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Racial differences in the association of insulin-like growth factor pathway and colorectal adenoma risk

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Abstract

Purpose—Insulin resistance is believed to play an important role in the link between energy imbalance and colon carcinogenesis. Emerging evidence suggests that there are substantial racial differences in genetic and anthropometric influences on insulin-like growth factors (IGFs); however, few studies have examined racial differences in the associations of IGFs and colorectal adenoma, precursor lesions of colon cancer.

Methods—We examined the association of circulating levels of IGF-1, IGFBP-3 and IGFBP-1, and SNPs in the IGF-1 receptor (*IGF1R*), IGF-2 receptor (*IGF2R*), and insulin receptor genes with risk of adenomas in a sample of 410 incident adenoma cases and 1,070 controls from the Case Transdisciplinary Research on Energetics and Cancer (TREC) Colon Adenomas Study.

Results—Caucasians have higher IGF-1 levels compared to African Americans; mean IGF-1 levels are 119.0 ng/ml (SD = 40.7) and 109.8 ng/ml (SD = 40.8), respectively, among cases (p = 0.02). Mean IGF-1 levels are also higher in Caucasian controls (122.9 ng/ml, SD = 41.2) versus

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African American controls (106.9, SD = 41.2), $p = 0.001$. We observed similar differences in IGFBP3 levels by race. Logistic regression models revealed a statistically signifi-cant association of IGF-1 with colorectal adenoma in African Americans only, with adjusted odds ratios (ORs) of 1.68 (95 % CI 1.06–2.68) and 1.68 (95 % CI 1.05–2.71), respectively, for the second and third tertiles as compared to the first tertile. One SNP (rs496601) in *IGF1R* was associated with adenomas in Caucasians only; the per allele adjusted OR is 0.73 (95 % CI 0.57–0.93). Similarly, one *IGF2R* SNP (rs3777404) was statistically significant in Caucasians; adjusted per allele OR is 1.53 (95 % CI 1.10–2.14).

Conclusion—Our results suggest racial differences in the associations of IGF pathway biomarkers and inherited genetic variance in the IGF pathway with risk of adenomas that warrant further study.

Keywords

Colorectal adenoma; Insulin-like growth factor; Obesity; African American; Candidate gene

Introduction

Colorectal cancer is a significant public health concern. In developed countries, twenty percent of all cancer mortality can be attributed to colorectal cancer [1]. While obesity and diets high in calories and fat have been studied extensively and are recognized as risk factors for colorectal cancer, the specific biological mechanisms responsible for the association of adiposity and colorectal cancer risk are not well established [2].

Racial disparities in colorectal cancer have been well documented, with African Americans having higher incidence and mortality compared to Caucasians [3–5]. Furthermore, while the mortality rates have been steadily declining for Caucasians, mortality from colorectal cancer among African Americans has not followed the same trend [3]. Because such disparities exist, it is important to understand the inherent biological mechanisms at play. Unfortunately, to date, very little research has been performed to study racial disparities in colorectal cancer or colorectal adenomas—the precursor lesion to colorectal cancer. Research to date on colorectal cancer and adenomas largely supports that obesity and inflammation pathways are involved in the promotion and progression of colorectal cancer, as well as many other types of cancer [6]. It has also been established that many biomarkers in these pathways differ by race or ethnicity [7]. Therefore, it is important to determine which ones may play a role in carcinogenesis by race. For African Americans in particular, with such elevated incidence and mortality rates, it is important to better elucidate the biomarkers involved in the development of colorectal cancer.

Insulin-like growth factors (IGFs) are candidates for study due to their influence on cell proliferation, differentiation, and apoptosis [1, 8, 9]. IGFs, and insulin-like growth factor-1(IGF-1) in particular, influence cell proliferation, differentiation, and apoptosis [8], and these effects are mediated through binding with the IGF-1 receptor and the insulin receptor [10, 11]. The majority of circulating IGF-1 is bound to IGF-binding proteins, and its main binding protein is IGF-binding protein-3 (IGFBP-3). Binding prolongs IGF-1 in circulation and slows its ability to react with the IGF-1 receptor, while unbound IGF-1 is free to react with the IGF-1 receptor to stimulate cell proliferation and angiogenesis and inhibit apoptosis [12].

Some studies that have examined circulating IGF-1 and IGFBP-3 report a statistically significant association with colorectal cancer and adenomas [13], while others have not [14]. Other research that has focused on genetic polymorphisms in *IGF-1* and *IGFBP-3* is similarly inconsistent, showing no associations [15, 16] or very weak associations with

colorectal cancer [1, 17]. Because IGFs are important factors associated with obesity and inflammation, and therefore may well be involved in carcinogenesis, they warrant thorough study.

In African Americans, biomarker levels of IGF pathway peptides are somewhat different than Caucasians in which mean plasma levels of IGF-1 and IGFBP-3 are usually lower in African Americans [18, 19]. Whether these markers are also significantly associated with risk of colorectal cancer and adenoma in African Americans has not been thoroughly studied. Because plasma levels of IGF-1 and IGFBP-3 consistently differ between African Americans and Caucasians, and because of the significant racial disparities in colorectal cancer incidence and mortality, it is important to determine whether these peptides also play a role in colon carcinogenesis in African Americans specifically with regard to adenomas, precursor lesions of colorectal cancer. We sought to determine whether IGF-1, IGFBP-3, IGFBP-1, and the IGF-1/IGFBP-3 molar ratio as well as inherited genetic polymorphisms differ in their associations with colorectal adenoma by race.

Materials and methods

Study population

Participants were recruited according to the Case Transdisciplinary Research on Energetics and Cancer (TREC) Colon Adenomas Study protocol [20]. Patients scheduled for routine colonoscopy for colorectal cancer screening at University Hospitals Case Medical Center (UHCMC) and affiliated clinics were recruited and surveyed using computer-assisted personal interviews for epidemiological risk factors prior to endoscopy [20]. At the time of colonoscopy, a nurse drew a fasting blood sample and obtained anthropometric measurements. Patients were excluded if they were ever diagnosed with inflammatory bowel disease, cancer, or colorectal adenomas or were younger than 30 years of age [20]. Our outcome of interest, the presence or absence of colorectal adenomas, was determined with histopathologically confirmed diagnosis of adenomatous polyps. Advanced adenoma is defined as adenoma with size ≥10 mm or with high-grade dysplasia. In the entire study sample, there were 432 incident adenoma cases and 1,139 adenoma-free controls; we excluded participants if they were missing data for relevant biomarkers or covariates for our analysis. There were six colorectal cancers identified through screening, and these individuals were excluded from the study. We included only Caucasians and African Americans in the analysis due to low numbers in other groups. The UHCMC approved this study, and all patients provided written informed consent [20].

Measurement of biomarkers

Plasma IGF-1, IGFBP-1, and IGFBP-3 were assayed using ELISAs with reagents from Diagnostic Systems Laboratory, Inc. (Webster, TX) according to standard protocol. Frozen pools and lyophilized control materials were used in each assay. All assays were carried out blinded to case–control status. Quality control samples were included within assay runs. The inter-assay coefficients of variation (CV) ranged from 6.41 to 10.88 % for IGF-1, from 4.21 to 7.32 % for IGFBP-1 and 6.36–8.19 % for IGFBP-3.

Selection and genotyping of SNPs in candidate genes

To study the contribution of genes in the IGF pathway, we selected *IGF1R*, *IGF2R*, and *INSR* haplotype-tagging SNPs using the Genome Variation Server (GVS) (http://gvs.gv.washington.edu/GVS/) from within each candidate gene as well as 5 kb up- and downstream. Tag SNPs were identified using GVS from the HapMap Yoruba population with an r^2 threshold of 0.8, 85 % data coverage, and 70 % clustering, and functional and/or non-synonymous SNPs were preferentially chosen. We limited our selection to SNPs with a

minor allele frequency of 0.05 or greater. SNPs were genotyped using the Illumina Custom Golden Gate Panel (Illumina, Inc., San Diego, CA).

We selected 14 SNPs in *IGF1R*, 8 SNPs in *IGF2R*, and 15 SNPs in *INSR* for genotyping and of those, five failed genotyping and were thus excluded, resulting in 13 SNPs in *IGF1R*, 6 SNPs in *IGF2R*, and 10 SNPs in *INSR* for analysis. The overall call rate for these SNPs was 99.2 % (range 93.6–100 %). We looked for deviations in Hardy–Weinberg equilibrium (HWE) among the control patients, separately by race, and excluded rs2059806 in *INSR* because of deviations from HWE (<0.01). We further excluded SNPs with a minor allele frequency less than 5 % (estimated separately by race) because of low power to detect genetic associations; this resulted in the exclusion of two SNPs for both Caucasians and African Americans (rs3743262 and rs1058696), one SNP excluded from analysis in Caucasians only (rs3743260), and one from analysis in African Americans only (rs1864193).

Measurement of covariates

Patients were surveyed for risk factors over the phone prior to colonoscopy. Smoking status was elicited and categorized as never (smoked <6 months in his or her lifetime), former, or current. Individuals were classified as non-steroidal anti-inflammatory drug (NSAID) users if they reported having taken aspirin or ibuprofen at least twice per week for at least 1 month. Family history of colorectal cancer was considered positive if individuals reported having at least one first-degree family member diagnosed with colon or rectal cancer [21]. At the time of the colonoscopy, height, weight, and waist circumference were measured by a study nurse according to standardized protocols [21]. Body mass index (BMI) was calculated as kilograms per height in meters squared (kg/m^2).

Statistical analysis

We calculated descriptive statistics by race and case–control status using chi-square tests for categorical variables and independent sample *t* tests for continuous variables. The *p* value for statistical significance was determined a priori at <0.05. We estimated partial correlation coefficients to analyze the correlation of IGF biomarkers and obesity measures adjusted for age and sex, with stratification by race and case–control status.

We used binary logistic regression models (using SPSS version 19) to analyze the relationship between adenomas and tertiles of circulating IGF-1, IGFBP-3, IGFBP-1, and molar ratio based on the control distributions and separately by race, using tertile 1 as the reference group. We controlled for the following covariates due to their previous association with colon cancer: age, sex, family history of colorectal cancer, NSAID use, and BMI. Age and sex were included in both the crude and adjusted models for both races because they are significantly associated with the presence of adenoma in both Caucasians and African Americans. Smoking status and family history of colorectal cancer are included in the model for both Caucasians and African Americans because they are risk factors for colon adenoma and colorectal cancer in both races. We include NSAID use because it is considered to be a protective factor for colon neoplasia. Some evidence has indicated that different adiposity measures are associated with disease in Caucasians and African Americans. However, in our data, there were no appreciable differences in the point estimates or 95 % confidence intervals when the models were adjusted for any of the adiposity measures (data not shown). Therefore, we present final models adjusted for BMI. Given our race-specific a priori hypothesis, we chose two methods for examining IGF–adenoma associations by race. We stratified by race and then also formally tested for statistical interaction by race, considering *p* values<0.10 statistically significant for multiplicative interaction terms in models.

Because Caucasians and African Americans differ with respect to BMI, waist circumference, and waist/hip ratio, we evaluated whether obesity is an important confounder for racial differences. We did this by estimating crude and adjusted means IGF-1, IGFBP1, and IGFBP3 adjusted for different measures of obesity; here, we evaluated whether adjustment for obesity would remove the race differences in circulating IGF pathway biomarkers. We also examined trends in biomarker levels by tertile of adiposity (stratified by race) to examine linear trends.

For SNP analyses, we used unconditional logistic regression and log additive genetic models to analyze the association of SNPs and adenoma status separately by race to estimate crude ORs and ORs adjusted for the aforementioned covariates. We did further adjust for multiple testing in the analysis of these SNPs [22]. We analyzed whether SNPs in *IGF1R, IGF2R,* and *INSR* are associated with circulating IGF-1 levels by analyzing mean levels for each genotype and testing for statistical significance using general linear models with and without adjustment for covariates mentioned above.

Results

Table 1 summarizes descriptive characteristics of our colonoscopy screening sample by race. Approximately 63 % of study participants are Caucasian and 38 % are African American. Notable differences by race include measures of adiposity (all $p < 0.001$), smoking status (more current smokers in African Americans), family history, insulin, and fasting glucose. In our sample, the prevalence of advanced adenoma is slightly higher for African Americans (6.17 %) versus 4.27 % in Caucasians, but this difference was not statistically significant.

Table 2 shows differences in IGF biomarkers according to race and case–control status. Caucasian colorectal adenoma cases have significantly higher IGF-1 and IGFBP-3 levels than African American cases in our sample, and the same is true for controls (all $p < 0.002$). Caucasian controls have higher circulating levels of IGFBP-1 than African American controls ($p = 0.001$). Other notable differences include Caucasian cases having higher IGFBP-3 than Caucasian controls ($p = 0.02$).

We observed no statistically significant correlations of IGF-1 or IGFBP3 with any obesity measure, including BMI, WHR, or waist circumference for any group examined. For IGFBP-1, however, we found negative correlation coefficients that were strongest for BMI and waist circumference and ranging from −0.20 to −0.48 that were very similar for Caucasians and African Americans. One interesting observation in African Americans is that correlations of IGF-1 with obesity measures range from 0.03 to 0.13 in African American cases and −0.02 to −0.06 in African American controls; however, these correlations were not statistically significant (data not shown).

In Caucasians, we observed no statistically significant association of IGF-1 and adenomas (Table 3). In African Americans, however, IGF-1 levels are statistically significantly associated with increased odds of colorectal adenomas: Compared to the bottom tertile, the adjusted OR for the second and third tertiles was almost identical [1.68 (95 % CI 1.06–2.68) and 1.68 (95 % CI 1.05–2.71), respectively (p-trend = 0.12)], suggesting a threshold effect.

In Caucasians, higher levels of IGFBP-3 are associated with a reduced but non-significant risk of adenomas. In contrast, for African Americans, the ORs are, albeit non-significant, in the opposite direction to that of the Caucasians. For both African Americans and Caucasians, there are no statistically significant associations of IG-FBP-1 and colorectal adenomas. Similarly for both African Americans and Caucasians, there were no statistically

significant associations of the IGF-1/IGFBP-3 molar ratio with colorectal adenomas. We tested for and identified a statistical interaction between race and IGF-1 (*p*-interaction = 0.08). Tests for multiplicative interaction of race and IGFBP-3 and IGFBP-1 were not statistically significant.

When we performed analyses limited to cases with advanced adenomas, our results showed no significant associations for any of the biomarkers for either race or when we analyzed the whole sample (data not shown). However, caution must be exercised in interpreting these results given the relatively small number of advanced adenomas.

Circulating levels of IGF-1, IGFBP-1, and IGFBP-3 differed significantly between African Americans and Caucasians regardless of adjustment for any of the adiposity measures; differences in circulating levels of IGF-1, IGFBP-1, and IGFBP-3 between African Americans and Caucasians are not entirely due to adiposity differences. For both African Americans and Caucasians, we observed a trend in circulating levels of IGFBP-1; increased tertiles of adiposity were associated with lower levels of IGFBP-1 (data not shown). IGF-1 levels by adiposity are nonlinear, and this is consistent for both groups; for both African Americans and Caucasians, we observed an inverse trend in circulating levels of IGFBP-1, where the highest tertiles of adiposity have the lowest levels of IGFBP-1 (data not shown). Table 4 shows the association of SNPs in candidate genes and odds of adenomas. Of the 13 SNPs analyzed in *IGF1R*, one SNP (rs4966011) is statistically significantly associated risk of colorectal adenoma in Caucasians only (adjusted per allele OR = 0.73 (95 % CI 0.57–0.93). Of the six SNPs analyzed in *IGF2R*, one SNP, rs3777404, is significant in Caucasians only; the adjusted per allele OR = 1.53 (95 % CI 1.10–2.14). There are no statistically significant associations identified for any of the 10 *INSR* SNPs. Only one of the two significant SNPs survives a gene-specific Bonferroni correction, *IGF2R* rs3777404. However, when we adjust for all SNP tests performed, no SNPs remain statistically significant.

In analyses of mean IGF-1 levels according to *IGF1R*, *IGF2R*, and *INSR* genotypes, one SNP in *INSR* (rs891087) showed statistically significant differences in IGF-1 in African Americans only ($p = 0.038$); IGF-1 levels for CC (common) and TT (rare) genotypes were 106.7 ng/mL (SD = 38.19) and 127.5 (SD = 52.2), respectively. However, it is important to note that this trend becomes non-significant ($p = 0.07$) when we adjust the means for covariates. Differences in biomarker means for other candidate genotypes did not reach statistical significance (data not shown).

Discussion

We identified modest race-specific differences in the association between IGF-1 and adenomas. In particular, we observed an association between circulating levels of IGF-1 and adenomas in African Americans only. We also demonstrated a genetic association of one SNP in *IGF1R*, rs4966011, and one SNP in *IGF2R*, rs3777404, in Caucasians only. To our knowledge, we are the first to report race-specific differences with regard to the association of both circulating IGF pathway biomarkers and SNPs in IGF candidate genes. While these results require further rigorous study in other samples by race, our results implicate the IGF axis in colorectal adenomas.

Because IGF-1 plays a role in cell proliferation and displays anti-apoptotic properties, it has been implicated in the development of cancer. Unbound IGF-1 will bind the IGF1 receptor and the insulin receptor [10, 11] and activate pathways that stimulate cell proliferation and survival. Our result in African Americans supports our hypothesis that increased circulating IGF-1 is associated with the presence of adenomas and purports a differential contribution of

insulin resistance to adenoma risk by race that deserves further study. Essentially, what we observed in Caucasians is that though they had higher IGF-1 levels than African Americans, there was no association with colorectal adenomas. As mentioned previously, the literature is inconsistent with regard to IGF-1 and its association with colorectal cancer. However, few if any studies have examined racial differences in this pathway, and our study indicates that there may be race-specific differences in the association with the IGF pathway and colorectal adenoma. Therefore, further studies should make efforts to understand these differences.

Racial variation in IGF pathway genes and peptides has been established and implicated in prostate cancer carcinogenesis [18, 23]. These studies indicate that African Americans have lower IGF-1 and IGFBP-3 levels than Caucasians, and though it did not reach statistical significance for IGF-1, IGFBP-3 levels are associated with prostate cancer risk for African Americans [18, 23].

To our knowledge, three studies have examined the relationship between IGF biomarkers and colorectal adenomas [13, 14, 24] and those that have, have not included large numbers of African Americans, or other minorities. The first study, conducted in the Nurses' Health Study, reported that those in the higher tertiles of IGF-1 were at elevated risk of intermediate- or late-stage adenomas [13]. The next study reported no differences in circulating IGF-1 or IGFBP-3 between adenoma cases and controls, nor statistically significant associations of IGF-1 or IGFBP-3 with adenomas [14]. The final study reported a positive and statistically significant association between an ever-increase in IGF-1 and IGF-1/IGFBP-3 ratio levels over 10 years and adenoma risk when compared to those with no increase [24].

Many studies have investigated serum IGF-1 and its relationship with colorectal and other cancers. A meta-analysis summarized evidence for an association between IGF-1 and IGFBP-3 and prostate, colorectal, breast, and lung cancer [25]. For colorectal cancer, the meta-odds ratio comparing highest and lowest IGF-1 levels was 1.58 (95 % CI 1.11–2.27) and not statistically significant for IGFBP-3 levels and colorectal cancer [25]. A second meta-analysis investigating the IGF pathway and colorectal cancer reported a positive and significant association between IGF-1 and colorectal cancer; RR = 1.07, 95 % CI 1.01–1.14 [26]. These meta-analyses did not examine differences by race or ethnicity, nor did they adjust for race or ethnicity; they only indicated that IGF-1 levels were positively and significantly associated with colorectal cancer risk.

Other cancers shown to be associated with IGF-1 to date, in addition to colorectal cancer, include prostate and breast cancer. Meta-analyses suggest that IGF-1 is positively associated with risk of prostate [27] (meta-OR = 1.31, 95 % CI 1.03–1.67) and pre-menopausal breast cancer (meta-OR = 1.98, 95 % CI 1.38–2.69) [25]. The results of studies with IGFBP-3 have been highly inconsistent with some meta-analyses, indicating an inverse relationship with prostate cancer risk (meta-OR = 0.88, 95 % CI 0.79–0.98) [28] and others suggesting no association with prostate, colorectal, post-menopausal breast cancer, or lung cancer [25]. While the meta-analyses suggest that there is an association of the IGF pathway and multiple cancer types, it is important to note that these meta-analyses include samples that are primarily of European ancestry.

The association of insulin resistance and cancer is poorly studied in minority populations, with the possible exception of breast cancer [29–32]. The Rancho Bernardo Study only included Caucasian women, and in their sample, the authors reported no association of IGF-1 with breast cancer [29]. Results from cross-sectional and case–control studies within the Multiethnic Cohort indicated that Latina women had the lowest IGF-1 levels and the

lowest rates of breast cancer [30]. The Multiethnic Cohort also includes African Americans, but did not directly assess associations between IGF-1 levels and colorectal cancer; rather, they assessed associations between IGF-1 levels and race/ethnicity and correlations between race/ethnicity and colon cancer incidence [30, 31]. The authors reported that African American women had statistically significantly higher IGF-1 levels than did Native Hawaiians, Japanese, Latina, or White women ($p = 0.002$) [31]. However, the same association was not reported in African American men [31]. The 4 Corners Breast Cancer study indicated that among non-Hispanic white women, IGF-1 was associated with post-menopausal breast cancer, though this same association was not identified in Hispanic women [9].

Many studies have examined genetic polymorphisms in the IGF-1 pathway [32–36] and suggest small and inconsistent associations. Slattery et al. [15] examined SNPs in *IGF1* and *IGFBP3* and reported no significant associations with colorectal cancer. A recent study from the North Carolina Colon Cancer study investigated the associations of polymorphisms in the following genes: *IGF-1* $(CA)_n$ repeat, *IGF-II* rs680, *IGFBP-3* rs2854744, and *AMP1* rs1501299 with colon cancer risk in Whites and African Americans. While the authors do not report whether IGF-1 differs by case status, their results further implicate the IGF pathway genes in the development of colorectal cancer. However, these associations were only observed in Whites and were not significant in African Americans [37]. As we similarly observed statistically significant associations between SNPs and adenomas in Caucasians only, this may indicate that inherited genetic variance in the IGF pathway may be more important in Caucasians.

Increases in circulating serum levels may represent a disturbance in GH/IGF-1 homeostasis, which could favor malignancy [24]. In light of what is known about IGF-1, primarily that it promotes cell proliferation and differentiation and inhibits apoptosis, the result that we observed in African Americans is biologically plausible [1]. However, the fact that we did not see the same association of circulating IGF-1 and adenomas in Caucasians, coupled with the fact that other adenoma studies (that studied primarily Caucasians) observed no statistically significant association of IGF-1 and adenomas [14, 24], may indicate that the relationship is race-specific or potentially modified by race. The results that we observed for IGFBP-3 are not what would be expected in the light of the biological role of IGFBP-3, but our results contribute to the inconsistency in published literature, leaving unanswered questions with this particular biomarker. In addition, it may be that SNPs in additional genes play a role in altered GH/IGF-1 homeostasis.

Some studies have examined whether circulating levels of IGF biomarkers vary according to inherited genetic variation in IGF pathway-related genes. One study found that the variant allele of rs1520220 in *IGF1* is associated with higher circulating levels of IGF-1, while the variant allele rs2854744 in *IGFBP3* is associated with higher levels of IGFBP-3 [38]. A study in China reported that circulating levels of IGFBP-3 was lowest for carriers of each of the five *IGFBP3* rare variants in a sample of 235 healthy female controls [39]. A study of Norwegian women reported no differences in circulating IGF-1 or IGFBP-3 according to *IGF1* or *IGFBP3* genotype; however, they did report that two haplotype variants in *IGF2R* are associated with lower IGF-1 levels [40]. Our study differs from these in terms of the SNPs analyzed; we focused on whether IGF1 receptors specifically are associated with circulating IGF1 and report null findings in Caucasian and African American samples. Collectively, these results suggest that IGF pathway polymorphisms may be associated with differences in circulating levels of IGF1 and IGFBP3; however, further studies are necessary.

There are several strengths to our study. We have a large sample that included a significant number of African Americans. We also specifically selected tag SNPs to represent variation in both Caucasians and African Americans, and to our knowledge, our study is the first to attempt a more comprehensive measurement of genetic variation across our candidate genes by race. With regard to our SNP findings, post hoc power calculations indicate that our study had approximately 65 % power to detect the genetic association of rs49666011 and approximately 83 % power to detect the association of rs37777404 given the allele frequencies in our Caucasian sample [41].

Weaknesses of our study include the reliance on single measures of IGF biomarkers taken from samples collected at the time of colonoscopy. Current IGF-1 and IGFBP-3 levels may not be representative of serum levels over time. However, several longitudinal studies have suggested that though there is some within-individual variability in IGF-1 and IGFBP-3 biomarker levels, the ranking of individuals within a sample remains fairly well correlated [18, 19]. Another limitation of our study is that biomarker collection occurred at the time of colonoscopy. As such, we cannot exclude the possibility of reverse causality. However, previous longitudinal studies indicate that changes in the IGF pathway precede malignancy development.

We did not investigate the entire IGF pathway; therefore, our results do not allow us to rule out associations of other biomarkers or SNPs not yet studied. An important limitation herein is the fact that we examined several SNPs in three candidate genes (*IGF1R*, *IGF2R*, and *INSR*), and none of them remained significant after applying a conservative Bonferroni correction for all SNPs tested. Caution thus needs to be exercised in interpreting our SNP results, and further studies are necessary. The unknown functional significance of the tag SNPs selected for study is another important consideration. The final important limitation in our study is sample size; we had somewhat limited power to detect modest differences in biomarker levels by case–control status and by race. Larger studies are needed to tease apart the influences of both race and adenoma status.

To our knowledge, our study is the first to examine the IGF pathway using circulating biomarkers and SNPs in candidate genes separately in a large sample that includes both Caucasians and African Americans. We examined SNPs at several locations in the *IGF1R*, *IGF2R*, and *INSR* genes and found that polymorphisms in SNPs rs4966011 (*IGF1R*) and rs3777404 (*IGF2R*) were associated with adenomas, rs4966011 positively and rs3777404 inversely. However, these associations were only observed in Caucasians, which may suggest that the candidate genes influencing adenoma risk in Caucasians may be different from those influencing risk in African Americans or the inherited genetic variance is a smaller contributor to overall IGF pathway “phenotype.”

Our study is the first to demonstrate a significant relationship between IGF-1 biomarker levels and the presence of colorectal adenomas in African Americans. Furthermore, our results were consistent with previous studies [18, 19] that indicate that IGF-1 and IGFBP-3 levels significantly differ between African Americans and Caucasians (*p* values for differences between African American and Caucasian controls for IGF-1 and IGFBP-3 were each <0.001, and *p* values for differences between African American and Caucasian cases were 0.02 and 0.002 for IGF-1 and IGFBP-3, respectively). The association between IGF-1 and IG-FBP-3 levels and adenomas requires further exploration, particularly in different race/ethnic groups and with larger samples. Further studies should also explore whether there may be other modifiable factors in the obesity and insulin-resistance pathways that impact the development of colorectal adenomas and colorectal cancer.

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Table 1

Descriptive characteristics of the study population by race

Characteristic mean (SD) or *n* (%)	Caucasians (*n* = 913)	African Americans (*n* = 567)	*p* value
Age (years)	55.1 (8.7)	55.9 (8.7)	0.08
Gender			<0.001
Male	381 (41.7 %)	171 (30.2 %)	
Female	532 (58.3 %)	396 (69.8 %)	
Body mass index (kg/m^2)	28.1 (6.0)	32.0 (7.8)	<0.001
Waist circumference (cm)	37.6 (6.4)	41.1 (7.3)	<0.001
Waist/hip ratio	0.90 (0.09)	0.94 (0.08)	<0.001
NSAID use			
Non-user	584 (64.0 %)	363 (64.0 %)	0.51
User	329 (36.0 %)	204 (36.0 %)	
Smoking status			
Never	455 (49.8 %)	204 (36.0 %)	<0.001
Former	360 (39.4 %)	197 (34.8 %)	
Current	98 (10.7 %)	165 (29.2 %)	
Pack years of smoking	10.1 (31.3)	11.7 (22.8)	0.28
Family history of colorectal cancer	235 (25.7 %)	121 (21.3 %)	0.03
Insulin (μIU/mL)	6.4 (8.4)	11.7 (36.8)	0.005
Fasting glucose (mg/dL)	85.7 (23.4)	96.0 (35.4)	<0.001
Advanced adenoma[a]	39 (4.27 %)	35 (6.17 %)	0.10

The significance of the differences between cases and controls for categorical variables was assessed using a Pearson chi-square test and for continuous variables was assessed using an independent samples *t* test

[a]Defined as if adenoma size ≥10 mm or high-grade dysplasia

Table 2

IGF biomarkers according to race and case–control status

Characteristic mean (SD) or *n* (%)	Caucasians			African Americans			*p* value for differences between Caucasian and African American cases	*p* value for differences between Caucasian and African American controls
	Cases (*n* = 230)	Controls (*n* = 683)	*p* value	Cases (*n* = 180)	Controls (*n* = 387)	*p* value		
IGF-1 (ng/mL)	119.0 (40.7)	122.9 (41.2)	0.22	109.8 (40.8)	106.9 (41.2)	0.45	0.02	0.001
IGFBP-3 (ng/mL)	3,727.7 (839.0)	3,868.4 (801.5)	0.02	3,448.6 (933.7)	3,446.8 (840.7)	0.98	0.002	0.001
IGFBP-1 (ng/mL)	29.5 (25.8)	32.5 (27.3)	0.14	24.6 (28.3)	24.9 (27.3)	0.93	0.07	0.001
IGF-1:IGFBP-3 ratio	0.12 (0.03)	0.12 (0.03)	0.93	0.12 (0.04)	0.11 (0.03)	0.17	0.63	0.17

The significance of the differences between cases and controls for categorical variables was assessed using a Pearson chi-square test and for continuous variables was assessed using an independent samples *t* test

Table 3

Association of IGF biomarkers and adenoma risk

	n cases–controls	Crude model[a]		Adjusted model[b]	
		OR (95 % CI)	*p*-trend	OR (95 % CI)	*p*-trend
IGF-1					
Caucasians					
Tertile 1	76/228	1.00	0.22	1.00	0.26
Tertile 2	94/229	1.23 (0.85–1.77)		1.28 (0.88–1.84)	
Tertile 3	60/226	0.80 (0.53–1.21)		0.83 (0.55–1.25)	
African Americans					
Tertile 1	47/129	1.00	0.45	1.00	0.12
Tertile 2	68/129	1.60 (1.01–2.53)		1.68 (1.06–2.68)	
Tertile 3	65/129	1.59 (0.99–2.54)		1.68 (1.05–2.71)	
IGFBP-3					
Caucasians					
Tertile 1	101/228	1.00	0.036	1.00	0.51
Tertile 2	66/228	0.75 (0.52–1.09)		0.80 (0.55–1.17)	
Tertile 3	63/227	0.77 (0.53–1.13)		0.80 (0.55–1.17)	
African Americans					
Tertile 1	59/129	1.00	0.98	1.00	0.07
Tertile 2	61/129	1.36 (0.86–2.15)		1.45 (0.91–2.30)	
Tertile 3	60/129	1.39 (0.87–2.21)		1.44 (0.90–2.31)	
IGF-1/IGFBP-3 ratio					
Caucasians					
Tertile 1	69/227	1.00	0.93	1.00	0.17
Tertile 2	84/228	1.17 (0.80–1.71)		1.23 (0.84–1.82)	
Tertile 3	77/228	0.94 (0.62–1.43)		0.96 (0.63–1.46)	
African Americans					
Tertile 1	51/129	1.00	0.18	1.00	0.50
Tertile 2	64/129	1.21 (0.77–1.90)		1.22 (0.77–1.94)	
Tertile 3	65/129	1.11 (0.70–1.77)		1.16 (0.72–1.87)	

	n cases–controls	Crude model[a]		Adjusted model[b]	
		OR (95 % CI)	*p*-trend	OR (95 % CI)	*p*-trend
IGFBP-1					
Caucasians					
Tertile 1	83/218	1.00	0.14	1.00	0.72
Tertile 2	75/226	0.86 (0.60–1.25)		0.95 (0.64–1.40)	
Tertile 3	72/231	0.83 (0.57–1.21)		0.98 (0.64–1.51)	
African Americans					
Tertile 1	57/129	1.00	0.91	1.00	0.11
Tertile 2	63/126	1.08 (0.69–1.70)		0.99 (0.62–1.58)	
Tertile 3	58/130	0.80 (0.51–1.28)		0.72 (0.43–1.18)	

[a] Adjusted for age and sex

[b] Adjusted for age, sex, body mass index, smoking status, non-steroidal inflammatory drug use, and family history of colorectal cancer

Table 4

Association of *IGF1R*, *IGF2R*, and *INSR* genotypes with colorectal adenomas stratified by race

Gene	SNP	Alleles (m/M)	MAF cases		MAF controls		Caucasians OR[a] (95 % CI)	African Americans OR[a] (95 % CI)
			Caucasians (*n* = 230)	African Americans (*n* = 180)	Caucasians (*n* = 683)	African Americans (*n* = 387)		
IGF1R	rs4966011	A/G	0.32	0.12	0.40	0.13	0.73 (0.57–0.93)	0.90 (0.58–1.40)
IGF1R	rs2715423	T/C	0.25	0.10	0.27	0.09	0.96 (0.73–1.25)	1.09 (0.67–1.78)
IGF1R	rs4426332	A/G	0.06	0.18	0.06	0.21	1.10 (0.67–1.79)	0.77 (0.54–1.10)
IGF1R	rs875686	T/A	0.27	0.34	0.31	0.34	0.80 (0.62–1.04)	0.93 (0.70–1.25)
IGF1R	rs1513643	C/T	0.54	0.35	0.49	0.32	1.21 (0.97–1.53)	1.17 (0.86–1.59)
IGF1R	rs4966035	T/C	0.32	0.38	0.30	0.42	1.08 (0.85–1.38)	0.80 (0.60–1.07)
IGF1R	rs3743260	T/C	<5 %	0.06	<5 %	0.08	–	0.70 (0.40–1.21)
IGF1R	rs2229765	A/G	0.45	0.26	0.44	0.29	1.06 (0.84–1.34)	0.88 (0.64–1.21)
IGF1R	rs2684788	G/A	0.55	0.42	0.53	0.39	1.07 (0.85–1.36)	1.11 (0.84–1.46)
IGF1R	rs1815009	G/A	0.25	0.48	0.27	0.51	0.93 (0.71–1.21)	0.89 (0.68–1.18)
IGF1R	rs2684787	A/G	0.23	0.11	0.22	0.10	1.03 (0.78–1.35)	1.03 (0.65–1.64)
IGF2R	rs3822844	C/T	0.28	0.46	0.30	0.44	0.91 (0.70–1.16)	1.05 (0.79–1.40)
IGF2R	rs3777404	T/C	0.16	0.13	0.11	0.15	1.53 (1.10–2.14)	0.79 (0.53–1.19)
IGF2R	rs3822843	G/A	0.15	0.24	0.15	0.23	1.04 (0.75–1.44)	1.08 (0.77–1.52)
IGF2R	rs1570070	G/A	0.33	0.31	0.33	0.27	1.01 (0.79–1.29)	1.31 (0.95–1.80)
IGF2R	rs998075	A/G	0.51	0.43	0.56	0.38	0.81 (0.64–1.02)	1.16 (0.87–1.53)
IGF2R	rs7753051	G/A	0.24	0.39	0.23	0.43	1.01 (0.76–1.33)	0.86 (0.64–1.15)
INSR	rs2962	T/C	0.06	0.12	0.07	0.10	0.88 (0.55–1.41)	1.29 (0.81–2.05)
INSR	rs2963	A/G	0.07	0.27	0.08	0.25	0.93 (0.59–1.45)	1.14 (0.82–1.59)
INSR	rs1864193	T/G	0.13	<5 %	0.15	<5 %	0.86 (0.62–1.20)	–
INSR	rs3745551	G/A	0.35	0.25	0.36	0.28	1.00 (0.78–1.27)	0.84 (0.62–1.16)
INSR	rs3745550	A/G	0.20	0.47	0.20	0.53	0.99 (0.74–1.33)	0.77 (0.58–1.02)
INSR	rs1051690	A/G	0.16	0.16	0.14	0.15	1.21 (0.87–1.67)	1.13 (0.78–1.64)
INSR	rs891087	T/C	0.08	0.22	0.08	0.21	1.05 (0.68–1.62)	1.09 (0.77–1.52)
INSR	rs890860	A/G	0.24	0.32	0.21	0.30	1.25 (0.95–1.66)	1.10 (0.81–1.49)
INSR	rs10402346	G/A	0.29	0.48	0.29	0.52	1.00 (0.78–1.28)	0.92 (0.69–1.23)

m/M minor/major allele, *MAF* minor allele frequency

[a]Odds ratios and 95 % confidence intervals adjusted for age, sex, non-steroidal inflammatory drug use, body mass index, family history of colorectal cancer, and smoking status