Impact of Abdominal Adipose Depots and Race on Risk for Colorectal Cancer: A Case-Control Study

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Abstract

Visceral (VAT) but not subcutaneous adipose tissue (SAT) is associated with obesity-related diseases including colorectal cancer (CRC). Superficial SAT (SSAT) and deep SAT (DSAT), components of SAT, also appear to independently influence disease risk. These abdominal adipose tissues (AAT) are not extensively studied in connection with CRC and have not been explored in the United States (US) despite known racial variations in body composition. We conducted a case-control study that compared associations between AAT with CRC risk and race of AA and NHW males with incident CRC matched by age, BMI and race (N=158, 79/group). Cross-sectional computed tomography (CT) images were used for assessment of AAT. Overall cases and controls had similar VAT areas (140 ± 192 vs 149 ± 152 cm^2, p-value=0.93), however cases had lower SSAT than controls (88 ± 39 vs 112 ± 65 cm^2, p<0.01). Among controls, AA had significantly lower VAT (114 ± 168 vs 180 ± 167, p<0.01) than NHW. Conditional logistic regression revealed AA males with greater SSAT had lower odds for CRC (OR: 0.24, 95%CI 0.07–0.85). Our findings indicate

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VAT does vary between cases and controls by race, however this variation is not a risk factor for CRC. The negative association between CRC and SSAT in AA men warrants further investigation.

Keywords

colorectal cancer; abdominal adipose tissues; visceral adipose tissue; race; computed tomography; body composition

Introduction

Obesity is significantly associated with both colon and rectal cancers in men(1). Central adiposity increases risk for colorectal cancer (CRC) (1, 2) and other obesity related chronic diseases (3–5). For many of these diseases excess visceral adipose tissue (VAT) as opposed to subcutaneous adipose tissue (SAT) quantified using computed tomography (CT) images has been linked to the increased risks (3, 4, 6). The influence of VAT vs SAT in risks for CRC in a United States (US) population has not been explored and findings from non-US populations have not been consistent(6, 7). Further, in the US, African Americans (AA), particularly AA men have higher risks for CRC than Non-Hispanic White (NHW) men, yet healthy AA men have lower VAT than their NHW counterparts(8, 9). Also, examinations of the two distinct SAT compartments, superficial SAT (SSAT) and deep SAT (DSAT) which are anatomically separated by the *fascia of Scarpa* may vary in their contribution to metabolic disruption (10, 11). Specifically, DSAT has been associated with insulin resistance, a risk factor associated with CRC, whereas SSAT has not (3, 11). Therefore the purpose of this study is to determine the association between excess VAT and other abdominal fat depots and CRC risk in urban males and if these risks vary by race.

Materials and Methods

Study Population, Design and Procedures

A case-control study of 79 males with incident CRC cases (51 AA and 28 NHW) matched for age (±5 years), body mass index (BMI; ±0.05kg/m^2) and race to 79 cancer-free male controls with abdominal CT scans was conducted. CRC cases were selected from participants of the Chicago Colorectal Cancer Consortium Study (CCCC) at three medical centers and through medical records at these centers. The CCCC study was a prospective cohort conducted between 2009 and 2013 to examine the relationship between genetic and environmental risk factors in a race/ethnically diverse population. Participants were recruited at the time of their colonoscopy from three university medical centers in Chicago, Illinois. Males 40 years of age and older with a good quality CT image were eligible for inclusion in our case-control study. Cases with newly diagnosed with non-hereditary CRC (Stage 0-III, non-metastatic) were matched to controls that had received a CT abdominal scan for a non-cancer diagnosis during a 24 hour emergency room visit or outpatient setting (Table 1) at the CCCC hospitals during the same historical time period of cases. Patients were excluded if they had hereditary CRC, a history of inflammatory bowel disease, Stage IV CRC diagnosis, end stage renal disease, abdominal gastric surgery or organ transplant.

Demographic and clinical information obtained from medical records included age, marital status, race, blood pressure, medical history of diabetes and hypertension (yes/no), history of gastrointestinal malignancies, current smoker (yes/no), current alcohol consumption (yes/no), self-reported unintentional weight loss within the past 6 months (yes/no). Height and weight for calculation of BMI was measured by CCCC staff for cases during enrollment or obtained from medical records within 3 days of CT procedure. BMI was calculated according to the Quetelet's index as weight (kg)/stature (m^2) and classified according to National Institutes of Health guidelines (18.5–24.9 for normal weight, 25.0–29.9 for overweight and 30.0 or higher for obese). Cancer staging was obtained from pathology reports and based on TNM (Tumor, Node, Metastases) cancer staging system.

Single archived diagnostic CT images were selected for assessment of cross-sectional area of abdominal adipose tissues at the standard landmark of L3 vertebra (12–14). Abdominal adipose tissues quantified for each image included total abdominal adipose tissue (TAT), SAT, SSAT, and DSAT. Each cross-sectional image for TAT, SAT and VAT was analyzed using three separate evaluations with SliceOmatic v4.3 (TomoVision, Montreal, QC, Canada) (Fig 1); waist circumference (WC), SSAT and DSAT were measured with IMAGEJ 1.47v (National Institutes of Health, Bethesda, USA) using the abdominal perimeter for an estimate of waist as previously published (15) and the subcutaneous and outer abdominal musculature perimeters for derivation of SSAT and DSAT areas. These medical imaging software packages permit specific tissue demarcation of abdominal adipose tissues according to Hounsfield Unit (HU) thresholds of −150 to −50 for VAT, −190 to −30 for SAT and −29 to 150 for skeletal muscle. The TAT estimate was calculated as sum of the areas of SAT + VAT. Intra-class coefficient of variations of imaging analysis between investigators was less than 2%.

Sample Size Estimation

Sample size was based on the area of VAT reported by Katzmarzyk et al (9) comparing NHW males (mean age: 44.9 ± 13.4 years) and AA males (mean age: 38.4±13.9 years). Sample size was calculated with PS – Power and Sample Size Version 3.0.43 using paired t-test for continuous variables (16). Based on a mean VAT area of 148.6 ± 73.4 cm^2 in NHW and of 97.7± 63.9 cm^2 in AA, a minimum of 19 males per race/ethnic group were needed within cases and controls to detect a difference of 50.9 cm^2 with a significance level of 0.05 and a power of 0.80. Our study sample consisted of 51 AA and 28 NHW males per group (cases vs. controls).

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Boards at the University of Illinois at Chicago (CCCC IRB Protocol # 2010-0168; IRB Protocol # 2014-0837), Rush University Medical Center (IRB Protocol # 10031003) and John H. Stroger Hospital (IRB Protocol # 10-142). A waiver of informed consent and HIPAA was obtained at each institution for retrospective use of protected health information.

Statistical Analyses

Statistical analysis was conducted using Statistical Analysis System (SAS) for Windows 9.3 (SAS Institute Inc., Cary, NC, USA). Variables were examined for presence of outliers and distributions and presented as medians with interquartile ranges in tables. Paired t-tests or Wilcoxon signed – rank tests were performed for continuous variables. Categorical data were analyzed using McNemar Chi-square test. Pearson and Spearman (non-parametric) correlation coefficients were computed to quantify the relationships between continuous and non-parametric variables. Collinearity was determined using correlation matrices. Variables with correlation >0.8 were not included in the same model. Severe collinearity was defined as a variance inflation factor greater than 4 (17). Conditional logistic regression was used to determine crude and adjusted significant predictors of CRC for the entire sample and then for each race/ethnic group using Stepwise and Forward selection. To control for the impact of unintended disease-associated weight loss the CT analysis of the abdominal adipose depots were compared in a subset of weight stable cases and controls (n=49 per group). Statistical significance set at a p-value<0.05. Bonferroni adjustment for statistical significance based on two hypotheses was calculated to be a p<0.025.

Results

The participants median and interquartile for age and BMI were 62(11) years and 27(6) kg/m^2, respectively and by design cases and controls were similar for age, BMI and race (Table 2). There also had similar demographic characteristics including smoking and alcohol use and prevalence of diabetes and hypertension. As commonly observed in patients with CRC diagnosis, self-reported unintentional weight loss was significantly higher in our cases than controls.

As anticipated VAT was highly correlated with TAT (r = 0.94, p<0.01), SAT (r = 0.71, p<0.01), SSAT (r = 0.59, p<0.01), DSAT (r = 0.68, p<0.01) and other measures of obesity [BMI (r = 0.67, p<0.01) and WC (r=0.83, p<0.01)]. However, only TAT had a correlation coefficient greater than 0.80, suggestive of high collinearity with other AAT (SAT, r = 0.89, p<0.01; SSAT r = 0.78, p<0.01; DSAT, r = 0.86, p<0.01), BMI (r = 0.76, p<0.01) and waist (r = 0.92, p<0.01) therefore, it was excluded from models. Also, as expected the SAT subtypes (SSAT and DSAT) were highly correlated (r >0.80, p< 0.01) with SAT and each other and were analyzed separately in models.

Unadjusted stratified analysis of cases vs controls

VAT did not differ between cases and controls (Table 3) overall, however, cases had significantly lower SAT, SSAT and DSAT than controls. Dichotomizing by race, unadjusted comparisons of abdominal adipose tissues (Table 4) revealed significantly lower SAT (p=0.02) and SSAT (p=0.002) in AA cases than AA controls but no differences in any other depot. Among NHW case-control pairs no difference in any abdominal adipose tissue was found, although a trend for lower SSAT (p = 0.09) in cases was present. Comparisons *between racial groups* revealed AA controls had significantly lower VAT than NHW controls, similar to those previously reported in healthy populations (8, 9). In contrast among

cases the difference in VAT area trended but was not significantly lower in AA than their NHW counterparts (p = 0.06).

Conditional logistic regression analysis

As shown in Table 5, significant predictors of CRC for the full sample included SSAT (OR = 0.22, 95%CI: 0.07 – 0.70) and self-reported unintentional weight loss (OR = 3.92, 95%CI: 1.43 – 10.74). After exploring significant predictors of CRC for each of the racial groups separately, the odds ratio for SSAT suggests that AAs with higher SSAT had 24% lower risk of CRC (OR = 0.24, 95%CI: 0.07 – 0.85).

Subset analysis in weight stable participants (n= 49 pairs)

Among weight stable pairs (n= 49 pairs), the median difference for waist (p=0.40), VAT, (p=0.40), and DSAT (p=0.22) did not differ between cases and controls (Table 3), however median SSAT was significantly higher in controls than cases (p<0.01, n = 43 per group). When this group was dichotomized by race (Table 4), only AA controls had significantly lower VAT than NHW controls (p=0.04). A trend for higher VAT was noticed between AA cases compared to AA controls (p=0.07) and higher SSAT in AA controls compared to AA cases (p=0.05).

Discussion

Few studies have explored associations between obesity-related body compositional changes and cancer in racially diverse, populations at high risk for obesity and colorectal cancer. Here, we provide important initial data in this area that expands our understanding of the influence of the race/ethnic variations in abdominal adipose tissue on the risks for colorectal cancer in AAs compared to NHW males. An association between VAT and CRC risk was not found in this racially diverse case control study of urban men. Six studies have studied the relationship between VAT area and CRC (6, 7, 18–21), however none of these studies were conducted in US populations. Our findings are similar to the study reported by Choe et al, of Korean adults with and without early stage CRC (Stage 0-I) (18) and two smaller cross-sectional studies in Turkish patients (7, 19). Three other investigations in Asian populations have reported larger VAT depots in patients with CRC compared to non-CRC counterparts (6, 20, 21), however differences in study design, race and non-BMI matched comparison groups limit the implications of their findings and the comparisons that can be made with our findings.

Although the association between VAT and CRC is unclear, its association with colorectal adenomas, which are precursors of CRC (22–26) is quite well established. Insulin resistance and pro-inflammatory pathways promoted by obesity and excess VAT are speculated as the mechanisms for the increased risks (27). Thus excess VAT, a frequent consequence of obesity and mechanistically linked to inflammatory and insulin resistant pathways, remains an important risk factor for CRC via its link with adenomas. The interval between adenoma development and CRC diagnosis can range from months to years. This long interval may have impeded detection of the association between VAT and other abdominal adipose depots in our case-control study. This is particularly important in uninsured or asymptomatic

populations. It is likely that abdominal adipose tissues change during this interval particularly within the intra-abdominal cavity (i.e., fluctuations of VAT deposition). To understand the role of VAT on CRC etiology, a prospective study is required that enrolls cancer-free participants assessed for body composition using CT or MRI at screening colonoscopy with subsequent study visits at regular intervals over a minimum of 10–15 years. Our findings of lower VAT in both AA cases and controls compared to their NHW BMI-matched pairs is consistent with reports between healthy AA and NHW (8, 9) and extends this relationship to men with CRC. The current study is the first to explore these relationships in a population of AA and NHW men with and without CRC, enabling robust comparisons of body composition between groups. More research is needed to clarify the biological implications of racial differences and how VAT contributes to CRC risk.

An important unexpected finding of our study was the significant negative association of SSAT with CRC observed in AA, but not NHW participants. This association has not been reported for CRC, however higher SAT to VAT body fat distribution has been found to be favorable for reduced risks for diabetes and cardiovascular disease. It is thought that the structural and functional difference between adipose depots confers the variation in risks (28, 29). Recently, evidence indicates the subcomponents of SAT, i.e. SSAT and DSAT, are distinct and may contribute to disease risk differently. DSAT metabolically resembles VAT and is more pathogenic than SSAT (30). Conversely, higher SSAT has been associated with improved blood pressure and heart rates in patients with Type 2 diabetes (31). Further, recent biopsy studies have determined SSAT has lower saturated to monounsaturated fatty acid content and lower expression of numerous pro-inflammatory genes than DSAT (11, 32). The negative association observed in our AA patients with SSAT and CRC was only apparent when the statistical analysis of the individual components of SAT (SSAT and DSAT) were separately explored; SAT was not significantly associated with CRC risk. The potential lower odds of CRC with higher SSAT in the AA participants provides an intriguing virtually unexplored area for future studies which has the potential to expand our understanding of the racial disparities in CRC.

This study had several limitations that should be considered. First, although case-control studies are prone to both subject and observation bias, given the limited knowledge in this area of and the efficiency and cost-effective nature of this study design render it ideal for the initial assessment of the disease to body composition relationship. A superior design would have enrolled cases and controls from the same pool of patients at the time of endoscopy and collected data on diet and physical activity behaviors as well as serum and mucosal tissue biopsies. Secondly, limited resources dictated selection of cases and controls from different sources and utilizing archived CT data for body composition analysis. Controls were selected from patients with a diagnostic CT for acute health conditions, primarily for abdominal, epigastric or flank pain, thus as is common in case control studies undiagnosed sub-clinical disease may have been present. Additionally, although controls with a history of any cancer were excluded, undiagnosed CRC or other types of cancer may have been unintentionally included as a control. Adenomas develop over 10–20 years(33) and patients may have polyps or undiagnosed disease for months or years, particularly in underserved populations not routinely screened with various health access disparities. Finally, the variety of cancer stages (Stage 0-III, non-metastatic) and the racial groups included in our study

restricts generalizability to these populations. Our study has important strengths. It provides data of the relationship between CRC, race and abdominal body composition of a US population an area which heretofore has been largely unexplored. Additionally, the impact of body composition on CRC risks was explored with rigorous control for age, BMI and race. We used CT scans for assessment of the body fat depots which are the gold standards for body composition analysis. The analysis of CT images was conducted using detailed, standardized body composition analysis protocols, including accurate measurements of VAT (fat within kidneys, intestines were not included in estimate). CT scans are routinely performed for a variety of reasons throughout the clinical care continuum and for our study we included only those that had a CT for acute illness, mostly in an outpatient setting or with an ER visit with a discharge within 23 hours. Finally, information about weight loss in both cases and controls were identically obtained, limiting bias concerns for this measurement.

Conclusions

VAT area did not significantly differ between cases and controls and greater VAT area was not associated with increased CRC risks. Further, the differences observed between the racial groups in our cases and controls were very similar to those reported in healthy populations. Specifically, AA controls had significantly lower VAT than their NHW counterparts and these differences remained after exploring in a weight stable subgroup. These findings may support the accumulating evidence suggesting VAT's role occurs earlier in the CRC pathogenic pathway, between the normal mucosa and adenoma sequence. Additionally, for AA who commonly display a low VAT phenotype other mechanisms and other abdominal adipose depots, including SSAT, should be explored in light of their increased risks for adenomas and CRC.

Acknowledgments

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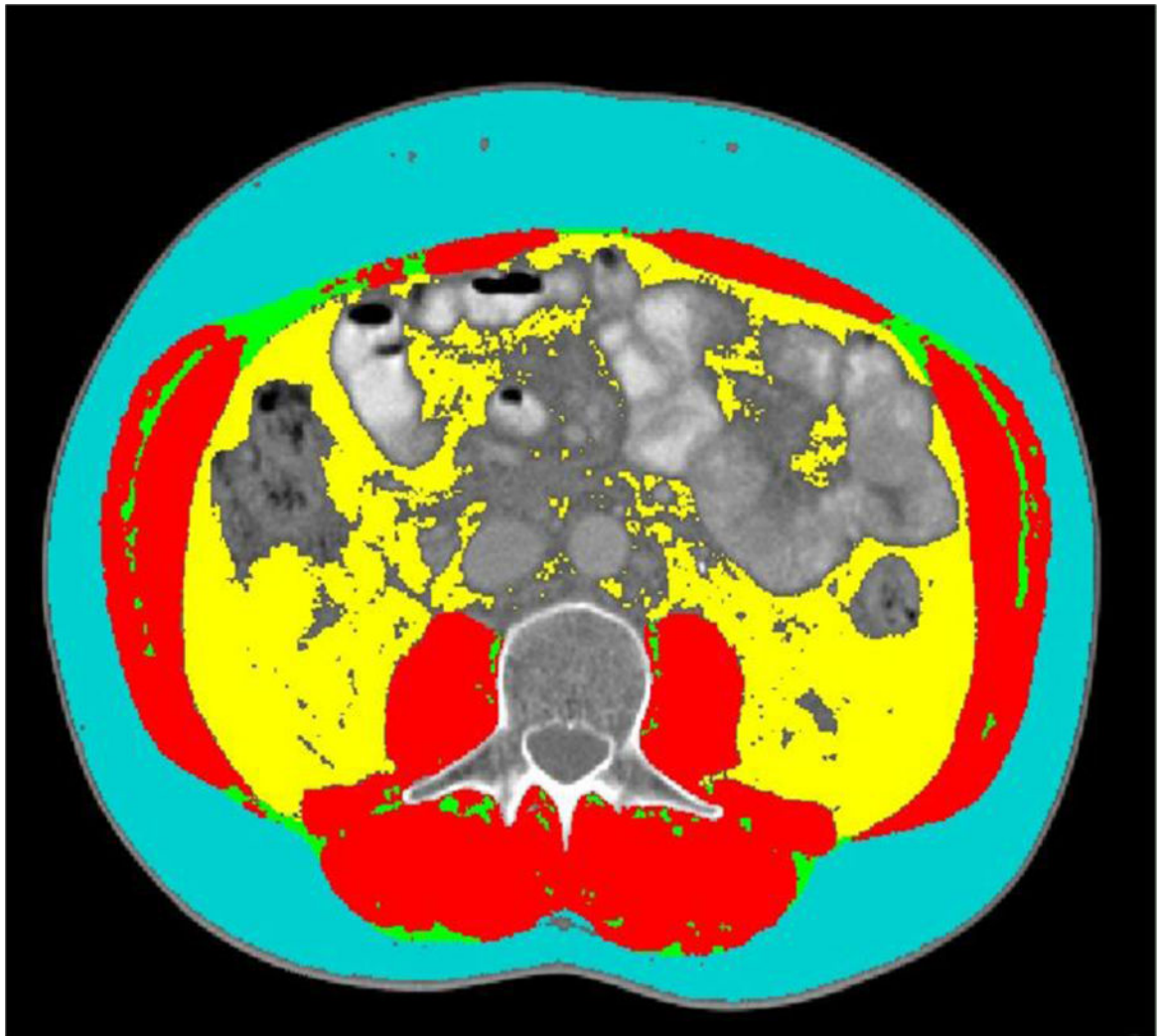
Fig. 1.
Cross-sectional image of the third lumbar (L3) analyzed for subcutaneous adipose tissue (blue), visceral adipose tissue (yellow), intermuscular adipose tissue (green) and skeletal muscle (red) using SliceOmatic medical imaging software (TomoVision, Montreal, QC, Canada).

Table 1

List of Diagnoses Requiring Computed Tomography Scan of Cancer-Free Controls

Diagnosis	Frequency (n/79)	Percent (%)
Abdominal/back/leg pain	41	51.3
Acute illness (i.e., fever, hernia repair evaluation)	14	17.5
Acute gastrointestinal event (i.e., perforation)	13	16.3
Other (i.e., transplant evaluation, aortic aneurysm)	8	10.0
Rule out malignancy	4	5.0

Table 2

Characteristics of Cases and Controls

	Cases (n= 79)	Controls (n= 79)	p-value[c]
Demographics & Anthropometrics	**Median(IQ) or %(n)**	**Median(IQ) or %(n)**	
African Americans (AA), %(n)	64.5(51)	64.5(51)	—
Non-Hispanic Whites (NHW), %(n)	35.4(28)	35.4(28)	—
Normal BMI (18.5–25), %(n)	26.6(21)	27.9(22)	0.59
Overweight BMI (25–30), %(n)	49.4(39)	43.0(34)	0.43
Obese BMI (30), %(n)	24.1(19)	29.1(23)	0.54
Cancer Stages 0-I, %(n)	30.7(23)	—	—
Cancer Stage 2 (II, IIA, IIB, IIC), %(n)	40.0(30)	—	—
Cancer Stage 3 (III,IIIA, IIIB, IIIC),%(n)	29.3(22)	—	—
Married, yes,%(n)	30.8(24)	42.9(33)	0.45
Current Smoker, yes, %(n)	27.9(22)	25.6(20)	0.76
Alcohol consumption, yes, %(n)	44.9(35)	37.3(28)	0.38
Diabetes, yes. %(n)	25.0(19)	26.6(21)	0.75
Hypertension, yes, %(n)	67.1(51)	63.3(50)	0.92
Unintentional Weight Loss, yes, %(n) (within 6 months)	27.6(21)	7.6(6)	**<0.01***

[a]Paired t-test & Wilcoxon-rank sum test used for continuous data; McNemar test for categorical data.

[b]Sample size for WC, SSAT and DSAT = 68 per group.

[c]Significant p-value < 0.05.

Table 3

Unadjusted Comparison of Abdominal Adipose Tissues for Cases and Controls[a]

Abdominal Depots	Cases (n= 79) Median (IQR)	Controls (n= 79) Median (IQR)	p-value[b]
TAT(cm^2)	294(294)	347(259)	0.29
SAT (cm^2)	133(91)	170(134)	**0.03** [*]
SSAT (cm^2)[b]	88(39)	112(65)	**<0.01** [*]
DSAT (cm^2)[b]	67(49.8)	176(35)	**0.04** [*]
VAT (cm^2)	140(192)	149(152)	0.93
SM (cm^2)	162(38)	176(35)	0.10
VAT/TAT (%)	44(23)	40(21)	0.11
VAT/SAT (%)	91(93)	75(75)	0.05
SAT/TAT (%)	50(21)	54(23)	**0.02** [*]
SSAT/TAT (%)	35(23)	39(24)	0.45
DSAT/TAT (%)	25(12)	28(12)	0.28
Weight Stable Sub-Group[c]			
WC (cm^2)	105(18)	109(18)	0.40
SSAT (cm^2)	95(48)	124(58)	**<0.01** [*]
DSAT (cm^2)	86(47)	88(68)	0.22
VAT (cm^2)	171(155)	167(148)	0.64

[a] Paired t-test used for comparisons between cases and controls for continuous data.

[b] Sample size for WC, SSAT and DSAT was 68 males per group.

[c] Sample size for weight stable sub-group was 49 per group and 43 per group for WC, SSAT and DSAT.

[*] Significant p-value < 0.05.

Table 4

Demographics, Anthropometrics and Body Composition by Race/Ethnicity of Cases and Controls

Demographics and Anthropometrics	AA Cases (n=51) Median (IQ)	AA Controls (n=51) Median (IQ)	AA Cases vs AA Controls *a* p-value	NHW Cases (n=28) Median (IQ)	NHW Controls (n=28) Median (IQ)	NHW Cases vs NHW Controls *a* p-value	AA Cases vs NHW Cases *b* p-value	AA Controls vs NHW Controls *b* p-value
BMI (kg/m²)	27(7)	27(7)	0.45	28(5)	28(5)	0.59	0.40	0.27
WC (cm)^c	99(14)	106(19)	0.16	104(23)	111(17)	0.41	0.08	0.03*
Abdominal Depots								
TAT (cm²)	263(264)	320(288)	0.45	366(253)	369(239)	0.46	0.05*	0.02*
SAT (cm²)	127(72)	165(146)	0.02*	144(101)	185(107)	0.71	0.25	0.18
SSAT (cm²)^c	88(40)	111(68)	<0.01*	88(41)	112(50)	0.09	0.85	0.54
DSAT (cm²)	62(50)	71(72)	0.06	77(65)	96(73)	0.39	0.10	0.06
VAT (cm²)	98(178)	114(168)	0.47	190(162)	180(167)	0.42	0.06	<0.01*
SM (cm²)	172(39)	178(33)	0.30	150(31)	172(46)	0.20	<0.01*	0.18
VAT/TAT (%)	42(25)	34(25)	0.01*	47(21)	48(17)	0.58	0.28	<0.01*
VAT/SAT (%)	81(89)	55(65)	0.01*	99(84)	103(75)	0.97	0.25	<0.01*
SAT/TAT (%)	52(21)	61(20)	<0.01*	47(20)	46(18)	0.78	0.24	<0.01*
SSAT/TAT (%)^c	35(23)	43(25)	0.20	34(20)	30(8)	0.58	0.13	<0.01*
DSAT/TAT (%)	24(13)	30(12)	0.01*	25(12)	25(12)	0.18	0.95	0.03*
Weight Stable Sub-Group^d								
WC (cm²)	104.6(16)	109(23)	0.96	106(21)	111(13)	0.28	0.63	0.25
SSAT (cm²)	96(37)	123(76)	0.05	91(38)	124(47)	0.07	0.26	0.80
DSAT (cm²)	78(42)	86(76)	0.32	88(63)	91(68)	0.47	0.53	0.53
VAT (cm²)	170(148)	138(147)	0.07	172(181)	186(163)	0.18	0.83	0.04*

*
Significant p-value <0.05.

*a*Paired t-test used for comparisons between cases and controls for continuous data.

*b*Dependent t-test & Wilcoxon-rank sum test used for within cases or controls based on normality.

[c]Sample size for WC, SSAT and SSAT/TAT = 45 for AA and 23 NHW per group.

[d]Sample size for weight stable sub-group: AA = 30 per group (sample for WC and SSAT = 26) and NHW = 19 per group (sample for WC and SSAT = 17).

Table 5

Predictors of Colorectal Cancer for Overall Sample and Race/Ethnic Groups using Conditional Logistic Regression

Model		B	OR	Lower CI	Upper CI	p-value
				CRC (yes/no)		
Full Sample (n=158, 78 pairs)	Median SSAT[a]	−1.51	0.22	0.07	0.70	0.01[*]
	Unintentional Weight Loss	1.37	3.92	1.43	10.74	0.01[*]
African Americans Only (n=102, 51 pairs)	Median SSAT[a]	−1.52	0.24	0.070	0.852	0.03[*]
	Unintentional Weight Loss	1.76	7.91	2.559	24.438	<0.01[*]
Non-Hispanic Whites Only (n=56, 28 pairs)	Alcohol	1.6094	5.00	1.096	22.82	0.04[*]

[*]
Significant p-value <0.05.

[a]
Median splits defined as: SSAT = 109.9cm^2