Carcinogenesis vol.32 no.5 pp.748–756, 2011
doi:10.1093/carcin/bgr026
Advance Access publication February 11, 2011

FTO polymorphisms are associated with adult body mass index (BMI) and colorectal adenomas in African-Americans

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Obesity is a known risk factor for colon cancer and higher body mass index (BMI) has been associated with colorectal adenomas, which are precursor lesions to most colorectal cancers. Polymorphisms in the fat-mass and obesity-associated (FTO) gene have been associated with BMI and larger effects in older versus younger children have been reported. However, no studies have examined associations between FTO polymorphisms, BMI throughout adulthood and colorectal adenomas. Therefore, we evaluated associations between FTO polymorphisms (rs1421085, rs17817449, rs8050136, rs9939609, rs8044769), adult BMI (at recruitment, 50s, 40s, 30s, 20s age decades) and colorectal adenomas in 759 Caucasians and 469 African-Americans. We found that the highest versus the lowest BMI tertile at recruitment [odds ratio (OR) = 1.82; 95% confidence interval (CI): 1.07–2.16] and in the 30s (OR = 1.50; 95% CI: 1.04–2.15) was associated with higher adenoma risk. Stratification by ethnicity revealed that these associations only remained significant in Caucasians. We found that, in Caucasians, having two versus no copies of the variant allele in rs17817449, rs8050136 and rs9939609, which are all in strong linkage disequilibrium, was associated with higher BMI in the 30s and 40s but none of the polymorphisms were associated with adenomas. In African-Americans, having one or two copies of the variant in rs17817449 (OR = 0.61; 95% CI: 0.39–0.95) and rs8050136 (OR = 0.59; 95% CI: 0.38–0.93) was associated with colorectal adenomas and, having two variant copies in rs17817449 and rs8050136 was associated with higher BMI at recruitment and in the 40s, respectively. Our results are consistent with prior studies and show for the first time that FTO polymorphisms are associated with colorectal adenomas in African-Americans.

Introduction

Colorectal cancer is the third most common non-skin cancer in the USA, affecting ∼150 000 individuals annually, and is the third leading cause of cancer death each year in the USA, accounting for ∼50 000 deaths annually (1). 'Sporadic' colorectal adenomas, which are precursor lesions to most colorectal cancers (2,3) likely develop through a combination of lifestyle and genetic risk factors (4–6).

Obesity has been consistently associated with an increased risk of colon cancer (7–9) but its role in the development of colorectal adenomas is not as well established. Some studies have shown a positive association between obesity-related measures including body mass index (BMI) and colorectal adenomas (10–15), while others have failed to find an association (16–18). The inconsistencies may be due, in part, to differences in the attributes of the populations such as ethnicity and genetic profiles as well as the time period when BMI was assessed. Many prior studies have examined BMI at recruitment or within a few years prior to colonoscopy screening, leaving potentially important earlier periods much less explored.

Polymorphisms in the fat-mass and obesity-associated (FTO) gene have been associated with obesity-related measures including BMI and waist circumference in several studies (19–22). The rs9939609 variant allele (A) was first found to be associated with BMI in a genome-wide association study (GWAS) comprising a large sample ($N = 38\ 759$) of Caucasians of European descent (19). Subsequently, this finding has been replicated in several other GWAS (20,22), and a recent meta-analysis of GWAS, which included 15 cohorts of European ancestry, concluded that the rs9939609 polymorphism is strongly associated with BMI (23). Similar associations have been observed for the rs8050136 'A' allele, which is in strong linkage disequilibrium (LD) with the rs9939609 'A' allele in Caucasians (20,22). The variant alleles in FTO rs17817449 (G) and rs1421085 (C) have also been associated with higher BMI and waist circumference levels in populations of European descent (24). However, the potential association between FTO polymorphisms and obesity-related measures has not been as well studied in African-Americans. Two studies reported no association between rs9939609 or rs8050136 and BMI or waist circumference (21,25). More recently, the Insulin Resistance Atherosclerosis Family Study, which evaluated 27 FTO single nucleotide polymorphisms including those most prominently cited in the literature (rs9939609, rs17817449, rs1421085, rs8050136), found that the 'A' alleles of rs9939609 and rs8050136 were both associated with BMI and waist circumference in African-Americans (26,27). Recently, among African-Americans in the Atherosclerosis Risk in Communities study, the 'C' allele of rs1421085 was observed to be associated with higher BMI but no associations were observed between rs9939609, rs17817449 and rs8050136 and any obesity-related traits (28). Although an association between rs9939609 and BMI was found in African-American youths, the rs9939609 polymorphism was not associated with percent body fat (29). Other recent studies in African-American youths have identified novel associations between previously unreported FTO polymorphisms rs3751812 (30) and rs8057044 (31) and obesity-related traits.

Some evidence suggests that FTO polymorphisms may exert larger effects with older age. In a longitudinal study, Haworth *et al.* (32) found that the association between the FTO rs9939609 'A' allele and BMI was stronger in children at age 11 compared with age 4, and they reported that this increase was paralleled by a rise in heritability. However, very little is known about how rs9939609 and other common variants in the FTO gene might contribute differentially to body size measures throughout adulthood.

Therefore, we examined potential associations between FTO polymorphisms (rs1421085, rs17817449, rs8050136, rs9939609, rs8044769), BMI in adulthood (recruitment, 50s, 40s, 30s and 20s age decades) and colorectal adenomas in a population of 759 Caucasians and 469 African-Americans undergoing colonoscopy screening.

Abbreviations: BMI, body mass index; CI, confidence interval; FTO, fat-mass and obesity-associated; LD, linkage disequilibrium; OR, odds ratio.

Materials and methods

Study population

The study population consisted of patients undergoing routine colonoscopy screening at the University Hospitals Health System in Cleveland, OH, from January, 2006 through August, 2009. Patients were required to complete an initial screening questionnaire over the telephone to determine if they were eligible to participate in the study. Patients were considered ineligible if they reported having a personal history of any cancer, ulcerative colitis, Crohn's disease, prior colorectal adenomatous polyps, a family history of Hereditary Nonpolyposis Colon Cancer, a family history of Familial Adenomatous Polyposis.

Eligible patients with histologically confirmed colorectal adenomatous polyps, including tubular, sessile serrated or tubulovillis subtypes, were defined as

'cases'. Four patients (2 Caucasians and 2 African-Americans) with histologically confirmed colorectal cancer found during the colonoscopy were excluded from the case–control analyses. Patients who had no observed adenomas (negative colonoscopy) or who had hyperplastic polyps were defined as 'controls' in this study.

The recruitment rate among eligible participants was ~64.9%. Subjects who declined to participate in the study were demographically similar to those who agreed to participate. Specifically, patients who declined to participate compared with those who enrolled in the study were of similar age (55.2 versus 56.3 years), gender (59.6 versus 52.7% female) and ethnic composition (60.4 versus 67.1% Caucasian and 37.1 versus 32.9% African-Americans). The study protocol was approved by the Institutional Review Board of University Hospitals Case Medical Center and the University of Southern California.

BMI and other risk factor measures

Weight, height and waist circumference were measured (without shoes and in light clothes) by a research nurse at the time of the colonoscopy (at recruitment). BMI was calculated as the ratio of weight in kilograms divided by height in meters squared. Self-reported height and usual weight in prior age decades (20s, 30s, 40s and 50s) were determined using a questionnaire, and these data were used to calculate BMI in the corresponding age decades. We categorized subjects into BMI tertiles based on cut points defined in controls and within each ethnic group, as applicable. Subjects were also classified as obese (BMI $\geq$ 30.0 kg/m^2), overweight (BMI $\geq$25.0 to $<$30.0 kg/m^2) or normal weight (BMI $\geq$18.5 to $<$25.0 kg/m^2) as per the criteria set forth by the World Health Organization (33).

Patients were also required to complete a computer-aided personal interview, prior to their colonoscopy, to assess lifestyle and behavioral risk factors. This computer-aided personal interview was based on a questionnaire developed by the National Cancer Institute Colon Cancer Familial Registry (http://epi.grants.cancer.gov/documents/CFR/center_questionnaires/Colon/LA/ColonRiskFactor_USC.pdf). A positive family history of colorectal cancer was defined as having one or more first degree relatives with colon or rectal cancer. Smokers were defined as patients who reported ever smoking cigarettes for $\geq$6 months. Alcohol users were defined as those subjects who reported regular intake of alcohol defined as two or more drinks/week for $\geq$6 months. Non-steroidal anti-inflammatory drug (NSAID) users were defined as those using aspirin or ibuprofen for at least twice a week for $>$1 month.

Genotyping

Blood was collected just prior to the patient's colonoscopy and aliquots of concentrated buffy coat were frozen within $<$8 h. DNA was extracted from the buffy coat using the Qiagen Biorobot EZ1 (Valencia, CA) and quantitated with PicoGreen (Life Technologies, Carlsbad, CA).

Genotyping of FTO single nucleotide polymorphisms was performed by using Taqman Genotyping Assays (Life Technologies) with RealMasterMix Probe with ROX (5′; Gaithersburg, MD) following manufacturer's instructions. Assays were measured using an Applied Biosystems 7900HT (Life Technologies) and genotypes determined using the manufacturer's software (SDS2.3). The overall genotype call rate was $>$99% (rs9939609: 100%; rs8050136: 99.8%; rs17818449: 99.8%; rs1421085: 99.8%; rs8044769: 99.4%). Two percent of samples were duplicated and the concordance rate was 100% for all single nucleotide polymorphisms assayed.

Statistical analysis

We used unconditional logistic regression modeling to evaluate the potential associations between body size tertiles in each age period (at recruitment, 50s, 40s, 30s and 20s age decades) and colorectal adenomas and between FTO polymorphisms and colorectal adenomas. We used least squares means to evaluate potential associations between FTO polymorphisms and body size measures as continuous traits. We also examined potential associations between FTO polymorphisms and body size categories in each age period using polytomous regression. We adjusted all analyses for potential confounding by other known risk factors including age, race, income, family history of colon cancer, smoking, alcohol and NSAID use. In addition, we conducted analyses stratified by major ethnic group (Caucasians, African-Americans) to reveal potentially important differences by ethnicity and to minimize the potential for population stratification in genetic associations.

We tested for Hardy–Weinberg Equilibrium in Caucasian and African-American controls, separately, using the chi-square goodness-of-fit test and 10 000 permutations of the exact test (34). We estimated LD with both Lewontin's D' and correlation coefficient (R^2) measures (35).

All P-values reported are from two-sided tests and significance was set at $\leq$0.05. Because evaluation of the potential associations between FTO polymorphisms and colorectal adenomas is a new discovery rather than a confirmatory hypothesis, we also performed correction of these P-values for multiple correlated tests under different modes of inheritance using p_ACT v1.2 (36). In addition, we conducted post-hoc power calculations using QUANTO (37). All other analyses were undertaken with SAS (Version 9.2, SAS Institute Inc., Cary, NC).

Results

Characteristics of the study population are provided in Table I. On average, cases compared with controls were older and more likely to be male, smoke and have less income. Although the mean BMI of cases was similar to controls in all adult age periods examined, the mean waist circumference at recruitment was significantly greater in cases compared with controls. Genotype and allele frequencies for all FTO polymorphisms examined (rs1421085 C/T, rs17817449 T/G, rs8050136 C/A, rs9939609 T/A, rs8044769 C/T) were not significantly different between cases and controls. Caucasians compared with African-Americans were, on average, more likely to be male, have a higher income and be less likely to smoke and more likely to drink alcohol. Mean BMI at recruitment and in the 50s, 40s and 30s age decades was significantly higher in African-Americans compared with Caucasians. In addition, waist circumference at recruitment was significantly greater in African-Americans compared with Caucasians. Genotype and allele frequencies were significantly different between Caucasians and African-Americans for FTO polymorphisms rs1421085, rs9939609 and rs8044769.

All FTO polymorphisms were found to be in Hardy–Weinberg equilibrium when examining Caucasian (C) and African-American (AA) controls, separately, using the chi-square and exact test methods (34). The variant alleles of the five FTO polymorphisms examined were in fairly strong LD in Caucasians ($D' \geq 0.98$; $R^2 \geq 0.74$), with rs17817449, rs8050136 and rs9939609 having nearly perfect LD ($D' = 1.00$; $R^2 \geq 0.99$); however, the LD pattern in African-Americans was considerably weaker ($D' \geq 0.70$; $R^2 \geq 0.20$).

We first examined potential associations between body size measures and colorectal adenomas (Table II). We found that the highest versus the lowest BMI tertile at recruitment (R) [odds ratio (OR) = 1.82; 95% confidence interval (CI): 1.07–2.16; P = 0.02] and in the 30s (OR = 1.50; 95% CI: 1.04–2.15; P = 0.03) was associated with higher adenoma risk. Stratification by major ethnic group revealed that these associations only remained statistically significant in Caucasians (R: OR = 1.63; 95% CI: 1.04–2.25; 30s: OR = 1.71; 95% CI: 1.04–2.83). When using the body size categories established by the WHO (33), we found that, in Caucasians, being obese (BMI $\geq$ 30 kg/m^2) compared with normal weight (BMI $\geq$18.5 to $<$25 kg/m^2) at recruitment was marginally positively associated with colorectal adenomas (OR = 1.55; 95% CI: 0.97–2.47; P = 0.06) (data not shown). No other statistically significant associations were observed between obesity and overweight, as defined by the WHO, and adenomas in the other age periods examined (data not shown). Waist circumference, which was only measured at recruitment, in the highest ($\geq$99.38 cm) compared the lowest ($<$86.36 cm) tertile was positively associated with colorectal adenomas in Caucasians (OR = 2.10; 95% CI: 1.21–3.34; P = 0.007; P-trend = 0.01) but no statistically significant association was observed with waist tertiles in African-Americans.

Potential associations between FTO polymorphisms and adult body size were also examined. In Caucasians (Table III), we found that having two versus no copies of the rs17817449 variant allele (G) was associated with a significantly higher BMI in the 40s (27.42 ± 0.54 versus 26.13 ± 0.38 kg/m^2; P = 0.05) and 30s (25.32 ± 0.45 versus 24.19 ± 0.31 kg/m^2; P = 0.04) age decades. Similar associations were observed in Caucasians for rs8050136 and rs9939609, which were in strong LD with rs17817449. In African-Americans (Table IV), having two versus no copies of the rs1421085 variant allele (C) was significantly associated with a higher BMI at recruitment (42.61 ± 3.10 kg/m^2 versus 31.88 ± 0.41 kg/m^2; P = 0.0007) and in the 50s (41.92 ± 3.29 kg/m^2 versus 31.20 ± 0.46 kg/m^2; P = 0.001), 40s (37.49 ± 2.85 kg/m^2 versus 28.28 ± 0.35 kg/m^2; P = 0.001), 30s (31.02 ± 2.41 kg/m^2 versus 25.22 ± 0.30 kg/m^2; P = 0.02) and 20s (28.07 ± 2.09 kg/m^2 versus 22.81 ± 0.26 kg/m^2; P = 0.01) age decades but only a small number of African-Americans had the rs1421085 C/C

Table I. Characteristics of the colorectal adenoma study population

Characteristic	Cases	Controls	Caucasians	African-Americans
Sample size	321	903	759	469
Age (years)	58.13 (8.33)	54.54 (8.93)[a]	55.98 (8.93)	55.18 (8.87)
Males	149 (46.42%)	311 (34.29%)[a]	321 (42.29%)	141 (30.06%)[a]
Caucasians	184 (57.32%)	573 (63.17%)[a]	—	—
Income				
<$15 K	62 (19.31%)	121 (13.34%)	33 (4.35%)	151 (32.20%)
$15–30 K	43 (13.40%)	112 (12.35%)	43 (5.67%)	112 (23.88%)
$30–45 K	42 (13.08%)	109 (12.02%)	73 (9.62%)	79 (16.84%)
$45–70 K	38 (11.84%)	165 (18.19%)	150 (19.76%)	53 (11.30%)
>$70 K	125 (38.94%)	343 (37.82%)[a]	411 (54.15%)	58 (12.37%)[a]
Smoking	203 (63.24%)	462 (50.94%)[a]	393 (51.78%)	366 (78.04%)[a]
Alcohol	220 (68.54%)	596 (65.71%)	534 (70.36%)	284 (60.55%)[a]
NSAIDs	29 (9.03%)	76 (8.38%)	66 (8.70%)	39 (8.32%)
Family history CRC	70 (21.81%)	213 (23.48%)	189 (24.90%)	95 (20.26%)
Waist (cm)	102.44 (17.91)	98.09 (17.07)[a]	85.76 (16.59)	104.57 (17.25)[a]
BMI[b]	30.29 (7.39)	29.65 (10.48)	28.51 (10.57)	31.95 (7.86)[a]
BMI in 50s decade	28.78 (6.88)	28.45 (6.40)	27.34 (5.30)	30.48 (7.79)[a]
BMI in 40s decade	26.83 (5.51)	26.98 (6.32)	26.21 (5.63)	28.17 (6.66)[a]
BMI in 30s decade	24.99 (4.60)	24.77 (5.30)	24.48 (4.81)	25.43 (5.55)[a]
BMI in 20s decade	23.10 (3.99)	22.71 (4.23)	22.75 (3.82)	22.96 (4.72)
FTO rs1421085				
T/T	165 (51.40%)	440 (48.83%)	240 (31.75%)	365 (78.32%)
T/C	126 (39.25%)	352 (39.07%)	383 (50.66%)	95 (20.39%)
C/C	30 (9.35%)	109 (12.10%)	133 (17.59%)	6 (1.29%)[a]
Allele C	186 (28.87%)	570 (31.63%)	649 (42.92%)	107 (11.48%)[a]
FTO rs17817449				
T/T	117 (36.45%)	294 (32.63%)	247 (32.72%)	164 (35.19%)
T/G	155 (48.29%)	456 (50.61%)	386 (51.13%)	225 (48.28%)
G/G	49 (15.26%)	150 (16.65%)	122 (16.16%)	77 (16.53%)
Allele G	253 (39.41%)	756 (42.00%)	630 (41.72%)	379 (40.67%)
FTO rs8050136				
C/C	111 (34.58%)	282 (31.30%)	248 (32.80%)	145 (31.11%)
C/A	158 (49.22%)	457 (50.72%)	387 (51.19%)	228 (48.93%)
A/A	52 (16.20%)	162 (17.98%)	121 (16.01%)	93 (19.96%)
Allele A	262 (40.81%)	781 (43.34%)	629 (41.60%)	414 (44.42%)
FTO rs9939609				
T/T	102 (31.78%)	266 (29.46%)	250 (33.02%)	118 (25.27%)
T/A	160 (49.84%)	463 (51.27%)	385 (50.86%)	238 (50.96%)
A/A	59 (18.38%)	174 (19.27%)	122 (16.12%)	111 (23.77%)[a]
Allele A	278 (43.30%)	811 (44.91%)	629 (41.55%)	460 (49.25%)[a]
FTO rs8044769				
C/C	124 (38.75%)	344 (38.35%)	201 (26.73%)	267 (57.42%)
C/T	147 (45.94%)	408 (45.48%)	391(51.99%)	164 (35.27%)
T/T	49 (15.31%)	145 (16.17%)	160 (21.28%)	34 (7.31%)[a]
Allele T	245 (38.28%)	698 (38.91%)	711(47.27%)	232 (24.95%)[a]

[a]$P \leq 0.05$ for chi-square or *t*-test as applicable between cases/controls or Caucasians/African-Americans.
[b]BMI is expressed in kg/m^2.

genotype. African-Americans having two versus no copies of the variant allele in rs17817449 and rs8050136 had a higher BMI at recruitment (33.96 ± 0.89 versus 31.81 ± 0.62 kg/m^2; P = 0.05) and in the 40s (29.24 ± 0.72 versus 27.49 ± 0.57 kg/m^2; $P = 0.05$), respectively, and, those with the one versus no copies of the rs8044769 variant allele (T) had a lower BMI in the 30s (24.76 ± 0.44 versus 25.85 ± 0.35 kg/m^2; $P = 0.05$) and 20s (22.34 ± 0.39 versus 23.35 ± 0.30 kg/m^2; $P = 0.04$). Using obesity and overweight categories as defined by the WHO, we found that African-Americans with one or two versus no copies of the rs1421085 variant allele (C) had an increased risk of obesity in the 30s (OR = 1.93; 95% CI: 1.03–3.63; $P = 0.04$) and 20s (OR = 3.37; 95% CI: 1.49–7.22; $P = 0.004$) (data not shown). In African-Americans, having one or two versus no copies of the rs8044769 variant allele (T) was inversely associated with overweight in the 40s (OR = 0.57; 95% CI: 0.35–0.94; $P = 0.03$), 30s (OR = 0.50; 95% CI: 0.30–0.82; $P = 0.006$) and 20s (OR = 0.53; 95% CI:0.30–0.93; $P = 0.03$). No other statistically significant associations were observed between FTO polymorphisms and overweight or obesity as defined by the WHO (data not shown).

We next examined potential associations between FTO polymorphisms and colorectal adenomas (Table V). In African-Americans, the rs17817449 T/G versus the T/T genotype was inversely associated with adenomas (OR = 0.54; 95% CI: 0.34–0.87; $P = 0.01$). Under a dominant genetic model (i.e. having one or two copies of the rs17817449 'G' allele), we also observed a decreased risk of adenomas in African-Americans (OR = 0.61; 95% CI: 0.39–0.95; $P = 0.03$). Similar associations were observed for rs9939609 (TA or AA versus TT: OR = 0.59; 95% CI: 0.38–0.93; $P = 0.02$) and rs8050136 (TA or AA versus TT: OR = 0.64; 95% CI: 0.40–1.03; $P = 0.07$), which were both in fairly strong LD with rs17817449 ($D' \geq 1.00$; $R^2 \geq 0.84$). Because evaluation of the potential associations between FTO polymorphisms and colorectal adenomas is a new discovery rather than a confirmatory hypothesis, we also corrected the P-values for multiple correlated tests under different models of inheritance. We found that the associations between rs8050136 and rs1817449 (using a dominant genetic model) and colorectal adenomas in African-Americans were marginally significant after correction for multiple tests (rs8050136: $P_{corrected} = 0.06$; rs17817449: $P_{corrected} = 0.07$). No statistically

Table II. OR for body size measures and colorectal adenomas by age decade and ethnicity[a]

Body size	At recruitment		50s age decade		40s age decade		30s age decade		20s age decade	
	n_{cases}/ n_{ctls}[b]	OR (95% CI)	n_{cases}/ n_{ctls}[b]	OR (95% CI)	n_{cases}/ n_{ctls}[b]	OR (95% CI)	n_{cases}/ n_{ctls}[b]	OR (95% CI)	n_{cases}/ n_{ctls}[b]	OR (95% CI)
Total Population										
BMI < 25.62[c]	80/301	1.00 (Referent)	85/226	1.00 (Referent)	87/273	1.00 (Referent)	78/285	1.00 (Referent)	87/286	1.00 (Referent)
BMI 35.62–31.01	123/301	1.38 (0.98–1.94), $P = 0.07$	97/226	1.01 (0.70–1.46), $P = 0.95$	106/274	1.12 (0.79−1.59), $P = 0.53$	108/286	1.29 (0.91–1.85), $P = 0.16$	100/286	1.22 (0.86–1.73), $P = 0.26$
BMI > 31.01	118/301	1.82 (1.07–2.16), $P = 0.02$	91/226	1.06 (0.72–1.55), $P = 0.77$	107/273	1.22 (0.85–1.74), $P = 0.28$	122/286	1.50 (1.04–2.15), $P = 0.03$	119/286	1.29 (0.91–1.84), $P = 0.16$
Waist < 88.90[d]	68/301	1.00 (Referent)	—	[T1: <25.10]	—	[T1: <23.91]	—	[T1: <22.14]	—	[T1: <20.67]
Waist 88.9–104.14	118/301	1.31 (0.91–1.87), $P = 0.15$	—	[T2: 25.10–29.29]	—	[T2: 23.91–27.45]	—	[T2: 22.14–25.10]	—	[T2: 20.67–23.58]
Waist > 104.14	135/301	1.50 (1.04–2.15), $P = 0.03$	—	[T3: >29.29]	—	[T3: >27.45]	—	[T3: >25.10]	—	[T3: >23.58]
Caucasians										
BMI < 24.87[c]	43/191	1.00 (Referent)	39/145	1.00 (Referent)	39/176	1.00 (Referent)	39/184	1.00 (Referent)	43/186	1.00 (Referent)
BMI 24.87–29.43	65/191	1.24 (0.78–1.96), $P = 0.37$	50/145	1.09 (0.66–1.81), $P = 0.73$	67/175	1.51 (0.93−2.44), $P = 0.09$	67/185	1.65 (1.02–2.66), $P = 0.04$	65/186	1.50 (0.94–2.38), $P = 0.08$
BMI > 29.43	76/191	1.63 (1.04–2.55), $P = 0.03$	67/145	1.48 (0.90–2.42), $P = 0.12$	67/175	1.52 (0.94–2.52), $P = 0.09$	71/185	1.71 (1.04–2.83), $P = 0.03$	71/185	1.40 (0.87–2.26), $P = 0.17$
Waist: < 86.36[d]	33/191	1.00 (Referent)	—	[T1: <24.39]	—	[T1: <23.43]	—	[T1: <21.94]	—	[T1: <20.74]
Waist: 86.36–99.38	66/191	1.50 (0.90–2.49), $P = 0.36$	—	[T2: 24.39–28.24]	—	[T2: 23.43–26.60]	—	[T2: 21.94–24.96]	—	[T2: 20.74–23.49]
Waist: >99.38	85/191	2.10 (1.21–3.34), $P = 0.007$	—	[T3: >28.24]	—	[T3: >26.60]	—	[T3: >24.96]	—	[T3: >23.49]
African-Americans										
BMI < 27.63[c]	47/110	1.00 (Referent)	47/81	1.00 (Referent)	46/99	1.00 (Referent)	40/101	1.00 (Referent)	43/100	1.00 (Referent)
BMI 27.63–34.56	50/110	1.17 (0.70–1.94), $P = 0.55$	37/81	0.80 (0.46–1.41), $P = 0.44$	44/98	0.93 (0.55−1.59), $P = 0.79$	53/101	1.34 (0.79–2.27), $P = 0.27$	44/101	1.04 (0.61–1.76), $P = 0.89$
BMI > 34.56	40/110	1.27 (0.68–2.02), $P = 0.57$	33/81	1.05 (0.58–1.90), $P = 0.86$	37/99	1.16 (0.66–2.01), $P = 0.61$	38/101	1.22 (0.69–2.14), $P = 0.49$	40/100	1.01 (0.58–1.76), $P = 0.98$
Waist < 96.52[d]	43/110	1.00 (Referent)	—	[T1: <26.58]	—	[T1: <24.96]	—	[T1: <22.66]	—	[T1: <20.59]
Waist 96.52–111.00	48/110	1.10 (0.66–1.86) $P = 0.71$	—	[T2: 26.58–32.28]	—	[T2: 24.96–29.99]	—	[T2: 22.66–26.57]	—	[T2: 20.59–24.00]
Waist > 111.00	46/110	1.17 (0.69–1.98), $P = 0.56$	—	[T3: >32.28]	—	[T3: >29.99]	—	[T3: >26.57]	—	[T3: >24.00]

[a]Adjusted for age, ethnicity, gender, income, smoking, alcohol, family history of colorectal cancer, NSAIDs.
[b]n_{cases} = number of cases in the tertile; N_{ctls} = number of controls in the tertile. The total number of subjects for BMI in the 50s (N_{cases} = 273; N_{ctls} = 678), 40s (N_{cases} = 300; N_{ctls} = 820), 30s (N_{cases} = 308; n_{ctls} = 857) and 20s (N_{cases} = 306; N_{ctls} = 858) varies from that of BMI at recruitment due to differences in age at recruitment (e.g. subjects 40 to <50 years of age at recruitment would not have a value for BMI in the 50s and subjects 30 to <40 years of age at recruitment would not have a value for BMI in the 50s and 40s).
[c]BMI tertiles (kg/m^2) were defined in controls for each time period in each ethnic group. Tertiles (T) for 50s, 40s, 30s and 20s decades denoted in [ ] below ORs in waist rows.
[d]Waist circumference was only measured at recruitment. Tertiles (cm) were defined in controls for each ethnic group.

Table III. Associations between FTO SNPs and body size measures as continuous traits by age: Caucasians only[a]

FTO SNP	Waist[b]	BMI[b]	BMI in 50s	BMI in 40s	BMI in 30s	BMI in 20s
rs1421085						
T/T	96.35 ± 1.03 (n = 240)	28.17 ± 0.40 (n = 240)	27.73 ± 0.41 (n = 184)	26.12 ± 0.38 (n = 219)	24.11 ± 0.32 (n = 195)	22.64 ± 0.25 (n = 231)
T/C	95.98 ± 0.82, P = 0.78 (n = 385)	28.19 ± 0.32, P = 0.98 (n = 385)	27.42 ± 0.32, P = 0.53 (n = 308)	26.26 ± 0.30, P = 0.77 (n = 360)	24.54 ± 0.25, P = 0.30 (n = 379)	22.70 ± 0.20, P = 0.84 (n = 375)
C/C	96.34 ± 1.41, P = 0.99 (n = 133)	28.66 ± 0.55, P = 0.48 (n = 133)	28.08 ± 0.55, P = 0.60 (n = 100)	27.15 ± 0.52, P = 0.10 (n = 121)	25.15 ± 0.43, P = 0.05 (n = 153)	23.12 ± 0.33, P = 0.24 (n = 131)
rs17817449						
T/T	96.12 ± 1.02 (n = 201)	28.17 ± 0.40 (n = 201)	27.69 ± 0.40 (n = 153)	26.13 ± 0.38 (n = 185)	24.19 ± 0.31 (n = 229)	22.73 ± 0.24 (n = 199)
T/G	95.98 ± 0.82, P = 0.91 (n = 393)	28.19 ± 0.32, P = 0.97 (n = 393)	27.45 ± 0.32, P = 0.62 (n = 316)	26.21 ± 0.30, P = 0.87 (n = 366)	24.48 ± 0.25, P = 0.47 (n = 373)	22.64 ± 0.20, P = 0.80 (n = 380)
G/G	96.93 ± 1.47, P = 0.65 (n = 160)	28.78 ± 0.57, P = 0.38 (n = 160)	28.17 ± 0.57, P = 0.48 (n = 121)	27.42 ± 0.54, P = 0.05 (n = 146)	25.32 ± 0.45, P = 0.04 (n = 129)	23.21 ± 0.35, P = 0.25 (n = 154)
rs8050136						
C/C	96.08 ± 1.01 (n = 248)	28.13 ± 0.40 (n = 248)	27.66 ± 0.40 (n = 190)	26.10 ± 0.38 (n = 227)	24.17 ± 0.31 (n = 237)	22.71 ± 0.24 (n = 239)
C/A	96.03 ± 0.82, P = 0.97 (n = 389)	28.19 ± 0.32, P = 0.91 (n = 389)	27.44 ± 0.32, P = 0.74 (n = 312)	26.21 ± 0.30, P = 0.83 (n = 364)	24.47 ± 0.25, P = 0.44 (n = 377)	22.64 ± 0.20, P = 0.81 (n = 378)
A/A	96.77 ± 1.48, P = 0.70 (n = 121)	28.78 ± 0.57, P = 0.35 (n = 121)	28.22 ± 0.58, P = 0.41 (n = 90)	27.45 ± 0.54, P = 0.04 (n = 109)	25.34 ± 0.45, P = 0.03 (n = 117)	23.24 ± 0.35, P = 0.21 (n = 120)
rs9939609						
T/T	96.03 ± 1.01 (n = 250)	28.10 ± 0.39 (n = 250)	27.66 ± 0.40 (n = 191)	26.10 ± 0.37 (n = 228)	24.15 ± 0.31 (n = 239)	22.72 ± 0.24 (n = 241)
T/A	96.14 ± 0.82, P = 0.93 (n = 387)	28.26 ± 0.32, P = 0.75 (n = 387)	27.49 ± 0.32, P = 0.74 (n = 311)	26.24 ± 0.30, P = 0.77 (n = 363)	24.49 ± 0.25, P = 0.41 (n = 375)	22.63 ± 0.20, P = 0.79 (n = 376)
A/A	96.66 ± 1.47, P = 0.72 (n = 122)	28.74 ± 0.57, P = 0.35 (n = 122)	28.19 ± 0.58, P = 0.44 (n = 91)	27.42 ± 0.54, P = 0.04 (n = 110)	25.34 ± 0.45, P = 0.03 (n = 118)	23.24 ± 0.34, P = 0.21 (n = 121)
rs8044769						
C/C	96.26 ± 1.15 (n = 247)	28.58 ± 0.45 (n = 247)	27.78 ± 0.49 (n = 189)	26.99 ± 0.42 (n = 226)	24.80 ± 0.35 (n = 236)	22.79 ± 0.27 (n = 238)
C/T	96.42 ± 0.81, P = 0.91 (n = 388)	28.33 ± 0.32, P = 0.65 (n = 388)	27.56 ± 0.32, P = 0.68 (n = 311)	26.17 ± 0.30, P = 0.11 (n = 363)	24.52 ± 0.25, P = 0.52 (n = 376)	22.75 ± 0.19, P = 0.90 (n = 377)
T/T	95.72 ± 1.27, P = 0.75 (n = 122)	27.85 ± 0.50, P = 0.28 (n = 122)	27.71 ± 0.50, P = 0.91 (n = 91)	26.18 ± 0.47, P = 0.19 (n = 110)	24.20 ± 0.39, P = 0.26 (n = 118)	22.82 ± 0.30, P = 0.94 (n = 121)

[a]Least squares means adjusted for age, gender, income, smoking, alcohol, family history of colorectal cancer, NSAIDs use. SNP, single nucleotide polymorphism.
[b]Measures from age at study recruitment.

Table IV. Associations between FTO SNPs and body size measures as continuous traits by age: African-Americans only[a]

FTO SNP	Waist[b]	BMI[b]	BMI in 50s	BMI in 40s	BMI in 30s	BMI in 20s
rs1421085						
T/T	103.35 ± 0.91 (n = 367)	31.88 ± 0.41 (n = 367)	31.20 ± 0.46 (n = 285)	28.28 ± 0.35 (n = 330)	25.22 ± 0.30 (n = 338)	22.81 ± 0.26 (n = 336)
T/C	102.99 ± 1.79, P = 0.50 (n = 95)	31.52 ± 0.80, P = 0.69 (n = 95)	29.85 ± 0.91, P = 0.17 (n = 72)	27.68 ± 0.69, P = 0.44 (n = 89)	25.75 ± 0.58, P = 0.42 (n = 92)	23.34 ± 0.51, P = 0.36 (n = 88)
C/C	120.06 ± 6.93, P = 0.03 (n = 6)	42.61 ± 3.10, P = 0.0007 (n = 6)	41.92 ± 3.29, P = 0.001 (n = 5)	37.49 ± 2.85, P = 0.001 (n = 5)	31.02 ± 2.41, P = 0.02 (n = 5)	28.07 ± 2.09, P = 0.01 (n = 5)
rs17817449						
T/T	104.23 ± 1.37 (n = 269)	31.81 ± 0.62 (n = 269)	31.48 ± 0.67 (n = 206)	27.72 ± 0.54 (n = 242)	25.00 ± 0.45 (n = 248)	23.03 ± 0.40 (n = 243)
T/G	102.96 ± 1.15, P = 0.44 (n = 164)	31.38 ± 0.51, P = 0.59 (n = 164)	30.31 ± 0.60, P = 0.18 (n = 127)	28.39 ± 0.45, P = 0.34 (n = 151)	25.47 ± 0.37, P = 0.43 (n = 155)	22.93 ± 0.33, P = 0.84 (n = 153)
G/G	108.70 ± 1.98, P = 0.06 (n = 34)	33.96 ± 0.89, P = 0.05 (n = 34)	32.71 ± 0.97, P = 0.29 (n = 28)	29.14 ± 0.79, P = 0.14 (n = 30)	26.08 ± 0.67, P = 0.18 (n = 31)	23.08 ± 0.58, P = 0.94 (n = 32)
rs8050136						
C/C	104.19 ± 1.46 (n = 147)	31.71 ± 0.66 (n = 147)	31.28 ± 0.70 (n = 121)	27.49 ± 0.57 (n = 133)	24.77 ± 0.48 (n = 134)	22.85 ± 0.42 (n = 133)
C/A	103.19 ± 1.50, P = 0.59 (n = 228)	31.52 ± 0.51, P = 0.82 (n = 228)	30.51 ± 0.60, P = 0.40 (n = 170)	28.37 ± 0.45, P = 0.23 (n = 209)	25.52 ± 0.37, P = 0.21 (n = 217)	23.02 ± 0.33, P = 0.76 (n = 213)
A/A	107.18 ± 1.80, P = 0.20 (n = 93)	33.39 ± 0.81, P = 0.10 (n = 93)	32.44 ± 0.91, P = 0.31 (n = 71)	29.24 ± 0.72, P = 0.05 (n = 82)	26.08 ± 0.60, P = 0.09 (n = 84)	23.15 ± 0.53, P = 0.66 (n = 83)
rs9939609						
T/T	104.55 ± 1.62 (n = 120)	31.90 ± 0.72 (n = 120)	31.08 ± 0.77 (n = 100)	27.62 ± 0.63 (n = 109)	24.79 ± 0.54 (n = 109)	22.80 ± 0.47 (n = 108)
T/A	103.14 ± 1.13, P = 0.47 (n = 238)	31.46 ± 0.50, P = 0.61 (n = 238)	30.66 ± 0.59, P = 0.67 (n = 179)	28.19 ± 0.44, P = 0.46 (n = 217)	25.39 ± 0.36, P = 0.35 (n = 226)	22.98 ± 0.32, P = 0.76 (n = 222)
A/A	106.36 ± 1.65, P = 0.43 (n = 111)	33.01 ± 0.74, P = 0.28 (n = 111)	32.17 ± 0.85, P = 0.34 (n = 84)	29.08 ± 0.65, P = 0.11 (n = 99)	26.04 ± 0.55, P = 0.10 (n = 101)	23.19 ± 0.48, P = 0.57 (n = 100)
rs8044769						
C/C	105.65 ± 1.05 (n = 166)	31.36 ± 0.47 (n = 166)	31.41 ± 0.54 (n = 136)	28.70 ± 0.42 (n = 150)	25.85 ± 0.35 (n = 152)	23.35 ± 0.30 (n = 151)
C/T	102.96 ± 1.37, P = 0.12 (n = 225)	31.38 ± 0.62, P = 0.21 (n = 225)	30.46 ± 0.70, P = 0.27 (n = 164)	27.68 ± 0.53, P = 0.13 (n = 206)	24.76 ± 0.44, P = 0.05 (n = 214)	22.34 ± 0.39, P = 0.04 (n = 209)
T/T	99.42 ± 3.15, P = 0.06 (n = 77)	31.48 ± 1.42, P = 0.56 (n = 77)	32.32 ± 1.49, P = 0.56 (n = 62)	27.62 ± 1.23, P = 0.40 (n = 68)	24.75 ± 1.04, P = 0.32 (n = 69)	23.39 ± 0.89, P = 0.96 (n = 69)

[a]Least squares means adjusted for age, gender, income, smoking, alcohol, family history of colorectal cancer, NSAIDs use.
[b]Measures from age at study recruitment. SNP, single nucleotide polymorphism.

Table V. OR for FTO polymorphisms and colorectal adenomas by ethnicity[a]

FTO SNP	Total population		Caucasians		African-Americans	
	n (cases/controls)	OR (95% CI); P-value	*n* (cases/controls)	OR (95% CI); P-value	*n* (cases/controls)	OR (95% CI); P-value
rs1421085						
T/T	165/440	1.00 (Referent)	60/180	1.00 (Referent)	105/260	1.00 (Referent)
T/C	126/352	1.08 (0.79–1.47), $P = 0.63$	97/286	1.06 (0.72–1.56), $P = 0.77$	29/66	1.05 (0.62–1.78), $P = 0.86$
C/C	30/109	0.94 (0.57–1.54), $P = 0.81$	27/106	0.84 (0.49–1.44), $P = 0.52$	3/3	—[b]
TC or CC versus TT	156/461	1.05 (0.78–1.42), $P = 0.74$	124/392	1.00 (0.69–1.45), $P = 0.99$	32/69	1.15 (0.69–1.92), $P = 0.59$
rs17817449						
T/T	117/294	1.00 (Referent)	59/188	1.00 (Referent)	58/106	1.00 (Referent)
T/G	155/456	0.87 (0.65–1.17), $P = 0.35$	101/285	1.18 (0.80–1.74), $P = 0.39$	54/171	0.54 (0.34–0.87), $P = 0.01$
G/G	49/150	0.84 (0.56–1.27), $P = 0.41$	24/98	0.84 (0.48–1.47), $P = 0.53$	25/52	0.85 (0.46–1.57), $P = 0.61$
TG or GG versus TT	204/606	0.86 (0.65–1.14), $P = 0.30$	125/283	1.10 (0.76–1.59), $P = 0.63$	79/223	0.61 (0.39–0.95), $P = 0.03$
rs8050136						
C/C	111/282	1.00 (Referent)	59/189	1.00 (Referent)	52/93	1.00 (Referent)
C/A	158/457	0.88 (0.65–1.18), $P = 0.39$	101/286	1.19 (0.81–1.75), $P = 0.39$	57/171	0.54 (0.33–0.87), $P = 0.01$
A/A	52/162	0.83 (0.56–1.24), $P = 0.37$	24/97	0.85 (0.49–1.49), $P = 0.58$	28/65	0.75 (0.41–1.36), $P = 0.34$
CA or AA versus CC	210/619	0.87 (0.65–1.15), $P = 0.32$	125/383	1.10 (0.76–1.60), $P = 0.61$	85/236	0.59 (0.38–0.93), $P = 0.02$
rs9939609						
T/T	102/266	1.00 (Referent)	60/190	1.00 (Referent)	42/76	1.00 (Referent)
T/A	160/463	0.89 (0.66–1.21), $P = 0.47$	99/286	1.14 (0.77–1.67), $P = 0.52$	61/177	0.57 (0.35–0.96), $P = 0.03$
A/A	59/174	0.89 (0.60–1.33), $P = 0.57$	25/97	0.87 (0.50–1.52), $P = 0.63$	34/77	0.81 (0.45–1.46), $P = 0.48$
TA or AA versus TT	219/637	0.89 (0.67–1.19), $P = 0.44$	124/383	1.07 (0.74–1.55), $P = 0.71$	95/254	0.64 (0.40–1.03), $P = 0.07$
rs8044769						
C/C	124/344	1.00 (Referent)	42/159	1.00 (Referent)	82/185	1.00 (Referent)
C/T	147/408	1.06 (0.78–1.43), $P = 0.73$	103/288	1.26 (0.83–1.94), $P = 0.28$	44/120	0.85 (0.54–1.35), $P = 0.49$
T/T	49/145	0.94 (0.61–1.44), $P = 0.78$	38/122	1.04 (0.62–1.76), $P = 0.88$	11/23	0.91 (0.39–2.12), $P = 0.82$
CT or TT versus CC	196/553	1.03 (0.77–1.38), $P = 0.85$	141/410	1.20 (0.80–1.80), $P = 0.39$	55/143	0.86 (0.56–1.33), $P = 0.49$

[a]Adjusted for age, ethnicity, gender, income, BMI, smoking, alcohol, family history of colorectal cancer, NSAIDs.
[b]Unstable estimate due to small cell/sample size. SNP, single nucleotide polymorphism.

significant associations were observed between any of the FTO polymorphisms and colorectal adenomas in Caucasians.

Discussion

We found that having one or two copies of the variant allele in FTO rs17817449 (G) and rs8050136 (A) polymorphisms was inversely associated with colorectal adenomas in African-Americans, which persisted after correction for multiple tests, albeit with marginal significance (rs8050136: $P_{corrected} = 0.06$; rs17817449: $P_{corrected} = 0.07$). In addition, we found that being in the highest versus the lowest BMI tertile at recruitment and in the 30s was associated with a higher risk of adenomas, and stratification by major ethnic group revealed that these associations only remained statistically significant in Caucasians. We observed that having two copies of the variant allele in rs17817449, rs8050136 and rs9939609, which are in strong LD with each other, was associated with higher BMI levels in the 30s and 40s age decades in Caucasians and in African-Americans, having two copies of the variant allele in rs1421085 (C) was associated with higher BMI in all age periods examined but only a small number ($n = 6$) of African-Americans had the C/C genotype; thus, these results may be spurious and should be interpreted with caution. Nevertheless, our results for associations between FTO polymorphisms and obesity-related measures are generally consistent with previous GWAS and candidate gene association studies (19,20,22–24,26–28,30,31).

Our results confirm previous findings of an association between obesity-related measures and colorectal adenomas (10–15). For example, Sedjo *et al*. (14) observed a positive association between obesity at colonoscopy and colorectal adenomas in the multi-ethnic Insulin Resistance Atherosclerosis Study cohort but they found no association between obesity at 5 and 10 years prior to the colonoscopy and colorectal adenomas. Furthermore, stratification by ethnicity revealed that their association between obesity at the time of colonoscopy only remained statistically significant in non-Hispanic whites (14). Using the same body size cut points (33), we also observed a positive association between obesity at the time of colonoscopy screening (recruitment) and adenomas in Caucasians, albeit marginal. In addition, Sedjo *et al.* (14) reported a significant P-value for trend with increasing waist circumference tertiles at the time of colonoscopy. In our study, we found a significant association for a trend with increasing tertiles of waist circumference at the time of colonoscopy (recruitment) and when comparing the highest with the lowest tertiles in Caucasians. Although we observed a positive association between the highest versus the lowest BMI tertile and colorectal adenomas in the 30s age decade, we did not find a statistically significant association between overweight or obesity using the WHO definitions in

the 30s (or 40s and 20s) age decades. Thus, these results and those from other prior studies evaluating obesity-related measures 3–10 years prior to colonoscopy (10,14) suggest that obesity at the time of colonoscopy appears to be a much stronger risk factor for colorectal adenomas than obesity observed during earlier adult age periods and provide further evidence to the hypothesis that excess adiposity appears to be more involved with growth promoting than cancer cell-initiating factors (38).

Our results also confirm previous findings between FTO polymorphisms and obesity-related measures (19,20,22–24,26–28,30,31) and, show for the first time, in African-Americans, that the FTO rs1421085 variant allele (C) seems to confer increased risk of higher BMI throughout adulthood while heterozygosity for the rs8044769 variant allele (T) may be potentially protective of higher BMI levels earlier in adulthood (20s and 30s age decades). These findings lend further support for differential effects of FTO polymorphisms by age previously observed in children. For example, Haworth *et al.* (32) found that the association between the FTO rs9939609 'A' allele and BMI was stronger in children at Age 11 compared with Age 4. Grunnett *et al.* (39) found a significant positive association between the rs9939609 'A' allele and higher BMI in younger and not elderly twins. They also found that the younger twins had significantly higher FTO messenger RNA (mRNA) levels in adipose tissue and muscle (in the basal state and after insulin stimulation) compared with the elderly twins, suggesting an age-related decline in FTO expression; however, the FTO rs9939609 polymorphism was not associated with these expression level changes (39). Additional studies evaluating the effects of FTO polymorphisms on mRNA and protein expression levels at multiple ages across adulthood are clearly needed.

Moreover, we report for the first time that, in African-Americans, having one or two copies of the variant allele in FTO rs17817449 (G), rs9939609 (A) or rs8050136 (A), which are in fairly strong pair-wise LD with each other, was inversely associated with colorectal adenomas. Because FTO variants were recently identified through GWAS, the functional effects of FTO polymorphisms remain largely unknown. However, inactivation of the FTO gene has been shown to protect mice from obesity and may be involved in peripheral energy homeostasis, mitochondrial coupling and/or substrate cycling (40). The rs9939609 'A' allele, in particular, has been associated with higher total energy and fat intake in several studies (41–43). Furthermore, an age-dependent decline in FTO expression has been observed in adipose tissue and skeletal muscle but the FTO rs9939609 polymorphism was not associated with the changes in FTO expression (39). A larger functional role for FTO is supported by results from a recent study that reported that the FTO rs9939609 'T' allele was associated with a decrease in all-cause mortality, independent of obesity (fatness), in a cohort of Danish men (44). Furthermore, Bressler *et al.* (28) reported that although the rs1421085 variant 'C' allele increased susceptibility to obesity, it conferred an apparent protective effect against diabetes in African-Americans. The rs17817449 and rs8050136 polymorphisms are located within Cutl-like 1 transcription factor recognition sequences and, the rs8050136 A allele appears to preferentially bind to Cutl-like 1 in human fibroblast DNA (45), and in a recent human study, rs8050136 was found to be strongly correlated ($P = 2.7 \times 10^{-5}$) with expression of retinoblastoma-like 2 (RBL2/p130), which is a tumor suppressor/cell cycle-repressing gene (46). Other putative mechanisms that might help explain the inverse associations we observed between FTO polymorphisms and colorectal adenomas include FTO's hypothesized role in apoptosis (47) and demethylation (48); however, further mechanistic work is needed to determine if the FTO polymorphisms functionally affect these processes in the human colon and rectum.

In Caucasians, we found higher BMI at recruitment and in the 30s, age decade was associated with increased colorectal adenoma risk, and FTO polymorphisms (rs1421085, rs17817449, rs8050136, rs9939609) were associated with higher BMI in the 30s age decade but none of these FTO polymorphisms were associated with adenomas. Thus, the increased risk of colorectal adenomas conferred by higher BMI in Caucasians does not appear to be mediated by any of the FTO polymorphisms examined in this study. We had 90.56 and 86.82% power to detect the effect sizes observed in Caucasians for the association between the highest tertile of BMI and colorectal adenomas at recruitment and in the 30s age decade, respectively. In African-Americans, we observed associations between FTO polymorphisms (rs8050136, rs17817449, rs9939609) and colorectal adenomas, and between FTO rs17917449 and rs8050136 and higher BMI at recruitment and in the 40s, respectively, but higher BMI in all age periods examined (recruitment, 50s, 40s, 30s, 20s) was not associated with adenomas. Thus, the apparent decreased risk conferred by the FTO polymorphisms in African-Americans (rs8050136, rs17817449, rs9939609) does not appear to be mediated by higher BMI. We had 81.64 and 80.26% power to detect the effect sizes observed in African-Americans for the association between dominant models of the FTO polymorphisms, rs8050136 and rs17817449 and colorectal adenomas, respectively.

Although initial GWAS discovered associations between FTO polymorphisms and obesity-related measures using an additive genetic model, the associations we observed in African-Americans were found using different genetic models. Specifically, the associations we observed between rs17817449 and rs8050136 and higher BMI at recruitment and in the 40s were found with having two copies of the variant allele, whereas the decreased risk we observed between these two polymorphisms and colorectal adenomas was found under a dominant genetic model (i.e. having one or two copies of the variant allele). Other candidate gene studies in African-Americans have reported that the association between FTO rs8050136 (and rs9939609) and BMI was strongest using a dominant model (data not shown) (26). Thus, although it is customary to evaluate additive genetic models in GWAS, perhaps, the effects of certain FTO variant alleles in African-Americans may be stronger under other genetic models that may only be revealed in follow-up candidate gene studies.

There are several limitations in our study. The most important issue relates to our retrospective evaluation of self-reported weight in the 20s, 30s, 40s and 50s age decades, which could lead to bias in our results. However, we compared the BMI calculated from the measured height and weight at recruitment with the BMI calculated from self-reported current (recruitment period) height and weight obtained from the questionnaire and found that the BMI based on self-reported height and weight (mean = 29.50; SD = 6.99) was not statistically significantly different from the BMI based on measured height and weight (mean = 29.69; SD = 7.09) (paired *t*-test: $t(1173) = 1.30$; $P = 0.19$). In addition, other studies have shown that correlations between self-reported and measured weight are generally quite high (49) and self-reported weight has been shown to be accurately recalled for up to 28 years prior in elderly subjects (50). We may have also missed potentially important periods by examining BMI only in these age decades versus at finer cut points. The possibility of selection bias also cannot be ruled out. Subjects in this study were recruited from those who underwent colonoscopy screening and may reflect a healthier (or at least a more health conscious) population. In addition, to minimize the potential for population stratification, we performed analyses stratified by major ethnic group and focused our results on those obtained in Caucasians and African-Americans, separately. Although our total sample size was fairly large, we did not have ample sample size to stratify by major ethnic group and gender, which may mask potentially important differences between males and females in these ethnic groups.

In summary, our results show, for the first time, that FTO polymorphisms (rs17817449 and rs8050136) are associated with colorectal adenomas, as well as adult BMI, in African-Americans. Additional prospective and mechanistic studies which evaluate the functional impact of these FTO polymorphisms in the human colon and rectum are needed to support our findings.

Funding

This work was supported in part by the National Institutes of Health National Cancer Institute (K07CA129162 to N.L.N.; U54CA116867 and R01CA136726 to L.L.)

References

1. Jemal,A. *et al*. (2009) Cancer statistics, 2009. *CA Cancer J. Clin.*, **59**, 225–249.
2. Atkin,W.S. *et al*. (1992) Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N. Engl. J. Med.*, **326**, 658–662.
3. Hill,M.J. *et al*. (1978) Aetiology of adenoma—carcinoma sequence in large bowel. *Lancet*, **1**, 245–247.
4. Giacosa,A. *et al*. (2004) Epidemiology of colorectal polyps. *Tech. Coloproctol.*, **8** (suppl 2), s243–s247.
5. Gupta,S. (2008) Colorectal polyps: the scope and management of the problem. *Am. J. Med. Sci.*, **336**, 407–417.
6. Young,J. *et al*. (2006) The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. *Cancer Epidemiol. Biomarkers Prev.*, **15**, 1778–1784.
7. Dai,Z. *et al*. (2007) Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J. Gastroenterol.*, **13**, 4199–4206.
8. Moghaddam,A.A. *et al*. (2007) Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol. Biomarkers Prev.*, **16**, 2533–2547.
9. Renehan,A.G. *et al*. (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*, **371**, 569–578.
10. Bird,C.L. *et al*. (1998) Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am. J. Epidemiol.*, **147**, 670–680.
11. Larsen,I.K. *et al*. (2006) Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals. *BMC Gastroenterol.*, **6**, 5.
12. Lee,G.E. *et al*. (2008) Association between BMI and metabolic syndrome and adenomatous colonic polyps in Korean men. *Obesity (Silver. Spring)*, **16**, 1434–1439.
13. Neugut,A.I. *et al*. (1991) Obesity and colorectal adenomatous polyps. *J. Natl Cancer Inst.*, **83**, 359–361.
14. Sedjo,R.L. *et al*. (2007) Change in body size and the risk of colorectal adenomas. *Cancer Epidemiol. Biomarkers Prev.*, **16**, 526–531.
15. Wise,L.A. *et al*. (2008) Anthropometric risk factors for colorectal polyps in African-American women. *Obesity (Silver. Spring)*, **16**, 859–868.
16. Anderson,J.C. *et al*. (2007) Body mass index: a marker for significant colorectal neoplasia in a screening population. *J. Clin. Gastroenterol.*, **41**, 285–290.
17. Omata,F. *et al*. (2009) Modifiable risk factors for colorectal neoplasms and hyperplastic polyps. *Intern. Med.*, **48**, 123–128.
18. Wallace,K. *et al*. (2005) The association of physical activity and body mass index with the risk of large bowel polyps. *Cancer Epidemiol. Biomarkers Prev.*, **14**, 2082–2086.
19. Frayling,T.M. *et al*. (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, **316**, 889–894.
20. Scott,L.J. *et al*. (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science*, **316**, 1341–1345.
21. Song,Y. *et al*. (2008) FTO polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. *Obesity (Silver. Spring)*, **16**, 2472–2480.
22. Zeggini,E. *et al*. (2007) Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*, **316**, 1336–1341.
23. Willer,C.J. *et al*. (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat. Genet.*, **41**, 25–34.
24. Do,R. *et al*. (2008) Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study. *Diabetes*, **57**, 1147–1150.
25. Scuteri,A. *et al*. (2007) Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet.*, **3**, e115.
26. Wing,M.R. *et al*. (2009) Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. *Hum. Genet.*, **125**, 615–626.
27. Wing,M.R. *et al*. (2010) Analysis of FTO gene variants with obesity and glucose homeostasis measures in the multiethnic Insulin Resistance Atherosclerosis Study cohort. *Int. J. Obes. (Lond)*.
28. Bressler,J. *et al*. (2010) Risk of type 2 diabetes and obesity is differentially associated with variation in FTO in whites and African-Americans in the ARIC study. *PLoS One*, **5**, e10521.
29. Liu,G. *et al*. (2010) FTO variant rs9939609 is associated with body mass index and waist circumference, but not with energy intake or physical activity in European- and African-American youth. *BMC Med. Genet.*, **11**, 57.
30. Grant,S.F. *et al*. (2010) Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. *PLoS One*, **3**, e1746.
31. Bollepalli,S. *et al*. (2010) Association of FTO gene variants with adiposity in African-American adolescents. *Obesity (Silver. Spring)*, **18**, 1959–1963.
32. Haworth,C.M. *et al*. (2008) Increasing heritability of BMI and stronger associations with the FTO gene over childhood. *Obesity (Silver. Spring)*, **16**, 2663–2668.
33. The World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech. Rep. Ser.*, **854**, 1–452.
34. Guo,S.W. *et al*. (1992) Performing the exact test of Hardy-Weinberg proportion for multiple alleles. *Biometrics*, **48**, 361–372.
35. Devlin,B. *et al*. (1995) A comparison of linkage disequilibrium measures for fine-scale mapping. *Genomics*, **29**, 311–322.
36. Conneely,K.N. *et al*. (2007) So many correlated tests, so little time! Rapid adjustment of P values for multiple correlated tests. *Am. J. Hum. Genet.*, **81**, 1158–1168.
37. Gauderman,W.J. *et al*. (2006) *QUANTO 1.1: A Computer Program for Power and Sample Size Calculations for Genetic-Epidemiology Studies*. http://hydra.usc.edu/gxe (27 December 2010, date last accessed).
38. Almendingen,K. *et al*. (2001) Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up in situ for 3 years? *Am. J. Gastroenterol.*, **96**, 2238–2246.
39. Grunnet,L.G. *et al*. (2009) Regulation and function of FTO mRNA expression in human skeletal muscle and subcutaneous adipose tissue. *Diabetes*, **58**, 2402–2408.
40. Fischer,J. *et al*. (2009) Inactivation of the Fto gene protects from obesity. *Nature*, **458**, 894–898.
41. Cecil,J.E. *et al*. (2008) An obesity-associated FTO gene variant and increased energy intake in children. *N. Engl. J. Med.*, **359**, 2558–2566.
42. Haupt,A. *et al*. (2009) Variation in the FTO gene influences food intake but not energy expenditure. *Exp. Clin. Endocrinol. Diabetes*, **117**, 194–197.
43. Timpson,N.J. *et al*. (2008) The fat mass- and obesity-associated locus and dietary intake in children. *Am. J. Clin. Nutr.*, **88**, 971–978.
44. Zimmermann,E. *et al*. (2009) Fatness-associated FTO gene variant increases mortality independent of fatness—in cohorts of Danish men. *PLoS. Genet.*, **4**, e4428.
45. Stratigopoulos,G. *et al*. (2008) Regulation of FTO/FTM expression in mice and humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **294**, R1185–R1196.
46. Jowett,J.B. *et al*. (2010) Genetic variation at the FTO locus influences RBL2 gene expression. *Diabetes*, **59**, 726–732.
47. van der Hoeven,F. *et al*. (1994) Programmed cell death is affected in the novel mouse mutant Fused toes (Ft). *Development*, **120**, 2601–2607.
48. Gerken,T. *et al*. (2007) The obesity-associated FTO gene encodes a 2-oxoglutaratedependent nucleic acid demethylase. *Science*, **318**, 1469–1472.
49. Willett,W.C. (1998) *Nutritional Epidemiology.* Oxford University Press, New York, NY.
50. Stevens,J. *et al*. (1990) Accuracy of current, 4-year, and 28-year self-reported body weight in an elderly population. *Am. J. Epidemiol.*, **132**, 1156–1163.

Received November 1, 2010; revised January 31, 2011; accepted February 6, 2011