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# Anthropometric Correlates of Insulin-Like Growth Factor 1 (IGF-1) and IGF Binding Protein-3 (IGFBP-3) Levels by Race/Ethnicity and Gender

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## Abstract

**Purpose—**Insulin-like growth factor 1 (IGF-1) levels are positively related to some cancers and negatively related to cardiovascular disease. These conditions are also related to insulin resistance and high body weight leading to the hypothesis that IGF-1 levels may, in part, mediate the association of high body weight with these health outcomes. Using the National Health and Nutrition Examination Survey (NHANES) III population, we examined the associations between IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 molar ratio with anthropometric measures in a large, United States population-based study where these associations could also be stratified by race/ethnicity and gender.

**Methods—**The study population consisted of 3168 women and 2635 men (44% non-Hispanic white, 28.2% non-Hispanic black and 27.7% Mexican-American). Anthropometric measures were obtained by trained personnel in the NHANES mobile examination centers. IGF-1 and IGFBP-3 were measured using immunoassays by staff at Diagnostic System Laboratories (DSL) Inc. (Webster, TX). Associations of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 molar ratio with anthropometric variables across race/ethnicity and gender were evaluated using linear regression modeling.

**Results—**Body mass index (BMI) was inversely associated with IGF-1 levels across all of the race/ethnicity and gender subgroups. In contrast, BMI, waist:hip ratio (WHR), and waist circumference were positively associated with IGFBP-3 levels only in non-Hispanic black men and non-Hispanic white women. The IGF-1/IGFBP-3 molar ratio was inversely associated with all anthropometric measures, except height, in all subgroups of the population.

**Conclusion—**The significant inverse associations of BMI with IGF-1 levels and of all anthropometric variables, except height, with the IGF-1:IGFBP-3 molar ratio in all subgroups do not support existing hypotheses that associations of excess weight with negative health outcomes, such as specific cancer diagnoses, are mediated through high IGF-1 levels.

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**Keywords**

BMI; obesity; cancer; IGF

## Introduction

Recent analysis of data collected from the National Health and Nutrition Examination Survey (NHANES) conducted in 2003–2004 demonstrated that there are significant differences in the prevalence of obesity by race/ethnicity in the US population. In this study, 30% of non-Hispanic Whites, 36.8% of Mexican Americans, and 40% of non-Hispanic Black adults were obese as determined by measurement of body mass index (BMI, a measure of weight relative to height) (1). Obesity is associated with many health risks and, among them, increased risk of developing certain types of cancers and increased mortality related to these cancers. Specifically, high BMI has been associated with increased risk and mortality of breast (postmenopausal), endometrial, esophageal, colon, and kidney cancers (2–6). High BMI also has been associated with prostate cancer aggressiveness and mortality (7).

The biological mechanisms linking obesity with increased cancer risk and/or mortality are not fully understood and many hypotheses have been generated to explain this association. One of these hypotheses is that a persistent state of high insulin-like growth factor 1 (IGF-1) levels may be associated with excess weight and promote multiple aspects of tumorigenesis (8). In both *in vitro* and animal models, IGF-1 signaling has been shown to increase cell proliferation, angiogenesis, metastasis, and cell survival (9). Furthermore, numerous epidemiology studies have shown that high serum levels of IGF-1 correlate with increased cancer risk, including prostate (10–12), colon (13–15), ovarian (16,17), and premenopausal breast cancer (18,19). Therefore, high IGF-1 levels have been associated both with cancers where there is strong evidence that obesity may play a role in the development and/or aggressiveness of the cancer (e.g., prostate and colon cancer) and also with cancers where the association with obesity is less clear (e.g., ovarian cancer) or even protective (e.g. premenopausal breast). It is possible that IGF-1 levels may mediate part of the association of anthropometric risk factors with cancer risk and other health outcomes.

Several prior studies have examined the association of IGF-1 levels with various anthropometric measures; however, the results have been mixed (20–27). For most of these studies the populations have been relatively homogeneous or the sample sizes too small to examine these associations stratified by race/ethnicity and gender. Therefore, the goals of the analyses presented here were to assess the relationship between IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio and anthropometric factors in a large, US population-based study where it could be determined if the associations vary across race/ethnicity and gender. These analyses were conducted using data from a subset of the population of the Third NHANES (NHANES III) that was carried out from 1988–1994. We previously published on analyses from these population-based data and showed differences in IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio by race/ethnicity (28). We now expand these analyses to determine if the associations between a variety of anthropometric factors and IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio differ by race/ethnicity and gender.

## Methods and Procedures

This study population is from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative sample of the US population with a stratified multistage probability design and over-sampling of African-and Mexican-Americans (29). The survey, carried out from 1988–1994, included questionnaires, serum collection, and physical

examination. A subset (n = 6,226) of the total sample of adults (n = 20,024) were selected at random and asked to fast overnight before attending a morning examination at which they supplied a serum sample. Response rates for adults aged 20 years and older were approximately 97% (30).

IGF-1 and IGFBP-3 were measured using Diagnostic System Laboratories (DSL, Inc., Webster, TX) IGF-I ELISA (Cat. # 10-5600) and IGFBP-3 IRMA (Catalog # 6600). The IGF-1/IGFBP-3 molar ratio was calculated using a conversion of 1 ng/ml IGF-1 = 0.13 nM IGF-1 and 1 ng/ml IGFBP-3 = 0.036 nM IGFBP-3, which results in multiplying the IGF-1/IGFBP-3 ratio by a constant of 3.61 to arrive at the molar ratio. Prior to measuring IGF-1 and IGFBP-3 in the entire sample of 5803 subjects, extensive evaluation of assay performance was conducted (31). These quality control studies demonstrated that assay batch, day of run, and freeze-thaw cycle can affect the reported IGF-1 or IGFBP-3 concentration. The IGF-1 and IGFBP-3 values reported here are from aliquots that were shipped directly to the National Center for Health Statistics/NHANES collection center and stored in liquid nitrogen. The assays were performed by a single technician and with a single batch of reagents. 10% blinded quality controls samples were in each batch and monitored throughout the laboratory assays. Samples were assayed in duplicate and repeated if the coefficient of variation was greater than 15% from a single vial.

Anthropometric measures were obtained in the Mobile Examination Centers (MEC) from trained interviewers with a standardized protocol and skill level. Anthropometric measures included height, weight, four measures of skin fold thickness (triceps, subscapular, supriliac, and thigh), and waist and hip circumferences and percent body fat. Percent body fat was obtained through bioelectrical impedance analysis (32). Additional data from the NHANES records concerning respondent's age, gender, race/ethnicity, and education was extracted. To account for the complex survey design used in NHANES III, data were analyzed using SUDAAN (33), following recommendations discussed in Korn and Graubard (34).

Analysis of variance was used to detect differences in age and anthropometric variables across race/ethnicity for each gender and to detect differences in IGF-1, IGFBP-3 or the molar ratio across deciles of BMI. Regression analyses were used to determine the association of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 molar ratio with anthropometric measures. In the analyses presented here, age is a linear variable. Age was modeled as a cubic and quadratic term to evaluate non-linear relationships, however, for the associations presented here, there was little influence on the results. In addition, models were adjusted for confounders such as smoking (current, former, never) and stratified on menopausal status (age <50 or 50+) were evaluated. These additional models did not substantially change the results preesented. Therefore, a more straight-forward model including adjusting for age and stratifying by race/ethnicity and gender was used for all analyses. The regression coefficients are presented Age-adjusted least-square means of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio were estimated by deciles of BMI (weighted to the NHANES study population) and stratified by race/ethnicity and gender. Significance for all analyses was determined at $p<0.05$.

## Results

For these analyses, data from a subset of the NHANES III population including 1156 non-Hispanic white men, 702 non-Hispanic black men, 777 Mexican-American men and 1400 non-Hispanic white women, 939 non-Hispanic Black women, and 831 Mexican-American women were examined. Mean age, anthropometric measures, and biomarker concentrations for each subgroup of the study population are presented in Table 1. Mean age was significantly different across all race/ethnicity subgroup comparisons for each gender. Among men, Mexican-Americans were shorter and weighed less than non-Hispanic whites or blacks. Non-Hispanic blacks had a lower sum of skinfolds and waist-to-hip ratio (WHR) than the other two subgroups

and non-Hispanic whites had the highest waist circumference. With regard to biomarker measures, Mexican-American men had the lowest levels of IGF-1. Non-Hispanic black men had among the highest levels of IGF-1 and the lowest levels of IGFBP-3, resulting in this group have the highest IGF-1:IGFBP-3 molar ratio.

Among women, all three subgroups were significantly different from each other for height and percent body fat, while non-Hispanic black women weighed more than non-Hispanic whites or Mexican-Americans. Non-Hispanic white women had a lower BMI, sum of skin folds, WHR, and waist circumference than the other two groups of females. Similar to the males, Non-Hispanic black women had the highest IGF-1:IGFBP-3 molar ratio due to high IGF-1 levels and low IGFBP-3 levels when compared to the other groups.

Given the significant differences in anthropometric measures and IGF-1, IGFBP-3, and IGF1/IGFBP-3 molar ratio between the groups shown in Table 1, we stratified our subsequent analyses by race/ethnicity and gender, while also adjusting for age. We found that the relationships between levels of IGF-1, IGF-BP3, and IGF-1/IGFBP-3 molar ratio and anthropometric measurements did vary by race/ethnicity and gender (Table 2). BMI was inversely associated with IGF-1 levels in all population groups, while waist-to-hip ratio (WHR) and waist circumference were inversely associated with IGF-1 levels in all groups except non-Hispanic black men and Mexican-American females. Percent body fat was inversely associated with IGF-1 levels in all groups of women, as was sum of skin folds except for non-Hispanic Black women. While, among men, only Mexican-Americans had a significant inverse association with sum of skin folds and only Non-Hispanic white men exhibited a significant inverse association with percent body fat. Height was positively associated with IGF-1 levels only in Mexican-Americans, both male and female. Interestingly, none of the anthropometric measures, other than BMI, were associated with IGF-1 levels in non-Hispanic Black Men and the lower 95% confidence bound for the BMI regression coefficient was −0.09.

Among women, all three subgroups exhibited significant inverse associations of BMI and percent body fat with IGF-1 levels. The significant inverse association of WHR with IGF-1 in non-Hispanic black women but not Mexican-Americans is also interesting because these two groups did not have statistically different mean WHR, yet the estimates of the regression coefficients and 95% CI reflect notable differences in this relationship between the two subgroups. Height was positively associated with IGF-1 levels only in Mexican-Americans, both male and female.

The pattern of IGFBP-3 association with anthropometric variables also showed great variation by race/ethnicity and gender (Table 3). In non-Hispanic Black men, IGFBP-3 levels were positively associated with all anthropometric measures, except height. The only other statistically significant association among men was the positive relationship of height with IGFBP-3 in Mexican-American men. Among women, non-Hispanic whites showed a significant positive association of IGFBP-3 levels with BMI, WHR, and waist circumference. WHR also was positively associated with IGFBP-3 in non-Hispanic Black women, while height was positively associated in both non-Hispanic Black and Mexican-American women. In contrast, inverse associations of the IGF-1/IGFBP-3 molar ratio with anthropometric variables were mostly consistent across all race/ethnicity and gender groupings (Table 4); however, there was still a great deal of variation in the regression coefficients, especially among women when examining BMI, WHR and percent body fat.

The analyses of the association of IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 molar ratio with WHR by race/ethnicity and gender were repeated including BMI in the model to determine if adjustment for overall adiposity (i.e. BMI) altered the association with central adiposity or fat distribution pattern, as measured by WHR. When including both BMI and WHR in the same

model, the significance of the association of WHR with IGF-1 and IGFBP-3 was largely attenuated in most groups. For BMI, the significance of the association with IGF-1 levels in non-Hispanic white and Mexican-American men and with IGFBP-3 levels in non-Hispanic white women was attenuated when WHR was added to the model. However, when examining the IGF-1/IGF-BP-3 molar ratio, the significance of the associations with both BMI and WHR remained in all populations after mutual adjustment, with the exception of WHR for Mexican-American males and females.

Prior reports of the association of IGF-1 levels with BMI suggested a peak near or in the overweight range (BMI of 24–27) in both men and women (20,23,26,35). We sought to determine if this observation would be evident in this large population-based study by examining IGF-1 levels by BMI deciles (Table 5). The BMI deciles were weighted to the NHANES III population and the analyses were age-adjusted. Overall, the decrease in IGF-1 across BMI deciles was more pronounced among women. Among men, a general decrease in IGF-1 by BMI deciles was also seen but the difference across BMI deciles reflected by the p value was largely from the comparison of the highest BMI decile to the other deciles. Across all deciles of BMI, non-Hispanic Black men and women had the highest IGF-1 levels. IGFBP-3 levels slightly increased across BMI deciles for non-Hispanic white and black men, while largely remaining the same across BMI deciles for the other subgroups (data not shown). Since increasing BMI was associated, with decreasing IGF-1 and slightly increasing or little change in IGFBP-3, all groups showed a significant inverse association of the IGF-1/IGF-BP-3 molar ratio with BMI (data not shown). Consistent with the mean measures in Table 1, Non-Hispanic black men and women had the highest IGF-1/IGFBP-3 molar ratio across all deciles of BMI by race/ethnicity and gender.

## Discussion

These data demonstrate an inverse association of IGF-1 levels with BMI. The inverse association of BMI with IGF-1 has been reported or suggested previously from smaller studies, many of which focused predominantly on participants of Caucasian background and/or on one gender (19–26,36,37). We were able to replicate this finding in a much larger study population and also to examine this association by race/ethnicity and gender. The inverse association is consistent in all populations in our study.

Conversely, BMI and other measures of adiposity were positively associated with IGFBP-3 levels in non-Hispanic black men but not in the other subgroups of men. These results, in this study population in which all subgroups of men had the same mean BMI, demonstrate the association of BMI with IGFBP-3 levels is differentially modulated across race/ethnicity in men. Similarly, mean percent body fat was the same across all three male subgroups yet there was a significant inverse association of this measure with IGF-1 levels only in the non-Hispanic white men and a significant positive association with IGFBP-3 levels only in non-Hispanic black men. Most prior studies have focused on BMI as a measure of adiposity (19–26,36,37). We further extended these studies to examine other measures of adiposity, including sum of skin folds, WHR, waist circumference, and percent body fat. BMI, WHR, and waist circumference were the measures most consistently inversely associated with IGF-1 levels, thereby, demonstrating that IGF-1 levels are related to both overall and central adiposity, with the exception of non-Hispanic black men. Adjusting for WHR and BMI in the same model mutually attenuated some associations; however, for IGF-1 and IGFBP-3 these changes were not consistent across race/ethnicity and gender. Both BMI and WHR were significantly inversely associated with the IGF-1/IGFBP-3 molar ratio after mutual adjustment in all subgroups except for Mexican-American males and females where the association with WHR was no longer significant. Therefore, in non-Hispanic white and black subgroups, BMI and

WHR each exhibit independent significant inverse associations with IGF-1:IGFBP-3 molar ratio.

The strengths of this study include that the population is from a large nationally-representative sample of the United States population and therefore the results have greater external validity than studies of more selected populations. The composition and size of the study population provided us with the opportunity to stratify our analyses by race/ethnicity and gender. We were able to confirm prior observations regarding the relationship between BMI and IGF-1 levels that were reported in smaller studies and also demonstrate that the association is largely consistent across race/ethnicity and gender in this population. Also, in this study, anthropometric measures were obtained from highly trained and standardized interviewers rather than from self-report and percent body fat was obtained by bioelectrical impedance analysis (32). IGF-1 and IGFBP-3 assays were performed following rigorous evaluation of assay performance and multiple measures were taken to ensure assay accuracy and reproducibility. These efforts included employing a dedicated laboratory technician to run all assays, preparation of one batch of reagents for the duration of the study, and selection of aliquots that were carefully stored. Therefore, the accurate measurements of anthropometric measures, as well as IGF-1 and IGFBP-3 concentrations, and the large population should minimize any potential for bias.

A limitation of this study is that it is cross-sectional and our results are based on total circulating IGF-1 levels. IGF-1 levels are routinely assessed in the clinic and in large epidemiology studies using immunoassays that detect total IGF-1 in circulation. However, circulating levels may not reflect the levels present locally in tissue. We are unable to assess these localized tissue concentrations in our study. Furthermore, free IGF-1 is the bioactive form of the protein, and recent studies have shown an association of free IGF-1, but not total IGF-1, with health outcomes (38,39). Methods to measure free IGF-1 are not yet amenable to large epidemiology studies. The IGF-1/IGFBP-3 ratio, as a surrogate measure of free IGF-1, was incorporated into our analyses. IGFBP-3 is bound to the majority, approximately 80%, of IGF-1 in circulation (40,41). The IGF-1:IGFBP-3 molar ratio has been suggested to be a reasonable approximation of free IGF-1 levels as the direction of change of the molar ratio, under normal physiological conditions, mirrors the direction of the change of free IGF-1 levels (42). However, it has also been shown that free IGF-1 can be influenced by the levels of other IGFBPs (41).

The highest decile of BMI also had the lowest levels of IGF-1 with this decrease being more pronounced across deciles in women. Concomitantly, there also was a decrease in IGF-1:IGFBP-3 molar ratio across BMI deciles for all subgroups of the population. The decrease in the IGF-1:IGFBP-3 molar ratio is largely reflective of the IGF-1 measurements as the IGFBP-3 measurements exhibited little change or only a slight increase across BMI deciles, which is consistent with prior publications of IGFBP-3 and BMI (8,36,42). These data are contradictory of the hypothesis that the associations of certain health outcomes such as cancer risk and mortality with obesity are mediated by high IGF-1 levels. In the NHANES III population, and in other reports, the most extreme BMI cut points are associated with the lowest IGF-1 levels. Others have hypothesized that the levels of free IGF-1 increase with body weight until a threshold is reached that triggers a negative feedback loop. This negative feedback would suppress growth hormone secretion, which in turn would result in decreased IGF-1 production in the liver, the major site of IGF-1 synthesis in the human body (40). The data presented here support this hypothesis in that the individuals in the highest decile of BMI have, on average, the lowest levels of IGF-1.

In rodent models, high IGF-1 levels are associated with diabetes and obesity (43–45). However, the rodent models may not capture the complexity of the human system with respect to IGF-1 regulation by excess body weight maintained over a period of many years. The proposed

negative feedback loop whereby high body weight results in downregulation of IGF-1 in humans (40) may be a phenomenon that occurs only after the individual has maintained the higher body weight for a period of time. This negative regulation with increasing body weight is not evident in the rodent models. However, rodent and human studies are consistent regarding caloric restriction modulating a decrease in IGF-1 levels (37,46,47). More research is needed to understand the different pathways that modulate the IGF axis with respect to aspects of energy balance (e.g. caloric restriction and excess body weight) and to understand the limitations and strengths of the animal models.

As noted in our prior publication (28), results from this NHANES III subpopulation demonstrate racial/ethnic differences in the IGF axis and we extend these studies to examine racial/ethnic differences in the associations of anthropometric measures with IGF-1, IGFBP-3 and the IGF-1:IGFBP-3 molar ratio. There are racial/ethnic differences in the prevalence of obesity (1) and in the prevalence of certain cancers (e.g. colon, prostate, and premenopausal breast) (48) that have been associated with high IGF-1 levels (11,15,19,49–52). In this study, we sought to determine if racial/ethnic variation in the associations of anthropometric measures with levels of IGF-1, IGFBP-3 or the IGF-1:IGFBP-3 molar ratio exist and could be a starting point for exploring the hypothesis that these differences may be a contributing factor to the disproportionate diagnosis of specific cancers that also been associated with high IGF-1 levels. We found that, across all deciles of BMI, non-Hispanic black men and women had the highest levels of IGF-1 and IGF-1/IGFBP-3 molar ratio. In addition, in all subgroups of the population, BMI was inversely associated with IGF-1 levels and all anthropometric measures, except height, were inversely associated with the IGF-1:IGFBP-3 molar ratio. Although the molar ratio data were relatively consistent across subgroups, differences in the associations of anthropometric measures with IGF-1 and IGFBP-3 across race/ethnicity and gender do exist, especially with IGFBP-3 levels in non-Hispanic black men. The differences in overall levels of IGF-1 by race/ethnicity and the associations of IGF-1, IGFBP-3 and the IGF-1/IGFBP-3 molar ratio with anthropometric measures are interesting and suggest that the influence of adiposity on circulating IGF-1 and IGFBP-3 levels may differ by race/ethnicity and gender. Further evaluation of these differences with respect to subsequent health outcomes in these subgroups is warranted.

## References


1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. Jama 2006;295:1549–1555. [PubMed: 16595758]
2. National Cancer Institute Fact Sheet. Obesity and cancer: questions and answers. Bethesda: MNCIM; 2004 [Accessed [6/13/2008]]. NCI fact sheet 3.70 http://www.cancer.gov/cancertopics/factsheet/Risk/obesity
3. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. Jama 2007;298:2028–2037. [PubMed: 17986696]
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638. [PubMed: 12711737]
5. Pan, SY.; DesMeules, M. Energy intake, physical activity, energy balance, and cancer: Epidemiological evidence. In: Verma, M., editor. Methods of Molecular Biology, Cancer Epidemiology. Totowa, NJ: Humana Press; 2009. p. 191-215.
6. Pan SY, Johnson KC, Ugnat AM, et al. Association of obesity and cancer risk in Canada. Am J Epidemiol 2004;159:259–268. [PubMed: 14742286]
7. Giovannucci E, Liu Y, Platz EA, et al. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer 2007;121:1571–1578. [PubMed: 17450530]
8. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab 2006;17:328–336. [PubMed: 16956771]

9. Samani AA, Yakar S, LeRoith D, Brodt P. The role of the IGF system in cancer growth and metastasis: overview and recent insights. Endocr Rev 2007;28:20–47. [PubMed: 16931767]
10. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–566. [PubMed: 9438850]
11. Chan JM, Stampfer MJ, Ma J, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 2002;94:1099–1106. [PubMed: 12122101]
12. Stattin P, Rinaldi S, Stenman UH, et al. Plasma prolactin and prostate cancer risk: A prospective study. Int J Cancer 2001;92:463–465. [PubMed: 11291087]
13. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109S–3120S. [PubMed: 11694656]
14. Ma J, Pollak M, Giovannucci E, et al. A prospective study of plasma levels of insulin-like growth factor I (IGF-I) and IGF-binding protein-3, and colorectal cancer risk among men. Growth Horm IGF Res 2000;10:S28–S29. [PubMed: 10984282]
15. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–625. [PubMed: 10203281]
16. Lukanova A, Lundin E, Toniolo P, et al. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. Int J Cancer 2002;101:549–554. [PubMed: 12237896]
17. Peeters PH, Lukanova A, Allen N, et al. Serum IGF-I, its major binding protein (IGFBP-3) and epithelial ovarian cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2007;14:81–90. [PubMed: 17395977]
18. Renehan AG, Egger M, Minder C, et al. IGF-I, IGF binding protein-3 and breast cancer risk: comparison of 3 meta-analyses. Int J Cancer 2005;115:1006–1007. [PubMed: 15723358]author reply 1008
19. Renehan AG, Harvie M, Howell A. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. Endocr Relat Cancer 2006;13:273–278. [PubMed: 16728563]
20. Allen NE, Appleby PN, Kaaks R, et al. Lifestyle determinants of serum insulin-like growth-factor-I (IGF-I), C-peptide and hormone binding protein levels in British women. Cancer Causes Control 2003;14:65–74. [PubMed: 12708727]
21. DeLellis K, Rinaldi S, Kaaks RJ, et al. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2004;13:1444–1451. [PubMed: 15342444]
22. Gapstur SM, Kopp P, Chiu BC, et al. Longitudinal associations of age, anthropometric and lifestyle factors with serum total insulin-like growth factor-I and IGF binding protein-3 levels in Black and White men: the CARDIA Male Hormone Study. Cancer Epidemiol Biomarkers Prev 2004;13:2208–2216. [PubMed: 15598782]
23. Gram IT, Norat T, Rinaldi S, et al. Body mass index, waist circumference and waist-hip ratio and serum levels of IGF-I and IGFBP-3 in European women. Int J Obes (Lond) 2006;30:1623–1631. [PubMed: 16552400]
24. Henderson KD, Goran MI, Kolonel LN, et al. Ethnic disparity in the relationship between obesity and plasma insulin-like growth factors: the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2006;15:2298–2302. [PubMed: 17119061]
25. Lukanova A, Lundin E, Zeleniuch-Jacquotte A, et al. Body mass index, circulating levels of sex-steroid hormones, IGF-I and IGF-binding protein-3: a cross-sectional study in healthy women. Eur J Endocrinol 2004;150:161–171. [PubMed: 14763914]
26. Lukanova A, Soderberg S, Stattin P, et al. Nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations (Sweden). Cancer Causes Control 2002;13:509–516. [PubMed: 12195640]
27. Platz EA, Pollak MN, Rimm EB, et al. Racial variation in insulin-like growth factor-1 and binding protein-3 concentrations in middle-aged men. Cancer Epidemiol Biomarkers Prev 1999;8:1107–1110. [PubMed: 10613344]
28. Berrigan D, Potischman N, Dodd KW, et al. Race/ethnic variation in serum levels of IGF-I and IGFBP-3 in US adults. Growth Horm IGF Res. 2008

29. National Center for Health Statistics. NCHS plan and operation of the Third National Health and Nutrition Examination Survey, 1988–1994. Vital Health Stat 1994;1
30. National Center for Health Statistics. Analytic and reporting guidelines: the Third National Health and Nutrition Examination Survey, NHANES III (1988–1994). Hyattsville, MD: 1996. p. 47
31. Berrigan D, Potischman N, Dodd KW, et al. Serum levels of insulin-like growth factor-1 and insulin like growth factor-1 binding protein-3: Quality control for studies of stored serum. Cancer Epidemiol Biomarkers Prev 2007;16:1017–1022. [PubMed: 17507631]
32. Chumlea WC, Guo SS, Kuczmarski RJ, et al. Body composition estimates from NHANES III bioelectrical impedance data. Int J Obes Relat Metab Disord 2002;26:1596–1609. [PubMed: 12461676]
33. Shah, BV.; Barnwell, G.; Bieler, GS. SUDAAN user's manual, release 8.0. Research Triangle Park, NC: Research Triangle Institute; 1997.
34. Korn, EL.; Graubard, BI. Analysis of health surveys. New York: John Wiley and Sons; 1999.
35. Holmes MD, Pollak MN, Hankinson SE. Lifestyle correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 2002;11:862–867. [PubMed: 12223430]
36. Chang S, Wu X, Yu H, Spitz MR. Plasma concentrations of insulin-like growth factors among healthy adult men and postmenopausal women: associations with body composition, lifestyle, and reproductive factors. Cancer Epidemiol Biomarkers Prev 2002;11:758–766. [PubMed: 12163330]
37. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001;60:91–106. [PubMed: 11310428]
38. Gunter MJ, Hoover DR, Yu H, et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev 2008;17:921–929. [PubMed: 18398032]
39. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. Cancer Res 2008;68:329–337. [PubMed: 18172327]
40. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–591. [PubMed: 15286738]
41. Frystyk J. Utility of free IGF-I measurements. Pituitary 2007;10:181–187. [PubMed: 17429595]
42. Frystyk J. Free insulin-like growth factors -- measurements and relationships to growth hormone secretion and glucose homeostasis. Growth Horm IGF Res 2004;14:337–375. [PubMed: 15336229]
43. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006;444:337–342. [PubMed: 17086191]
44. Hursting SD, Nunez NP, Varticovski L, Vinson C. The obesity-cancer link: lessons learned from a fatless mouse. Cancer Res 2007;67:2391–2393. [PubMed: 17363554]
45. Yakar S, Nunez NP, Pennisi P, et al. Increased tumor growth in mice with diet-induced obesity: impact of ovarian hormones. Endocrinology 2006;147:5826–5834. [PubMed: 16959846]
46. Berrigan D, Perkins SN, Haines DC, Hursting SD. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. Carcinogenesis 2002;23:817–822. [PubMed: 12016155]
47. Hursting SD, Lashinger LM, Wheatley KW, et al. Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link. Best Pract Res Clin Endocrinol Metab 2008;22:659–669. [PubMed: 18971125]
48. American Cancer Society Cancer Facts and Figures 2008. Altanta: American Cancer Society; 2008.
49. Allen NE, Roddam AW, Allen DS, et al. A prospective study of serum insulin-like growth factor-I (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. Br J Cancer 2005;92:1283–1287. [PubMed: 15756268]
50. Giovannucci E, Pollak MN, Platz EA, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9:345–349. [PubMed: 10794477]

51. Renehan AG, Zwahlen M, Minder C, et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–1353. [PubMed: 15110491]

52. Stattin P, Bylund A, Rinaldi S, et al. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. J Natl Cancer Inst 2000;92:1910–1917. [PubMed: 11106682]

**Table 1**

Demographic and anthropometric variables of NHANES III subset

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| **Variable**[1] | **NH White n=1156 (19.9%)** | **NH Black n=702 (12.1%)** | **Mexican, American n=777 (13.4%)** | **p value**[d] | **NH White n=1400 (24.1%)** | **NH Black n=937 (16.1%)** | **Mexican, American n=831 (14.3%)** | **p value**[e] |
| **Age (yr)**[2] | 43.9[a] (42.4, 45.3) | 40.8[b] (39.4, 42.2) | 35.9[c] (34.8, 37.0) | <.0001 | 45.7[a] (44.2, 47.3) | 41.2[b] (40.2, 42.3) | 37.2[c] (36.0, 38.4) | <.0001 |
| **Height (cm)** | 176.7[a] (176.2, 177.3) | 176.5[a] (175.8, 177.2) | 169.9[b] (169.1, 170.7) | <.0001 | 162.4[a] 161.8, 162.98) | 163.2[b] (162.7, 163.6) | 157.1[c] (156.5, 157.8) | <.0001 |
| **Weight (kg)** | 84.2[a] (82.9, 85.6) | 83.0[a] (81.8, 84.3) | 78.0[b] (76.5, 79.5) | <.0001 | 68.1[a] (66.9, 69.3) | 77.3[b] (75.7, 78.9) | 69.6[a] (68.2, 71.0) | <.0001 |
| **BMI (kg/m2)** | 26.9[a] (26.5, 27.3) | 26.6[a] (26.2, 27.0) | 26.9[a] (26.5, 27.4) | 0.61 | 25.8[a] (25.4, 26.3) | 29.0[b] (28.4, 29.6) | 28.2[b] (27.7, 28.6) | <.0001 |
| **Waist, Hip ratio** | 0.96[a] (0.95, 0.96) | 0.92[b] (0.91, 0.93) | 0.96[a] (0.95, 0.96) | <.0001 | 0.86[a] (0.85, 0.86) | 0.87[b] (0.87, 0.88) | 0.89[b] (0.88, 0.89) | <.0001 |
| **Waist circumference (cm)** | 96.4[a] (95.4, 97.4) | 92.0[b] (90.9, 93.1) | 93.6[b] (92.4, 94.7) | <.0001 | 87.3[a] (86.2, 88.5) | 93.2[b] (91.8, 94.6) | 91.3[b] (90.0, 92.7) | <.0001 |
| **Sum of skinfolds (mm)**[3] | 68.0[a] (65.6, 70.3) | 61.0[b] (58.2, 63.8) | 66.7[a] (64.3, 69.1) | 0.0004 | 86.6[a] (84.1, 89.15) | 92.5[b] (89.6, 95.4) | 95.1[b] (91.5, 98.7) | 0.0003 |
| **% body fat** | 21.5[a] (20.8, 22.1) | 21.5[a] (20.9, 22.1) | 20.8[a] (20.0, 21.6) | 0.68 | 22.2[a] (21.4, 23.0) | 27.9[b] (26.9, 29.0) | 25.2[c] (24.4, 26.0) | <.0001 |
| **IGF-1 (ng/ml)** | 287 (279, 294) | 284 (276, 293) | 265 (257, 274) | 0.03 | 256 (246, 266) | 282 (272, 291) | 249 (236, 262) | <.0001 |
| **IGFBP-3 (ng/ml)** | 4437 (4346, 4529) | 4072 (3993, 4151) | 4184 (4108, 4259) | <.0001 | 4584 (4512, 4656) | 4368 (4250, 4487) | 4337 (4216, 4458) | <.0001 |
| **IGF-1/IGFBP-3 (molar ratio)** | 234 (228, 240) | 252 (244, 259) | 228 (223, 234) | 0.0001 | 199 (192, 207) | 234 (226, 242) | 204 (196, 212) | <.0001 |

[1] Values weighted to account for the survey design

[2] Mean (95% confidence interval)

[3] Triceps +Subscapular + Suprailiac + Thigh

[a,b,c] Means with the same letter designation are statistically the same within each gender

[d] p value for differences among males

[e] p value for differences among females

**Table 2**

Age-adjusted regression coefficients for average IGF-1 related to anthropometric variables, stratified by race/ethnicity and gender

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Variable** | **NH White** | **NH Black** | **Mexican-American** | **NH White** | **NH Black** | **Mexican-American** |
| **BMI** | −2.49* (−3.60, −1.38) | −1.33* (−2.57, −0.09) | −2.61* (−4.40, −0.81) | −1.47* (−2.32, −0.63) | −2.82* (−4.03, −1.61) | −3.65* (−5.52, −1.79) |
| **Waist:Hip** | −193.71* (−306.59, −80.83) | −109.96 (−257.15, 37.24) | −216.61* (−364.56, −68.65) | −95.94* (−177.11, −14.77) | −193.80* (−309.76, −77.83) | −75.35 (−236.65, 85.94) |
| **Waist Circumference** | −0.89* (−1.34, −0.43) | −0.40 (−0.87, 0.07) | −0.85* (−1.60, −0.10) | −0.8219* (−1.16, −0.48) | −1.24* (−1.76, −0.72) | −1.43* (−2.32, −0.54) |
| **Sum of skinfolds** | −0.20 (−0.43, 0.04) | 0.06 (−0.34, 0.46) | −0.34* (−0.65, −0.02) | −0.24* (−0.48, −0.003) | −0.23 (−0.54, 0.07) | −0.66* (−0.91, −0.41) |
| **% body fat** | −1.70* −2.86, −0.55 | −0.11 (−1.91, 1.69) | −1.06 (−2.27, 0.14) | −1.89* (−2.59, −1.20) | −2.45* (−3.38, −1.52) | −3.80* (−5.39, −2.20) |
| **Height** | 0.76 (−0.31, 1.84) | 1.22 (−0.15, 2.60) | 1.91* (0.83, 2.99) | −0.31 (−1.37, 0.76) | 1.05 (−0.62, 2.72) | 1.38* (0.19, 2.58) |

*p<0.05 for regression coefficient not equal to 0

**Table 3**

Age-adjusted regression coefficients for average IGFBP-3 related to anthropometric variables, stratified by race/ethnicity and gender

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Variable** | **NH White** | **NH Black** | **Mexican-American** | **NH White** | **NH Black** | **Mexican-American** |
| **BMI** | 4.90 (−10.60, 20.41) | 26.24* (16.61, 35.87) | 7.77 (−5.95, 21.49) | 8.68* (1.43, 15.93) | −9.90 (−20.17, 0.37) | −10.24 (−25.46, 4.98) |
| **Waist:Hip** | 785.42 (−496.67, 2067.50) | 2084.83* (886.60, 3283.05) | 23.61 (−1231.41, 1278.64) | 836.16* (40.77, 1631.54) | 1141.46* (78.56, 2204.37) | 909.75 (−100.51, 1920.02) |
| **Waist Circumference** | 2.92 (−3.10, 8.95) | 12.44* (8.37, 16.50) | 5.22 (−0.48, 10.92) | 4.05* (1.07, 7.03) | −0.63 (−4.72, 3.46) | −1.45 (−8.06, 5.15) |
| **Sum of skinfolds** | 1.14 (−2.41, 4.69) | 6.23* (3.37, 9.09) | 2.14 (−0.05, 4.33) | 1.60 (−0.84, 4.05) | −1.82 (−4.48, 0.84) | 0.85 (−1.89, 3.58) |
| **% body fat** | 9.80 −3.40, 23.00 | 28.37* (17.43, 39.30) | 2.90 (−7.65, 13.45) | 1.25 (−7.38, 9.88) | −1.16 (−11.62, 9.29) | −6.62 (−23.71, 10.48) |
| **Height** | 3.44 (−6.12, 13.01) | 11.40 (−1.51, 24.32) | 26.16* (16.50, 35.81) | 5.00 (−3.72, 13.72) | 13.19* (1.52, 24.87) | 18.78* (5.21, 32.35) |

*p<0.05 for regression coefficient not equal to 0

**Table 4**

Age-adjusted regression coefficients for average IGF-1:IGFBP-3 (Molar Ratio) related to anthropometric variables, stratified by race/ethnicity and gender

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| **Variable** | **NH White** | **NH Black** | **Mexican-American** | **NH White** | **NH Black** | **Mexican-American** |
| **BMI** | −2.27* (−2.99, −1.55) | −2.63* (−3.56, −1.71) | −2.77* (−4.07, −1.47) | −1.50* (−2.05, −0.95) | −1.88* (−2.87, −0.89) | −2.72* (−3.82, −1.63) |
| **Waist:Hip** | −191.18* (−264.10, −118.26) | −212.95* (−312.34, −113.52) | −194.88* (−290.10, −99.59) | −121.65* (−176.58, −66.62) | −228.62* (−295.52, −163.72) | −129.84* (−235.18, −24.51) |
| **Waist Circumference** | −0.85* (−1.17, −0.52) | −0.34* (−0.56, −0.10) | −1.07* (−1.55, −0.59) | −0.84* (−1.07, −0.61) | −1.04* (−1.45, −0.63) | −1.24* (−1.75, −0.71) |
| **Sum of skinfolds** | −0.21* (−0.38, −0.03) | −0.38* (−0.57, −0.10) | −0.42* (−0.69, −0.14) | −0.24* (−0.38, −0.11) | −0.11 (−0.35, 0.14) | −0.56* (−0.72, −0.41) |
| **% body fat** | −1.83* (−2.53, −1.12) | −1.67* (−3.05, −0.30) | −1.08* (−1.78, −0.37) | −1.55* (−2.07, −1.03) | −1.90* (−2.94, −0.85) | −2.91* (−3.92. −1.89) |
| **Height** | 0.38 (−0.29, 1.03) | 0.42 (−0.45, 1.28) | 0.10 (−0.57, 0.77) | −0.45 (−1.11, 0.21) | 0.10 (−0.89, 1.09) | 0.32 (−0.64, 1.28) |

* p<0.05 for regression coefficient not equal to 0

**Table 5**

Age-adjusted IGF-1 means by weighted BMI deciles stratified by race/ethnicity and gender, NHANES III

| | Male | | | | Female | | |
|---|---|---|---|---|---|---|---|
| | **White NH (n=1156)** | **Black NH (n=702)** | **Mexican-American (n=777)** | | **White NH (n=1400)** | **Black NH (n=937)** | **Mexican-American (n=831)** |
| **IGF-1 levels** | | | | **IGF-1 levels** | | | |
| **BMI <=21.4** (n=289) | 257.0 | 261.5 | 249.0 | **BMI<=19.9** (n=256) | 252.6 | 307.4 | 255.5 |
| **21.5–22.8** (n=261) | 268.6 | 301.9 | 260.2 | **20.0–21.3** (n=237) | 228.4 | 292.2 | 294.3 |
| **22.9–3.9** (n=237) | 272.3 | 272.1 | 256.5 | **21.4–22.3** (n=217) | 249.7 | 277.3 | 249.1 |
| **24.0–24.9** (n=264) | 273.5 | 264.8 | 255.6 | **22.4–23.7** (n=286) | 227.3 | 302.7 | 252.0 |
| **25.0–25.8** (n=235) | 269.6 | 294.9 | 257.6 | **23.8–25.0** (n=319) | 239.3 | 294.9 | 271.0 |
| **25.9–27.0** (n=291) | 261.4 | 272.2 | 256.2 | **25.1–26.3** (n=313) | 219.0 | 280.6 | 238.3 |
| **27.1–28.3** (n=302) | 265.8 | 276.4 | 259.9 | **26.4–28.1** (n=386) | 242.3 | 292.0 | 258.3 |
| **28.4–30.0** (n=305) | 260.2 | 313.8 | 247.6 | **28.2–30.9** (n=445) | 226.8 | 288.7 | 236.0 |
| **30.1–32.7** (n=280) | 258.0 | 277.2 | 247.6 | **31.0–34.6** (n=404) | 244.3 | 252.9 | 220.2 |
| **32.8+** (n=278) | 217.5 | 241.9 | 211.7 | **34.7+** (n=449) | 204.5 | 249.0 | 194.8 |
| **p value*** | <.0001 | 0.001 | 0.007 | **p value*** | 0.0002 | <.0001 | <.0001 |

* p<0.05, for difference across BMI deciles within each subgroup