Published in final edited form as:
Int J Cancer. 2012 September 15; 131(6): E1038–E1043. doi:10.1002/ijc.27592.

Susceptibility variants for obesity and colorectal cancer risk: the Multiethnic Cohort and PAGE Studies

Unhee Lim[1], **Lynne R. Wilkens**[1], **Kristine R. Monroe**[2], **Christian Caberto**[1], **Maarit Tiirikainen**[1], **Iona Cheng**[1], **Sungshim Lani Park**[1], **Daniel O. Stram**[2], **Brian E. Henderson**[2], **Laurence N. Kolonel**[1], **Christopher A. Haiman**[2], and **Loïc Le Marchand**[1]

[1]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA

[2]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of, Medicine, University of Southern California, Los Angeles, CA, USA

Abstract

Obesity is a leading contributor to colorectal cancer risk. We investigated whether the risk variants identified in genome-wide association studies of body mass index (BMI) and waist size are associated with colorectal cancer risk, independently of the effect of obesity phenotype due to a shared etiology. Twenty four SNPs in 15 loci (*BDNF, FAIM2, FTO, GNPDA2, KCTD15, LYPLAL1, MC4R, MSRA, MTCH2, NEGR1, NRXN3, SEC16B, SH2B1, TFAP2B,* and *TMEM18*) were genotyped in a case-control study of 2,033 colorectal cancer cases and 9,640 controls nested within the Multiethnic Cohort Study, as part of the Population Architecture using Genomics and Epidemiology (PAGE) consortium. Risk alleles for two obesity SNPs were associated with colorectal cancer risk – *KCTD15* rs29941 [odds ratio (OR) for C allele = 0.90, 95% confidence interval (CI) 0.83–0.98; $p = 0.01$] and *MC4R* rs17782313 (OR for C allele = 1.12, 95% CI 1.02–1.22; $p = 0.02$). These associations were independent of the effect of BMI. However, none of the results remained significant after adjustment for multiple comparisons. No heterogeneity was observed across race/ethnic groups. Our findings suggest that the obesity risk variants are not likely to affect the risk of colorectal cancer substantially.

Keywords

genotype-phenotype interactions; obesity; pleiotropy; prospective nested case-control studies; race/ethnicity

INTRODUCTION

Obesity is a leading modifiable risk factor for colorectal cancer. About 35% of new colorectal cancer cases among men and 21% of cases among women have been attributed to obesity in the U.S.[1] Furthermore, larger waist size has been associated with risk of colon cancer independently of body mass index (BMI; kg/m^2).[2] Just as there are common behavioral factors (e.g., diet and physical inactivity) that independently increase the risk of obesity or colorectal cancer, inherited susceptibility may also contribute to the development of both conditions. Accordingly, risk variants identified for obesity in genome-wide association studies (GWAS) have been considered for potential pleiotropic effects in

Corresponding Author: Unhee Lim, PhD, University of Hawaii Cancer Center, 1236 Lauhala Street, Suite, 407, Honolulu, HI 96813; phone (808) 440-5211; fax (808) 586-2982; ulim@cc.hawaii.edu.

CONFLICT OF INTEREST
The authors declared no conflict of interest.

carcinogenesis. In particular, the best-replicated obesity risk locus in *FTO* has been associated inversely with lung [3] and low-grade prostate [4] cancers but positively with high-grade prostate cancer [4] and endometrial cancer,[5] although the associations were weak and of borderline significance or attenuated with BMI adjustment. To date, there has been no epidemiologic study on colorectal cancer in relation to *FTO* or other GWAS-replicated risk variants of obesity.

GWAS to date have identified over 30 common single nucleotide polymorphisms (SNPs) associated with overall adiposity, assessed by BMI, [6] and additional SNPs associated with abdominal obesity, assessed by waist size.[7] Some of these variants appear to be involved in the hypothalamic regulation of energy balance, such as *BDNF*, *MC4R, POMC,* and *SH2B1*,[6] but other GWAS variants for obesity, including those in the *FTO* locus, [8] are still being investigated for their functional effects, which may involve potentially carcinogenic disturbances.

We examined the effects of 15 risk loci for obesity identified in GWAS of BMI [9, 10] and waist size[11, 12] as of September 2009 for their effects on the risk of colorectal cancer in a nested case-control study of the Multiethnic Cohort, as part of the Population Architecture using Genomics and Epidemiology (PAGE) consortium.[13]

MATERIALS AND METHODS

Study Population and Baseline Data

The Multiethnic Cohort (MEC) Study, established between 1993 and 1996 in Hawaii and Los Angeles, is a prospective investigation of the roles of lifestyle and genetic risk factors in common cancers among five ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians and whites), as described in detail previously.[14] A questionnaire was mailed to men and women of ages 45–75 and of the five ethnicities who were identified primarily through the drivers' license files for the state of Hawaii and the county of Los Angeles, California. The over 215,000 MEC Study participants are broadly representative of the study area populations, as reflected in the distribution of various census demographics.[14]

The baseline questionnaire queried information on demographics and risk factors for cancer: ethnicity, medical and reproductive history, smoking history, dietary intake and physical activity. Medical history questions included family history of colon or rectal cancer among first-degree relatives, history of intestinal polyps and aspirin use.[14] Participants were asked to write in their current weight and height, from which BMI was calculated. Usual dietary intake in the past year was assessed using a quantitative food frequency questionnaire (QFFQ) with over 180 items, developed and calibrated specifically for this multiethnic population.[15] Physical activity was assessed as numbers of hours spent in various sedentary, sports and work-related activities, expressed as metabolic equivalents (METs). History of diabetes in the current analysis also incorporated self-reports in the follow-up questionnaires (approximately 5 and 10 years after baseline), medication use reported at the time of specimen collection, and records of hospital discharge and insurance.

Case/Control Ascertainment and Biospecimen Collection

All primary cancer cases within the MEC occurring during follow-up since the baseline have been identified by regular linkage with NCI Surveillance, Epidemiology, and End Results (SEER) registries: the Hawaii Tumor Registry, the Los Angeles County Surveillance Program and the State of California Cancer Registry. Case ascertainment in the MEC has been observed to be close to complete with a low out-migration rate.[14] Blood samples for genetic studies were collected in two phases: first, in 1996–2001, specimens were obtained retrospectively from incident colorectal, breast and prostate cancer cases, together with a

random sample of the cohort to serve as controls; secondly, in 2001–2006, specimens were obtained from over 67,000 consenting surviving cancer-free participants who have been followed for cancer incidence. The distribution of established risk factors for colorectal cancer was similar in the entire cohort and in the biospecimen subgroup. Among the MEC participants with biospecimens, we identified 1,125 male and 908 female incident colorectal cancer cases (ICD-O-3: C180–187, C199, C209) by October, 2010 (median of 8 years since entry). Controls for the current analysis consisted of men and women without colorectal cancer diagnosis identified by October, 2010 and with blood samples available (n = 9,640). The Institutional Review Boards at the University of Hawaii and at the University of Southern California (USC) approved the study, and all study participants provided informed consent.

SNP Selection and Genotyping

DNA was purified from buffy coat samples stored in vapor phase of liquid nitrogen. Twenty four SNPs in 15 loci (*BDNF, FAIM2, FTO, GNPDA2, KCTD15, LYPLAL1, MC4R, MSRA, MTCH2, NEGR1, NRXN3, SEC16B, SH2B1*, *TFAP2B,* and *TMEM18*) were considered in the current analysis, comprising all the published risk variants for BMI [9, 10] or body weight [10] and waist size [11, 12] as of September 2009. Genotyping was conducted using the standard TaqMan and the OpenArray systems (Applied Biosystems, Carlsbad, CA) at the University of Hawaii Cancer Center (UHCC) and USC. Laboratory technicians were blinded to case-control status. Quality assurance data indicated high genotype call rates (>97%), high concordance (≥ 99.9%) between the UHCC and USC labs for all 24 variants on the 375 HapMap samples, and high concordance (>99.5%) among the 8.8% blinded duplicate samples. All SNPs were consistent with the Hardy-Weinberg distributions (p>0.01 in 5 ethnic groups).

Statistical Analysis

Each biallelic SNP was examined in relation to BMI in general linear models that adjusted for age, sex, and ethnicity. The association between each SNP and colorectal cancer risk was estimated by the odds ratios (ORs) and 95% confidence intervals (CIs) from unconditional logistic regression models. The number of obesity risk allele in each SNP was coded as 2 dichotomous indicator variables for nominal associations (1 or 2 *vs.* 0) and as a continuous variable for trend tests. The base model was adjusted for age, sex, ethnicity, and the interaction between sex and ethnicity. BMI was added in the model to examine whether it mediated the associations of the SNPs with colorectal cancer. Effect modification by sex, ethnicity, and levels of BMI and physical activity was assessed by a Wald test of the cross-product terms of the SNP trend variable and each covariate in separate models. For the *FTO* and *KCTD15* loci, for which two or more SNPs were genotyped, haplotypes were reconstructed using PHASE v2.1.1[16, 17] and tested for an association with CRC. Polytomous logistic regression was used to examine the SNP-cancer associations by tumor site of colon *vs.* rectum in reference to common controls. Analyses were conducted using SAS v9.2, and significance was considered at p<0.05 (two-sided). To control the potentially inflated Type 1 error due to multiple comparisons, we performed false discovery rate (FDR)-adjustments, [18] permutation testing,[19] and false positive report probability (FPRP) estimation.[20]

RESULTS

The obesity risk variants and their allele frequencies among controls for each ethnic group are described in Supplemental Table 1. Allele frequencies in whites in the MEC were similar to those observed in populations of European descent.[6, 9, 10]

Among the MEC controls, we confirmed the positive associations between BMI and 13 variants in 6 loci (*BDNF, FTO, KCTD15, NEGR1, NRXN3* and *SH2B1*) and also between BMI-adjusted waist circumference and 19 SNPs in 10 loci (the 6 loci above plus *LYPLAL1, MSRA, SEC16B* and *TMEM18*) (reported separately by the PAGE consortium).

Cases were slightly older than controls (Table 1). After controlling for age, cases were more likely than controls to have a higher BMI and personal history of diabetes, to be a former smoker, with higher mean pack-years among smokers, and to have consumed more alcohol. Cases had slightly fewer years of education and were likely to consume less multivitamins, dietary fiber and total calcium. Among women, cases were less likely to use postmenopausal hormone treatment than controls.

In the main effect analysis of the obesity risk variants on colorectal cancer, adjusted for age, sex and ethnicity, two out of the 24 SNPs showed a significant association (Table 2; results for all SNPs are shown in Supplemental Table 2). The *KCTD15* rs29941 obesity risk allele (C) was associated with a lower colorectal cancer risk, whereas the *MC4R* rs17782313 obesity risk allele (C) showed a positive association with colorectal cancer. Further adjustments for BMI or for the risk factors that differed between cases and controls in Table 1 did not materially change the risk estimates (i.e., difference <10%). However, neither association was statistically significant when corrected for multiple comparisons, either by FDR-adjustment (adjusted *p-value* for both rs29941 and rs17782313 = 0.24), by case-control status permutation in sex/race/SNP-strata (permutation *p*-value = 0.056 for rs29941, $p = 0.060$ for rs17782313) or by the FPRP approach (FPRP = 0.650 for rs17782313 and 0.752 for rs29941, at a prior probability level of 0.01 and power to detect an OR of 1.5). Similarly, haplotypes estimated from the 8 *FTO* variants and 2 *KCTD15* variants did not show a significant association with CRC (Supplemental Table 3).

We also examined individuals' risk score by summing the number of risk alleles for the 15 loci (including two SNPs in low linkage disequilibrium (LD) for *BDNF*, rs8050136 for *FTO*, and rs29941 for *KCTD15*). The risk score, ranging between 4 and 22, showed a significant positive association with BMI ($p < 0.0001$) but not with colorectal cancer ($p = 0.47$). The *MC4R* rs17782313 variant, but not *KCTD15* rs29941, showed a slightly stronger association with rectal cancer (n = 444 cases; OR = 1.29, 95% CI 1.10–1.51) than with colon cancer (n = 1,369 cases; OR = 1.07, 0.96–1.18; *p-heterogeneity* = 0.03).

In a subgroup (1,640 cases, 8,878 controls) that had 109 ancestry informative markers (AIMs) data available, the SNP-colorectal cancer associations were examined with and without adjustment for the four principal components that represented the differential AIMs patterns for the 5 race/ethnic groups in the cohort.[21] The results were similar, indicating no evidence of population stratification (data not shown).

BMI was positively associated with colorectal cancer risk (OR for a 5 kg/m^2 increment = 1.19, 95% CI 1.12–1.26), with a slightly stronger association for colon cancer (OR = 1.21, 95% CI 1.13–1.29) than for rectal cancer (OR = 1.10, 95% CI 0.99–1.23), as reported previously.[2] These risk estimates were not changed after adjustment for the rs29941 and rs17782313 variants (data not shown).

Because some of the obesity variants have shown different associations with obesity phenotypes by sex,[7] race,[22] or physical activity,[23] we tested for evidence of heterogeneity. Results for *FTO* and *KCTD15* that showed significant heterogeneity by weight status in some or all variants examined are presented in Table 2 ($P_{het} < 0.05$). Three of the 8 variants in *FTO* (r2 of 80–95% in whites, 54–98% in the other ethnic groups) and both *KCTD15* variants (rs11084753 and rs29941; r^2 ranging from 31% in African Americans to 60% in Japanese Americans and Native Hawaiians) had a significant inverse association with

colorectal cancer among obese individuals, but not among normal-weight or overweight individuals. As in the main effects analysis, adjusting for BMI did not yield a notable change in the risk estimates (data not shown).

The SNP-cancer associations did not vary across ethnicity (see Supplemental Table 4), except for the *NRXN3* rs10146997 variant, which was inversely associated with colorectal cancer risk in whites only (*p-heterogeneity* = 0.02). Similarly, there was no evidence of heterogeneity by sex, age (by median age of 70) or physical activity (by median 1.60 METs; data not shown).

DISCUSSION

Considering that total and abdominal fatness is an established risk factor for colorectal cancer, we examined whether risk variants for higher BMI or larger waist size from GWAS may contribute to the risk of this cancer through shared etiology. Our study is one of the first analyses of the *FTO* and other obesity GWAS variants for pleiotropic effects on colorectal cancer and utilized the uniquely wide range of genetic and pre-diagnostic phenotype data in a multiethnic cohort. Only 2 of the 24 variants examined showed an initial significant association, but after accounting for multiple comparisons, these findings were no longer significant. Carriers of the obesity risk allele for the *KCTD15* rs29941 variant, which, as expected, was positively correlated with BMI in our study, showed a reduced risk for colorectal cancer, whereas for *MC4R* rs17782313, the obesity risk allele carriers had an elevated risk. Furthermore, variants in *FTO* and *KCTD15* had a stronger inverse association among the obese than non-obese. These findings suggest that the potential effects of obesity variants on colorectal cancer risk are likely to be small and, possibly, vary by weight status.

We did not find an overall association between any of the *FTO* variants considered here and colorectal cancer risk. This is consistent with a previous study of *FTO* and colorectal adenoma.[24] Among whites and African Americans with (n = 321) and without (n = 903) colonoscopy-confirmed adenomas, the obesity risk alleles for rs8050136 and rs9939609 in *FTO* were associated with higher self-reported adult BMI (in 30s and 40s), and higher BMI in turn was associated with greater risk of colorectal adenoma; however, the *FTO* variants showed no overall association with adenoma and a significant inverse association among African Americans.[24] We observed no associations between 8 *FTO* obesity risk variants and incident colorectal cancer across ethnicity, including African Americans. However, we found an inverse association of the obesity risk alleles in *FTO* and *KCTD15* with colorectal cancer among obese individuals. Thus, the role of the obesity-associated variants in colorectal carcinogenesis may entail more complex mechanisms.

The *KCTD15* gene encodes a protein, “potassium channel tetramerisation domain containing 15”, whose function remains largely undetermined. Its variant (rs29941) explained less than 0.01% of the variance in BMI in previous GWAS, as compared to the 0.34% explained by the *FTO* risk alleles (rs1558902).[6] Several other genes encoding potassium channel-regulating proteins have been identified in GWAS of obesity [25] as well as of Type 2 diabetes and other metabolic diseases. This may implicate genetic alterations in potassium channel regulator proteins as likely candidates for pleiotropic effects in metabolic disorders. Carriers of the risk allele in *MC4R* showed increased risk of colorectal cancer, despite the lack of clear association with BMI or waist size in our data, possibly due to our relatively limited sample size. Also, imprecision in BMI based on self-reported weight and height in our study might have contributed to a slight misclassification, resulting in some attenuation of any genotype-phenotype associations – however, the association between the *FTO* variants and BMI in our data was comparable to that observed in studies with measured BMI.

Our study constitutes an initial examination of the potential association between genetic susceptibility to increased adiposity and colorectal cancer risk and suggests no substantial effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Population Architecture Using Genomics and Epidemiology (PAGE) program is funded by the National Human Genome Research Institute (NHGRI), supported by U01HG004803 (CALiCo), U01HG004798 (EAGLE), U01HG004802 (MEC), U01HG004790 (WHI), and U01HG004801 (Coordinating Center), and their respective NHGRI ARRA supplements. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The complete list of PAGE members can be found at http://www.pagestudy.org.

The Multiethnic Cohort study (MEC) characterization of epidemiological architecture is funded through the NHGRI PAGE program (U01HG004802 and its NHGRI ARRA supplement). The MEC study is funded through the National Cancer Institute (R37CA54281, R01 CA63, P01CA33619, U01CA136792, and U01CA98758). The UHCC Genomics Shared Resource (GSR) is supported by NCI CCSG 3P30CA071789-12S8. The authors thank study participants and acknowledge the dedicated efforts of the following staff of the GSR and the MEC at the University of Hawaii Cancer Center: Ann Seifried, Annette Lum-Jones, Maj Earle, and Wileen Mau.

References

1. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004; 4:579–91. [PubMed: 15286738]
2. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr. 2007; 86:556–65. [PubMed: 17823417]
3. Brennan P, McKay J, Moore L, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, et al. Obesity and cancer: Mendelian randomization approach utilizing the FTO genotype. Int J Epidemiol. 2009; 38:971–5. [PubMed: 19542184]
4. Lewis SJ, Murad A, Chen L, Davey Smith G, Donovan J, Palmer T, Hamdy F, Neal D, Lane JA, Davis M, Cox A, Martin RM. Associations between an obesity related genetic variant (FTO rs9939609) and prostate cancer risk. PLoS One. 2010; 5:e13485. [PubMed: 20976066]
5. Lurie G, Gaudet MM, Spurdle AB, Carney ME, Wilkens LR, Yang HP, Weiss NS, Webb PM, Thompson PJ, Terada K, Setiawan VW, Rebbeck TR, et al. The obesity-associated polymorphisms FTO rs9939609 and MC4R rs17782313 and endometrial cancer risk in non–Hispanic white women. PLoS One. 2011; 6:e16756. [PubMed: 21347432]
6. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Allen HL, Lindgren CM, Luan J, Magi R, Randall JC, Vedantam S, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42:937–48. [PubMed: 20935630]
7. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, Thorleifsson G, Zillikens MC, Speliotes EK, Magi R, Workalemahu T, White CC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet. 2010; 42:949–60. [PubMed: 20935629]
8. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007; 318:1469–72. [PubMed: 17991826]
9. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009; 41:25–34. [PubMed: 19079261]

10. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, Styrkarsdottir U, Gretarsdottir S, Thorlacius S, Jonsdottir I, Jonsdottir T, Olafsdottir EJ, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet. 2009; 41:18–24. [PubMed: 19079260]
11. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L, Speliotes EK, Thorleifsson G, Willer CJ, Herrera BM, Jackson AU, Lim N, et al. Genome-wide association scan meta-analysis identifies three Loci influencing adiposity and fat distribution. PLoS Genet. 2009; 5:e1000508. [PubMed: 19557161]
12. Heard-Costa NL, Zillikens MC, Monda KL, Johansson A, Harris TB, Fu M, Haritunians T, Feitosa MF, Aspelund T, Eiriksdottir G, Garcia M, Launer LJ, et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. PLoS Genet. 2009; 5:e1000539. [PubMed: 19557197]
13. Matise TC, Ambite JL, Buyske S, Carlson CS, Cole SA, Crawford DC, Haiman CA, Heiss G, Kooperberg C, Marchand LL, Manolio TA, North KE, et al. The Next PAGE in understanding complex traits: design for the analysis of Population Architecture Using Genetics and Epidemiology (PAGE) Study. Am J Epidemiol. 2011; 174:849–59. [PubMed: 21836165]
14. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol. 2000; 151:346–57. [PubMed: 10695593]
15. Stram DO, Hankin JH, Wilkens LR, Pike MC, Monroe KR, Park S, Henderson BE, Nomura AM, Earle ME, Nagamine FS, Kolonel LN. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. Am J Epidemiol. 2000; 151:358–70. [PubMed: 10695594]
16. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 2001; 68:978–89. [PubMed: 11254454]
17. Stephens M, Donnelly P. A comparison of bayesian methods for haplotype reconstruction from population genotype data. Am J Hum Genet. 2003; 73:1162–9. [PubMed: 14574645]
18. Storey JD, Tibshirani R. Statistical significance for genomewide studies. Proc Natl Acad Sci USA. 2003; 100:9440–5. [PubMed: 12883005]
19. Han B, Kang HM, Eskin E. Rapid and accurate multiple testing correction and power estimation for millions of correlated markers. PLoS Genet. 2009; 5:e1000456. [PubMed: 19381255]
20. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst. 2004; 96:434–42. [PubMed: 15026468]
21. Wang H, Haiman CA, Kolonel LN, Henderson BE, Wilkens LR, Le Marchand L, Stram DO. Self-reported ethnicity, genetic structure and the impact of population stratification in a multiethnic study. Hum Genet. 2010; 128:165–77. [PubMed: 20499252]
22. Wing MR, Ziegler J, Langefeld CD, Ng MC, Haffner SM, Norris JM, Goodarzi MO, Bowden DW. Analysis of FTO gene variants with measures of obesity and glucose homeostasis in the IRAS Family Study. Hum Genet. 2009; 125:615–26. [PubMed: 19322589]
23. Rampersaud E, Mitchell BD, Pollin TI, Fu M, Shen H, O'Connell JR, Ducharme JL, Hines S, Sack P, Naglieri R, Shuldiner AR, Snitker S. Physical activity and the association of common FTO gene variants with body mass index and obesity. Arch Intern Med. 2008; 168:1791–7. [PubMed: 18779467]
24. Nock NL, Plummer SJ, Thompson CL, Casey G, Li L. FTO polymorphisms are associated with adult body mass index (BMI) and colorectal adenomas in African-Americans. Carcinogenesis. 2011; 32:748–56. [PubMed: 21317302]
25. Jiao H, Arner P, Hoffstedt J, Brodin D, Dubern B, Czernichow S, Van't Hooft F, Axelsson T, Pedersen O, Hansen T, Sorensen TI, Hedebrand J, et al. Genome Wide Association Study Identifies KCNMA1 Contributing to Human Obesity. BMC Med Genomics. 2011; 4:51. [PubMed: 21708048]

Novelty/Impact

This is the first report on testing pleiotropic effects of obesity risk variants on the risk of colorectal cancer. The findings suggest that, although obesity is the leading modifiable risk factor for colorectal cancer, the effect of obesity risk variants is likely small.

Table 1

Characteristics* of colorectal cancer cases and controls

	Cases n = 2,033	Controls n = 9,640	*P* *
Age at case diagnosis or control blood draw, years	70.0 (8.6)	68.0 (8.6)	<.0001
Sex, n (%)			.29
Male	1125 (55%)	5260 (55%)	
Female	908 (45%)	4380 (45%)	
Ethnicity, n (%)			.002
White	381 (19%)	1915 (20%)	
African American	406 (20%)	2474 (26%)	
Japanese American	694 (34%)	2623 (27%)	
Latino	439 (22%)	1984 (21%)	
Native Hawaiian	113 (6%)	644 (7%)	
Education, years of school	13.2 (3.0)	13.6 (3.1)	.0002
Body mass index (BMI), kg/m^2	27.2 (4.9)	26.8 (4.8)	<.0001
Family history of colorectal cancer, % yes	219 (11%)	876 (9%)	.05
History of intestinal polyps, % yes	131 (6.4%)	659 (6.8%)	.10
Diabetes, %	500 (24%)	1928 (20%)	<.0001
Cigarette-smoking history, n (%)			.001
Never	762 (38%)	4006 (42%)	
Former	954 (47%)	4191 (44%)	
Current	300 (15%)	1342 (14%)	
Pack-years among ever smokers	19.6 (16.7)	17.9 (15.4)	.004
Physical activity, metabolic equivalents (METs)	1.62 (0.29)	1.62 (0.29)	.28
Aspirin, % current use	418 (21%)	2062 (21%)	.11
Multivitamin, % current use of ≥1/week	926 (46%)	4793 (50%)	.0005
Dietary intake**			
Alcohol, servings/day	0.83 (2.15)	0.66 (1.76)	.0003
Fiber, g/1000kcal/day	11.6 (4.4)	11.9 (4.3)	<.0001
Total calcium, mg/day	958 (578)	1010 (639)	.0002
Hormone treatment, % current use among women	225 (25%)	1520 (35%)	<.0001

* Mean (standard deviation) for continuous traits and number of subjects (percent) for categorical traits. *P*-values for case-control comparisons are from general linear models. All comparisons, other than for age, were adjusted for age.

** Dietary intake of alcohol was compared in servings (14g ethanol per serving). Intake of dietary fiber was adjusted for total energy intake by nutrient density (per 1,000 kcal). Total intake of calcium from foods and supplements was not energy-adjusted.

Table 2

Association* of selected genetic risk variants for obesity with colorectal cancer, overall and by BMI level

			Combined		By Obesity Level				
					BMI < 30		BMI ≥ 30		
Gene	**SNP**	**Genotype**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	***P*-het**
FTO	rs1121980	GG	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		GA	1.09 (0.96, 1.23)	0.18	1.14 (0.99, 1.32)	0.06	0.86 (0.66, 1.13)	0.28	
		AA	1.08 (0.90, 1.29)	0.40	1.21 (0.98, 1.49)	0.08	**0.68 (0.47, 0.98)**	**0.04**	
		trend	1.05 (0.97, 1.14)	0.24	**1.11 (1.01, 1.22)**	**0.04**	**0.84 (0.70, 0.99)**	**0.04**	**0.005**
FTO	rs1421085	TT	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		TC	0.98 (0.86, 1.10)	0.69	1.01 (0.88, 1.16)	0.88	0.82 (0.63, 1.06)	0.13	
		CC	0.99 (0.79, 1.24)	0.93	1.04 (0.80, 1.34)	0.80	0.78 (0.49, 1.23)	0.28	
		trend	0.99 (0.90, 1.08)	0.77	1.02 (0.92, 1.13)	0.71	0.84 (0.70, 1.01)	0.07	0.07
FTO	rs1558902	TT	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		TA	0.94 (0.83, 1.06)	0.30	0.97 (0.85, 1.12)	0.72	0.81 (0.61, 1.06)	0.13	
		AA	1.02 (0.81, 1.28)	0.85	1.07 (0.82, 1.39)	0.63	0.82 (0.51, 1.32)	0.42	
		trend	0.98 (0.89, 1.07)	0.63	1.01 (0.91, 1.13)	0.79	0.84 (0.69, 1.01)	0.07	0.08
FTO	rs3751812	GG	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		GT	0.96 (0.87, 1.07)	0.50	0.99 (0.88, 1.12)	0.89	0.84 (0.67, 1.06)	0.14	
		TT	0.99 (0.80, 1.21)	0.90	1.04 (0.82, 1.32)	0.77	0.77 (0.50, 1.18)	0.23	
		trend	0.98 (0.90, 1.06)	0.61	1.01 (0.92, 1.11)	0.82	0.84 (0.71, 1.00)	0.05	0.06
FTO	rs8050136	CC	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		CA	1.04 (0.93, 1.16)	0.47	1.08 (0.95, 1.22)	0.24	0.89 (0.70, 1.12)	0.31	
		AA	1.04 (0.87, 1.24)	0.64	1.17 (0.95, 1.44)	0.14	**0.70 (0.49, 0.99)**	**0.04**	
		trend	1.03 (0.95, 1.11)	0.49	1.08 (0.99, 1.19)	0.08	**0.84 (0.72, 0.99)**	**0.03**	**0.006**
FTO	rs9930506	AA	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		AG	1.07 (0.95, 1.21)	0.28	1.14 (0.99, 1.31)	0.06	0.89 (0.68, 1.16)	0.38	
		GG	1.03 (0.85, 1.26)	0.75	1.08 (0.86, 1.37)	0.51	0.83 (0.55, 1.26)	0.38	
		trend	1.04 (0.95, 1.13)	0.43	1.08 (0.99, 1.20)	0.12	0.88 (0.73, 1.05)	0.16	**0.04**

			Combined		By Obesity Level				
					BMI < 30		BMI ≥ 30		
Gene	**SNP**	**Genotype**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	***P*-het**
FTO	rs9939609	TT	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		TA	1.03 (0.91, 1.16)	0.68	1.05 (0.91, 1.21)	0.51	0.89 (0.68, 1.17)	0.40	
		AA	1.03 (0.85, 1.24)	0.78	1.17 (0.94, 1.46)	0.16	**0.64 (0.44, 0.95)**	**0.02**	
		trend	1.02 (0.93, 1.11)	0.70	1.06 (0.96, 1.17)	0.23	0.84 (0.71, 1.01)	0.06	**0.02**
FTO	rs9941349	CC	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		CT	1.02 (0.92, 1.13)	0.75	1.07 (0.95, 1.20)	0.29	0.87 (0.68, 1.07)	0.17	
		TT	1.02 (0.84, 1.23)	0.86	1.07 (0.87, 1.32)	0.57	0.81 (0.57, 1.18)	0.27	
		trend	1.01 (0.94, 1.09)	0.76	1.05 (0.96, 1.15)	0.25	0.86 (0.73, 1.01)	0.06	**0.03**
KCTD15	rs11084753	AA	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		AG	0.92 (0.80, 1.05)	0.21	0.95 (0.81, 1.11)	0.49	0.80 (0.59, 1.08)	0.14	
		GG	0.88 (0.75, 1.02)	0.10	0.94 (0.78, 1.12)	0.49	**0.68 (0.49, 0.94)**	**0.02**	
		trend	0.94 (0.87, 1.01)	0.10	0.99 (0.91, 1.09)	0.89	**0.77 (0.66, 0.90)**	**0.0008**	**0.004**
KCTD15	rs29941	TT	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		TC	0.86 (0.75, 1.00)	**0.045**	0.89 (0.76, 1.05)	0.17	0.68 (0.49, 0.95)	0.02	
		CC	**0.81 (0.68, 0.96)**	**0.01**	0.90 (0.74, 1.09)	0.27	**0.54 (0.38, 0.78)**	**0.001**	
		trend	**0.90 (0.83, 0.98)**	**0.01**	0.97 (0.88, 1.06)	0.49	**0.70 (0.60, 0.82)**	**<0.0001**	**0.0003**
MC4R	rs17782313	TT	1.0 (reference)		1.0 (reference)		1.0 (reference)		
		TC	1.10 (0.98, 1.23)	0.10	1.07 (0.94, 1.23)	0.29	1.18 (0.92, 1.50)	0.19	
		CC	**1.28 (1.01, 1.61)**	**0.04**	1.31 (1.00, 1.70)	0.05	1.15 (0.69, 1.92)	0.60	
		trend	**1.12 (1.02, 1.22)**	**0.02**	1.10 (1.00, 1.22)	0.06	1.16 (0.97, 1.41)	0.11	0.61

*Odds ratios (ORs) and 95% confidence intervals (CIs) estimated in logistic regression models that adjusted for age and ethnicity, and also sex for the obesity-stratification. *P*-het.: *P*-values for heterogeneity by sex or BMI (<30 or ≥ 30).