,000 kcal/d	Q1	<0.00015	139.2	2,495	0.21	Q1	<0.0002	188.1	2,609	0.27
	Q2	0.00015–0.00032	139.7	2,545	0.20	Q2	0.00021–0.0763	177.6	2,495	0.26
	Q3	0.00033–0.0684	138.4	2,740	0.19	Q3	0.07631–0.5555	176.9	2,559	0.26
	Q4	0.0685+	152.2	2,907	0.20	Q4	0.5556+	169.7	2,703	0.23
		P†	0.34	0.003	0.24		*P*†	0.36	0.33	0.02
Total fat intake density, g/1,000 kcal/d	Q1	<23	144.0	2,633	0.20	Q1	<29	185.4	2,876	0.24
	Q2	23–27	139.8	2,653	0.20	Q2	29–34	183.1	2,601	0.26
	Q3	28–38	142.5	2,721	0.20	Q3	35–39	178.4	2,461	0.27
	Q4	39+	143.3	2,622	0.20	Q4	40+	170.3	2,528	0.25
		P†	0.73	0.80	0.61		*P*†	0.15	0.001	0.18
Saturated fat intake density, g/1,000 kcal/d	Q1	<7	138.8	2,764	0.19	Q1	<8	184.2	2,877	0.24
	Q2	7–9	146.4	2,654	0.21	Q2	8–9	181.1	2,589	0.26
	Q3	10–11	143.7	2,748	0.19	Q3	10–11	176.9	2,560	0.26
	Q4	12+	138.7	2,572	0.20	Q4	12+	175.3	2,480	0.26
		P†	0.53	0.16	0.75		*P*†	0.23	0.01	0.25
Fat from meat intake density, g/1,000 kcal/d	Q1	<2.68	146.8	2,818	0.19	Q1	<3.58	183.9	2,734	0.25
	Q2	2.68–4.59	140.5	2,645	0.20	Q2	2.58–5.88	188.0	2,611	0.27
	Q3	4.60–6.92	141.1	2,601	0.20	Q3	5.89–8.12	178.6	2,626	0.25
	Q4	6.93+	141.6	2,643	0.20	Q4	8.13+	167.1	2,485	0.25
		P†	0.43	0.06	0.37		*P*†	0.001	0.003	0.28
Total protein intake density, g/1,000 kcal/d	Q1	<33	140.4	2,707	0.19	Q1	<33	169.9	2,692	0.23
	Q2	33–36	145.4	2,687	0.20	Q2	33–36	202.7	2,759	0.27
	Q3	37–40	146.0	2,661	0.20	Q3	37–40	175.6	2,557	0.26
	Q4	41+	139.3	2,651	0.20	Q4	41+	173.2	2,473	0.26
		P†	0.69	0.98	0.57		*P*†	0.60	0.05	0.23
Total dairy intake density, g/1,000 kcal/d	Q1	<51	138.9	2,664	0.19	Q1	<35	168.5	2,587	0.24
	Q2	51–98	141.9	2,634	0.20	Q2	35–73	181.1	2,612	0.26
	Q3	99–156	139.9	2,612	0.20	Q3	73–142	184.3	2,568	0.27
	Q4	157+	149.4	2,792	0.20	Q4	143+	183.3	2,684	0.25
		P†	0.48	0.27	0.86		*P*†	0.41	0.24	0.91

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Table 2. Age-adjusted and race/ethnicity–adjusted LS mean levels for IGF-I, IGFBP-3, and IGFMR by sex, race/ethnicity, age, height, BMI, parity, and lifestyle variables (Cont'd)

		Females					Males			
		Variable	IGF-I	IGFBP-3	IGFMR		Variable	IGF-I	IGFBP-3	IGFMR
Total milk intake density, g/1,000 kcal/d	Q1	<19	138.0	2,623	0.20	Q1	<16	163.5	2,622	0.23
	Q2	19–63	137.1	2,547	0.20	Q2	16–44	185.2	2,478	0.28
	Q3	64–119	141.0	2,671	0.20	Q3	45–103	187.3	2,671	0.26
	Q4	120+	154.3	2,868	0.20	Q4	104+	182.0	2,685	0.25
		P†	0.27	0.09	0.84		*P*†	0.66	0.16	0.42
Total low-fat milk intake density, g/1,000 kcal/d	L1	0	140.4	2,674	0.19	L1	0	178.5	2,693	0.25
	L2	1–15.5	137.7	2,684	0.19	L2	1–9.92	185.3	2,613	0.26
	L3	15.54–48.74	143.4	2,610	0.20	L3	9.93–35.19	186.9	2,463	0.28
	L4	48.75–98.12	146.5	2,621	0.21	L4	35.20–83.04	166.6	2,394	0.26
	L5	98.13+	151.9	2,793	0.20	L5	83.05+	180.2	2,649	0.25
		P†	0.20	0.74	0.18		*P*†	0.82	0.11	0.22
Vitamin D intake density from food sources, g/1,000 kcal/d	Q1	<38	139.0	2,636	0.20	Q1	<33	173.6	2,658	0.24
	Q2	38–64	141.6	2,690	0.19	Q2	33–58	173.0	2,590	0.25
	Q3	65–89	141.7	2,610	0.20	Q3	59–85	183.3	2,505	0.27
	Q4	90+	147.4	2,760	0.20	Q4	86+	187.5	2,701	0.26
		P†	0.14	0.12	0.73		*P*†	0.32	0.67	0.43
Calcium intake density from food sources, g/1,000 kcal/d	Q1	<308	139.7	2,642	0.20	Q1	<262	165.4	2,611	0.24
	Q2	308–389	137.8	2,654	0.19	Q2	262–333	183.1	2,568	0.27
	Q3	390–483	147.8	2,696	0.20	Q3	334–429	185.3	2,617	0.26
	Q4	484+	144.9	2,707	0.20	Q4	430+	184.1	2,653	0.26
		P†	0.43	0.34	0.93		*P*†	0.38	0.66	0.52

NOTE: The means presented are LS means of natural log-transformed hormone levels exponentiated back to physiologic levels.
*P for homogeneity, categorical variable.
†P for trend, continuous variable.

White and Latino women rest at the low end of both measures. No other cancer incidence comparison across races/ethnicities seemed to have any clear relationship in this crude analysis.

Discussion

Our results confirmed the existence of statistically significant associations between plasma IGF-I and IGFBP-3 levels with race/ethnicity, sex, age, and body size. We also found an inverse association of IGF-I and IGFBP-3 levels with fat intake in men, possibly driven by fat intake from meat sources, and a direct association between IGFP-3 levels and alcohol in women. In addition, we observed associations between current smoking and low IGF-I levels and between low-fat milk intake and low IGFBP-3 levels in men. Finally, we found ecological evidence supporting an association between IGF-I and colorectal but not breast or prostate cancer. Overall, our models have explained only a small fraction of the variance in hormone levels.

Several factors have been investigated as potential determinants of the IGF-related proteins. The extensive epidemiologic literature on the determinants of IGF-I and IGFBP-3 has been reviewed recently (24, 25). Dietary findings have pointed to associations between improved nutritional status and increasing circulating IGF-I and IGFBP-3 levels, the exact drivers of these associations remain elusive possibly due to difficulty in deciphering independent effects among highly correlated and inexactly measured covariates. In this analysis, our primary aims were to test in our multiethnic population the reproducibility of our previous racial/ethnic finding and to investigate the cross-sectional relationship between plasma IGF-I and IGFBP-3 with various lifestyle and dietary factors, which had been previously implicated in determining circulating levels of these proteins.

After adjustment for possible confounders, IGF-I and IGFBP-3 levels varied significantly by racial/ethnic group among women in our data. Among men, IGFBP-3 differed strongly across racial/ethnic groups, but IGF-I did not. In a previous article, we reported that race/ethnicity was independently associated with plasma IGF-I levels in women (15). We confirmed that circulating IGF-I levels in postmenopausal women were significantly lower in Latino women compared with African American, Native Hawaiian, and Japanese women. Few past studies had sufficient power to test for differences in IGF levels across race/ethnicity. However, several studies have suggested that Latino neonates, girls, and premenopausal women have lower IGF-I compared with Whites or African Americans (26-28). In contrast to our finding in women of a higher mean IGF-I level for African Americans compared with Whites, Chang et al. (29) have reported no statistically significant difference in mean serum IGF-I between age-matched and weight-matched postmenopausal African American and White women. Chang et al. (29) reported no statistically significant difference in age-adjusted median IGF-I levels in middle-aged Caucasian, Asian, and African American men (224, 208, and 205 ng/mL, respectively; $P_{diff} = 0.08$) but found a statistically significant difference in IGFBP-3 levels across races (3,868, 3,926, and 3,373 ng/mL, respectively; $P_{diff} = 0.01$). These higher IGFBP-3 levels in White men compared with African American men agree with our findings, and the cause of this variation across racial/ethnic groups clearly warrants further investigation as it may shed light on the relationships between IGF proteins and disease incidence.

Our findings were also consistent with the reported relationships of these IGF-related proteins with sex and

Table 3. Multiple regression of IGF-I and IGFBP-3 on variables selected among race/ethnicity, age, parity, age at menarche, age at natural menopause, smoking, weight, height, BMI, physical activity, and dietary variables using Mallow's Cp selection and R^2 selection

	Females					Males				
	Variable		Regression coefficient	P	R^2	Variable		Regression coefficient	P	R^2
IGF-I, ng/mL	Age, y		−0.0105	0.0002		Age, y		−0.0088	<0.0001	
	Race/ethnicity	AA	0.1271	0.048		Race/ethnicity	AA	0.0145	0.821	
		L	−0.1237	0.050			L	−0.0267	0.673	
		J	0.0241	0.700			J	0.0637	0.344	
		H	0.0483	0.474			H	0.0623	0.320	
	BMI, kg/m^2	Q2	0.0352	0.553		Height, in.		0.0201	0.007	
		Q3	−0.0321	0.583		Fat from meat, g/1,000 kcal/d		−0.0182	0.002	
		Q4	−0.1571	0.009		Smoking, current (vs never + past)		−0.1597	0.004	
					0.08					0.08
IGFBP-3, ng/mL	Age, y		−0.0119	<0.0001		Age, y		−0.0104	<0.0001	
	Race/ethnicity	AA	−0.0329	0.515		Race/ethnicity	AA	−0.1541	0.002	
		L	−0.1916	0.0001			L	−0.0723	0.146	
		J	0.0809	0.105			J	−0.0105	0.843	
		H	0.0472	0.370			H	−0.0194	0.692	
	BMI, kg/m^2	Q2	0.1543	0.001		Height, in.		0.0123	0.035	
		Q3	0.0941	0.040		Fat from meat, g/1,000 kcal/d		−0.0143	0.002	
		Q4	−0.0091	0.846		Low-fat milk, g/1,000 kcal/d		−0.0661	0.037	
	Alcohol		0.0530	0.0003						
					0.18					0.12
IGFMR	Race/ethnicity	AA	0.2057	0.0001		Race/ethnicity	AA	0.1339	0.013	
		L	0.1185	0.0229			L	0.0302	0.563	
		J	−0.0039	0.940			J	0.0310	0.557	
		H	0.0373	0.501			H	0.0691	0.1863	
	BMI, kg/m^2	Q2	−0.0910	0.064		Smoking, current (vs never + past)		−0.1394	0.002	
		Q3	−0.1177	0.015		Alcohol		−0.0391	0.009	
		Q4	−0.1411	0.004						
					0.05					0.04

NOTE: Whites are reference group. Abbreviations for race/ethnicity: AA, African American; J, Japanese; H, Native Hawaiian; L, Latino; W, White.

age. In our data, women had statistically significantly lower plasma IGF-I and higher IGFBP-3 than men independent of race, age, and BMI. IGF-I and IGFBP-3 declined linearly (log-linearly) with age. These findings agree with previous reports (18, 19, 23, 29). In contrast, the association between these proteins and body size seemed to be complex. In our data, IGF-I and IGFBP-3 seemed to have sex-specific relationships with body size. IGF-I seemed to have a direct correlation with BMI in women until some critical BMI point at which IGF-I began to decline, a nonlinear relationship that Lukanova et al. also described in a Swedish cohort (30). However, unlike in the MEC, this pattern was also observed in males in this Swedish cohort. In addition, we found that height is better correlated with IGF-I and IGFBP-3 than BMI in men. The literature on this topic is not consistent possibly because of this nonlinear, sex-dependent relationship (20, 30, 31). Differences in body fat distribution, which may be driven in large part by genetics (32-34), may contribute to differences in hormonal regulation of the IGF system. Further investigation of these relationships may clarify regulatory pathways for IGF and eventually explain inconsistencies in IGF-cancer incidence relationships.

Potential lifestyle determinants of IGF-I and IGFBP-3 include physical activity, smoking, and alcohol, calorie, fat, and protein intakes (24, 35). Among women in our data, the only association found with diet was an inverse

Table 4. Mean plasma protein levels from 955 Hawaii-Los Angeles MEC controls and age-adjusted incidence rates in the MEC through 1999 by race/ethnicity

Females								Males							
IGF-I*		IGFBP-3*		Colon cancer†		Breast cancer†		IGF-I*		IGFBP-3*		Colon cancer†		Prostate cancer†	
AA	160	J	2,951	AA	139	H	556	J	178	W	2,723	J	221	AA	1,124
H	148	H	2,897	H	138	J	399	H	176	J	2,717	H	198	L	459
J	145	W	2,768	J	119	W	360	AA	167	H	2,649	AA	192	W	443
W	141	AA	2,616	W	79	AA	332	W	165	L	2,518	W	129	H	402
L	126	L	2,254	L	77	L	246	L	162	AA	2,291	L	115	J	314

NOTE: Abbreviations: H, Native Hawaiian; J, Japanese; W, White; AA, African American; L, Latino.
*Protein concentrations are adjusted for covariates found to be significant in multivariate model (see Table 3) LS mean levels in ng/mL.
†Cancer incidence rates are truncated to ages 50–74 years per 100,000 and age-adjusted to the U.S. 1970 standard population.

one between alcohol and IGFBP-3. In the Rancho Bernardo Study, IGF-I showed a relationship in the opposite direction with alcohol intake among women (18). In men, we found other associations in our data. Fat intake from meat sources and current smoking seemed to be inversely associated with IGF-I levels. Fat intake from meat sources and low-fat milk were also inversely associated with IGFBP-3. In contrast, in a cohort of U.S. men, Ma et al. (36) found a direct association between low-fat milk intake and both IGF-I and IGFBP-3 levels and no association with red meat intake. Thus, the data on diet and IGF proteins are inconsistent. The relationship between smoking and IGF levels is also not clear. In five studies that addressed smoking and IGF-I, two found a positive association, one found an inverse association, as we did in women, and two found no association. The study that addressed smoking and IGFBP-3 reported an inverse association between current smoking and IGFBP-3 levels (24).

The main result from this study was that, overall, our models did not explain much of the variance in plasma IGF-I or IGFBP-3 as indicated by the low R^2 values. Previous investigators have reported similarly low R^2 values (29), which may be indicative of an as yet ill-defined set of IGF-I and IGFBP-3 determinants. Either we have poorly measured or analyzed the relevant covariates or we have failed to identify the true determinants. Measurement error may have attenuated the relationships under study, although most of the variables measured in the MEC that we included in this analysis have been valid in previous studies (16, 37). Another potential explanation for the low explanatory value of our models is that IGF-I and IGFBP-3 levels are largely driven by factors we have not measured in this study, such as genetic factors. Harrela et al. (38) reported that the proportions of variance in IGF-I and IGFBP-3 attributable to genetic effects were 38% and 60%, respectively. The genetic contribution to interindividual variation in circulating IGF-I and IGFBP-3 levels merits further study. A genetic marker has not yet been confirmed, but inherited variants in the growth hormone gene (39), IGF-I (15, 40), and the gene for IGFBP-3 (41) have been studied for possible association with adult IGF hormone levels.

A potential limitation of our study is that it relied on a single measurement of IGF-I and IGFBP-3 to represent long-term circulating levels. Although many studies have shown measurable interindividual variation in IGF-I and IGFBP-3 (42-45), data from the Rancho Bernardo Study suggest that the intraindividual variation in IGF-I is minimal (45) and that a single measurement may be adequate. It is also possible that adult levels of these peptides are, at least partially, determined early in life. Our finding of an association with height in men suggests that factors (possibly nutritional) during adolescence may have long-lasting effect on IGF-I hormone levels.

If differences in IGF-I and IGFBP-3 levels are related to the risk of breast, prostate, and colon cancers, as has been hypothesized, then one might expect mean levels of these proteins to correlate with racial/ethnic–specific cancer incidence rates in the MEC. The correlation between IGF-I levels and colon cancer incidence rates across racial/ethnic groups shown here provided support for this hypothesis. The cross-sectional nature of the data precluded our drawing conclusions about causation; however, we plan to use future analyses to follow up on these findings. In future work investigating the IGF system and cancer, it will be of value to use the blood samples that are being prospectively collected from the MEC to carry out nested case-control studies.

It is unclear whether the risk factors found here to be associated with IGF-I and IGFBP-3 have confounded previous association studies, leading to the inconsistency in the epidemiologic data on circulating levels of these proteins and cancer risk. However, it would be prudent to adjust for these factors in ongoing and future studies. Because of the relatively weak differences in IGF-I and IGFBP-3 across racial/ethnic groups, it seems unlikely that the identified determinants of these proteins would be a major source of population stratification in studies with significant admixture. However, we intend to further explore racial/ethnic differences in the determinants of IGF-I and IGFBP-3 levels in the MEC as additional data become available.

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