Plasma Concentrations of Insulin-like Growth Factors among Healthy Adult Men and Postmenopausal Women: Associations with Body Composition, Lifestyle, and Reproductive Factors

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Abstract

As evidence builds for cancer risk associated with insulin-like growth factors (IGFs) and their binding proteins (BPs), capitalizing on such associations for cancer prevention requires identifying the determinants of IGF levels. We measured plasma IGF-I, IGF-II, and IGF BP-3 in a cross-section of 210 men and 171 postmenopausal women enrolled in research as healthy controls. Using linear regression adjusted for age and ethnicity, we evaluated associations between IGF and IGF BP levels and gender, height, body mass index (BMI), smoking, caloric intake, physical activity, and reproductive factors. As expected, women using hormone replacement therapy (HRT) recently had significantly lower IGF-I levels than nonusers. Overall, IGF-I and IGF BP-3 levels did not differ by gender, although men had significantly higher molar ratios of IGF-I to IGF BP-3 and lower plasma IGF-II than women without recent HRT use. For men, BMI was a better predictor of IGF-I levels than height, whereas for women, height was more important. Lower IGF-II levels for both genders were associated with higher BMI and lower physical activity. Lower physical activity was associated with lower IGF BP-3 levels among men. Miscarriage number and menopausal age were positively associated with IGF BP-3 levels. HRT use strongly depressed IGF-I levels among smokers, and additional analysis revealed no remarkable associations. Caloric intake was negatively associated with IGF-I levels among men. Results for ratios of IGF-I and IGF-II to IGF BP-3 generally reflected those for IGF-I and IGF-II levels, respectively. In conclusion, whereas some traditional cancer risk factors were associated with IGF levels, altogether, they accounted for <15% of the total variability in plasma levels for each IGF, suggesting that other factors influence IGF levels.

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Introduction

As evidence accumulates for an association between cancer risk and plasma levels of IGFs[2] and their BPs, it becomes increasingly important to identify modifiable factors that determine IGF levels. In several epidemiological studies, elevated levels of plasma IGF-I, decreased levels of the most abundant IGF BP, IGF BP-3, and higher ratios of IGF-I to IGF BP-3, an indicator of unbound, biologically active IGF-I, were associated with increased risk of premenopausal breast cancer (1, 2), prostate cancer (3–6), lung cancer (7), and colon cancer (8, 9). Altogether, these cancers will account for 55% of the 1,284,900 new cancer cases diagnosed among all men and women in the United States in 2001 (10), suggesting that the contribution of IGFs to the public health burden of cancer could be sizeable.

In vitro and *in vivo* research has demonstrated that IGFs act as potent mitogens of both normal and cancerous cells, and reduce apoptosis (11), qualities that are important in promoting carcinogenesis. Of the six IGF BPs that bind with high affinity to IGF-I and IGF-II, and regulate their bioavailability, IGF BP-3 is the most abundant in the blood (12). Whereas much effort has gone into characterizing the IGF system and its effects, particularly on acromegalics and patients deficient in growth hormone, few studies have investigated the determinants of plasma IGF levels in healthy men and women.

To identify lifestyle factors associated with IGF levels, we analyzed data from a cross-sectional group of healthy adult men and postmenopausal women who participated in research conducted at The University of Texas M. D. Anderson Cancer Center. In addition to identifying factors associated with plasma levels of IGF-I, IGF-II, and IGF BP-3, we assessed the ratio of IGF-I to IGF BP-3. We hypothesized that higher levels of plasma IGF-I, lower levels of IGF BP-3, and higher ratios of IGF-I to IGF BP-3 would be associated with common risk factors for cancer, including tall stature, obesity, smoking, physical inactivity, high daily caloric intake, nulliparity, and later age at menopause, only some of which have been evaluated previously for their relationship with IGFs. On the basis of other published studies (13–15), we also predicted that plasma IGF-I levels would be lower among women with recent use of HRT.

Materials and Methods

Study Population. The data used in this analysis were collected from healthy men and women serving as controls for an ongoing lung cancer case-control study conducted in the Department of Epidemiology at The University of Texas M. D. Anderson Cancer Center. The study participants have been

[2] The abbreviations used are: IGF, insulin-like growth factor; BP, binding protein; HRT, hormone replacement therapy; BMI, body mass index.

described previously (16). In brief, the participants were identified from a control-pool database established from registrants of a large, private, multispecialty health care provider that includes a health maintenance organization, and managed-care and fee-for-service patients in the Houston metropolitan area. Each control subject was contacted by telephone to confirm his or her willingness to participate, and an appointment for study enrollment and blood draw was scheduled at a clinic site convenient to the participant.

Specimen and Data Collection. After obtaining informed consent, trained interviewers conducted in-person interviews with each participant by using a structured questionnaire followed by weighing, measurement of height, and collection of a 10-ml blood specimen. The blood was collected in heparinized tubes and transported immediately to the laboratory where the specimens were processed. The plasma was isolated by centrifugation of the blood at 1500 rpm for 10 min at room temperature and was stored at −80°C.

Measurement of IGFs and IGF BP-3. We used three commercially available ELISA kits (Diagnostic Systems Laboratories, Webster, TX) to determine the plasma levels of IGF-I, IGF-II, and IGF BP-3. To separate IGFs from their BPs, we mixed plasma specimens with acid-ethanol extraction buffer before measurement. The extraction procedure has been evaluated and is as efficient as acid-column chromatography (data not shown). To measure IGF BP-3, the specimens were diluted 100-fold in assay buffer before analysis.

Statistical Analysis. For descriptive analysis after evaluating distributions for normality, we used Student's *t* tests and standard χ^2 tests to compare means and distributions of several characteristics between men and women. We compared IGF plasma concentrations by gender and evaluated for linear trends in the plasma levels of IGFs by arbitrary categories of height, BMI, level of weekly physical activity (high *versus* low), and smoking. Daily total caloric intake was divided into sex-specific tertiles. Height categories were arbitrarily defined as <5′4”, 5′4” to 5′7”, and ≥5′8” for women, and <5′8”, 5′8” to 6′, and ≥6′ for men. The cut points for BMI were based on those suggested by the National Heart, Lung, and Blood Institute/NIH (17). Higher weekly physical activity was defined as self-reporting of participating in “active sports” or “jogging or running” at least once a week. Smoking characteristics evaluated included smoking status (never, former, or current), pack-years smoked (tertiles), number of cigarettes smoked daily (1–19, 20–39, or ≥40), age at smoking initiation (≤15 *versus* >15 years), inhaling deeply into the chest, and use of menthol cigarettes. Among women, we also evaluated parity, total number of children, miscarriage (ever *versus* never and total number of miscarriages), age at menopause (<50 *versus* ≥50), and HRT within the past 6 months.

After establishing the normality of the plasma IGF concentration distributions, we used linear regression to evaluate for men and women separately the associations between IGF-I, IGF-II, IGF BP-3, and the ratio of IGF-I to IGF BP-3 and factors of interest (*i.e.*, BMI, height, total daily caloric intake, physical activity, smoking, and, among women, reproductive factors). To accommodate the opposing effects of IGFs and IGF BPs, models for IGF-I and IGF-II were also adjusted for IGF BP-3 (18). Models were adjusted for age and ethnicity because of concern for age-related declines in IGF levels and the possible confounding effects of ethnicity.

In combined multivariate linear regression models, we constructed models using all of the factors significantly associated with dependent variable ($P \leq 0.10$) and removed, in a stepwise fashion, each factor that did not contribute significantly except for age and ethnicity. The contribution of each factor was evaluated by using the partial F test comparing the full and diminished models (19), and applying a significance level of $P \leq 0.05$. As per Michels *et al.* (20), we initially included both BMI and height in each model to capture information on body composition related to weight and height together (*i.e.*, BMI) and additional information on body size (*i.e.*, height). In models for which height did not contribute significantly ($P \leq 0.05$) in addition to BMI, height was removed to evaluate the influence of BMI alone. In addition to reporting the β estimates for individual predictor variables, we report the total model r^2 to provide a sense of the model variability and strength of fit.

Results

Selected Characteristics and Gender Differences in Plasma IGF and IGF BP Levels. For the 210 adult men and 171 postmenopausal women in our analysis, mean BMI was similar [26.8 (SD = 3.9) and 26.2 (SD = 5.9), respectively; $P = 0.24$], although the men were significantly taller ($P < 0.0001$) and heavier ($P = 0.0001$) than the women were. A larger proportion of men were overweight (25 ≤ BMI <30) and obese (BMI ≥30; 51% and 19%, respectively) than women (36% and 20%, respectively). The men were older [63.2 (SD = 9.2) *versus* 61.4 (SD = 10.0); $P = 0.05$] and consumed more total calories daily [2188 (SD = 732) *versus* 1760 (SD = 634); $P = 0.0001$] than the women did. In our sample, there was a higher proportion of former smokers among men (61%) than among women (40%), and the men had smoked more pack-years on average than the women did (51.6 and 38.3, respectively; $P = 0.0001$). Most of our subjects reported low levels of weekly physical activity (90% and 94% in men and women, respectively), and differences by gender were not significant ($P = 0.11$). The modal age at menopause was 50 years, and the proportion of women who had used HRT in the past 6 months was 53% ($n = 98$). Among women, 88% ($n = 151$) reported having children and 33% ($n = 56$) reported ever having a miscarriage, the number ranging from one to seven miscarriages.

As we expected, plasma IGF-1 levels and the molar ratio of IGF-1 to IGF BP-3 were significantly higher in women who used HRT within the past 6 months than those who had not (Table 1). Recent HRT use did not appear to influence plasma levels of IGF-II, IGF BP-3, or the molar ratio of the two. Overall, plasma levels of IGF-I and IGF BP-3 did not differ by gender, although men had significantly higher molar ratios of IGF-I to IGF BP-3 than women who had not used HRT recently. Compared with women who had not used HRT recently, men had significantly lower plasma IGF-II and molar ratios of IGF-II to IGF BP-3. These gender differences remained apparent after stratification on a variety of characteristics, including smoking status, tertiles of pack-years smoked, and total daily caloric intake (data not shown). In models adjusted for age and ethnicity among men and women without recent HRT use, gender was significantly associated with plasma levels of IGF-I ($\beta = 21.2$; SE = 7.05; $P = 0.003$; $r^2 = 0.33$, also adjusted for IGF BP-3) and the molar ratio of IGF-I to IGF BP-3 ($\beta = 0.71$; SE = 0.20; $P = 0.0003$; $r^2 = 0.08$). Gender was also associated in age- and ethnicity-adjusted models with plasma levels of IGF-II ($\beta = -77.2$; SE = 11.98; $P = < 0.0001$; $r^2 = 0.45$, also adjusted for IGF BP-3) and the molar ratio of IGF-II to IGF BP-3 ($\beta = 0.067$; SE = 0.01; $P < 0.0001$; $r^2 = 0.08$). However, gender was not significantly associated with levels of IGF BP-3 ($\beta = -113.5$; SE = 94.2; $P = 0.23$; $r^2 = 0.06$). As

Table 1 Mean plasma concentrations (SDs) of IGF-I, IGF-II, and IGF BP-3, and the molar ratios of IGF-I and IGF-II to IGF BP-3 by gender, HRT use, height, and BMI

	n (%)	IGF-I in ng/ml		IGF-II in ng/ml	IGF BP-3 in ng/ml	IGF-I/IGF BP-3		IGF-II/IGF BP-3
Women	171 (100)	137.1 (65.5)		640.0 (165.3)	3778 (891)	3.4 (1.4)		0.64 (0.15)
HRT within 6 months								
Yes	90 (53)	114.8 (53.8)		624.3 (150.7)	3739 (923)	3.0 (1.1)		0.63 (0.14)
No	80 (47)	153.9 (67.1)[a]		655.6 (185.4)[a]	3819 (864)[a]	3.9 (1.5)[a]		0.65 (0.16)[a]
P		<0.0001		0.23	0.56	<0.0001		0.56
Height in feet and inches		No HRT	HRT			No HRT	HRT	
<5'4"	65 (38)	139.6 (63.0)	106.9 (44.2)	614.9 (170.6)	3651 (898)	3.6 (1.4)	3.0 (1.0)	0.64 (0.17)
5'4" to 5'7"	83 (49)	155.7 (66.5)	119.7 (63.4)	657.3 (165.4)	3832 (865)	3.9 (1.3)	3.1 (1.2)	0.65 (0.14)
≥5'8"	23 (13)	192.6 (72.0)[b]	118.1 (39.8)	641.4 (166.0)	3941 (960)	5.0 (2.2)	3.0 (0.8)	0.61 (0.13)
P for trend		0.01	0.64	0.26	0.10	0.02	0.38	0.49
BMI in kg/m^2		No HRT	HRT			No HRT	HRT	
<25	75 (44)	169.6 (70.6)[c]	114.8 (57.2)	669.0 (149.6)	3779 (898)	4.4 (1.8)[c]	3.0 (1.2)	0.67 (0.12)
25–30	61 (36)	146.1 (51.8)[c]	107.4 (48.4)	608.9 (182.4)	3758 (772)	3.7 (1.0)[c]	2.9 (1.0)	0.61 (0.18)
≥30	35 (20)	138.1 (73.6)[c]	135.2 (55.7)	627.4 (171.2)	3812 (1078)	3.5 (1.3)[c]	3.3 (0.8)	0.63 (0.13)
P for trend		0.30	0.61	0.17	0.57	0.08	0.60	0.02
Men	210 (100)	164.9 (62.4)[a]		544.9 (130.1)[a]	3629 (962)[a]	4.6 (1.5)		0.58 (0.12)
Height in feet and inches								
<5'8"	36 (19)	150.0 (74.1)		516.9 (140.1)	3380 (1216)	4.5 (1.5)		0.61 (0.15)
5'8" to 6'	134 (64)	169.3 (59.6)		556.8 (126.1)	3674 (889)	4.6 (1.5)		0.58 (0.11)
≥6'	40 (19)	163.6 (59.6)		530.4 (132.1)	3696 (941)	4.5 (1.6)		0.54 (0.12)
P for trend		0.13		0.50	0.01	0.98		0.0003
BMI in kg/m^2								
<25	63 (30)	171.2 (55.1)		577.2 (118.4)	3725 (833)	4.7 (1.7)		0.60 (0.12)
25–30	108 (51)	166.9 (65.4)		543.2 (130.8)	3611 (1053)	4.6 (1.4)		0.58 (0.11)
≥30	39 (19)	149.5 (64.2)		497.5 (134.1)	3521 (894)	4.3 (1.5)		0.54 (0.13)
P for trend		0.10		0.005	0.35	0.11		0.02

[a] To compare mean IGF levels of men and women without recent use of HRT, we used the Student *t* test to test for significance. The *P* for IGF-I was 0.16; for IGF-II, $P < 0.0001$; for IGF BP-3, $P = 0.12$; for the molar ratio of IGF-I. IGF BP-3, $P = 0.0009$; and for the molar ratio of IGF-II:IGF BP-3, $P = 0.0004$.

[b] When we compared mean levels of IGF-I of men and women without recent use of HRT by height, the $P = 0.56$ for those shorter than 5'8" and $P = 0.24$ for those 5'8" and taller. When we compared molar ratios of IGF-I to IGF BP-3 for men and women without recent use of HRT by height, the $P = 0.006$ for those shorter than 5'8" and $P = 0.79$ for those 5'8" and taller. When we compared molar ratios of IGF-II to IGF BP-3 for men and women without recent use of HRT by height, the $P = 0.12$ for those shorter than 5'8" and $P = 0.08$ for those 5'8" and taller.

[c] When we compared mean levels of IGF-I of men and women without recent use of HRT by BMI categories, the $P = 0.90$ for those with BMI <25, the $P = 0.10$ for those with BMI 25–30, and for those with BMI ≥30, $P = 0.53$. When we compared molar ratios of IGF-I to IGF BP-3 for men and women without recent use of HRT by BMI categories, the $P = 0.56$ for those with BMI <25, the $P = 0.0008$ for those with BMI 25–30, and for those with BMI ≥30, $P = 0.03$. When we compared molar ratios of IGF-II to IGF BP-3 for men and women without recent use of HRT by BMI categories, the $P = 0.001$ for those with BMI <25, the $P = 0.41$ for those with BMI 25–30, and for those with BMI ≥30, $P = 0.01$.

expected, age was negatively associated with plasma levels of all of the IGFs (men: for IGF-I, $\beta = -0.81$; SE = 0.45; for IGF-II, $\beta = -0.92$; SE = 1.04; for IGF BP-3, $\beta = -16.0$; SE = 7.1; women: for IGF-I, $\beta = -0.68$; SE = 0.55; for IGF BP-3, $\beta = -2.9$; SE = 8.0), except for IGF-II ($\beta = 2.73$; SE = 1.49) among women. Because of the gender differences in plasma levels of IGFs, we present the results for men and women separately in subsequent tables.

Height and BMI. In both men and women, we observed the lowest IGF-I levels among those in the shortest height categories, and there were nonsignificant trends for decreasing IGF-I levels with increasing BMI categories, as shown in Table 1. In a model adjusting for age, ethnicity, and IGF BP-3 level, this inverse pattern for BMI with IGF-I levels was statistically significant among men ($\beta = -1.94$; SE = 0.95; $P = 0.04$; $r^2 = 0.33$). In contrast, among women, BMI was not associated with IGF-I levels after adjustment for the same covariates ($\beta = -0.15$; SE = 0.70; $P = 0.82$; $r^2 = 0.33$). However, there was a borderline significant association with height for IGF-I levels after adjustment for BMI, age, ethnicity, and IGF BP-3 levels among women ($\beta = 118.3$; SE = 63.7; $P = 0.07$; $r^2 = 0.34$) but not among men ($\beta = 31.7$; SE = 55.5; $P = 0.57$; $r^2 = 0.33$). Reflecting the patterns of BMI and height with IGF-I levels, in models adjusted for age and ethnicity, the ratio of IGF-I to IGF BP-3 was significantly associated among men with BMI ($\beta = -0.06$; SE = 0.03; $P = 0.03$; $r^2 = 0.05$) but not height ($\beta = 0.96$; SE = 1.56; $P = 0.54$) and among women with height ($\beta = 3.38$; SE = 1.64; $P = 0.04$; $r^2 = 0.11$) but not BMI ($\beta = -0.02$; SE = 0.02; $P = 0.39$).

Obese men and women had the lowest mean IGF-II levels compared with their leaner respective counterparts, although the decreasing trend with BMI was consistent only among men. In models adjusted for age, ethnicity, and IGF BP-3 levels, BMI was significantly associated with plasma levels of IGF-II among men ($\beta = -5.59$; SE = 1.70; $P = 0.001$; $r^2 = 0.50$) and women ($\beta = -4.80$; SE = 1.75; $P = 0.007$; $r^2 = 0.39$). In other models adjusted for age and ethnicity, height was not associated with plasma IGF-II levels or the molar ratio of IGF-II to IGF BP-3 among either men or women. Neither height nor BMI were associated in models adjusted for age and ethnicity with plasma levels of IGF BP-3 among men or women.

Caloric Consumption and Physical Activity. Among men, increasing tertiles of daily caloric consumption were nonsignificantly associated with decreasing mean plasma IGF-I levels and increasing IGF BP-3 levels, which were reflected together as a significant decreasing trend in the mean ratio of IGF-I to IGF BP-3 (Table 2). In models adjusting for age, ethnicity, and IGF BP-3 levels, increasing total daily caloric intake was associated with decreasing IGF-I levels ($\beta = -0.01$; SE = 0.005; $P = 0.05$; $r^2 = 0.33$) and lower ratios of IGF-I to IGF BP-3 ($\beta = -0.0003$; SE = 0.0001; $P = 0.05$; $r^2 = 0.07$) among men. Caloric intake was not consistently associated with levels of

Table 2 Mean plasma concentrations (SDs) of IGF-I, IGF-II, and IGF BP-3, and the molar ratios of IGF-I and IGF-II to IGF BP-3 by gender, caloric intake, weekly physical activity level, and reproductive factors

	n (%)	IGF-I in ng/ml	IGF-II in ng/ml	IGF BP-3 in ng/ml	IGF-I/IGF BP-3	IGF-II/IGF BP-3
Men						
Caloric intake[a]						
Low	45 (21)	174.4 (74.7)	539.0 (131.6)	3557 (968)	4.8 (1.8)	0.58 (0.12)
Medium	75 (36)	159.4 (51.6)	541.2 (136.7)	3604 (989)	4.5 (1.3)	0.57 (0.13)
High	90 (43)	161.0 (58.3)	554.3 (123.2)	3726 (934)	4.4 (1.3)	0.57 (0.11)
P for trend		0.26	0.37	0.30	0.05	0.78
Weekly physical activity[b]						
High	22 (10)	167.1 (67.4)	604.7 (156.7)	3934 (796)	4.3 (1.6)	0.57 (0.11)
Low	188 (90)	164.7 (62.0)	537.9 (125.3)	3593 (975)	4.6 (1.5)	0.58 (0.12)
P for trend		0.87	0.02	0.12	0.29	0.90
Women						
Caloric intake[a]						
Low	56 (33)	131.7 (50.5)	641.9 (158.4)	3733 (783)	3.5 (1.2)	0.65 (0.16)
Medium	57 (33)	133.0 (71.5)	633.0 (204.3)	3815 (899)	3.4 (1.6)	0.62 (0.17)
High	58 (34)	134.0 (66.6)	642.2 (136.1)	3786 (991)	3.4 (1.4)	0.65 (0.12)
P for trend		0.85	0.99	0.76	0.74	0.91
Weekly physical activity[b]						
High	10 (6)	109.5 (53.9)	719.4 (142.9)	3542 (768)	3.0 (0.9)	0.76 (0.11)
Low	161 (94)	134.4 (63.6)	634.0 (168.2)	3793 (899)	3.5 (1.4)	0.63 (0.12)
P		0.23	0.12	0.39	0.27	0.008
Age at menopause						
<50 years	111 (65)	126.8 (59.8)	636.5 (163.2)	3733 (922)	3.3 (0.4)	0.65 (0.15)
≥50 years	58 (35)	145.3 (68.9)	642.5 (179.5)	3854 (826)	3.7 (1.4)	0.63 (0.15)
P		0.07	0.83	0.40	0.18	0.38
Report of miscarriage						
Yes	56 (33)	134.3 (61.9)	655.3 (168.5)	3864 (825)	3.4 (1.4)	0.64 (0.15)
No	115 (67)	132.2 (64.1)	631.1 (167.4)	3737 (923)	3.5 (1.4)	0.64 (0.15)
P		0.84	0.38	0.38	0.88	0.99
Parity						
Parous	150 (88)	133.7 (65.3)	644.2 (171.7)	3743 (889)	3.5 (1.4)	0.65 (0.12)
Nulliparous	21 (12)	127.5 (46.3)	602.5 (133.1)	4034 (892)	3.1 (1.1)	0.56 (0.15)
P		0.68	0.29	0.16	0.30	0.01

[a] Daily caloric intake was divided based on tertiles of consumption: among women, low was defined as <1375 calories, medium as 1375–1908 calories, and high as >1908 calories. Among men, low was defined as <1793 calories, medium as 1793–2395 calories, and high as >2395 calories.
[b] High weekly physical activity was defined as self-report of one or more weekly episodes of "active sports" or "jogging or running."

IGF-II or the molar ratio of IGF-II to IGF BP-3 among men or women.

Both less active men and women had significantly lower mean plasma levels of IGF-II than active people did. In age and ethnicity-adjusted models, high physical activity was associated with high IGF-II levels for women ($\beta = 104.3$; SE = 43.7; $P = 0.02$; $r^2 = 0.39$) and men ($\beta = 40.4$; SE = 22.1; $P = 0.07$; $r^2 = 0.48$). After adjusting for age and ethnicity, higher physical activity was associated with high levels of IGF BP-3 in a borderline fashion among men ($\beta = 369.2$; SE = 215.7; $P = 0.09$; $r^2 = 0.09$). Plasma levels of other IGFs were not associated with either total daily caloric intake or high weekly physical activity.

Reproductive Factors Among Women. As shown in Table 2, we observed that women who were older at menopause (*i.e.*, ≥50 years) had borderline higher plasma IGF-I levels than women who were younger at menopause. In separate models adjusted for age, ethnicity, and IGF BP-3, age at menopause ($\beta = 1.18$; SE = 0.51; $P = 0.02$; $r^2 = 0.36$) and HRT use ($\beta = -39.6$; SE = 8.16; $P < 0.0001$; $r^2 = 0.42$) were associated with plasma IGF-I levels. Age at menopause and recent HRT were also both associated in separate age- and ethnicity-adjusted models with the ratio of IGF-I to IGF BP-3 (for age at menopause, $\beta = 0.03$; SE = 0.01; $P = 0.04$; $r^2 = 0.11$; for HRT use; $\beta = -1.03$; SE = 0.21; $P < 0.0001$; $r^2 = 0.21$). Increasing number of miscarriages and age at menopause were associated with plasma IGF BP-3 levels in separate models adjusted for age and ethnicity (for miscarriages, $\beta = 182.2$; SE = 56.8; $P = 0.002$; $r^2 = 0.09$; for menopausal age, $\beta = 19.8$; SE = 8.4; $P = 0.02$; $r^2 = 0.06$). Among all of the IGFs evaluated for an association with parity, only a borderline significant association was evident for plasma IGF-II levels ($\beta = 9.69$; SE = 5.13; $P = 0.06$; $r^2 = 0.38$), and the ratio of IGF-II to IGF BP-3 ($\beta = 0.01$; SE = 0.006; $P = 0.05$; $r^2 = 0.05$) after adjustment for age and ethnicity.

Smoking. Men who had never smoked had higher plasma IGF-I levels than men who were former and current smokers (Table 3). Among male smokers, IGF-I levels declined with increasing pack-years of exposure. This pattern was less evident when cigarettes smoked per day were analyzed. Plasma levels of IGFs among men did not vary significantly by age at smoking initiation, depth of inhalation, or use of menthol cigarettes (data not shown).

Among women, there was a similar pattern for women using HRT compared with women who had not: plasma IGF-I levels were lower in every category of smoking among women who used HRT (Table 4). Among both women who used HRT and those who did not, current smokers had higher IGF-I levels than either former or never-smokers. Current smokers smoking 40 or more cigarettes daily had higher IGF-I levels than women smoking fewer cigarettes daily had. However, this pattern of higher IGF-I levels among heavier smokers was not supported by trends in pack-years: current female smokers with a longer history of smoking had lower mean IGF-I levels than other

Table 3 Mean plasma concentrations (SDs) of IGF-I, IGF-II, and IGF BP-3, and the ratios of IGF-I and IGF-II to IGF BP-3 by selected smoking characteristics in men

	n (%)	IGF-I in ng/ml	IGF-II in ng/ml	IGF BP-3 in ng/ml	IGF-I/IGF BP-3	IGF-II/IGF BP-3
Smoking status						
Never	7 (3)	187.1 (83.7)	576.8 (90.0)	4011 (655)	4.5 (1.3)	0.54 (0.07)
Former	127 (60)	158.2 (60.1)	542.5 (141.2)	3638 (969)	4.4 (1.4)	0.57 (0.11)
Current	46 (36)	174.1 (63.3)	546.0 (113.6)	3580 (975)	4.9 (1.6)	0.59 (0.13)
Current smokers, pack-years[a]						
Low	18 (24)	192.9 (80.8)	546.3 (141.4)	3777 (1258)	5.2 (2.1)	0.57 (0.16)
Medium	22 (29)	165.5 (54.3)	543.6 (116.0)	3745 (831)	4.4 (1.4)	0.55 (0.11)
High	36 (47)	169.9 (58.3)	547.3 (99.3)	3381 (882)	5.0 (1.3)	0.63 (0.12)
P for trend		0.28	0.96	0.12	0.78	0.07
Former smokers, pack-years[a]						
Low	42 (33)	170 (65.9)	545.2 (133.5)	3561 (938)	4.8 (1.7)	0.58 (0.10)
Medium	43 (34)	154.0 (55.5)	554.6 (139.1)	3571 (881)	4.4 (1.0)	0.59 (0.09)
High	42 (33)	150.8 (58.3)	527.4 (152.5)	3780 (1085)	4.0 (1.4)	0.53 (0.14)
P for trend		0.14	0.56	0.30	0.02	0.04
Current smokers, number of cigarettes smoked daily						
1–19	11 (9)	185.9 (96.9)	536.3 (141.7)	3515 (1378)	5.4 (2.2)	0.61 (0.15)
20–39	38 (52)	171.9 (56.2)	549.9 (123.9)	3748 (994)	4.6 (1.5)	0.57 (0.13)
≥40	24 (33)	172.3 (58.1)	544.5 (87.2)	3371 (771)	5.0 (1.4)	0.62 (0.12)
P for trend		0.63	0.92	0.57	0.94	0.13

[a] Pack-years were divided into tertiles based on the distribution of all smokers: low was defined as ≤32.5 pack-years, medium as >32.5 to <56.25 pack-years, and high as ≥56.25 pack-years.

current smokers did. In contrast, plasma IGF BP-3 and IGF-II levels did not vary remarkably by smoking status.

In adjusted models among men and women separately, smoking was not significantly associated with the plasma levels of IGF-I, IGF-II, and IGF BP-3 or the ratio of IGF-I to IGF BP-3, even after potential effect modification by HRT use was considered. Whether smoking was quantified by smoking status, tertile of pack-years, number of cigarettes smoked daily, use of menthol cigarettes, age at smoking initiation, or the depth of inhaling did not influence the results (data not shown).

Multivariate Models. For multivariable analyses evaluating the associations between height, BMI, caloric intake, weekly physical activity, reproductive factors, smoking, and plasma IGFs, we adjusted all of the models for age and ethnicity (Table 5). Among men, plasma IGF-I levels were inversely associated with BMI and caloric intake. Among women, IGF-I levels were positively associated height adjusted for BMI and negatively so with recent use of HRT. Whereas the multivariate models explained 34% of the variance in plasma IGF-I levels for men and 44% of the IGF-I variance for women, the largest contribution to IGF-I variance in both men and women was from IGF BP-3 (27% for both men and women).

For men, elevated plasma IGF BP-3 levels were associated with frequent weekly physical activity, although the association was of only borderline significance. Among women, plasma levels of IGF BP-3 were significantly elevated only with age at menopause and the total number of miscarriages reported.

In separate adjusted models for both men and women, the ratio of IGF-I to IGF BP-3 was weakly and negatively associated with BMI, although this association was significant only among men. Among men, the ratio was also associated with total daily caloric intake. Among women, the ratio was positively associated with height and inversely so with HRT use.

For age and ethnicity-adjusted models, IGF-II levels were negatively associated with BMI among both men and women, but only among women was high weekly physical activity also independently associated with IGF-II levels. Of the total variance in plasma IGF-II levels among men that was explained by the model including age, ethnicity, plasma IGF BP-3 levels, and BMI (50%), IGF BP-3 accounted for the largest part (43%). Among women, 30% of the total variance in plasma IGF-II levels was explained IGF BP-3 levels, and all of the factors together accounted for 42% of the total variance.

Discussion

Gender and Body Composition. In this analysis of healthy adult men and postmenopausal women, we found that gender predicted levels of IGFs: men had significantly higher levels of IGF-I, higher ratios of IGF-I to IGF BP-3, and lower levels of IGF-II and IGF BP-3 than women had. Similar findings have been reported by some investigators but not others (21–26). Landin-Wilhelmsen *et al.* (26) reported an association between gender and IGF-I levels similar to ours but only among older participants (*i.e.*, ages 55–64), not among younger ones (*i.e.*, ages 25–34), suggesting the possibility of an age-gender-IGF-I interaction.

The association in our report between plasma IGF-I levels and height adjusted for BMI among women, and BMI (but not height) among men was also observed by Maccario *et al.* (23) in obese people in northern Italy (Turin) but not in slimmer subjects from northern Italy (Parma; Ref. 24) and southern California (21). Body composition differences between study samples may also be important to consider when comparing studies, as Marin *et al.* (27) reported that plasma IGF-I levels in men were inversely associated with visceral but not subcutaneous or total fat mass and that men with more visceral fat had higher BMIs. We characterized body composition by using BMI, which does not reflect distribution of body mass, or proportion of fatness and leanness. Despite this limitation, we found that BMI was associated with plasma levels of several IGFs. This suggests that evaluating other more specific aspects of body composition may reveal more about the specific factors that determine IGF levels, as we found that height was a significant predictor of plasma IGF-I levels independent of BMI in women but not in men.

Caloric Intake and Weekly Physical Activity. Our findings for caloric intake and physical activity are interesting in the

Table 4 Mean plasma concentrations (SDs) of IGF-I, IGF-II, and IGF BP-3, and the ratios of IGF-I and IGF-II to IGF BP-3 by HRT use and selected smoking characteristics in women

	no HRT (n = 80)	HRT (n = 90)	no HRT	HRT	P
IGF-I in ng/ml					
Smoking status					
Never	14	8	114.6 (59.4)	91.6 (46.7)	0.35
Former	28	41	157.8 (72.4)	115.0 (52.9)	0.006
Current	38	41	165.4 (61.7)	119.1 (55.9)	0.0008
Current smokers, pack-years[a]					
Low	10	16	179.1 (66.4)	105.6 (38.5)	0.007
Medium	15	15	170.6 (67.4)	136.5 (67.5)	0.18
High	13	10	149.0 (51.6)	114.6 (59.2)	0.15
P for trend			0.24	0.55	
Former smokers, pack-years[a]					
Low	13	18	168.1 (78.8)	122.9 (63.1)	0.09
Medium	9	12	172.2 (68.9)	113.8 (49.0)	0.03
High	6	11	114.1 (53.3)	103.3 (38.7)	0.64
P for trend			0.19	0.34	
Current smokers, number of cigarettes smoked daily					
1–19	9	15	160.5 (48.8)	102.1 (38.5)	0.004
20–39	23	19	164.4 (70.5)	127.9 (63.7)	0.09
≥40	6	7	176.8 (48.2)	131.6 (63.9)	0.18
P for trend			0.64	0.18	
IGF BP-3 in ng/ml					
Smoking status					
Never	14	8	3435 (1013)	3378 (1005)	0.90
Former	28	41	4007 (792)	3816 (966)	0.39
Current	38	41	3824 (834)	3734 (868)	0.64
Current smokers, pack-years[a]					
Low	10	16	3479 (682)	3602 (725)	0.67
Medium	15	15	3879 (1015)	4072 (949)	0.59
High	13	10	4026 (667)	3436 (867)	0.25
P for trend			0.13	0.84	
Former smokers, pack-years[a]					
Low	13	18	4121 (639)	3851 (868)	0.35
Medium	9	12	4104 (632)	3946 (1209)	0.73
High	6	11	3615 (1237)	3614 (880)	0.99
P for trend			0.25	0.58	
Current smokers, number of cigarettes smoked daily					
1–19	9	15	3766 (907)	3624 (696)	0.67
20–39	23	19	3819 (844)	3911 (928)	0.74
≥40	6	7	3928 (822)	3486 (1054)	0.42
P for trend			0.72	0.98	
IGF-I/IGF BP-3					
Smoking status					
Never	14	8	3.2 (1.0)	2.6 (0.9)	0.21
Former	28	41	3.9 (1.6)	3.0 (1.1)	0.01
Current	38	41	4.3 (1.5)	3.2 (1.2)	0.0003
Current smokers, pack-years[a]					
Low	10	16	5.1 (2.0)	3.0 (1.1)	0.002
Medium	15	15	4.3 (1.4)	3.3 (1.2)	0.04
High	13	10	3.6 (0.8)	3.2 (1.2)	0.40
P for trend			0.01	0.53	
Former smokers, pack-years[a]					
Low	13	18	4.1 (1.9)	3.2 (1.4)	0.13
Medium	9	12	4.2 (1.5)	2.8 (0.9)	0.02
High	6	11	3.1 (1.0)	2.8 (0.9)	0.65
P for trend			0.28	0.42	
Current smokers, number of cigarettes smoked daily					
1–19	9	15	4.2 (1.1)	2.8 (1.0)	0.005
20–39	23	19	4.2 (1.7)	3.2 (1.2)	0.03
≥40	6	7	4.6 (1.6)	3.7 (1.2)	0.27
P for trend			0.72	0.11	
IGF-II in ng/ml					
Smoking status					
Never	14	8	606.5 (236.4)	584.1 (170.6)	0.81
Former	28	41	688.8 (200.0)	646.8 (151.8)	0.33
Current	38	41	649.2 (151.1)	609.7 (146.1)	0.24

Table 4 Continued

	no HRT (n = 80)	HRT (n = 90)	no HRT	HRT	P
Current smokers, pack-years[a]					
Low	10	16	608.9 (131.9)	658.8 (69.4)	0.29
Medium	15	15	633.1 (185.3)	605.5 (186.5)	0.69
High	13	10	698.9 (113.7)	537.3 (150.1)	0.008
P for trend			0.15	0.04	
Former smokers, pack-years[a]					
Low	13	18	738.7 (258.8)	666.0 (159.7)	0.34
Medium	9	12	653.1 (106.9)	662.2 (130.5)	0.87
High	6	11	634.2 (155.1)	598.5 (163.0)	0.67
P for trend			0.25	0.28	
Current smokers, number of cigarettes smoked daily					
1–19	9	15	634.3 (139.4)	653.5 (74.3)	0.71
20–39	23	19	653.8 (163.3)	612.2 (170.5)	0.43
≥40	6	7	645.4 (141.0)	509.0 (160.0)	0.11
P for trend			0.78	0.04	
IGF-II/IGF BP3					
Smoking status					
Never	14	8	0.67 (0.21)	0.65 (0.08)	0.76
Former	28	41	0.65 (0.18)	0.65 (0.14)	0.97
Current	38	41	0.64 (0.13)	0.62 (0.15)	0.53
Current smokers, pack-years[a]					
Low	10	16	0.67 (0.17)	0.70 (0.11)	0.57
Medium	15	15	0.61 (0.10)	0.56 (0.17)	0.33
High	13	10	0.66 (0.13)	0.59 (0.14)	0.25
P for trend			0.94	0.04	
Former smokers, pack-years[a]					
Low	13	18	0.66 (0.22)	0.65 (0.13)	0.88
Medium	9	12	0.60 (0.13)	0.65 (0.11)	0.40
High	6	11	0.68 (0.14)	0.63 (0.17)	0.58
P for trend			0.96	0.67	
Current smokers, number of cigarettes smoked daily					
1–19	9	15	0.65 (0.18)	0.69 (0.11)	0.51
20–39	23	19	0.64 (0.11)	0.59 (0.18)	0.33
≥40	6	7	0.63 (0.15)	0.55 (0.14)	0.35
P for trend			0.	0.	

[a] Pack-years were divided into tertiles based on the distribution of all smokers: low was defined as ≤32.5 pack-years, medium as >32.5 to <56.25 pack-years, and high as ≥56.25 pack-years.

context of our BMI findings but should not be overinterpreted, as there were limitations to our measurements. Using a food frequency questionnaire provided us with average daily caloric intake over the past 12 months, which may be only grossly associated with precisely measured, single samples of biomarkers like plasma IGF levels. Our measure of weekly physical activity only identified people who participated in high intensity activities at least once a week. Thus, estimating a dose-response association between IGF levels and frequency, duration, or type of physical activity was not possible. Despite these limitations, the relationship between caloric intake and physical activity and levels of IGFs is worth additional investigation, because risk of colon cancer has been associated with both plasma levels of IGF-I and IGF BP-3 (8, 9, 28) and physical inactivity (29–33). Moreover, colorectal cancer has been associated with elevated levels of serum IGF-II (34–36) and overexpression of IGF-II mRNA (37).

Reproductive Factors and Smoking. Our finding of significantly lower plasma IGF-I levels with recent HRT use is consistent with other published research (14, 15). In light of accumulating evidence for an effect of HRT on IGF-I levels and a role for IGF-I in the carcinogenesis of several forms of cancer, the importance of this finding needs to be considered more broadly by the scientific and public health community. HRT is already widely used in developed countries, and the magnitude of its effect on IGF-I levels is large enough to be considered for its use in prevention strategies. However, in our study, we did not determine the formulations or doses of HRT or mode of delivery used by the women in our analysis. We also did not consistently collect information to identify women without natural menopause. These issues and the limited sample size prohibited analysis of women who were older and younger at menopause by type of menopause (*i.e.*, natural or surgical). Other reproductive factors were associated with IGF levels, including the number of miscarriages and parity, suggesting that events during the reproductive years may indicate or determine IGF levels later in life.

Relevance to Cancer in Women. Our finding that height in postmenopausal women was associated with levels of plasma IGF-I is noteworthy in the context of breast cancer epidemiology, as several groups have identified adult height as a risk factor for breast cancer (38–41), but the determinants of height that relate to breast cancer risk remain unclear. However, adult height reflects a number of factors, including genetic inheritance, nutritional status during childhood development, and early life exposure to IGF-I, and it is not clear whether the factors critical for cancer development act early in life or later during adulthood. If future studies find that adult levels of IGF-I reflect childhood levels, it is plausible then, that for some people, elevated IGF-I levels may be a prolonged, if not a

Table 5 Multivariate linear regression models for plasma concentrations of IGFs by gender

	β (SE)[a]	*P*	r^2
IGF-I[b]			
Model for men			0.34
BMI	−2.05 (0.94)	0.03	
Total calories	−0.01 (0.005)	0.04	
Model for women			0.44
BMI	−0.51 (0.64)	0.43	
Height	120.1 (59.0)	0.04	
HRT	−40.46 (8.07)	<0.0001	
IGF BP-3			
Model for men			0.09
High weekly physical activity	369.0 (215.7)	0.09	
Model for women			0.13
Age at menopause	21.0 (8.15)	0.01	
Number of miscarriages	188.7 (55.9)	0.0009	
IGF-I/IGF BP-3			
Model for men			0.07
BMI	−0.06 (0.03)	0.02	
Total calories	−0.0003 (0.0001)	0.05	
Model for women			0.25
BMI	−0.02 (0.02)	0.14	
Height	3.35 (1.51)	0.03	
HRT	−1.06 (0.21)	<0.0001	
IGF-II[b]			
Model for men			0.50
BMI	−5.59 (1.70)	0.001	
Model for women			0.42
BMI	−5.13 (1.73)	0.003	
High weekly physical activity	113.42 (42.84)	0.009	
IGF-II/IGF BP-3			
Model for men			0.09
BMI	−0.005 (0.002)	0.03	
Height	−0.31 (0.12)	0.01	
Model for women			0.13
BMI	−0.004 (0.002)	0.03	
Age at menopause	−0.003 (0.001)	0.03	
High weekly physical activity	0.15 (0.05)	0.002	

[a] All models were adjusted for age and ethnicity.
[b] In addition to being adjusted for age and ethnicity, the models were adjusted for plasma levels of IGF BP-3.

lifelong exposure, and consequently, may result in increased cancer risk. Evidence for this comes from studies in which cancer risk remained elevated when the analysis was restricted to biological samples collected years before cancer diagnosis, long enough to minimize the possible effects of undetected cancer development on IGF-I plasma levels (3, 9, 42). Whereas our height-IGF-I finding was based on only postmenopausal women, evaluating this relationship among premenopausal women is of particularly interest, as increased breast cancer risk associated with elevated plasma IGF-I levels has been reported among only premenopausal women, not postmenopausal women (42).

Relevance to Cancer in Men. Our findings on plasma IGF levels and body composition among men are relevant to understanding the complex relationships among BMI, height, plasma IGF levels, and prostate cancer. Whereas there is consistent and increasing evidence that elevated IGF-I and lower IGF BP-3 plasma levels increase prostate cancer risk, the relationship between BMI and prostate cancer has been much more equivocal. It is possible that BMI is a poor proxy for the specific aspect of body composition that is related to prostate cancer, as is suggested by studies reporting prostate cancer risk associated with height (43–45). In a recent report by Rodrigues *et al.* (46), height was associated with increased prostate cancer mortality in the earlier but not the later of two large cohort studies that were started 23 years apart. Because the authors observed that average height increased for advancing birth cohorts in the earlier cohort study but not in the more recent one, they speculated that a significant finding among the older men might have been produced by differences between the cohorts. For example, differences in nutritional status would have affected the maximum height attained. Thus, it is possible that in well-nourished individuals, full adult height is determined less by nutritional status than by genetic background. Given the high prevalence rates of obesity in the United States, it may not be surprising that in our sample of people from Texas, height was not strongly associated with plasma IGF levels in men.

Conclusion. To build on our findings of risk factors associated with plasma levels of IGFs, we are preparing an analysis focused primarily on nutritional factors associated with plasma IGF concentrations. Future efforts need to be directed at understanding the influence of genetic polymorphisms involved in the IGF pathway on plasma IGF levels, as reported recently by Jernstrom *et al.* (47). Other efforts should focus on the relevance and relationship of circulating IGF levels to the levels in the tissues in which IGFs exert their effects on carcinogenesis. In the future, we speculate that in addition to interventions that modify IGF levels, we may be able to use nonmodifiable IGF-associated factors, like height and age at menopause, in conjunction with plasma IGF levels to identify and monitor people at elevated risk for IGF-related cancers.

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