Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites

BY

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DISSERTATION

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This dissertation is dedicated to my husband, Jorge and daughter, Sairis. They inspire me to do great things, to live life to its fullest potential and to have boundless courage.

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LIST OF ABBREVIATIONS

AA	African American
AMPK	5’ Adenosine Monophosphate Activated Protein Kinase
APN	Adiponectin
BMI	Body Mass Index
CCCC	Chicago Colorectal Cancer Consortium Study
CRC	Colorectal Cancer
CRP	C - Reactive Protein
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
DSAT	Deep Subcutaneous Adipose Tissue
ELISA	Enzyme - Linked Immunosorbent Assay
EMR	Electronic Medical Records
FFA	Free Fatty Acid
HFC	Hepatic Fat Content
HU	Hounsfield Unit
IBD	Irritable Bowel Disease
IGF-1	Insulin-like Growth Factor – 1
IGFBP-3	Insulin-like Growth Factor Binding Protein – 3
IL-6	Interleukin – 6
IMAT	Intermuscular Adipose Tissue
JHS	John H. Stroger Hospital
L3	Third lumbar vertebra
MetS	Metabolic Syndrome
MRI	Magnetic Resonance Imaging
mTOR	Mechanistic Target of Rapamycin

LIST OF ABBREVIATIONS (continued)

NAFLD	Non-Alcoholic Fatty Liver Disease
NFkB	Nuclear Factor kappa B
NHANES	National Health and Nutrition Examination Survey
NHW	Non-Hispanic White
NIH	National Institutes of Health
OR	Odds Ratio
RUMC	Rush University Medical Center
SAT	Subcutaneous Adipose Tissue
SES	Socioeconomic Status
SSAT	Superficial Subcutaneous Adipose Tissue
T12-L1	Between 12 Thoracic and First Lumbar Vertebrae
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
TNF-α	Tumor Necrosis Factor – alpha
UIHHSS	University of Illinois Hospital and Health Sciences System
US	United States
VAT	Visceral Adipose Tissue
WC	Waist Circumference
WHR	Waist-to-Hip Ratio

SUMMARY

A study was conducted to explore the associations between body composition and colorectal cancer using two approaches in 128 African American and Non-Hispanic White patients with colorectal cancer (cases) and a comparison group of 128 cancer-free patients (controls) matched on age, gender, body mass index and race/ethnicity. A case-control approach was conducted to examine the associations between abdominal adipose tissues and colorectal cancer and to determine if variations exist by race/ethnicity. A separate cross-sectional analysis on serum samples from a subgroup of cases was performed to assess the association between biomarkers of colorectal cancer risk and body composition. In addition, an exploratory analysis was carried out to determine the feasibility of using two techniques for calculating hepatic fat content and prevalence of hepatic steatosis in both groups. Information on demographics, anthropometrics and clinical data and two single-cross sectional computed tomography images for abdominal body composition analysis were collected from electronic medical records and radiology departments at three hospitals.

No differences in visceral adipose tissue in cases and controls were found although this depot is associated with increased colorectal cancer risk in the literature. Additionally, African American males in both cases and controls had lower visceral adipose tissue compared to Non-Hispanic White male counterparts as observed in healthy populations. Furthermore, another less studied abdominal adipose tissue, superficial subcutaneous adipose tissue was found to be significantly different between cases and controls. Results showed that African Americans with higher superficial subcutaneous adipose tissue had lower odds of colorectal cancer. This association was not found for Non-Hispanic Whites. Serum results revealed lower adiponectin and insulin-like growth factor binding protein-3 in African American male cases compared to Non-Hispanic White male cases.

I. INTRODUCTION

1.0. Background

Obesity is a widespread public health problem associated with metabolic complications including inflammation, insulin resistance, diabetes, cardiovascular disease and cancer however it is not a homogenous condition. Obese individuals with excess intra-abdominal adiposity, termed visceral adiposity, and those with elevated hepatic fat content (HFC) are much more predisposed to develop these diseases than those with abdominal fat located primarily, subcutaneously. The location and amount of adipose depots are determined by both non-modifiable (gender, age and race/ethnicity) and modifiable (diet, exercise) factors.

Obesity has been identified as significant risk factor for CRC for over 20 years. Recently, visceral adipose tissue (VAT) and HFC rather than overall adiposity have been found to be closely associated with colorectal adenomas and CRC.[1-6] Cohort studies have reported race/ethnic differences in risk and prevalence of CRC with increasing levels of obesity. Prevalence for CRC is greater in African Americans (AA) than Non-Hispanic Whites (NHW), however, AAs have less VAT and HFC[7] but higher prevalence of IR. The cause for the racial disparity in obesity-related CRC remains poorly understood. One study recently found that elevation in risk factors associated with cardiovascular disease (i.e., triglycerides, blood pressure and glucose) were observed at a significantly lower VAT area in AA men and women compared to NHWs (AA women = 82 cm^2, NHW women = 140 cm^2; AA men = 82 cm^2, NHW men = 141 cm^2).[8] These findings indicate that AAs are at greater risk for disease at a much lower VAT surface areas compared to NHWs. We speculate that racial differences in VAT area may also be associated with the greater CRC risk burden observed in AA adults. Furthermore, scientific evidence is completely lacking on the influence of HFC or other abdominal adipose depots such as intermuscular adipose tissue (IMAT), subcutaneous adipose tissue (SAT) subtypes, deep subcutaneous adipose tissue (DSAT), or superficial subcutaneous adipose tissue (SSAT) on CRC risk, particularly in a

racially/ethnically diverse population. There is almost no data exploring interrelationship between the various adipose depots, inflammation and insulin resistance in CRC minority populations. Such knowledge would provide important insight into CRC racial disparities.

Computed tomography (CT) scans provide high-quality images that precisely measure abdominal compartments, including VAT and HFC, however they are expensive, frequently inaccessible and require radiation exposure rendering them impractical for use in epidemiologic studies. In medical settings CT scans are used routinely for diagnostic purposes. Patients with CRC have diagnostic CT scans of their abdomen performed prior to surgery for tumor staging and evaluation of metastasis. Therefore, these scans can be exploited to quantify abdominal fat depots (i.e., VAT, SAT, IMAT, SSAT, DSAT) and HFC for research purposes. Exploitation of retrospective CT scans for assessment of abdominal fat distribution and HFC is inexpensive and requires no additional radiation exposure.

The purpose of this investigation was to determine if the area of the abdominal adipose depots and HFC using hepatic attenuation in patients with CRC (cases) were similar to age, gender, race and BMI matched patients (controls) requiring an abdominal CT scan for medical reasons (abdominal pain, gall bladder surgery, hiatal hernia repair, organ donor). We assessed the associations between various abdominal adipose depots and HFC with established serum risk factors for CRC and explore if these relationships vary by race/ethnicity.

1.1. Specific Aims and Hypotheses

A case-control study design was utilized to accomplish Specific Aims 1 and 2. Cases with incident CRC and a pre-surgical abdominal CT scan were compared to controls with retrospective abdominal CT scans for medical reasons (abdominal pain, gall bladder surgery, hiatal hernia repair, organ donor). For Specific Aim 3, a cross-sectional design was used to explore the association between abdominal and hepatic fat content and biomarkers associated with CRC in

pre-surgical serum in a subsample of CRC cases. Specific aim 4 was a cross sectional study of a subset of cases and controls with CT scans that enabled assessment of HFC.

SPECIFIC AIM 1: To determine if there is a unique abdominal adipose tissue phenotype in patients with CRC.

Hypothesis 1. For a given body mass index (BMI), patients with CRC will have > VAT than controls.

SPECIFIC AIM 2: To discern if patients with CRC retain the racial variation in abdominal adipose tissues that exists in healthy populations.

Hypothesis 2. For a given BMI in CRC patients, NHW will have > VAT than AA.

SPECIFIC AIM 3: To discern the associations between abdominal adipose depots on biomarkers of CRC risk in serum and explore if these relationships are modified by race/ethnicity.

Hypothesis 3. Associations between VAT and biochemical serum factors will be similar between NHW and AA.

SPECIFIC AIM 4. To determine the feasibility of using two techniques for assessment of hepatic fat content in patients with and without CRC and assess the prevalence of hepatic steatosis in these patients.

Hypothesis 4. Cases will have higher prevalence of HFC compared to controls.

1.2. Significance of the Study

The main objective of this study was to determine if the relationship between abdominal adiposity HFC and CRC assessed in NHW and AA patients with and without CRC were similar. The areas for HFC, VAT, IMAT, SAT and its subtypes, DSAT and SSAT, were assessed from diagnostic CT scans. Cases and controls were compared for similarities with particular focus on race/ethnicity variations. In cases the relationship between abdominal adiposity, cancer staging

and established serum markers of CRC risks (adiponectin, interleukin-6, tumor necrosis factor-α, leptin, testosterone, estradiol, insulin, insulin-like growth factor-1, insulin-like growth factor binding protein-3, homeostasis model of assessment-insulin resistance) were also assessed.

II. RELATED LITERATURE

2.0. Overview

The literature review is divided into 6 major sections. The first section is a brief review of the epidemiology of CRC, followed by a summary of surrogate markers of obesity, BMI and waist circumference (WC) and their associations with CRC risk. The third section describes body composition, methods for assessment and their association with CRC, followed by reviews of postulated obesity-related mechanisms and CRC pathogenesis. The fifth section explores the relationship between race/ethnicity, disparities and CRC. The final section summarizes the background information with a diagram depicting the theoretical framework for this investigation.

2.1. Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) is a slowly progressing disease that develops over 10-15 years and is characterized by the accumulation of mutations that arise from hereditary causes and/or spontaneous mutations of genes controlling cell proliferation, differentiation, apoptosis, and DNA repair in the colonic mucosa. [9] Only a small fraction of CRC results from hereditary causes, the vast majority (approximately 90%) are sporadic and non-hereditary.[10,11] Colorectal Cancer is third in incidence and mortality of all cancers in the United States. [12] Worldwide CRC incidence rates parallel economic development with common risk factors associated with obesity and Western lifestyles: physical inactivity, excessive dietary fat consumption, and disproportionate energy intakes. [10,13,14] Other known risk factors for CRC include older age, male gender, family history of CRC, history of colorectal polyps, inflammatory bowel disease, type 2 diabetes, excessive alcohol use, smoking, and diets high in red and processed meats. [15] The lifetime risk of having a diagnosis of CRC is 5% in the US. [15]

Data from 2003-2007 from the North American Association of Central Cancer Registries and National Center for Health Statistics reveal that African American (AA) men compared to Caucasians have the highest age-adjusted incidence rate (68.3/100,00 vs. 56.8/100,000) and ,

age-adjusted mortality rate (30.5/100,000 vs. 20.9/100,000) for CRC.[15] There is also evidence that AA are younger and have advanced CRC stage at diagnosis than their European American counterparts.[16] Overall, CRC mortality rates began declining in the 1980s for men and 1950s for women, possibly as a result of screening initiatives focused on earlier detection and removal of precancerous polyps.[15,17] Regardless, CRC remains the third most common cancer in men and second most common cancer in women. [14,18]

The projected annual medical cost for treating obesity –related health problems is a staggering $28 billion/year by 2020 and $66 billion/year by 2030.[19] Obese individuals have 30% higher healthcare costs and utilize more healthcare services than normal weight individuals.[20] Obesity has been identified as an independent risk factor for post-surgical infections and subsequent treatment of infections increasing hospital costs by approximately $17,000 in patients requiring total or segmental colonic resections for CRC, diverticulitis and irritable bowel disease (IBD).[21] Obese persons have reduced quality of life, reduced workforce productivity, functional limitations with early disability and shortened life expectancy.[20]

2.2. Surrogate Markers of Obesity (Body Mass Index and Waist Circumference) and Colorectal Cancer Risk

Obesity has been identified as a significant risk factor for CRC for over 20 years. [22] The obesity-induced chronic inflammation is thought to increase susceptibility of gene mutations. [9,23] The increasing spread of obesity across all race/ethnic, ages and gender renders this an extremely important area of research. Recently, higher incidence rates have been found in those younger than 50 years of age, possibly reflecting the impact of obesity on CRC risk.[24]

2.2.1. Body Mass Index and Colorectal Cancer

Several large prospective cohort studies have consistently demonstrated positive associations between obesity and CRC[3,25-27 28] and a dose-response has been reported for body mass index (BMI), waist circumference, and waist-to-hip ratio. [3,29] Campbell et al. reported a that

5kg/m2 increase in BMI increments was positively associated with greater odds in women (OR =1.20; 95% CI = 1.10-1.32) and men (OR = 1.24; 95% CI =1.15 -1.34) compared to sex-matched siblings.[30] Findings from a meta-analysis of 31 studies concluded that a 5-unit increase in BMI increased CRC risk by 30% in men (RR: 1.30;95%CI: 1.25, 1.35) and 12% in women (RR: 1.12;95% CI: 1.07, 1.18).[31] A nationally representative US sample (Cancer Prevention Study II, 1982-1998) reported the relative risk for CRC in women with a BMI ≥ 40 was 1.46 (95% CI, 0.94-2.24) and in men with a BMI 35-39.9 was 1.84 (1.39–2.41) compared to those with a normal BMI (18.5-24.9).[26] In a large prospective Norwegian study, increased risk of CRC occurred in men with a BMI ≥ 25 and a ≥ 10 kg weight gain from baseline assessment whereas no association was found in women (postmenopausal).[32] Women appear to have an increased risk of CRC when high BMI is accompanied by low physical activity (1).[33] A 5-unit increase in BMI and 10cm increase in waist circumference significantly increases CRC risk.[31]

2.2.2.. Waist Circumference and Colorectal Cancer

Unlike BMI, WC is a surrogate measure for regional fat distribution and increasing WC is associated with increased CRC risk. Central adiposity assessed indirectly by WC is associated with increased morbidity and mortality in CRC.[34,35] Men have greater CRC risks than women which may be due to their greater abdominal circumference.[36] WC in men has been associated with colorectal adenomas but not in women. [37] Risks for CRC increase by 33% per 10 cm increase in waist circumference and 43% per 0.1 unit increase in waist-hip ratio.[31] Risks for proximal and distal colon cancers have been observed with increasing WC in both genders.[36] WC has been shown to significantly and independently predict the presence of diabetes (HR 1.56) and hypertension (HR 1.7) in patients with CRC.[38]

2.2.3. Obesity and Colorectal Cancer Prognosis

Obese adults with CRC have worse prognosis and lower survival rates than normal weight counterparts. [39,40] A large nationally representative sample (NHANES 1971-1975) determined

mortality from CRC was 0.39, 0.68, and 0.96/1,000 person-years for normal weight (BMI 18.5 - 24.9), overweight (BMI 25-29.9), and obese (≥30) respectively (*P* value for log-rank trend test<0.001).[39] Doria-Rose et al. found postmenopausal obese women with CRC had increased risk of CRC death compared to normal weight postmenopausal women independent of hormone use, however, the impact of physical activity, other pre-existing comorbidities were not evaluated.[41] Advanced stage cancer, node positivity, and extent of nodal involvement which contribute to a worse prognosis has been observed in obese males[42] and in females within lowest and highest BMI quartiles. [43] Sakai et al. found obese CRC patients had significantly longer surgeries, significantly higher blood loss and a trend towards more infections than non-obese CRC patients.[44] Significant linear trends of age-adjusted death rates from CRC are observed with increasing BMI in both genders. [26,45]

2.3. Body Composition and Colorectal Cancer

Advances in imaging techniques enabled the exploration of the relationship between body composition, specifically abdominal adipose depots and HFC, and health.[46-48] The description of the biological and physiological properties of abdominal adipose depots by pioneers in the field improved our understanding of the connection between these depots and metabolic disease risk.[49-55] Internal adipose depots also referred to as intra-abdominal adipose depots (VAT) and hepatic fat content (ectopic fat accumulation) are designated as culprits of metabolic dysfunction. In this section, body composition will be discussed with emphasis on how abdominal adipose depots and hepatic fat deposition may contribute to the heterogeneity of obesity and how imaging technologies continue to advance our understanding of body composition and obesity, specifically ‘metabolically unhealthy’ or ‘malignant’ obesity.

2.3.1. Benign Obesity and Malignant Obesity (metabolic obesity or metabolically unhealthy)

Obesity is a heterogeneous condition. Some overweight or obese individuals have low levels of VAT, no metabolic dysfunction, few or no additional risk factors and relatively low disease risk.[55] On the other hand, some normal weight individuals with significant amounts of VAT have high risk for metabolic dysfunction, diabetes and other obesity-related health problems.[55] It is now recognized that malignant obesity or metabolic obesity is due to the type and distribution of intra-abdominal adipose depots rather than generalized adiposity.[33,55,56] VAT is more pathogenic, more metabolically active and contributes disproportionately to inflammation, atherosclerosis, dyslipidemia, hypertension, and certain types of cancer, such as CRC than other abdominal depots like SAT.[57,58] Traditional clinical measures of obesity – weight, BMI and WC are unable to distinguish metabolically healthy versus metabolically unhealthy obese individuals. However, initially, these clinical measures are useful in identifying individuals at increased risk for metabolic disease and compared to BMI, WC has more predictive power. Excess adiposity with or without metabolic disease is regardless of metabolic function is unhealthy and should be treated as such.

2.3.2. Assessment of Abdominal Adipose Depots and Colorectal Cancer

The BMI measures total adiposity but does not provide specific information of body fat distribution. In addition, generalized adiposity is not consistently associated with increased CRC risk. Whereas WC is often used as a surrogate marker of abdominal fat mass because it correlates with subcutaneous, visceral and intra-abdominal fat.[36,59] WC and BMI are also highly correlated (r^2 range of 0.86-0.95).[60] The CT and magnetic resonance imaging (MRI) scans allow for differentiation and quantification of abdominal adipose tissue and are currently the gold standards for direct assessment and quantification of abdominal fat distribution.[38,61] These CT or MRI derived images are used more frequently for diagnosis, evaluation, and treatment decisions in patients with CRC because they are less expensive and more readily accessible than MRIs. Diagnostic CT scans have been exploited for assessment of abdominal adipose depots and

skeletal muscle (SM) in many cancer populations[61-63] and in a variety of chronic diseases for more than 30 years.[48,54] There is also a body of literature exploring regional fat distribution assessed by CT and MRI in healthy adults and adolescents.[64] The MRI is preferred for regional fat distribution evaluation in children and healthy adults because it does not emit radiation.

2.3.2.1. Subcutaneous Adipose Tissue and Intra-Abdominal Adipose Tissues

The anatomical location, cellular composition and metabolic characteristics of abdominal adipose tissues have been described previously in great detail.[46,47,65] Briefly, there are two main adipose tissues in the body, subcutaneous located between the skin and visceral (intra-abdominal adipose tissue) found within the abdominal cavity and which surrounds the inner organs.[46,55] The main function of SAT is to provide insulation from heat/cold and consists of two subtypes SSAT and DSAT which are anatomically separated by the subcutaneous fascia.[46,47,55] The SAT also includes the adipose tissue of the mammary glands. In healthy weight individuals, approximately 80% of total body fat is SAT.[58,66] The VAT includes the intraperitoneal (omental and mesenteric) and extraperitoneal adipose tissues (preperitoneal and retroperitoneal).[46,47,55] In normal weight and obese men, VAT is approximately 10-20% of total body fat and for women it is 5-10% of total body fat.[66] A single cross-sectional CT image includes SAT (SSAT and DSAT) and VAT (mesenteric, omental and extraperitoneal).

These adipose depots are structurally different and have different biological functions. The VAT subtypes, mesentery and the omental, drain directly into the portal vein and are thought to be more closely related to metabolic dysfunction because of this characteristic.[46,47,55] There is some evidence that the mesenteric depot is the specific VAT sub-type linked to obesity-related diseases.[37,67,68] In contrast, abdominal SAT drains into systemic circulation and is thought to have less influence on metabolic dysfunction. There is continued interest in understanding the role of specific visceral sub-types and metabolic disease.

Another abdominal adipose depot that has been explored in relation to disease risk is IMAT and it results from the infiltration of fat within muscles. A cross-sectional slice taken of the abdomen displays the IMAT within the abdominal muscles: obliques, transverses abdominis, rectus abdominis, psoas and erector spinae. Since muscle, especially SM, is involved in insulin-mediated glucose uptake and fatty acid oxidation, the effects of IMAT to metabolic dysfunction within the muscle is of great interest. It is well known that SM is highly sensitive to insulin and increased triglyceride concentrations correlates with diminished insulin activity.[69,70] Increased IMAT is associated with metabolic syndrome (MetS) in women but not men.[71] Newer evidence suggests that excess lipid accumulation alone within the muscle may not be responsible for causing insulin resistance since elite athletes have similar amounts of fat deposition within muscle as do patients with Type 2 diabetes mellitus (T2DM) and yet are much more insulin sensitive.[72,73] The exact mechanism between IMAT and insulin resistance remains largely unexplained. Excess IMAT may potentially play a role in insulin resistance, obesity and MetS, however, whether it is a primary role in the onset of insulin resistance or if it is a cause or consequence remains to be determined.

2.3.2.2. Non-modifiable Factors that Influence Abdominal Adipose Tissue Distribution

Genetics, age and gender are non-modifiable factors that influence regional fat distribution. Identical twins have higher correlations for total body fat, trunk fat and lower body fat compared to fraternal twins suggestive of genetic etiology.[74] One study recently demonstrated that in addition to genetic phenotype for VAT accumulation, sharing of the same familial environment also seems to be an important factor in determining visceral adiposity.[55,75] This points to the important role of habits and behaviors formed at home such as food and diet behaviors and opportunities for physical activity shared by members of same family. Age is another very important mediator of abdominal fat deposition. In both genders, the amount of VAT increases with age.[58,76] In healthy women, total body and abdominal fat increases and fat-free

mass decreases in the years following menopause.[77] Younger women accumulate more fat in lower body adipose depots (hips, thighs) than men[78,79] and have less VAT and SAT than postmenopausal women.[80] During menopause and after menopause, women will transition from storing fat subcutaneously to accumulating fat viscerally.[81] Postmenopausal women may have up to 50% more VAT than premenopausal women.[80] On the other hand, premenopausal women are able to accumulate a higher body fat percentage before noticeable VAT accumulation is observed.[55] Men and women have very different body fat distribution phenotypes. In general, men tend to accumulate higher amounts of fat in the truncal region whereas women accumulate more in the lower regions of the body (hips, thighs) characteristically known as pear-shaped.[55,82,83] Compared to men, women have higher subcutaneous and less visceral fat.[82,84] Men have almost twice the amount of VAT at lower BMIs compared to similarly aged women.[85] In women, VAT is less affected by changes in total adiposity even when BMI, total fat and SAT are higher compared to men.[86] Studies have shown that increasing WC correlates with increasing VAT in men and in women.[76,87] However, for any given WC, men will have higher VAT amounts than women.[52] Differences in body fat distribution are attributed to the influence of fluctuating levels of sex hormones during the life trajectory.[55,65,78,88] Men and peri/post-menopausal women will have higher VAT deposition with increasing age compared to young pre-menopausal women. In terms of race/ethnicity, White adults have higher amounts of VAT compared to AA adults of same age and this trend continues even as age increases.[89,90]

2.3.2.3. Behavioral Factors that Influence Abdominal Adipose Tissue Distribution

Poor diet and behavioral factors such as physical inactivity are determinants of obesity and its related disorders. The Framingham Heart study reported lower VAT and SAT in physically active participants.[91] Physical activity decreases WC and improves metabolic abnormalities even without weight loss.[55] The effect of physical activity with or without changes in energy intake on abdominal fat is controversial.[92] In the presence of 5% weight reduction with or without exercise,

obese individuals decreased VAT and CRP levels and had improved IR.[93] In overweight and obese adults, moderate to high intensity exercise reduces VAT in the absence of a low calorie diet.[94] There is also evidence that VAT responds to small changes in energy deficit in the absence of any changes of physical activity.[92] The mechanism by which exercise decreases VAT in the absence of weight loss is not understood. It is postulated that increases in fat-free mass as observed with exercise may offset the detrimental effects of VAT since exercise causes the mobilization of lipids from VAT as a consequence of B-adrenergic action of VAT by exercise associated sympathetic stimulation.[55]

Where physical activity appears to be beneficial to body fat distribution, cigarette smoking adversely alters it. Participants from the Framingham Heart Study who were former and current smokers had significantly higher VAT than never smokers.[91] Heavy smokers (≥20 cigarettes per day) appear to be more prone to central fat accumulation as indicated by WC compared to light smokers.[95] A dose-dependent association has also been described for participants with VAT higher than 100 cm^2 and total pack-years (number of years smoking multiplied by the number of daily cigarette packs smoked).[96]

2.4. Visceral Adipose Tissue, Subcutaneous Adipose Tissue and Colorectal Cancer

Current studies exploring abdominal adipose depots, VAT and SAT, have shown that VAT, in particular, is a better predictor of obesity-related health risks.[34] VAT is a better predictor for colorectal adenoma risk than BMI[1,2,37,97-99] although evidence for this is inconsistent.[98] Kang et al. examined the association of VAT and CRC and found it was an independent risk factor (OR of 3.09, 95% CI 2.19-4.36).[100] Japanese adults with colorectal adenoma[101] had more VAT than controls.[97] VAT has been associated with colorectal adenomas in both males and females independent of BMI.[2]

In cancer populations, abdominal adipose depots associate with increased risk. Balentine et al (2010) evaluated if direct analysis of VAT by CT using a variety of anatomical landmarks

(L2/L3; L4/L5) are valid in patients with CRC (Stage 0-IV) and determined that VAT amounts at any given anatomical landmark, as did WC, correlated significantly with diabetes and hypertension confirming that direct measurement of VAT is valid in cancer patients.[38] Only a handful of studies have assessed VAT in patients with CRC. These studies have shown that VAT is an independent predictor of CRC but these findings are not consistent. Yamamoto et al. (2010) performed a study in mostly male Korean patients with early-stage CRC and cancer-free controls and found a positive association between VAT and CRC that increased significantly from lowest (designated as the reference tertile) to highest VAT tertile (mid-tertile OR 2.17, 95% CI 0.45-10.46; highest tertile OR 5.92 95% CI 1.22-28.65).[1] On the other hand in a smaller Turkish study, Erarslan et al (2009) examined 54 newly diagnosed patients with CRC (24.6±3.7) and 50 healthy controls (BMI 29.2±5.8) and found that VAT was similar in both groups.[102] In the latter study, BMI was statistically significant between the CRC patients and healthy controls and cancer staging was not reported. Gender differences were also not explored and this may have been due to small sample sizes overall and very few female participants. More studies assessing VAT in larger samples exploring gender differences and the relationship between VAT and CRC are needed.

2.5. Hepatic Fat Content and Colorectal Cancer

Hepatic fat content (HFC), also referred to as hepatic steatosis, liver fat infiltration or fatty liver is a metabolic consequence of obesity, associated with MetS and its components (IR, dyslipidemia and hypertension) and its manifestation is non-alcoholic fatty liver disease (NAFLD).[103-105] The prevalence of NAFLD is increasing[103] and currently affects 20-30% of the US population.[105,106] Liver fat deposition within hepatocytes causes inflammation which leads to scarring of the liver tissue and if left untreated, can lead to cirrhosis.[107] Simple hepatic steatosis is the mildest form and cirrhosis is the most extreme form of NAFLD which may lead to liver failure or hepatocarcinoma, however, this outcome is less common in NAFLD.[105,108] Persons with non-

alcoholic fatty liver disease (NAFLD) have an increased risk for colorectal adenomas and CRC.[109] This section will describe diagnostic and alternative non-invasive strategies for assessing hepatic fat content and the known associations between HFC and colorectal adenomas and CRC.

2.5.1. Liver Biopsy for Diagnosis of Hepatic Steatosis

The gold standard for diagnosing hepatic steatosis is the liver biopsy.[105,106] The liver biopsy is an invasive procedure with various complications, cannot be used for repeated measurements or to monitor response to treatment and its use is not practical in healthy populations.[105,107] Although various less invasive procedures such as assessment by CT, MRI or ultrasound are proposed as effective alternatives for the evaluation of hepatic steatosis,[110,111] a liver biopsy is ultimately required to confirm diagnosis and to describe histologically (hepatocyte changes, inflammation, and extent of fibrosis) the extent of liver damage due to fatty infiltration.[105] MRIs, CTs, and ultrasounds have been used to assess the prevalence of hepatic steatosis in asymptomatic adults and population-based studies and have proven to be reproducible, reliable, and valid measures of hepatic steatosis compared to liver biopsy.[110-114]

2.5.2. Computed Tomography Scans for Assessment of Hepatic Fat Content

The liver is a solid fat-free organ made up of soft tissues and an entire image of the liver can be seen using a cross-sectional CT slice at the Thoracic 12 - Lumbar 1 (T12-L1) vertebral landmark in most humans (90% of the time).[105,110,115] Various protocols for evaluation of HFC using CT images have been developed.[115,116] In brief, HFC is determined from the mean HU of circular regions manually traced on the liver, spleen and/or other anatomical parts such as the aorta using medical imaging software as specified in the protocol being applied. Under normal conditions, the liver has about the same or higher radiographic density to other similar solid organs of the upper abdomen (ie. spleen, pancreas, kidneys). The CT radiographic density, also known as x-ray attenuation, is measured in Hounsfield (HU) units and each body tissue and bone has a corresponding HU threshold.[117] In the normal liver, the mean attenuation has been reported at

56.7±11 HU a.[118,119] Hepatic attenuation values measured at different sections of the same liver fall within a narrow HU range suggesting that the liver is homogenous throughout.[105,115,120]

2.5.3. Factors that Influence Assessment of Hepatic Fat Content

Hepatic fat content is best visible and most accurately assessed using a CT scan of the abdomen without contrast.[112,117,121] Contrast enhanced CT scans have been used for hepatic fat quantification but are generally not recommended because the contrast yields potentially erroneous attenuation values.[110,111] The internal reference standards recommended for a contrast enhanced CT is abdominal SM and for a non-contrast enhanced CT, the reference standard is the spleen.[105,110] CT scans provide a reliable image of the liver and the measurement of amount of steatosis is possible due to the inverse relationship between the CT unit, Hounsfield attenuation unit, and hepatic fat content such that higher hepatic fat content yields lower the liver attenuation values.[110] Hepatic attenuation values less than or equal to 40 HU are representative of moderate-to-severe hepatic steatosis.[117]

2.6. Hepatic Fat Content, Colorectal Adenomas and Colorectal Cancer

The presence of NAFLD in patients is an independent predictor for colorectal adenomatous polyps which are precursors to CRC, after controlling for age, gender, smoking status, metabolic syndrome, hypertension and diabetes.[104] These findings have been corroborated internationally.[122-124] Contrary to these findings, Touzin et al did not find higher prevalence of adenomas in patients with NAFLD compared to controls.[125] A recent review of the literature by Armstrong et al on NAFLD and its association with increased metabolic complications concluded that NAFLD significantly increases risk for T2DM, cardiovascular disease, renal disease and CRC, however, more studies are needed, especially in CRC to further explore the impact of NAFLD.[126] Additionally, research evaluating the association of HFC, adenomas or CRC is sparse in the US. More studies in diverse populations are needed to explicate this association and its implications.

2.6.1. Postulated obesity-related mechanisms and Colorectal Cancer pathogenesis

The mechanisms involved in obesity-related CRC development are not completely understood. Associations between metabolic dysfunction and CRC may involve inflammatory and insulin resistance pathways. The obesity-related CRC as currently understood is complex and may involve pathogenic changes in abdominal fat distribution and hepatic fat content that independently or concurrently contribute to inflammatory and insulin resistance pathways leading to the pro-carcinogenic environment that ultimately causes CRC. This section describes how adipose tissue expansion contributes to metabolic dysfunction and summarizes several major, well known mechanistic pathways in obesity-related CRC.

2.6.1.1. Adipocyte Size and Adipose Tissue Expansion

Adipose tissue is composed of mostly of adipocytes and other cell types such as pre-adipocytes, blood cells and endothelial cells.[127] Adipocytes are the main storage depots of triglycerides.[58,127] The adipocyte size determines how effective the adipocyte is in storing free fatty acid (FFA) and triglyceride (TG) postprandially.[58] Small more insulin sensitive adipocytes are powerful buffers with high absorption capacity of FFAs and TGs after a meal.[58] However, as these small adipocytes grow larger or hypertrophy, they become less efficient, dysfunctional, insulin resistant and hyperlipolytic. With adipose tissue expansion, the adipose compartments accumulate fat by hypertrophy (adipocyte enlargement) or hyperplasia (generation of smaller, more functional adipocytes).[57] SAT contains a greater number of small adipocytes compared to VAT which contains a higher number of larger adipocytes.[58] In response to increased adiposity, adipocyte size and number increase within all adipose tissue compartments in both genders.[55] In conditions of excess energy, it is thought that impaired adipogenesis within the adipose tissue, possibly initially subcutaneously which normally creates hyperplastic adipocytes leads existing adipocytes to switch to hypertrophy to store excess fat.[57] It is postulated that visceral and ectopic fat accumulation results when SAT is no longer able to expand through hyperplasia and switches

instead to hypertrophic expansion.[128] Adipocyte hypertrophy will continue up to a certain point and then spillover of lipids into depots like VAT, liver, heart and pancreas ensues leading to metabolic abnormalities: dyslipidemia, inflammation and insulin resistance.[55,57,128]

2.6.1.2. Overview of Colorectal Cancer Pathogenesis

The majority of colon adenocarcinomas develop from adenomas or polyps. The well accepted model by Vogelstein[129] for the development of CRC from normal mucosa to premalignant adenoma involves several key genes: the *APC* gene, a tumor suppressor gene, is one of the first genes that may become mutated and is usually expressed in 80% of adenomas and adenocarcinomas[130,131]; the *K-ras* gene, an oncogene responsible for cell proliferation is also mutated in CRC; and *p53* gene, a tumor suppressor gene associated with apoptosis, is believed to be the gene mutation responsible for the conversion of an adenoma to adenocarcinoma.[131] This transformation is a long-term process characterized by an accumulation of mutations that disrupt the normal processes of cell proliferation, differentiation, apoptosis, and DNA repair. The reason for this loss of control remains unclear, however, chronic low-grade inflammation as seen in obesity has been hypothesized to play a central part.[9] White adipose tissue is an endocrine tissue and secretes bioactive molecules from adipocytes, preadipocytes, and macrophages.[132,133] These bioactive pro-inflammatory molecules also referred to as adipokines include IL-6 and tumor necrosis factor alpha (TNF-α) among others.[134] The release of these cytokines from macrophages lends to systemic low-grade inflammation.[9,135] Circulating IL-6 and TNF-α, elevated insulin levels and upregulation of insulin-growth-factor-1 (IGF-1) have been associated with adiposity and risk of colorectal adenomas[136] and increased CRC risk.[136,137] Studies demonstrate that low- grade inflammation and high circulating insulin (hyperinsulinemia) and upregulation of IGF-1 have effects on cell proliferation, angiogenesis, and tumor promotion.[138,139]

2.6.1.3. Chronic low-grade Inflammation and Colorectal Cancer

A chronic low-grade systemic inflammation accompanies obesity and is linked to CRC in both observational and clinical studies.[136,140,141] Chronic inflammation is described as an initiator and promoter of cancer progression.[141,142] IL-6 (interleukin-6) and C-reactive protein (CRP), have been identified as independent predictors of CRC risk and poor post-surgical outcomes and survival.[140] Obesity-related inflammation leads to the production of a host of pro-inflammatory adipokines (eg. leptin, resistin) and cytokines (eg. TNF-α, IL-6) while simultaneously reducing the release of an anti-inflammatory adipokines (eg. adiponectin) and cytokines (IL-10).[140-142] As the adipose tissue continues to expand, the existing blood vessels are insufficient at delivering adequate oxygen to the adipocytes leading to hypoxia. Hypoxia-inducible-factor 1, the possible mediator of hypoxia triggers an inflammatory response and angiogenesis to increase oxygen delivery to the hypertrophic adipocyte.[143] In addition, endoplasmic reticulum stress increases as metabolic and structural changes occur within the hypertrophic adipocyte.[143,144] Recently, chronic *colonic* inflammation has also been associated with obesity.[145] It is the continuous presence of these pro-inflammatory molecules in the colonic cellular environment that has the potential for carcinogenesis.

2.6.1.3.1. Adiponectin and Obesity

Adiponectin is an anti-inflammatory and insulin sensitizing adipokine.[146,147] It has two known cellular receptors: adiponectin receptor-1 and adiponectin receptor-2.[148] It is purported to having anti-carcinogenic properties but the mechanisms of action are unclear.[148,149] Adiponectin is highly expressed in visceral adipose tissue (VAT) and inhibits liver gluconeogenesis and promotes fatty acid oxidation in SM.[147] Expression of adiponectin is decreased in VAT of obese compared to non-obese subjects.[150] Women tend to have higher circulating adiponectin concentrations than men, possibly due to higher body fat mass and higher estrogen and androgens.[151] Testosterone has been shown to decrease circulating levels of adiponectin in men

and mice as demonstrated in vivo and in vitro studies.[151,152] , Adiponectin activates the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway thereby downregulating the mammalian target of rampamycin (mTOR) signaling pathway and inhibiting CRC cell growth[153] and may also suppress other tumor growth inhibitor enzymes downstream of AMPK, however, these have not been identified.[151,153] In obesity, adiponectin is down-regulated, possibly by TNF-α.[146] It has been shown that adiponectin receptors are expressed on many cancer cell types, however, how adiponectin and its receptors relate to obesity and cancer is less clear.[149]

2.6.1.3.2. Adiponectin and Colorectal Cancer

Patients with CRC have low levels of adiponectin compared to controls.[154] It is postulated that adiponectin has anti-carcinogenic effects by several mechanisms. Adiponectin activates the AMPK/mTOR pathway suppressing cell growth and proliferation by inhibiting the production of enzymes needed in protein regulation (mTOR)[153] and reducing the expression of a major transcriptional regulator, sterol regulatory element binding protein.[151] It also upregulates p53 and p21, important proteins involved in growth arrest and apoptosis.[151] Additionally, colonic tumors have been shown to have higher expression of adiponectin receptors than non-involved tissue in patients with CRC, however, what this means is not yet known.[148,155]

2.6.2. Reversal of chronic inflammation

Weight loss reverses the adverse effects of obesity on chronic inflammation. Common systemic markers of inflammation such as CRP, IL-6 and TNF-α decrease substantially with weight loss.[156] Pendyala et al examined the effects of weight loss on both systemic and colonic inflammation in obese women and found that weight loss between 5-10% not only decreases chronic systemic inflammatory cytokines (TNF-α, IL-8, IL-6), but also decreased colonic inflammatory cytokines (TNF-α, IL-6, IL-8) and pro-oncogenic genes (*IL-8, JUN, FOS*).[145,157]

2.6.3. Insulin Resistance, Metabolic Syndrome and Colorectal Cancer

A major metabolic consequence of obesity is T2DM which is characterized by insulin resistance, hyperinsulinemia and elevated levels of fasting blood glucose. Epidemiologic studies conducted in the US, Europe, and Asia consistently show that T2DM increases the risk for CRC.[31,158,159] The individual metabolic consequences of T2DM including hyperinsulinemia, insulin resistance and elevated fasting blood glucose levels, associate with increased CRC risk [160-162] in both genders however the associations are greater in men.[159] Similarly, colorectal adenomas, a precursor of CRC, have been associated with elevated insulin levels and insulin resistance.[100,163]

2.6.3.1. Metabolic Syndrome and CRC

The MetS is defined as having 3 or more of the following metabolic abnormalities: high blood pressure, increased waist circumference, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, or diabetes/hyperglycemia.[132,164] A large prospective study evaluating metabolic syndrome (≥ 3 components) as a risk factor CRC of 14,109 men and women found a stronger association for men (RR, 1.78; 95%CI, 1.0-3.6) than for women (RR, 1.16 95%CI, 0.6-2.2).[164] Similarly, a large European multi-center case-control study found that men (OR = 1.86; 95% CI 1.21–2.86) with MetS had stronger associations for CRC risk than women (OR =1.13; 95%CI 0.66-1.93).[165] Individual components of MetS, especially hyperglycemia, may influence CRC risk through several biological mechanisms.[166,167] A nested case control of a large prospective cohort (EPIC 1992-2000) found abdominal obesity (WC≥102 cm in men or ≥88 cm in women) and abnormal glucose levels (based on self-reporting having diabetes or glycosilated hemoglobin ≥5.7%) were strongly associated with CRC risk.[166] Similarly, a CRC case-control study showed cases had significantly higher insulin and homeostasis model assessment insulin resistance index (HOMA-IR) and decreased adiponectin (a pro-insulin sensitive and anti-inflammatory adipokine) than controls.[161]

2.6.3.2. Potential Mechanistic Pathways of Insulin, Insulin Growth Factor -1, Insulin Growth Factor Binding Protein -3 and Colorectal Cancer

Animal and human studies have provided new and relevant information on the mechanisms involving insulin, insulin-growth-factor 1 (IGF-1) and insulin-growth-factor 2 (IGF-2) in CRC.[168] The molecule, IGF - 1 is involved in the growth and maintenance of tissues. Under normal conditions, insulin-like growth factor binding proteins 1, 2 and 3 (IGFBPs 1,2,3) bind IGF and inactivate its effect.[6,169] Obesity induced adipocyte hypertrophy causes secretion of inflammatory markers and alterations of insulin release and decreased insulin sensitivity leads to changes in expression of insulin receptors and of intracellular insulin signaling pathways.[6,138,168,170] Interleukin-6 (IL-6) and TNF-α, for example are known pro-tumorigenic cytokines and potent inflammatory mediators that can alter insulin sensitivity by upregulating key steps in insulin signaling pathways.[146,171] High insulin levels lead to increased IGF-1 and IGF-2 levels and downregulation of IGFBP-1 and IGFBP-2 proteins leading to increased bioavailability of IGF.[45,172,173] IGFBP-3 is the predominant binding protein in plasma and has high affinity (sequesters about 90%) of the available IGF proteins.[169] The binding protein, IGFPB-3 appears to have a role apart from binding proteins which possibly involves regulation of cell growth, preventing proliferation, promoting apoptosis, and may inhibit NFkB, although exact mechanisms have not been completely determined.[169,174,175] Over-expression of IGF alters downstream metabolic pathways involved in proliferation, apoptosis, angiogenesis, cell adhesion, migration and wound healing.[6] Evidence from human and animal studies confirm that high levels of insulin and IGF acting via the insulin-IGF axis promote colorectal carcinogenesis.[6]

2.6.4. Obesity, Gender, Human Sex Hormones and Colorectal Cancer Risk

Gender differences in CRC risk exist and this risk differential is possibly due to body composition differences between men and women as described in section 2.3.2.2. The influence of human sex hormones primarily estrogen and testosterone on body composition throughout the life cycle and their influence on disease risk, specifically on carcinogenesis have been studied

extensively. The epidemiological evidence of the influence of gender on CRC risk, mostly based on self-reported BMI data is controversial. However, accumulating evidence on human sex hormones and body composition similarities between men and postmenopausal women and differences between pre and postmenopausal women suggest an important role for body fat distribution in augmenting CRC risk.

2.6.4.1. Epidemiological Evidence of Gender Influence on Colorectal Cancer Risk

An association between an increased risk of CRC mortality in overweight men was reported in a 1979 large prospective study of 750,000 men.[176] The age-adjusted incidence of CRC for adults 40 and older between 1975-2006 using nine registries from the Surveillance, Epidemiology and End Results (SEER) dataset was 149.7/100,000 in men and 108.4/100,000 for women.[177] The gender difference remained after stratifying by age, tumor stage, tumor location, and geographic location. More recent studies provide further evidence for a stronger association of obesity and CRC risk in men than in women, [32,178,179] however these inconsistencies may be due to reliance of self-reported heights and weights. [178] Findings from the Nurses' Health Study, the Physicians' Health Study and the Health Professionals Study, large prospective US studies, confirmed the association of increasing BMI with increased CRC risk in both genders.[4,180,181] These cohort studies revealed the association between physical inactivity and CRC development specifically for obese compared to lean women [4] but not in men. [3,5] These studies substantiated the clustering of MetS was a consequence of increasing obesity which was then associated with increased CRC risk.[181]

2.6.4.2. Female Sex Hormones, Obesity, and Colorectal Cancer Risk

There is evidence that estrogen is protective against CRC in females. Several large clinical and population-based studies observed that estrogen positive females (hormone replacement therapy or oral contraceptives) have reduced risk of CRC compared to estrogen

negative females (non-users). [182,183] There are several other studies including a recent publication by the Women's Health Initiative group that report no benefit of estrogen and progestin combined therapy in CRC.[184] The role of estrogen in the development of CRC remains debatable. Nonetheless, numerous findings regarding estrogen and its receptors have advanced the understanding of its metabolism and its potential involvement in CRC.

Estrogen binds two separate receptors : estrogen receptor –α (ER-α) and estrogen receptor – β (ER-β)[185] and while ERα is expressed in tissues involved in reproduction (breast, uterine, prostrate), white adipose tissue, bone, liver and muscle and has insignificant role in CRC, ER-β, on the other hand, is highly expressed in colonic mucosa, the epithelium of the prostrate, testes, bone marrow and vascular endothelial.[186] The ER-β expression is reduced in CRC[185,187] and its expression indicates advanced CRC and poor prognosis.[187] Estrogen may play important role the progression of CRC because it is involved in growth and regeneration of cells,[188] induces apoptosis and inhibits cell proliferation,[187] has beneficial effects on insulin sensitivity, [78] and affects body fat distribution.[78] Aging, a contributing factor to CRC, is associated with a natural decline of circulating estrogen resulting in loss of muscle mass, adipose tissue gain in females and loss of bone health in both genders.[186] How changing levels of circulating estrogen as a result of aging and obesity lead to CRC remains to be explained.

Estrogen levels decrease in postmenopausal women as weight increases.[55,189] In a population based case – control study of women with incident CRC and without in Los Angeles found no significant increase (*P trend* = 0.18) in risk with increasing BMI except for 50 (*P trend* <0.001) and 60 (*P trend* = 0.002) years of age.[190] Upon adjustment for BMI and other confounders, the association between estrogen use and CRC was similar between groups.[190] Data collected from the Nurses' Health Study, the Women's Health Study, the Health Professionals study, and the Physician's Study II was used to assess the relationship between estradiol, testosterone, and estradiol/testosterone ratio in CRC cases and controls adjusting for various factors including BMI, age at blood draw, smoking, current alcohol use and family history

and revealed that in men higher levels of total testosterone and estradiol/testosterone ratio were associated with decreased CRC risk.[191] In women, these researchers found that only the estradiol/testosterone ratio was associated with an inverse relationship for CRC. These studies imply an important role for estrogen and other sex hormones in CRC, however, more research is needed to clarify its role.

2.6.4.3. Male Sex Hormones, Obesity and Colorectal Cancer

Few studies have explored the association between CRC, obesity and testosterone in men. Available evidence shows that circulating testosterone decreases with increasing adiposity (visceral obesity).[192-194] Higher levels of testosterone are associated with decreased CRC risk in men with similar BMI after multi-variable adjustment (age at blood draw, fasting status, smoking etc).[191] Middle-aged obese men injected with testosterone showed improved insulin resistance.[195] Although, there is insufficient literature on testosterone and CRC, similar to other sex hormones, it may play a role in the development of CRC via its effect on obesity-induced insulin resistance.

2.7. Race/Ethnicity, Disparities and CRC

Disparities influence cancer incidence and mortality within different race/ethnic groups. These cancer disparities are complex and possibly include socioeconomic status (SES), culture, health care access, and to a lesser degree, genetics.[16,17,196] Ethnic/racial minorities tend to have lower SES, increased social barriers to education, less access to quality health care, and more risky behaviors associated with cancer risk (ie. smoking, inactivity, poor diet).[197,198] In regards to CRC, the factors that are speculated to contribute to the differences in cancer survival among race/ethnic groups are access and utilization of early detection screening, quality medical access, treatment, and supportive care and pre-existing co-morbidities such as obesity.[15] However, there is evidence that even after controlling for factors associated with health disparities, minorities, particularly African Americans (AA), are at increased risk for CRC.[101] Such findings indicate that

there are possible unknown mechanisms that perhaps involve differences in body fat distribution, biology and metabolism that increase risk disproportionately for certain race/ethnic groups.

2.7.1. Race/Ethnic Differences in Body Composition of Cancer-free populations

Barreira et al[199] reported race/ethnic body composition differences in cancer-free populations and found that AA women have larger WC, waist-to-hip ratio (WHR), higher BMI and total fat mass (kg) than NHW women, whereas AA men compared to NHW had lower WC, WHR and total fat mass (kg), although in this study, NHW men and women were significantly older.[199] The Pennington Longitudinal Study, examined body composition differences at baseline between AA and NHW and showed that AA men and women had significantly lower BMI and WC than NHW men and women.[200] As in the previous study, AAs were significantly younger than NHW counterparts.[200] Carroll et al (2008) examined various body composition parameters in a sample of AA and NHW men and women and determined that in similarly aged men, NHW men showed trend for higher BMI and WC ($p<0.10$) than AA but no differences in percent of body fat and WHR.[201] In similarly aged, NHW and AA women, this study found no differences in height, BMI, WC, and WHR with the exception of body fat percentage which was significantly higher in AA women (43.9±0.8%) compared to NHW women (39.7±1.5%).[201] Demerath et al[202] studied similarly aged men and women and compared body composition measures and found that NHW men had similar BMI, total body fat, WC and taller than AA counterparts whereas AA females had higher BMI, WC, total body fat and similar height compared to their NHW counterparts.[202] Despres et al (2000) found that AA and NHW males did not differ in weight, BMI, percent body fat and fat mass but AA had smaller WC and WHR than NHW however, in this study, NHW were significantly older than AA (36.2 ±14.8 vs. 32.7±11.9, respectively, $p <0.05$).[56] For females, these researchers reported significantly higher weight, BMI, percent body fat, fat mass, and WC in AA females compared to NHW females of similar age.[56] A study evaluating race/ethnic differences in NHW and AA postmenopausal women of similar age and stature, weight, BMI, total fat mass (kg) and

WC were significantly higher in AA women compared to NHWs.[203] In sum, these studies illustrate various race/ethnic variations in several different body composition parameters between AA and NHWs. Generally, these data suggest that AA females tend to have higher BMI, body fat, and WC than NHW women whereas AA men may have lower WC, WHR, and total fat mass than NHW men.

2.7.2. Race/Ethnic Differences in Body Composition of CRC populations

To our knowledge, no studies have explicitly explored race/ethnic differences in body composition in patients with CRC. Only one study, after an extensive literature review, has examined race/ethnic differences in body composition related to colorectal adenoma risk which is a precursor for CRC. This study was conducted by Thompson et al (2012) and it was a case-control study exploring racial differences in obesity and adenoma risk in adenoma cases versus adenoma-free controls in AA and NHW men and women.[204] This study showed that WHR was the only measure of obesity associated with increased adenoma risk in AA whereas BMI, WC, waist-to-height ratio, but not WHR were associated with increased risk in NHW cases.[204]

2.7.3. Abdominal Adipose Tissues, Hepatic Fat Content and Race/Ethnicity

Ethnicity and genetic ancestry influence adipose accretion and regional fat distribution. White men have more VAT than AA men even after controlling for total adipose tissue (TAT), sex hormones, age[205] and lower extremity fat.[206] Liver fat content and body fat percentages are significantly higher (p-value <0.001) in Caucasians (12.8 ± 1.7), then Hispanics (10.2 ±1.7) and lowest in AA (1.43±1.9)[207] with similar SAT. A study comparing older (between 70-80 yr) White and AA men, found that AA men had significantly greater intra-muscular adipose tissue (p <0.0001) and lower SAT (p < 0.0001) at all levels of adiposity compared to Caucasians.[208] Interestingly, recent evidence reveals that regional fat distribution appears to track from childhood. Children with African ancestry have lower total abdominal adipose tissue (TAT), VAT, SAT after adjusting for SES, age, gender, height, race, and pubertal status than children with European or

Hispanic ancestry.[209] To date, no studies have explored race/ethnic variation of abdominal adipose depots in patients with CRC.

2.7.3.1. Hepatic Fat Content and Race/Ethnicity

African Americans have less prevalence of NAFLD.[210,211] A study out of California of about 750 people showed that AA had lower prevalence of NAFLD than Hispanics, Asians, and Whites.[211] Furthermore, the lower prevalence of hepatic adiposity in AA was not explained by ethnic differences in BMI, insulin resistance, alcohol consumption, or medication use.[210] The frequency of NAFLD as seen in this study suggests that Hispanics are at greatest risk, followed by Whites, and AA have the lowest risk. Such findings are paradoxical since AA are at highest risk of adenomas and CRC, yet have the lowest risk of insulin resistance, VAT, and hepatic steatosis which are strong determinants of disease risk in Hispanics and Whites. To date, no studies have explored race-ethnic variation of hepatic fat in patients with CRC.

2.8. Summary

Obesity is a risk factor for CRC supported by epidemiological studies and newer emerging evidence. The proposed obesity, pathogenic abdominal fat distribution, hepatic fat infiltration and CRC theoretical framework is summarized in Figure I. Obesity is a heterogeneous condition and the pathology it involves is determined by many factors including genetic predisposition, gender, age, race/ethnicity, physical activity and other behavioral factors. Individuals with an increased propensity to store fat subcutaneously or who have functional SAT compartments that expands via hyperplasia instead of hypertrophy have fewer metabolic disturbances and lower risks. Individuals with disturbances of this process progress to an obesity phenotype characterized by increased VAT accumulation inflammation, insulin resistance, increased HFC leading to a disruption of cellular processes within the colon (increasing inflammation and disruption of normal insulin and hormonal signaling pathways) that are pathogenic in nature and eventually predisposes the individual to increased risk of CRC.

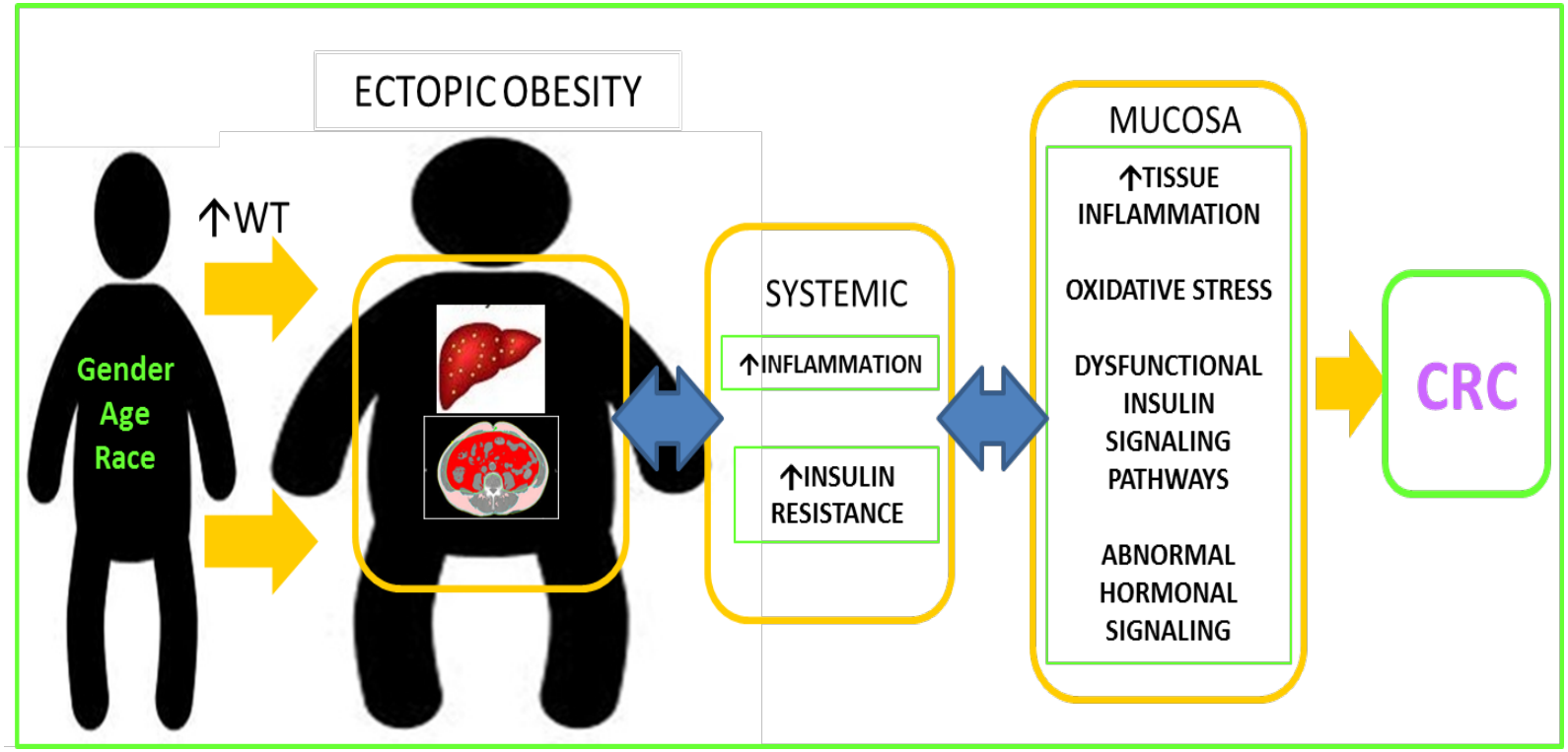

Figure 1. Theoretical framework for research study

III. PILOT STUDY AND PRELIMINARY FINDINGS

A small pilot study was conducted using data collected by Pusatcioglu et al[212] on men (n=14) with incident CRC from the Chicago Colorectal Cancer Consortium (CCCC) with a preoperative abdominal CT scan, serum (glucose, insulin, CRP, IL-6, TNF-α, Bone Morphogenic Protein-2), and colonic tissue (mRNA expression of IL-6, hepcidin, ferroportin, and divalent metal transporter-1). The aims of this study were two-fold: 1) to evaluate the correlations between abdominal fat depots in men with incident CRC and serum and colonic tissue biomarkers of inflammation and iron regulation and 2) to determine if it was feasible to acquire, retrieve and analyze archived CT scans of CCCC study patients.

3.0. Methods of Pilot Study

A cross-sectional CT slice at mid-point of L3 vertebrae was obtained and analyzed using IMAGEJ (NIH) to quantify abdominal circumference (WC, cm) and surface areas (cm^2) for TAT, SAT, SSAT, DSAT, and VAT. Median split for WC (98.9 cm) was used to investigate the influence of excess weight. Serum and tissue biomarkers examined were previously collected and analyzed by Pusatcioglu et al[212].

3.1. Results of Pilot Study

The results showed a mean age (yrs), BMI (kg/m^2), and WC (cm) was 58.4, 26.9, and 103.5, respectfully. The sample was 50% (7/14) African American, 64% Stages I-II and 34% Stages III-IV. TAT and VAT were significantly higher for WC above median-split ($p < 0.05$); BMI correlated with SAT ($r=0.81$, $p<0.001$) but not with VAT ($r=0.34$, $p=0.2301$); WC was correlated with all depots ($r \geq 0.65$, $p<0.01$). Correlations between TAT ($r=0.54$, $p=0.0451$), SAT ($r=0.68$, $p=0.006$), SSAT ($r=0.68$, $p=0.007$), DSAT ($r=0.68$, $p=0.007$) and serum TNF-α occurred but not with VAT ($r=0.02$, $p=0.9425$). No correlations were observed between adipose depots and colonic

tumor tissue biomarkers. Of 15 CRC patients with preoperative CT scans, 14 scans provided good quality images that were analyzed for regional fat distribution and included in this study.

3.2. Conclusions of Pilot Study

Despite our small sample size, significant correlations within adipose depots, BMI and AC were found and SAT was highly correlated with serum TNF-α. VAT was not associated with any tissue biomarker. Overall, it was feasible to acquire, retrieve and analyze scans of CCCC CRC patients. Larger studies assessing this area are needed.

IV. RESEARCH DESIGN AND METHODS

4.0. Study Design

To efficiently address our specific aims *two* distinct study designs were employed. To achieve ***specific aims 1 and 2***, a *case-control design* was used to characterize the relationship between abdominal adipose distribution and CRC and to assess race/ethnic variations. A total of 256 NHW and AA (128 cases and 128 controls) men and postmenopausal women were included in this case-control study. Patients with CRC (cases, n=128) were obtained from two sources: 1) Chicago Colorectal Cancer Consortium (CCCC) Study, (Principal Investigator: Barbara Jung, MD) which examines the genetic and environmental risk factors for CRC and 2) recently diagnosed incident CRC cases available retrospectively from electronic medical records (EMR) at the CCCC affiliated medical centers. The CCCC has established a CRC registry and has a bio-repository database of patients with and without CRC (adenomas and polyp-free) from 6 hospitals including University of Illinois Hospital & Health Sciences System (UIHHSS), Rush University Medical Center (RUMC) and John H. Stroger (JHS). Final entry of cases into the study depended on the availability and quality of archived abdominal/chest/pelvic CT images. Patients without CRC (Controls, n=128) matched to controls (n=128) were obtained from the radiology and medical records databases of two hospitals: UIHHSS and JHS.

To achieve ***specific aim 3***, a *cross-sectional design* was used to describe the association of abdominal adiposity with biomarkers from serum collected from a subgroup of incident CRC cases (N=59; 43 males, 16 females). The study design overview and statistical plan Figure 2.

To achieve specific aim 4, a cross-sectional design was used to assess the feasibility of two techniques to quantify HFC and to determine the prevalence of hepatic steatosis in our sample (cases and controls).

A case-control design was selected for AIMS 1 and 2 because precise documentation of baseline exposure (ie. diagnostic CT images for assessment of abdominal adiposity), major outcomes (ie. CRC risk factors, serum & tissue biomarkers), and many vital confounding factors

(ie. age, gender, BMI, race/ethnicity, health insurance, education) are available for the population selected within the CCCC bio-repository database (cases) and patient electronic medical records (additional cases and controls). A cross-sectional design was selected for AIM 3 because serum samples were obtained at initial colonoscopy appointment and available for cases only. A cross-sectional design for AIM 4 was used because CT images were used to explore the prevalence of hepatic steatosis for each group (cases and controls) separately without further analysis.

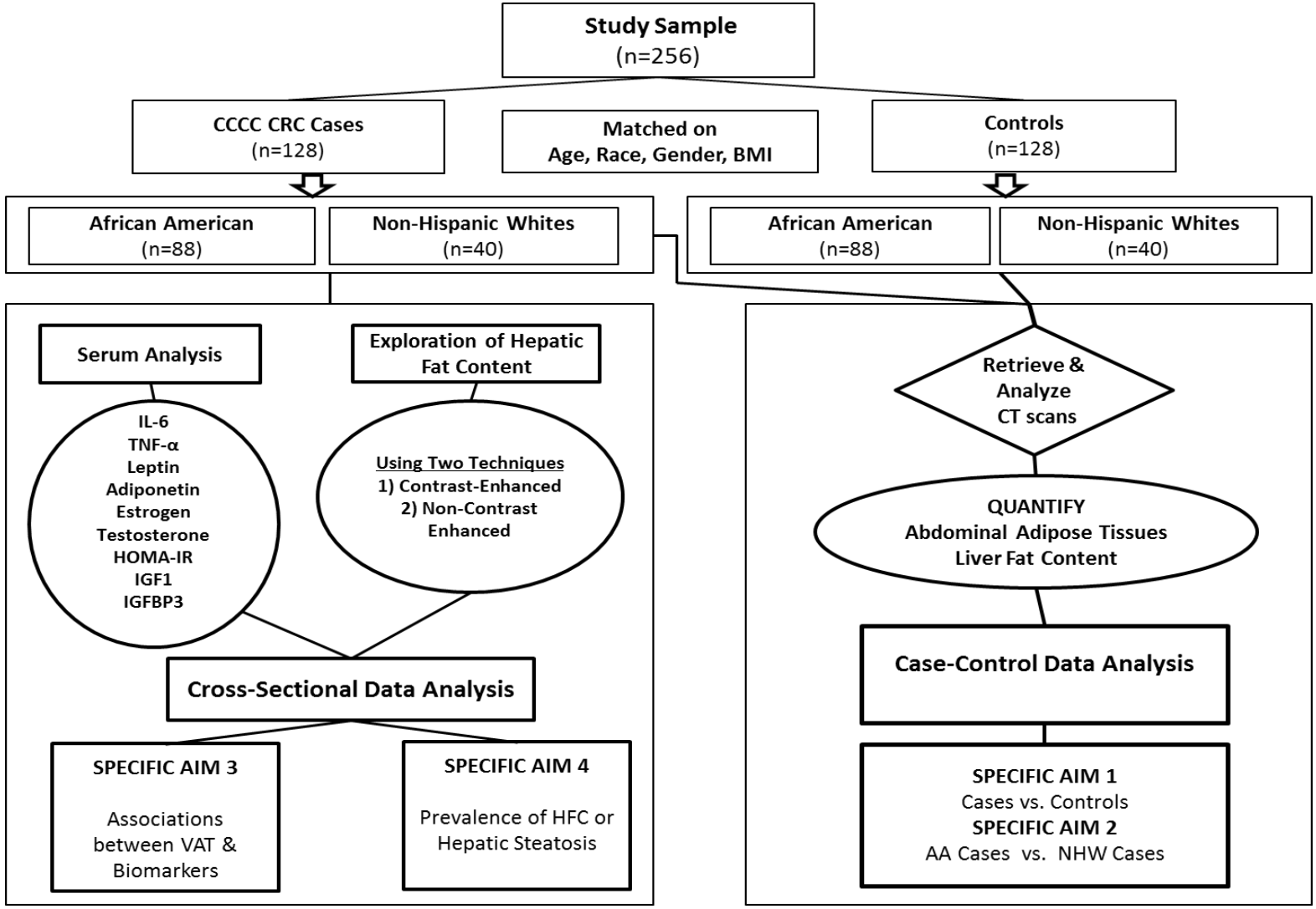

Figure 2. Study design overview and statistical plan

4.1. Study Population

A proportion of cases were identified from the CCCC participants and additional non-CCC cases were identified from EMR. All cases had newly diagnosed (incident) CRC. Controls were individuals without CRC matched for age (up to 5 yrs), race (self-reported African American and Non-Hispanic White), gender, and BMI (up to 0.5 units) to selected cases. All participants (cases and controls) had an abdominal CT scan. Males less than 40 years were excluded because CRC when not hereditary is a disease associated with older age. Females with age greater than 55 were included in an attempt to capture postmenopausal status.

Controls included patients that had a CT scan for diagnostic evaluation of non-cancer medical conditions (eg. abdominal pain, hiatal hernia repair, organ donor or gall bladder surgery). These patients were selected as potential controls because virtually all had diagnostic CT scans are performed routinely for a variety of medical complaints or for surgical planning.

4.2. Setting

The CCCC study enrolls patients from UIHHSS, JHS and RUMC. UIHHS is located three blocks from JHS and treats patients of similar race/ethnic backgrounds and from similar geographic regions. JHS is a Trauma I Center that treats a racially/ethnically diverse population of patients without health insurance from across the City of Chicago, the state of Illinois and Indiana. Similarly, the RUMC is located in the same medical district as UIHHSS and John H. Stroger Hospital however most patients at this hospital have medical insurance.

4.3. Sampling Procedure

4.3.1. Chicago Colorectal Cancer Study and Colorectal Cases

The study flowchart and sampling procedure is explained in Figure III for cases and Figure 4 for controls. Patients screened for CRC were eligible to participate in the CCCC study at participating hospitals (UIHHSS, JHS, RUMC). Following consent, questionnaires were

completed in designated private areas of the clinics and blood draws were obtained prior to colonoscopies or prior to surgery.

4.3.2. Additional Incident Colorectal Cancer Cases

Additional retrospective incident CRC cases with a CT scan from UIHHSS medical records database were obtained using EMR and radiology database review. Of 128 colorectal cancer cases initially obtained from the CCCC study, 38 did not have a CT scan or had a CT scan that did not provide good quality cross-sectional images at L3 and T12L1. Additional cases (non-CCCC) were needed to meet the sample size requirements of power analysis.

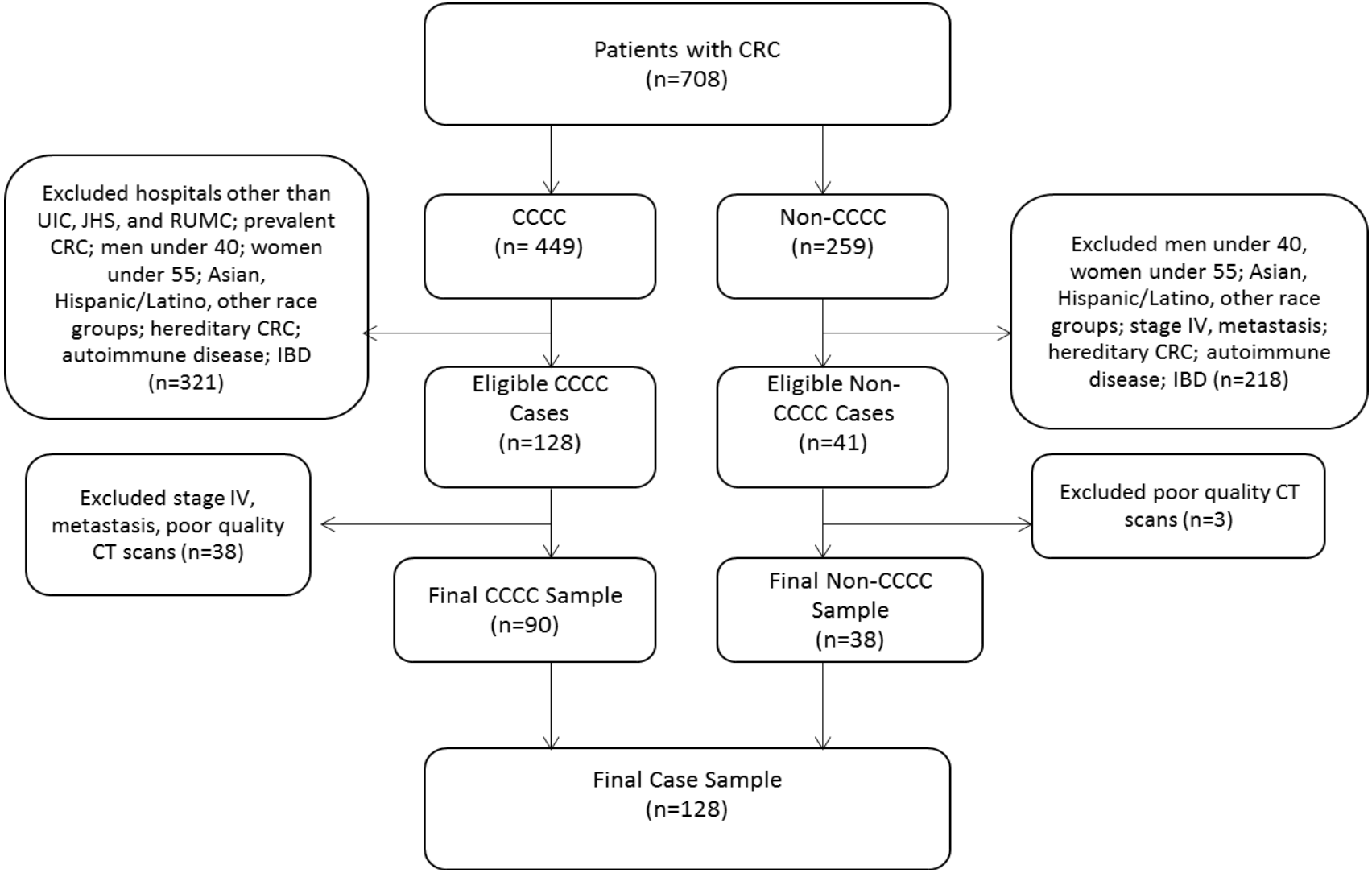

Figure 3. Flowchart and sampling procedure for cases

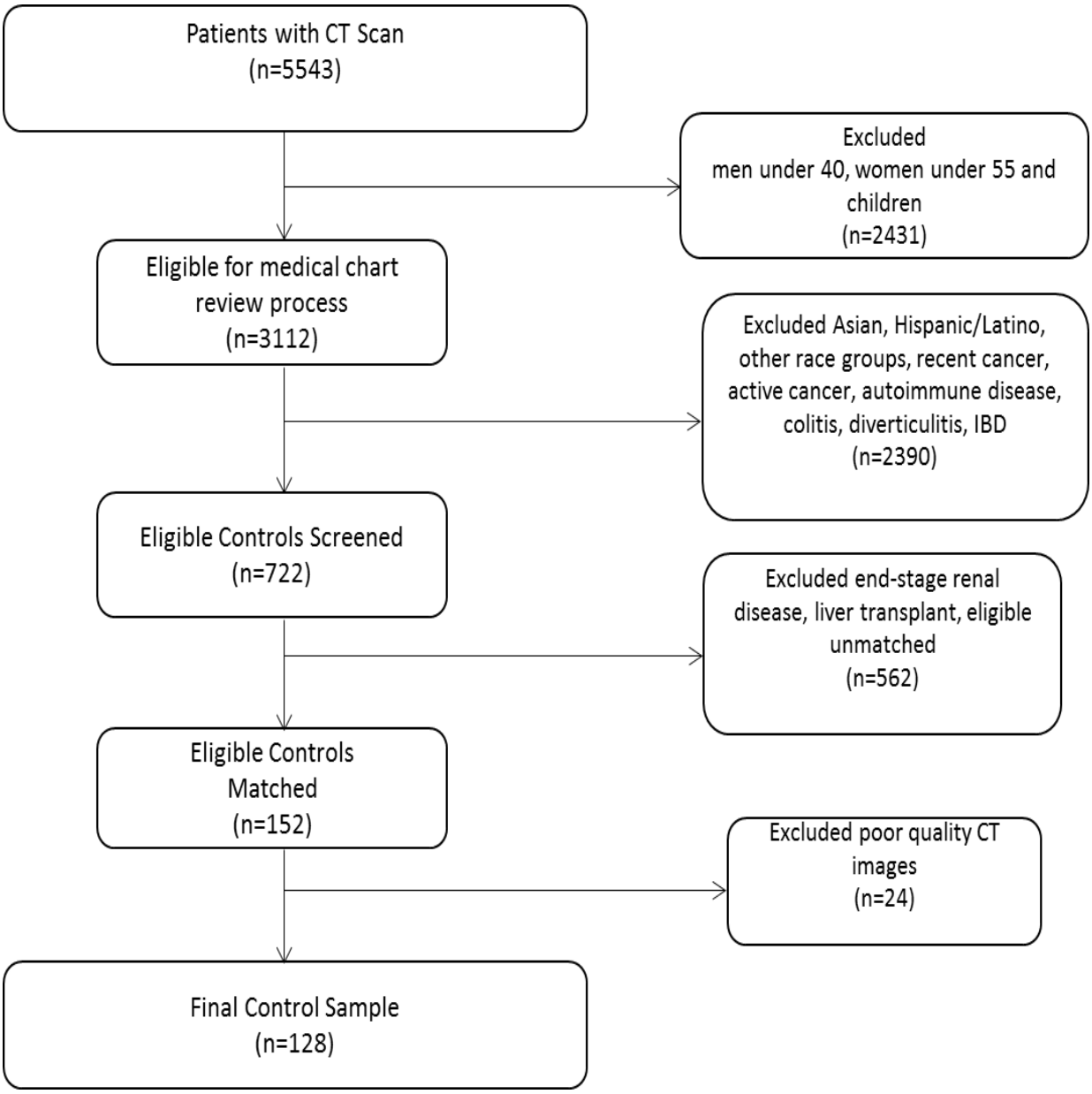

Figure 4. Flowchart and sampling procedure for controls

Controls were obtained (Figure IV) from UIHHSS and JHS hospitals and matched on age, BMI, race/ethnicity and gender. For this study, only cases with a high quality abdominal CT image were included. To achieve specific aim 3, a subsample of cases with CT scans and serum markers of inflammation and insulin resistance were measured from banked blood.

4.3.3. Selection of Controls

All patients requiring a CT scan for a non-cancer medical condition (eg. abdominal pain, hiatal hernia repair or gall bladder surgery) at UIHHSS between 2009 and February 2014 were eligible for consideration and screening process. The radiology databases were reviewed first by initial filter of patients requiring abdominal CT scans for the time period of interest (2009-2014). A medical record review and screening of patients that were age ≥ 40 for males and ≥ 55 for females and exclusion criteria followed (see Appendix C). The final number of qualified sample of controls with an abdominal CT image of high quality for body composition analysis were included in the study. A comprehensive medical records review followed for controls selected for the study for demographic information and medical history of interest.

4.3.3.1. Inclusion Criteria for Cases and Controls

Cases: Male Patients (≥40 yrs old) and female patients (≥55) with newly diagnosed non-hereditary CRC (Stage 0-III, non-metastatic) obtained from the CCCC bio-repository database at UIHHSS, JHS, or RUMC between the years 2009-2013 with a good quality retrospective CT image were eligible for inclusion. Additional incident CRC cases were determined using same criteria between the years of 2013-2014.

Controls: Male Patients (≥40 yrs old) and female patients (≥55) with a good quality retrospective CT image between 2009-2014 and for abdominal pain, hiatal hernia repair or gall bladder work-up at UIHHSS or JHS were eligible for this study.

4.3.3.2. Exclusion Criteria for Cases and Controls

Cases: Patients with hereditary CRC, with a history of inflammatory bowel disease (ie. Ulcerative Colitis, Chron's Disease), diagnosis of Stage V CRC, end stage renal disease, abdominal gastric surgery or organ transplant were excluded to reduce the influence of advanced disease on inflammation, insulin resistance, and regional fat distribution.

Controls: Patients with a history of recent cancer or active cancer, autoimmune disease, colitis, any IBD (ie. Chron's syndrome) end-stage renal disease, abdominal surgery or organ transplant were excluded.

4.4. Patient Privacy and Informed Consent

The privacy of study participants was protected through the use of assigned research identification numbers. Data was stored in a locked file cabinets to protect the confidentiality of obtained information. This bio-repository information of CCCC study participants and use of CT scans was approved by the Institutional Review Board at UIC (CCCC IRB Protocol # 2010-0168). Additional UIC (IRB Protocol # 2014-0837), JHS (IRB Protocol # 10-142) and RUMC (IRB Protocol # 10031003) approval was obtained under expedited IRB review process at each institution for use of retrospective EMR and CT scan data (APPENDIX C). A waiver of informed consent and HIPAA was obtained at each site (for retrospective use of protected health information). CT images were transported in password-protected, encrypted flash drives (Sandisk® Secure Access™ by YuuWaa). Computers containing the CT imaging software, SliceOmatic (TomoVision, Magog, Canada) and IMAGEJ (NIH) were password protected and encrypted with PGP Whole Disk Encryption (Symantec Corporation, Mountain View, CA).

4.5. Sample Size Estimation

The sample size for cases in this study was based on the number of incident CRC cases in the CCCC bio-repository database with an abdominal CT scan (N=128). Given this restriction, the statistical power it provided for specific aims 1 and 2 were determined to discern if it was

sufficient to detect adequate effect size differences between comparison groups. For **AIM 1**, sample size was determined based on VAT and disease status (cases vs. controls). For **AIM 2**, sample size was determined based on VAT and disease status (cases vs. controls) by race/ethnicity. We powered on our primary and secondary aims, the sample size for Aims 3 and 4 were based on availability.

Determination of sample size (***128 in each group per disease state: cases and controls for a total N of 256***) for **AIM 1** is based on VAT means and SDs from Yamamoto et al[1] and Oh et al[99] case-control studies of VAT areas with early CRC. The effect size for differences between cases (140±42 cm^2) and controls (115±54cm^2) was 25 cm^2 for VAT area for the Yamamoto et al study. A sample size of 59 per group is sufficient for identifying an effect size of this order of magnitude or larger with 80% statistical power based on a paired t-test at the 5% level of significance. This sample size estimation was based on a Japanese population. The effect size for determination of differences between cases (124.8±49.8) and controls (99.7±51.6) was 25.1cm^2 for VAT according to results published by Oh et al. A sample size of 64 per group is sufficient for identifying an effect size of this order of magnitude or larger with 80% statistical power based on paired t-test at the 5% level of significance. This sample size estimation was based on a Korean population. It was anticipated that AA and NHW patients in this study would be more heterogeneous, therefore, to account for this, the entire sample size based on the possibly eligible AA and NHW ***CRC cases (n=128)*** of the CCCC study were matched to an equal number of AA and NHW ***controls (n=128)*** to address **AIM 1**.

Determination of sample size (***27 males and 51 females in each group per race/ethnicity within cases and controls***) for **AIM 2** was based on rates of clinically detected differences for means and SDs for the area of VAT reported by Katzmarzyk et al [7] comparing NHW males (mean age: 44.9 ± 13.4 years) and AA males (mean age: 38.4±13.9 years) and between AA and NHW females (mean age NHW: 48.9±11.0 years; mean age AA: 40.8±11.4

years)**.** Thirteen percent of the AA females and 41% of the NHW females in their study were postmenopausal. Based on a mean VAT area in males of 148.6 ± 73.4 cm^2 in NHW and 97.7± 63.9 cm^2 in AA**, 27 men/ethnic group are needed** to detect this difference with a significance level of 0.05 and a power of 0.80 within cases and controls. In females based on a mean VAT area of 126.8 ± 63.7 cm^2 in NHW and 96.7± 50.7cm^2 in AA**, 51 women/ethnic group are needed** to detect this difference with a significance level of 0.05 and a power of 0.80 within cases and controls. The females in this study were more heterogeneous than those included in Katzmarzyk et al. due to matching and restriction to postmenopausal status. *The initial CCCC sample provided 32 AA and 12 NHW female CRC patients with a CT scan indicating insufficient sample size to explore AIM 2 in females. Despite insufficient power, results obtained from our investigation provide much needed data for sample size determination for future studies with a CRC focus conducted in older female populations.*

V. MEASUREMENT OF VARIABLES

5.0. Demographic Information, Medical History and Clinical Data

Demographic and medical information including age, marital status, race/ethnicity, level of education, employment status, blood pressure, family history of cancer and medical history of major chronic diseases (diabetes, cardiovascular disease), history of GI malignancies, medication use (anti-inflammatory agents), smoking/alcohol history, self-reported unintentional weight loss within the past 6 months (yes/no) and history of physical activity were obtained from the CCCC database and hospital EMR (see Appendix A) when available.

5.1. Height and Weight

Height and weight were obtained from the hospital medical records for controls and for additional CRC cases. For the CCCC cases, height was obtained from medical records and weight was measured wearing minimal clothing at bedside to the nearest 0.1kg or obtained from medical records and recorded into the CCCC research database.

5.2. Body Mass Index (BMI)

Body mass index was calculated using the height and weight corresponding to the weight and height nearest to CT scan date for cases and controls. BMI was calculated according to Quetelet's index: weight (kg)/stature $(m)^2$ classified according to the NIH guideline. [213] Body mass index was classified according to the guidelines where individuals with a BMI of 18.5-24.9 were normal weight, those with BMI 25.0-29.9 were overweight, while those with a BMI of 30.0 or above were obese.

5.3. Tumor Localization/Staging

Staging of tumors was obtained from the pathology report. Localization was categorized as left sided colon (splendic flexure, descending, sigmoid, rectum, recto-sigmoid) or right sided (transverse, ascending, hepatic flexure, cecum) whenever possible. Staging was based on the TNM guidelines.

5.4. Biomarkers in Serum

The following serum biomarkers were analyzed from fasting samples collected from incident CRC cases at endoscopy or pre-surgery. Postulated mechanisms of these biomarkers and carcinogenesis were discussed in the literature review, however, additional information and rationales for each are included in this section. Duplicate assay measurements were performed for all serum biomarkers.

5.4.1. Fasting Glucose

Rationale: Elevated fasting glucose levels are associated with increased risk of several gastrointestinal cancers including colon cancer in both men and women.[214] A subsample taken from the longitudinal study, Women's Health Initiative showed that baseline glucose levels in postmenopausal women were positively associated with colorectal cancer risk whereas serum insulin and HOMA – IR were not.[215] The normal range for fasting glucose is < 100 mg/dL.

Technique: Fasting glucose values was obtained from CCCC bio-repository database for cases or from EMR for additional cases enrolled.

5.4.2. Interleukin-6

Rationale: Interleukin-6 (IL-6) has been identified as independent predictors of CRC risk and poor post-surgical outcomes and survival.[140] **Technique:** Interleukin-6 was measured using the R&D systems Quantikine® High Sensitivity ELISA kit for human IL-6 (R&D Systems, Minneapolis, MN) using 200-300 µl of serum by the Fantuzzi lab in the Department of Kinesiology and Nutrition at UIC**.** The sensitivity of this assay is 0.7pg/m. The normal range for serum IL-6 in healthy populations is 0.48-9.96pg/mL based on ELISA kit reference range.

5.4.3. Tumor Necrosis Factor – α

Rationale: TNF-α has been identified as independent predictors of CRC risk and poor post-surgical outcomes and survival[140]. **Technique:** Tumor necrosis factor-α was measured using

the R&D systems Quantikine® ELISA kit for human TNF(R&D Systems, Minneapolis, MN) using 200-300 µl of serum by the Fantuzzi lab in the Department of Kinesiology and Nutrition at UIC**.** The sensitivity of this assay is 0.7pg/mL. The normal range of circulating TNF-α is 1.6 - 15.6 pg/mL based on ELISA kit reference range.

5.4.4. Systemic Estradiol levels

Rationale: Obesity alters estrogen levels.[216] Several large clinical and population-based studies observed that estrogen positive females (hormone replacement therapy or oral contraceptives) have reduced risk of CRC compared to estrogen negative females (non-users).[182,183] However, other studies have demonstrated that elevated estradiol concentrations are a risk factor for CRC.[217,218] Estrogen appears to have a role in CRC but whether that role is protective or harmful needs to be determined. **Technique:** Estradiol was assessed using Estradiol ELISA Kit (Diagnostic Automation/Cortez Diagnostics, Inc**.** USA) using 25 µl of plasma. The assay was done in duplicate by the Fantuzzi lab in the Department of Kinesiology and Nutrition at UIC. The sensitivity of the assay is 10 pg/mL. The normal range for circulating estrogen levels were 15-100pg/mL for males and 15-90 pg/mL for postmenopausal women based on ELISA kit reference range.

5.4.5. Systemic Testosterone levels

Rationale: Testosterone concentrations are altered in obesity in both genders.[219,220] Available research suggests that testosterone is protective against CRC in men [191], however, it decreases with increasing visceral obesity [192,193] and naturally with increasing age.[221] **Technique:** Testosterone will be assessed using Testosterone Elisa Kit (**Diagnostic Automation/Cortez Diagnostics, Inc**. USA) using 25 µl of plasma. The assay was done in duplicate by the Fantuzzi lab in the Department of Kinesiology and Nutrition at UIC. The sensitivity of the assay is 0.17pg/mL. The reference range for testosterone is 0.01-34.1pg/mL based on ELISA kit reference range.

5.4.6. Leptin

Rationale: Leptin is elevated in obesity and is positively associated with CRC.[222] **Technique:** Plasma Leptin was assessed using R&D systems Quantikine® Solid Phase Sandwich ELISA kit for human leptin with 10 µl of plasma or serum. The sensitivity for this assay is 5.5pg/ml. The reference interval of leptin is less than 7.8 pg/mL based on ELISA kit reference range.

5.4.7. Adiponectin

Rationale: Adiponectin is a marker of insulin resistance and inflammation.[151,223] Levels are low in obesity, diabetes and in patients with CRC.[155,224] **Technique:** Serum Adiponectin was assessed using R&D systems Quantikine® ELISA kit for human adiponectin with 10 µl of plasma or 10µL serum by the Fantuzzi Lab. The sensitivity for this assay is less than 0.891ng/mL. The normal range of adiponectin is 0.87-21.42µg/mL based on ELISA kit reference range.

5.4.8. Glucose Homeostasis

Rationale: Epidemiologic studies conducted in the US, Europe, and Asia have consistently shown T2DM increases the risk for CRC.[31,158,159] The individual metabolic consequences of T2DM including hyperinsulinemia, insulin resistance and elevated fasting blood glucose levels, associate with increased CRC risk [160-162] in both genders however the associations are greater in men.[159] Similarly, colorectal adenomas, a precursor of CRC, have been associated with elevated insulin levels and insulin resistance.[100,163] Therefore, we used glucose and insulin levels to estimate insulin resistance using the Homeostasis model assessment (HOMA-IR) of insulin sensitivity. This calculation is a simple and inexpensive alternative to more sophisticated techniques. This method derives an estimate of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations.[225] The equation is as follows: *HOMA-IR= Fasting Glucose * Fasting Insulin/405.* **Technique:** 100µl of serum was used to measure insulin using an ELISA by the Fantuzzi Lab in the Department of Kinesiology and Nutrition at UIC. Fasting

glucose levels were recorded from the clinical diagnostics before the endoscopy. The sensitivity of this assay is 0.5uU/mL and the normal level for insulin is 5-35 uU/mL based on ELISA kit reference range.

5.4.9. Insulin-like-growth factor – 1 (IGF-1)

Rationale: IGF-1 is a peptide hormone that binds to the IGF-1 receptor and initiates a host of intracellular signaling pathways involved in carcinogenic processes like cellular growth and proliferation.[173] IGF-1 along with insulin inhibit the production of sex hormone binding globulin (SHBG) in the liver and stimulates the ovaries to produce sex steroids which are known to promote proliferation and decrease apoptosis.[170] High levels are associated with tumor growth in cell and animal studies.[226] Higher circulating levels of IGF-1 are noted in patients with CRC compared to cancer-free controls.[227] **Technique:** Serum IGF-1 was assessed using R&D Systems Quantikine® ELISA kit for human IGF-1 with 20µL serum by the Fantuzzi Lab. The sensitivity for this assay ranges from 0.007- 0.056ng/mL. The normal level of IGF-1 is 40-258ng/mL based on ELISA kit reference range.

5.5.0. Insulin-like growth factor-binding protein – 3 (IGFBP-3)

Rationale: IGFBP-3 is peptide produced in the liver and appears to have a protective effect against CRC due to its stimulation of apoptosis in colonic epithelial cells.[174] Low levels of IGFBP-3 and high levels of IGF-1 have been associated with increased risk of CRC[174] but these findings are not consistently shown.[228] **Technique:** Serum IGFPB-3 was assessed using R&D Systems Quantikine® ELISA kit for human IGFPB-3 with 10 µl of serum or plasma by the Fantuzzi Lab. The sensitivity for this assay ranges from 0.02- 0.14ng/mL. The normal level of IGFBP-3 is 0.84 – 3.78 µg/mL based on ELISA kit reference range.

5.5. Computed Tomography

The diagnostic pre-surgical CT scans in cases and controls were exploited for assessment of abdominal adipose distribution and hepatic fat content in patients with and without CRC. Use of pre-surgical CT scans archived at three hospitals using different scanners was a limitation of this study. However, adhering to specific anatomical landmarks (ie.T12-L1 for hepatic fat content and L3 for abdominal adipose tissue) and standard analysis protocols we ensured reproducibility of study measures. Validated protocols from researchers in this specialty area were followed for each body fat depot. It is well documented that enhanced or unenhanced CT scans are appropriate to use for abdominal fat quantification, however, for hepatic fat content *only unenhanced CT scans* are recommended. Cross-sectional slice thicknesses, type of scanner (Brand, Model), CT scan protocols (abdominal, abdominal/chest, enhanced, unenhanced) and parameters employed, and CT scan dates were recorded for all patients included in the study. A checklist was developed to collect information about CT scans which was completed prior to abdominal and hepatic fat analysis to document this important information (see Appendix B). CT scans were anonymized using MIMICS® (Materialise HQ, Leuven, Belgium) software or internally by each hospital's PACS administrator.

5.5.1. Computed Tomography Scanners and Settings

Imaging data from multiple scanners were used in this study. A 7-56 HU variation between scanners has been reported.[229] However, we used a body composition analysis software (Slice-O-matic) that allows manual adjustment of tissue thresholds and this software and technique will minimize the effects of HU variation between scanners. CT scanners were calibrated daily at each hospital using standard industry phantoms and each hospital complied with annual physics and state evaluations. The CT data was obtained using 512X512 matrix (100% 256/256), 5mm slice thickness (70%; 179/256, range 1-5mm), 120kvp (90%, 251/256, range 100-140kvp), and 80-698 mA.

5.5.2. Assessment of Good Quality Images

Good quality CT images are important for body composition analysis. Poor images of retrospective CT images can occur for various reasons including patient movement, internal or external artifacts (bullet fragments or metal clips on hospital robes), or size of patient. Each CT image was evaluated for quality based on the following criteria: 1) Is CT image clear of any artifacts? 2) Is complete abdominal perimeter visible? 3) If image has cut-offs, where is it located and what depots are affected? 3) Is SAT easily identifiable? 4) Is VAT easily identifiable? 5) Is SM easily identifiable? Positive answers for questions 1, 2, 4 and 5 resulted in good quality images and thus included in the study. Images with cutoffs on either side or both sides were documented on and evaluated separately during body composition analysis. Only images with complete abdominal perimeter were included for assessment of WC and SSAT.

5.5.3. Quantification of Abdominal Adiposity

The L3 region for abdominal depots was isolated by a radiologist and forwarded to our lab for abdominal fat distribution analysis with Slice-O-matic v4.3 (TomoVision, Magog, Canada) software and IMAGEJ 1.47v (National Institutes of Health, Bethesda, USA) software following standard analysis protocols. These software permits specific tissue demarcation for abdominal adipose tissue by using HU thresholds of -150- to -50 for VAT and -190 to -30 for SAT and IMAT adipose tissue and -29 to +150 for SM. The imaging software quantifies cross-sectional surface areas (cm^2) automatically. Quantification of abdominal adipose tissue adhered to established and published techniques.[61] Trained investigators received formal body composition analysis CT training from experienced trained observer at lab of Vickie Baracos, PhD, Division of Palliative Care Medicine, Dept. of Oncology, University of Alberta (Canada). Trained investigators analyzed each image and performed data quality checks (up to 3 separate evaluations) per method for

Slice-O-matic and two separate evaluations for IMAGEJ and intra-class coefficient of variations were calculated.

5.5.3.1. Slice-O-matic Technique for Computed Tomography Body Composition Analysis

This medical imaging software allows the coloring or 'tagging' of abdominal adipose tissues on the L3 image based on attenuation thresholds as previously described. Thresholds were also adjusted manually to color tissue areas not 'tagging' appropriately. Each abdominal adipose depot and SM was assigned a different color and cross-sectional surface areas (cm^2) for each segmented tissues were calculated. Any abdominal adipose tissue found between the skin and abdominal musculature wall of the L3 image was considered SAT and was tagged in blue/teal. The boundary between SAT and the intra-abdominal cavity was the abdominal SM wall and this was tagged red. The fat deposits seen within the SM was identified as IMAT and this was tagged green. The intra-abdominal fat (VAT) surrounds the organs and found within the intra-abdominal cavity and this was tagged yellow. Once all the abdominal tissues were tagged, the software automatically calculated surface areas and these values were exported to Microsoft Excel for further manipulation. To calculate TAT, the sum of the surface areas of the major abdominal adipose tissues (SAT, VAT and IMAT) of the L3 image were added together (SAT + VAT + IMAT). The L3 image was evaluated three different times as part of the quality assurance process. The intra-individual coefficient of variation for this technique was less than 3%.

5.5.3.2. NIH IMAGEJ for Superficial and Deep Superficial Subcutaneous Analysis

The subtypes of SAT, SSAT and DSAT were calculated using IMAGEJ. This software requires manual tracing using a computer and graphics tablet with stylus interface to quantify cross-sectional surface areas of the L3 image. To calculate SSAT and DSAT, the outer abdominal perimeter was traced and the measures for surface area (mm^2) and perimeter (mm) of this region of interest (ROI) was calculated automatically by the software. Then, a second line was traced following the subcutaneous fascia and this ROI was quantified automatically and recorded. Finally

a third line around the outer abdominal musculature was drawn and measurement was taken. The measures for DSAT and SSAT were then calculated using subtraction process. To calculate SSAT surface area the subcutaneous fascia measurement was subtracted from outer abdominal perimeter and divided by 100 to derive cm^2 unit. To calculate DSAT surface area the outer abdominal musculature measurement was subtracted from subcutaneous fascia and divided by 100 to derive the cm^2 unit. This process was repeated twice for each image and the intra-individual coefficient of variation was less than 2%.

5.6.3. Abdominal Adipose Tissue Ratios

The ratios for various abdominal adipose tissues were determined. Ratios expressed as percentages for VAT, SAT, SSAT and DSAT to TAT were calculated by dividing TAT by these depots and multiplying by 100. The ratio for VAT/SAT was calculated similarly except that SAT replaced TAT in the equation.

5.6.4. Quantification of Hepatic Fat

The T12-L1 intervertebral space for HFC was isolated by a radiologist and forwarded to our lab for quantification of hepatic attenuation with Sliceomatic v4.3 (TomoVision, Magog, Canada). According to Davidson et al, the liver and spleen is visible at T12-L1 intervertebral space in 94% (108 of 113) of women and 96% (122 of 130) of men.[115]

5.6.4.1. Contrast-Enhanced Computed Tomography Image Technique for Quantifying Hepatic Fat Content

Hepatic attenuation in HU using a single cross-sectional slice of T12-L1 region was measured adhering to the HFC calculation by Kim et al[116] and simplified techniques by Monjardim et al[230] for CE images. The HFC calculation for CE images is based on the following equation by Kim et al[116]: $[L - 0.3 \times (0.75 \times P + 0.25 \times A)]/0.7$ where L represents the liver HU, P represents the main portal vein (MPV) HU and abdominal aorta (A) HU. The approach by

Monjardim et al[230] indicates one measure each of aorta, main portal vein and liver. This technique was applied using the geometrical mask feature of Slice-O-matic software. First, a circular ROI capturing most the diameter of each vessel but staying within lumen was drawn on the aorta and then another on the MPV on the CT image. This was followed by a third circular region drawn on the lower lobe of the liver (about 1 cm^2 in diameter) taking care not to include any vessels. The HU for each ROI was then calculated automatically by the software and incorporated into the Kim et al calculation for determination of HFC.

5.6.4.2. Non-contrast Enhanced Computed Tomography Image Technique for Quantifying Hepatic Fat Content

Hepatic attenuation in HU using a single cross-sectional slice of T12-L1 region was measured adhering to protocol as described by Davidson et al [115] for HFC using a NCE CT image. Fatty liver infiltration was assessed by two non-contrast enhanced (NCE) CT criteria previously published: 1) Hepatic attenuation levels ≤40 HU estimates moderate-to-severe hepatic steatosis and 2) liver-to-spleen attenuation ratio ≤ 1.1.[117,118] There is no clear reference standard for measuring hepatic fat content using CT. However, the 40-HU threshold has been tested and re-tested and correlates with a hepatic fat content of ≥30% indicating moderate hepatic steatosis.[118] One trained investigator analyzed each image using the snake and performed data quality checks (up to 2 separate evaluations) per recommended protocol. Radiologists supervised and hepatic fat content analysis and performed data quality checks on analyzed slices.

5.6.5. CT computed Abdominal Circumference

Using IMAGEJ (NIH) software, abdominal circumference was computed using the perimeter of the abdominal cavity at the L3 vertebrae of the abdominal/chest/pelvic CT scan each study participant. The abdominal circumference unit was measured in centimeters (cm). This abdominal circumference was used as a proxy for waist circumference.

VI. STATISTICAL ANALYSIS

The data for CRC cases was entered into Microsoft Excel by CCCC data management team. The data collected at hospitals for the control group was entered in Microsoft Access and Microsoft Excel. Data generated by imaging software was exported to Microsoft Excel. Data was then cleaned and exported for analysis. Data and statistical analyses were performed by using Statistical Analysis System (SAS) 9.3 (SAS Institute Inc., Cary, NC, USA). Variables were examined for presence of outliers and distributions and those that were not normally distributed were transformed to achieve normality. Non-parametric tests were used for variables that did not transform (Wilcoxon signed rank test, Mann-Whitney U test, Spearman Correlation).

6.0. Basic Statistics Overview

Standard descriptive statistics were used to summarize distributions for continuous and categorical variables. Means, medians, standard deviations, interquartile ranges, and standard errors were calculated for continuous variables (age, height, weight, BMI, abdominal adipose tissue surface areas, serum and tissue biomarkers, systolic and diastolic blood pressure). For data uniformity, data was presented as medians and interquartile ranges in tables. Frequencies and percentages were calculated for categorical variables (race/ethnicity, gender, marital status, level of education, history of GI malignancies, medical history, use of anti-inflammatory agents, smoking/alcohol history, unintentional weight loss, cancer stage). Descriptive statistics were examined based on gender, race/ethnicity, BMI and weight loss status. Level of significance were defined as p-value less than 0.05. The Bonferroni adjustment for statistical significance based on three hypotheses being tested is $p<0.017$.

Pearson and/or Spearman correlation (non-parametric) correlation coefficients were used to quantify the relationships between continuous and non-parametric variables. Collinearity was determined for variables using a correlation matrix. Variables with correlation >0.8 were not included in the same model. Variance inflation factors were evaluated for variables in regression

models. A VIF >4 is consistent with severe collinearity[231]. The highest collinearity encountered for any variable in our analysis was 2.5.

Simple and multiple linear regression and logistic regression were used to determine the effect of the exposure variables on the outcome variable with and without controlling for other covariates. In this study, age, race/ethnicity, gender, BMI, smoking/alcohol history and unintentional weight loss were potential confounders. These were controlled for doing analysis or with stratification according to potential dichotomous confounders (eg., gender, race/ethnicity, unintentional weight loss) evaluating its confounding effect. Model diagnostics were conducted to verify fitted models.

Variable entrance requirements in regression were based on collinearity, statistical significance and influence on the adjusted R-square of the model. Only variables with collinearity less than 0.80 entered into the models. Variables with statistically significant p-values (<0.05) after determination by Stepwise and Forward selection remained in the model. Variables making it into the final model but not statistically significant remained in the model only if their inclusion improved model fit (adjusted R-square changed dramatically). The best subset of variables remaining in the models were presented in results.

6.1. Case-Control Analysis: Specific Aims 1 & 2

Analysis between cases and controls was limited by the information available in medical records for controls and for additional cases. Matching variables to explore these hypotheses were age, gender, race/ethnicity, SAT and VAT. The main exposures were abdominal fat distribution: VAT (pre-operative diagnostic CT scan for quantification of abdominal adipose tissues) and other abdominal adipose tissues. The main outcome was CRC (yes/no) for logistic models. Matching variables, exposures and outcomes for AIM 2 were exactly the same as described under AIM 1. Statistical analyses for AIMS 1 and 2 were the same with the exception that for AIM 2, the analyses were stratified by race/ethnicity.

6.1.1. Statistical Analysis for AIM 1 and AIM 2

The goal of this aim was to determine if there is a unique abdominal and hepatic fat distribution phenotype in patients with CRC. For *comparisons between CASES and CONTROLS,* paired t-test, Wilcoxon signed rank test (continuous VAT) and McNemar test were conducted for comparisons between matched CRC cases to control pairs with McNemar test used for dichotomous variables: health insurance (yes/no), current smoker (yes/no), alcohol consumption (yes/no), level of education (≥High school vs <HS), medical history of diabetes (yes/no), medical history of hypertension (yes/no), and aspirin use (yes/no). *Conditional Logistic Regression between CASES and CONTROLS* was used to determine predictors of CRC. Forward selection method was used to identify significant predictors. The following variables included in selection method were median splits of abdominal adipose tissues, health insurance, smoking/alcohol history, level of education, medical history of diabetes and/or hypertension, self-reported unintentional weight loss and aspirin use.

The goal of AIM 2 was to discern if patients with CRC retain the racial variation in body fat depots that exists in healthy populations. For comparisons between CASES and CONTROLS we applied the same statistical strategies as described for AIM 1 stratified by stratified by race/ethnicity.

6.2. Cross-sectional Analysis: Specific Aim 3

This cross-sectional analysis was limited to cases only. Controls did not have serum available.

6.2.1. Statistical Analysis for AIM 3

The goal of this aim was to discern the associations between abdominal adipose depots and HFC on biomarkers of CRC risk in serum and non-tumor tissues and explore if these relationships are modified by race/ethnicity. Independent t-tests were used to examine the unadjusted difference of VAT and biomarkers in serum of normally distributed continuous

variables stratified by race/ethnicity. A non-parametric tests were used for variables that did not achieve normality following transformation. Simple and multiple linear regression model was used to examine the associations between VAT and other abdominal adipose depots with serum biomarkers for normally distributed continuous variables controlling for gender, age, and race. Stepwise and Forward selection methods were used to identify significant predictors of serum biomarkers. Pearson's product-moment and Spearman correlation analysis was used to explore associations between continuous variables and non-parametric variables, respectively.

6.3. Exploratory Analysis for AIM 4

This analysis is limited to participants (cases and controls) with a cross-sectional slice for liver, set at T12L1. There were a few images available for patients at T11, T10 or T12, however these were not included in the analyses. CT scans for cases were mostly contrast-enhanced (CE). Therefore, for hepatic fat analysis there were images with or without contrast enhancement. Both CE and non-contrast enhanced (NCE) techniques for evaluation of hepatic fat content will be utilized to explore the extent of hepatic fat content in cases and controls. The goal of this aim was to explore HFC in patients with and without CRC using two methods for evaluation for contrast and non-contrast enhanced CT images. Frequencies (%) of patients with hepatic steatosis for each HFC approach were determined. Descriptive statistics (medians, interquartiles) were generated for gender, race/ethnicity, obesity status, cancer stage, current smoker, alcohol consumption, medical history of diabetes and hypertension and unintentional weight loss of cases included in this analysis.

VII. RESULTS

The results for each specific aim and corresponding hypotheses are presented in this section. An overview of basic demographics and description of the study population introduces the section followed by Specific Aims 1-4, in chronological order. The appendix section contains supplemental analyses, which include additional tables and figures for each of the specific aims. This supplemental data provides additional information of results that are not addressed in Specific Aims 1-4.

7.0. Characteristics of Study Population

Approximately 79% (176/256) of our sample was AA and 63% (158/256) were male. Table I contains additional data on demographic, anthropometric and abdominal parameters for cases and controls. Briefly, the median age, BMI and WC of cases (62 years, 27 kg/m^2, and 103.9cm, respectively) and controls, (61 years, 27 kg/m^2, and 105cm, respectively) were very similar, as designed. Additionally, 28% of cases and 31% of controls were obese (BMI≥30kg/m^2). Most participants were either married (27%, 35/128) or single (44%, 56/128). Insufficient data on education (Table 1) was determined during analysis therefore this variable is incomplete and will be excluded from models. Available data on education suggests that 67% (86/128) of cases and 33.5% (43/128) completed high school. Cases and controls were also similar for smoking (approximately 27% (35/128), were current smokers. Overall 29% (37/128) of the cases and 86% (110/128) of controls had health insurance, however this variable was collected prior to and during the transition of the new health care law, therefore, it may not be an accurate measure of health insurance and a proxy for socioeconomic status. Due to the inconsistency, it was not included in the models. Table II shows results the prevalence of medical conditions, specifically diabetes and hypertension, as well as self-reported unintentional weight loss (within the last 6 months). Approximately 24% (31/128) of cases and 26% (33/128) of controls had medical history of

diabetes whereas 64% (82/128) of cases and 64% (85/128) of controls had HTN. Unintentional weight loss was reported in 31% (39/128) of cases and 9% (12/128) of controls.

7.0.1. Correlation Analysis of Body Composition Variables and Age

Correlation analysis was used to examine the associations of body composition variables with each other and with age. As expected, abdominal adipose tissues were highly correlated. Collinearity (r>0.80) was apparent between TAT and other abdominal adipose tissues with the exception of IMAT (r=0.66). Waist was highly correlated with TAT(r=0.88), SAT(r=0.76) and VAT (r=0.79). As expected SAT was highly collinear with SSAT(r=0.89) and DSAT(r=0.92). Only IMAT was significantly correlated with age (r=0.28). BMI was less correlated to VAT (r=0.52) than waist but association was still significant.

TABLE I

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION OF CASES AND CONTROLS[a]

	Cases (n= 128)	**Controls (n= 128)**	**p- value[c]**
Demographics & Anthropometrics	**Median(IQ) or %(n)**	**Median(IQ) or %(n)**	
Age (yrs)	62(10)	61(11)	0.1278
Height (cm)	170(15)	173(15)	**0.0087***
Weight (kg)	79(23)	80(26)	**0.0181***
BMI (kg/m^2)	27(7)	27(6)	0.8582
WC[b] (cm)	99.7(17)	105.2(17)	0.0529
Males, yes	61.7(79)	61.7(79)	NS[d]
African Americans (AA), %(n)	68.8(88)	68.8(88)	NS[d]
Non-Hispanic Whites (NHW), %(n)	31.3(40)	31.3(40)	NS[d]
Normal BMI (18.5-25), %(n)	30.5(39)	29.6(38)	NS[d]
Overweight BMI (25-30), %(n)	40.6(52)	39.8(51)	NS[d]
Obese BMI (≥30), %(n)	28.9(37)	30.5(39)	NS[d]
Cancer Stages 0-I, %(n)	25.6(33)	Not Applicable	---
Cancer Stage 2 (II, IIA, IIB, IIC), %(n)	33.6(43)	Not Applicable	---
Cancer Stage 3 (III,IIIA, IIIB, IIIC),%(n)	33.6(43)	Not Applicable	---
Married, yes,%(n)	27.6(35)	38.5(47)	---
High School of higher, yes, %(n)	67.2(86)	33.5(43)	0.6423
Health Insurance, yes, %(n)	28.9(37)	85.9(110)	**0.0001***
Current Smoker, yes, %(n)	27.3(35)	27.5(35)	NS[d]
Alcohol consumption, yes, %(n)	36.7(47)	36.7(47)	NS[d]
Abdominal Depots			
TAT(cm^2)	297(250)	339(249)	0.0601
SAT (cm^2)	159(117)	181(154)	**0.0105***
SSAT (cm^2)[b]	95(60)	121(80)	**0.0058***
DSAT (cm^2)	76(58)	87(74)	**0.0164***
VAT (cm^2)	87(131)	106(129)	0.6009
IMAT (cm^2)	14(14)	15(13)	0.7944
SM (cm^2)	147(55)	157(62)	**0.0100***
VAT/TAT	34(28)	32(26)	0.3181
VAT/SAT	56(78)	49(66)	0.1471
SAT/TAT	60(29)	64(23)	0.1916
SSAT/TAT[b]	43(27)	42(23)	0.5170
DSAT/TAT	27(13)	28(12)	0.2029

[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 =103 per group.

[c]Significant p-value < 0.05.

[d]NS = not significant.

TABLE II

CLINICAL CHARACTERISTICS AND UNINTENTIONAL WEIGHT LOSS[a]

	Cases (n= 128) %(n)	**Controls (n= 128) %(n)**	**p-value[b]**
Daily Aspirin Use, yes	36.7(47)	28.9(37)	0.2752
Diabetes, yes	24.2(31)	25.8(33)	0.8026
HTN, yes	64.1(82)	66.4(85)	0.8129
Unintentional Weight Loss, yes (within 6 months)	30.5(39)	9.4(12)	**0.0001***

[a]McNemar test used to examine differences of categorical variables

[b]Significant p-value < 0.05.

TABLE III

PEARSON CORRELATION MATRIX OF AGE AND ABDOMINAL ADIPOSE TISSUES[a]

	AGE	**BMI**	**WAIST**	**TAT**	**SAT**	**VAT**	**IMAT**	**SSAT**	**DSAT**
AGE	1								
BMI	-0.06	1							
WAIST	0.07	0.71**	1						
TAT	0.01	0.76**	0.88**	1					
SAT	-0.03	0.76**	0.76**	0.88**	1				
VAT	0.05	0.52	0.79**	0.83**	0.56**	1			
IMAT	0.28**	0.46**	0.61**	0.66**	0.56**	0.59**	1		
SSAT	-0.003	0.59**	0.67**	0.71**	0.89**	0.43**	0.46**	1	
DSAT	0.06	0.69**	0.83**	0.86**	0.92**	0.59**	0.60**	0.80**	1

**Significant p-value <0.01.

[a]Transformed variables used in analysis.

7.1. Specific Aim 1. Is there a unique body composition phenotype in cases?

We matched cases and controls for age, gender, race/ethnicity and BMI therefore these parameters were omitted from multiple regression and conditional logistic models. Results are presented first comparing cases to controls followed by stratification by gender.

7.1.2. Comparisons of Body Composition between Cases and Controls and Gender

The median surface areas (cm^2) for the abdominal adipose tissues and abdominal adipose tissue ratios (VAT/TAT, VAT/SAT, SAT/TAT, SSAT/TAT and DSAT/TAT) presented as percentages are compared in Table I. Contrary to our hypothesis, VAT did not differ significantly overall between cases and controls (p-value=0.6009). Abdominal adipose tissue SAT, SSAT & DSAT which were significantly lower in cases. Cases were found to have significantly lower SM (p-value = 0.01*)*. Further stratification by gender, indicated some differences between male cases and controls, between male and female cases, and between male and female controls (Table IV). Overall, VAT was not statistically different for either gender between cases and controls. Other abdominal parameters were also similar with the exception of SSAT which was statistically (p=0.005) lower in male cases (88cm^2) compared to controls (112cm^2). Significantly lower SAT (p=0.032) and SM (p=0.05) were also observed in male cases compared to controls. No differences between cases and controls for any abdominal adipose parameters occurred in women. As expected statistically significant differences between females and males were observed in SAT, SSAT, DSAT (male vs female cases only), VAT, SM and ratios (VAT/TAT, VAT/SAT, SAT/TAT, SSAT/TAT and DSAT/TAT) within case and control groups. Females have higher SAT, SSAT, DSAT and less VAT and SM than males. Female cases had significantly higher SAT (228cm^2) than male cases (133cm^2) but significantly less VAT (68cm^2 vs 140cm^2). Female controls had significantly less VAT (86cm^2 vs 149cm^2) and significantly higher SAT (197cm^2 vs 170cm^2) than male counterparts.

TABLE IV

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION BY GENDER OF CASES AND CONTROLS

	Male Cases (n=79)	Male Controls (n= 79)	Males Cases vs Controls	Female Cases (n=49)	Female Controls (n=49)	Females Cases vs Controls[a]	Males Cases vs Cases[b]	Males Controls vs Controls[c]
Demographics and Anthropometrics	**Median (IQ)**	**Median (IQ)**	**p- value**	**Median (IQ)**	**Median (IQ)**	**p-value**	**p- value**	**p-value**
Age (yrs)	62(11)	61(14)	0.1448	61(9)	60(9)	0.5677	0.8909	0.6349
Height (cm)	175(10)	178(10)	**0.0438***	160(8)	162(8)	0.0996	**<.0001***	**<.0001***
Weight (kg)	84(18)	87(24)	**0.0383***	68(19)	71(19)	0.7600	**0.0005***	**<.0001***
BMI (kg/m^2)	27(5)	27(6)	0.7237	95(13)	26(7)	0.5618	0.5755	0.9492
WC (cm)[c]	101(17)	107(18)	0.1048	95(13)	100(17)	0.2941	**0.0480***	0.0609
Abdominal Depots								
TAT(cm^2)	294(294)	347(259)	0.2904	303(193)	328(217)	0.0724	0.5347	0.7841
SAT (cm^2)	133(91)	170(134)	**0.0318***	228(133)	197(179)	0.1558	**<.0001***	**0.0073***
SSAT (cm^2)[c]	88(39)	112(65)	**0.0005***	137(69)	146(87)	0.8345	**<.0001***	**0.0155***
DSAT (cm^2)[c]	67(49.8)	176(35)	**0.0396***	86(58)	93(76)	0.2099	**0.0372***	0.2721
VAT (cm^2)	140(23)	149(152)	0.9316	68(74)	86(70)	0.2063	**0.0018***	**0.0040***
IMAT (cm^2)	15(14)	12(16)	0.3746	12(12)	18(9)	0.1128	0.5444	0.0813
SM (cm^2)	162(38)	176(35)	0.1035	109(27)	115(24)	0.0356	**<.0001***	**<.0001***
VAT / TAT (%)	44(23)	40(21)	0.1079	21(16)	22(9)	0.4761	**<.0001***	**<.0001***
VAT / SAT (%)	90(92)	74(75)	**0.0498***	29(31)	31(19)	0.4389	**<.0001***	**<.0001***
SAT/TAT (%)	50(20)	54(23)	**0.0240***	75(17)	71(10)	0.3489	**<.0001***	**<.0001***
SSAT/TAT (%)**	35(23)	39(24)	0.4501	53(16)	49(19)	0.8388	**<.0001***	**0.0080***
DSAT/TAT (%)	25(12)	28(12)	0.2847	29(11)	29(11)	**0.0492***	**0.0314***	0.4401

[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 DSAT was 68 males per group and 35 females per group.

*Significant p-value < 0.05.

7.1.3. Multiple Regression Analysis of Predictors of Abdominal Adipose Tissues

Tables V highlights the most significant independent variables determined for each abdominal adipose tissues and SM using Stepwise selection linear regression. Significant predictors of VAT were WC, SSAT, IMAT, CRC (yes/no), current smoker and self-reported history of unintentional weight loss. The model fit improves over WC alone with the addition of each variable. Approximately 66% of the variance in VAT, (F = 57.90, p<0.001, R^2=0.6793, Adjusted R^2=0.6676) was predicted with the final model. Significant predictors of SAT included WC and IMAT. Weight loss history did not enter the model. This model predicted approximately 62% of the variance in SAT, (F=141.90, p<0.0001, R^2=0.6282, Adjusted R^2=0.6237). Significant predictors of DSAT were waist and IMAT which predicted 73% of the variance in DSAT (F=226.53,p<0.0001, R^2=0.7295, Adjusted R^2= 0.7263). Significant predictors of IMAT were VAT, SAT, current smoker and alcohol use. This model predicts 46% of the variance in IMAT (F=36.92, p<0.0001, R^2=0.4708, Adjusted R^2 = 0.4581). Significant predictors of SM were waist, SSAT, IMAT, CRC and diabetes which explained 42% of the variance in SM (F=25.90, p<0.0001, R^2=0.4397, Adjusted R^2= 0.4227).

7.1.4. Unadjusted and Adjusted Conditional Logistic Regression of Body Composition of Cases and Controls and by Gender

Unadjusted conditional logistic regression of median splits of abdominal adipose tissues (Table VI) and WC showed that the crude OR for median VAT (defined as VAT ≥ or < than 94.2cm^2) was 0.32 (p=0.0083), crude OR for median SAT (defined as ≥ or < than 172.9cm^2) was 0.51 (p=0.382), crude OR for median SSAT (defined as ≥ or < than 109.9cm^2) was 0.29 (p=0.0025), and crude OR for median DSAT (defined as ≥ or < than 80.7cm^2) was 0.53 (p=0.0423). Each of these models showed the odds for having lower SAT, SSAT, and DSAT was greater in cases compared to controls.

TABLE V

PREDICTORS OF BODY COMPOSITION PARAMETERS FOR OVERALL CASES AND CONTROLS USING MULTIPLE LINEAR REGRESSION

	Body Composition Parameters					
Variable	**VAT**	**SAT**	**SSAT**	**DSAT**	**IMAT**	**SM**
Intercept	-14.06**	-8.09**	-220.91**	-6.81**	0.85**	5.99**
WC	0.25**	0.18**	3.45**	0.14**		0.12**
VAT			-3.79**		0.11**	
SAT					0.12**	
SSAT	-0.32**					-0.34**
DSAT						
IMAT	0.82**	0.67**	6.87**	0.41**		-0.47**
Smoker (yes/no)	-1.21**				0.28	
Aspirin (yes/no)						
Alcohol (yes/no)					0.30*	
Hypertension (yes/no)						
Diabetes (yes/no)						-0.71**
Unintentional Weight Loss (yes/no)	-1.15*					
CRC (yes/no)						-0.33
N	171	171	171	171	171	171
R^2	0.6743	0.6282	0.5293	0.7295	0.4708	0.4397
Adjusted R^2	0.6644	0.6237	0.5208	0.7263	0.4581	0.4227

*Significant p-value <0.05.

**Significant p-value <0.01

Unadjusted conditional logistic regression models of demographic variables (independent) and CRC (dependent, where Event = 1) variables are shown on Table VI. This analysis revealed

that unintentional weight loss history (Crude OR = 4.1, p=0.0001) and aspirin use (Crude OR = 3.3, p=0.0009) were statistically significant predictors for disease.

Adjusted conditional logistic regression using stepwise selection method determined a main effects model (Table VII) which included SSAT, aspirin, self-reported unintentional weight loss. The odds for taking aspirin for having a history of weight loss and lower SSAT were higher in cases compared to controls. Self-reported unintentional weight loss was a significant confounder between abdominal adipose tissues and CRC in cases compared to controls.

Stratification by gender of adjusted conditional logistic models (Table VII) showed that predictors of CRC for males were IMAT (OR: 2.75, CI: 1.08-7.00, p=0.03), SSAT (OR: 0.22, CI: 0.07-0.70, p=0.01) and unintentional weight loss (OR: 3.92, CI: 1.43-10.74 p = 0.008). For females, the only significant predictor to make it into the model as predictor of CRC was unintentional weight loss (OR: 5.33, CI: 1.55 -18.3, p=0.0078.

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TABLE VI

UNADJUSTED CONDITIONAL LOGISTIC REGRESSION OF ASSOCIATION OF MEDIAN SPLITS OF BODY COMPOSITION VARIABLES AND CRC

	CRC (yes/no)				
Variables[a]	B	OR	Lower CI	Upper CI	p-value
Median WC	-1.15	0.32	0.136	0.745	0.0083
Median SAT	-0.66	0.52	0.277	0.965	**0.0382***
Median SSAT	-1.22	0.30	0.135	0.652	**0.0025***
Median DSAT	-0.63	0.53	0.291	0.978	**0.0423***
Median VAT	-0.29	0.75	0.407	1.382	0.3562
Median IMAT	-0.07	0.93	0.544	1.584	0.7855
Median VAT/TAT	0.26	1.32	0.725	2.389	0.3672
Median VAT/SAT	0.27	0.60	0.316	1.138	0.1178
Median SAT/TAT	-0.51	0.76	0.451	1.274	0.2951
Median SSAT/TAT	0.15	0.76	0.451	1.274	0.2951
Median DSAT/TAT	-0.28	0.32	0.136	0.745	**0.0083***
Smoker	-0.04	0.96	0.555	1.665	0.8886
Aspirin	1.19	3.30	1.626	6.695	**0.0009***
Alcohol	-0.12	0.89	0.505	1.550	0.6684
Hypertension	0.04	1.04	0.589	1.849	0.8840
Unintentional Weight Loss	1.41	4.11	1.984	8.518	**0.0001***

*Significant p-value <0.05.

[a]Median splits defined as: WC = 101.4cm; VAT = 94.2cm^2; IMAT = 14.5cm^2; SAT = 172.9cm^2; SSAT = 109.9cm^2; DSAT = 80.7 cm^2; VAT/TAT = 32.5%; VAT/SAT = 52.1%; SAT/TAT = 61.4%; DSAT/TAT = 27.8%; SSAT/TAT = 42.2%.

TABLE VII

ADJUSTED CONDITIONAL LOGISTIC REGRESSION OF PREDICTORS OF CRC OVERALL AND BY GENDER

		CRC (yes/no)				
	Model	B	OR	Lower CI	Upper CI	p-value
Complete Sample	Median SSAT[a]	-1.66	0.19	0.06	0.65	0.0079
	Aspirin	1.48	4.39	1.78	10.70	0.0012
	Unintentional Weight Loss	2.08	8.01	2.65	24.19	0.0002
Males Only	Median IMAT[a]	1.01	2.75	1.08	7.00	0.0335
	Median SSAT[a]	-1.51	0.22	0.07	0.70	0.0102
	Unintentional Weight Loss	1.37	3.92	1.43	10.74	0.0078
Females Only	Unintentional Weight Loss	1.67	5.33	1.55	18.30	0.0078

*Significant p-value <0.05.

[a]Median splits defined as: SSAT = 109.9cm^2; IMAT = 14.5cm^2.

7.1.5. Subset Analysis of Body Composition and Anthropometrics for Weight Stable Group Overall

Self-reported unintentional weight loss entered the VAT model. A subset of weight stable matched pairs was created to explore possible differences (n=78/group) compared to main study sample (N=128/group). Stratified analysis was performed comparing cases to controls and by gender. Stratified results of the weight stable subset remained virtually identical to findings of the main study sample (Table VIII). Stratified analysis by gender of weight stable group showed significant lower IMAT for female cases compared to controls. The small sample of female cases and controls precluded further evaluation.

TABLE VIII

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION OF SELF-REPORTED WEIGHT STABLE GROUP OF CASES AND CONTROLS

	Cases (n=78)	**Controls (n=78)**	**Cases vs Controls**
Variables	**Median(IQ)**	**Median(IQ)**	**p-values**
Age (yrs)	62(10)	61(12)	0.1380
Height (cm)	170(18)	174(13)	**0.0020***
Weight (kg)	81(21)	84(22)	**0.0127***
BMI (kg/m^2)	28(5)	27(6)	0.7124
WC (cm)**	102(19)	108(16)	0.1596
TAT(cm^2)	334(228)	375(197)	0.1361
SAT (cm^2)	175(126)	192(128)	**0.0115***
SSAT (cm^2)**	105(60)	133(66)	**0.0011***
DSAT (cm^2)	87(57)	94(64)	**0.0356**
VAT (cm^2)	140(176)	131(117)	0.8509
IMAT (cm^2)	15(13)	17(15)	0.1675
SM (cm^2)	147(57)	94(64)	**0.0078***
VAT / TAT (%)	41(29)	34(23)	0.2519
VAT / SAT (%)	76(88)	57(63)	0.1119
SAT/TAT (%)	55(28)	60(21)	0.2180
SSAT/TAT (%)**	36(26)	40(18)	0.8643
DSAT/TAT (%)	26(11)	28(11)	0.3054

*Significant p-value <0.05.

[a]Waist, SSAT, and SSAT/TAT sample size = 64 per group.

7.2. Specific Aim 2. Do patients with CRC retain the racial variation of abdominal adipose tissues observed in healthy populations?

Cases and controls in this study were matched on age, gender, race/ethnicity and BMI, thus these parameters are by design omitted from multiple regression and conditional logistic models. Stratified analysis by race/ethnicity has been conducted to evaluate the predictors of selected variables within each of the race/ethnic groups. For each section the results are

presented for the AA group followed by the NHW group and concludes with a comparison of similarities and differences between the race/ethnic groups.

7.2.1. Comparisons of Body Composition Stratified by Race/Ethnicity

Results of further stratification by race/ethnicity of median and interquartile(IQ) surface areas of abdominal adipose tissues and ratios are presented in Table IX. In support of our hypothesis, VAT was significantly different between AA cases (73cm^2) and controls (87cm^2) compared to NHW cases (162cm^2, p-value = 0.0065) and controls (155cm^2, p-value = 0.0006). WC was also significantly smaller in AAs cases (98cm^2) and controls (101cm^2) compared to NHW cases (109cm^2, p – value = 0.0408) and controls (103cm^2, p-value = 0.0220). IMAT was significantly lower in AA cases (11cm^2) and controls (13cm^2) compared to NHW cases (18cm^2, p-value = 0.0008) and controls (19cm^2, p-value =0.0189). Significant differences between the various body composition derived ratios were noted between AA cases and controls and NHW counterparts. VAT/TAT was significantly lower in AA cases (30%) and controls (28%) compared to NHW cases (43%, p-value = 0.0309) and controls (41%, p-value = <.0001). VAT/SAT was significantly lower in AA cases (48%) and controls (40%) and NHW cases (83%, p-value = 0.0249) and controls (76%, p-value = <.0001).

Additional stratification by male gender (Table X) revealed several significant differences of TAT, VAT, IMAT, SM and ratios between groups. Primarily, VAT was statistically different only between AA male (114cm^2) and NHW male (180cm^2) controls (p-value = 0.0014). VAT was not significantly different between AA male cases (98cm^2) and AA controls (114cm^2, p-value=0.4562) nor between NHW male cases (190cm^2) and NHW male controls (180cm^2, p-value = 0.4206). However, AA cases showed a trend for lower VAT than NHW cases (p=0.0617). NHW cases and controls had significantly higher TAT than their race/ethnic counterparts. SSAT was significantly lower in AA male cases (88cm^2) compared to AA controls (111cm^2, p=0.0016). AA male cases had statistically higher VAT/TAT (42% vs 34%, p-value =0.0132), VAT/SAT (81% vs 55%, p-value

= 0.0050) and statistically lower SAT/TAT (52% vs 61%, p-value =0.0016) and DSAT/TAT (24% vs 30%, p-value = 0.0121) than AA male controls. IMAT was statistically lower in AA male cases (13cm^2) and controls (11cm^2) compared to NHW cases (19cm^2, p-value = 0.0092) and control (18cm^2, p =0.0078) counterparts. SM was statistically higher in AA male cases (172.9cm^2) compared to MHW male controls (150cm^2, p-value = 0.0018).

Comparisons of body composition variables in females by race/ethnic and group assignment are provided in table XI. As expected, the subset of NHW females (n=12) is small in comparison to AA females (n=37). Overall, no statistically significant differences between AA female cases and controls compared to NHW counterparts nor between race/ethnic group comparisons were found. Trends for lower VAT (p-value = 0.0931) and IMAT (p-value = 0.0569) in AA female cases and AA female controls were observed.

TABLE IX

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION BY RACE/ETHNICITY OF CASES AND CONTROLS

	AA Cases (n=88)	**AA Controls (n=88)**	**AA Cases vs AA Controls**	**NHW Cases (n=40)**	**NHW Controls (n=40)**	**NHW Cases vs NHW Controls**	**AA Cases vs NHW Cases**	**AA Controls vs NHW Controls**
Demographics and Anthropometrics	**Median (IQ)**	**Median (IQ)**	**p-value[a]**	**Median (IQ)**	**Median (IQ)**	**p-value[a]**	**p-value[b]**	**p-value[b]**
Age (yrs)	62(10)	61(12)	0.0932	62(10)	62(10)	0.8872	0.9263	0.6681
Height (cm)	169(14)	171(16)	0.0948	175(15)	173(18)	0.0110	0.5620	0.1670
Weight (kg)	78(23)	81(25)	0.0797	80(22)	81(22)	0.0756	0.4937	0.2600
BMI (kg/m^2)	27(7)	27(6)	0.8025	27(6)	28(6)	0.3477	0.4953	0.4292
WC (cm)[c]	98(15)	101(19)	0.1174	109(17)	103(20)	0.2626	**0.0408***	**0.0220***
Abdominal Depots								
TAT (cm^2)	284(248)	320(290)	0.0799	354(232)	357(253)	0.4676	**0.0317***	**0.0479***
SAT (cm^2)	157(120)	179(189)	**0.0086***	194(110)	165(121)	0.5751	0.5216	0.5367
SSAT (cm^2)[c]	97(68)	120(84)	**0.0456***	125(69)	94(60)	0.0547	0.6828	0.5343
DSAT (cm^2)	68(49)	83(68)	**0.0175***	97(73)	88(61)	0.4767	*0.0558*	*0.0967*
VAT (cm^2)	73(122)	87(120)	0.8834	162(186)	155(180)	0.5080	**0.0065***	**0.0006***
IMAT (cm^2)	11(12)	13(13)	0.5085	18(21)	19(16)	0.6144	**0.0008***	**0.0189***
SM (cm^2)	150(65)	158(63)	0.0617	148(55)	136(44)	0.0745	0.1905	0.7661
VAT / TAT (%)	30(28)	28(23)	0.1094	43(25)	41(21)	0.6155	**0.0309***	**<.0001***
VAT / SAT (%)	48(72)	40(53)	0.0542	83(79)	76(73)	0.9659	**0.0249***	**<.0001***
SAT/TAT (%)	63(29)	67(22)	0.0745	52(25)	54(22)	0.7984	**0.0182***	**<.0001***
SSAT/TAT (%)[c]	48(26)	45(23)	0.3210	33(22)	36(23)	0.7302	*0.0532*	**0.0006***
DSAT/TAT (%)	27(12)	30(11)	**0.0170***	26(9)	28(13)	0.2754	0.7602	**0.0294***

*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 = 71 for AA and 32 NHW per group.

TABLE X

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION BY RACE/ETHNICITY OF MALE CASES AND CONTROLS

	AA Male Cases (n=51)	**AA Male Controls (n=51)**	**AA Male Cases vs AA Male Controls**	**NHW Male Cases (n=28)**	**NHW Male Controls (n=28)**	**NHW Male Cases vs NHW Male Controls**	**AA Male Cases vs NHW Male Cases**	**AA Male Controls vs NHW Male Controls**
Demographics and Anthropometrics	**Median (IQ)**	**Median (IQ)**	**[a]p-value**	**Median (IQ)**	**Median (IQ)**	**[a]p- value**	**[b]p-value**	**[b]p-value**
Age (yrs)	63(10)	61(14)	0.1209	61(100	62(13)	0.8179	0.4499	0.9226
Height (cm)	175(10)	177(10)	0.1338	177(10)	179(10)	0.1605	0.5530	0.4493
Weight (kg)	82(18)	86(26)	0.0642	85(17)	88(25)	0.3649	0.2360	0.2896
BMI (kg/m^2)	27(7)	27(7)	0.4484	28(5)	28(5)	0.5919	0.3975	0.2685
WC (cm)[c]	99(14)	106(19)	0.1627	104(23)	111(17)	0.4082	0.0844	**0.0304***
Abdominal Depots								
TAT (cm^2)	263(264)	320(288)	0.4476	366(253)	369(239)	0.4578	**0.0453***	**0.0229***
SAT (cm^2)	127(72)	165(146)	**0.0152***	144(101)	185(107)	0.7090	0.2503	0.1752
SSAT (cm^2)[c]	88(40)	111(68)	**0.0016***	88(41)	112(50)	0.0919	0.8464	0.5444
DSAT (cm^2)	62(50)	71(72)	0.0555	77(65)	96(73)	0.3869	0.1040	0.0623
VAT (cm^2)	98(178)	114(168)	0.4652	190(162)	180(167)	0.4206	0.0617	**0.0014***
IMAT (cm^2)	13(13)	11(10)	0.4263	19(17)	18(25)	0.6773	**0.0092***	**0.0078***
SM (cm^2)	172(39)	178(33)	0.3049	150(31)	172(46)	0.2040	**0.0018***	0.1833
VAT / TAT (%)	42(25)	34(25)	**0.0132***	47(21)	48(17)	0.5812	0.2784	**0.0005***
VAT / SAT (%)	81(89)	55(65)	**0.0050***	99(84)	103(75)	0.9667	0.2483	**0.0004***
SAT/TAT (%)	52(21)	61(20)	**0.0016***	47(20)	46(18)	0.7819	0.2442	**0.0002***
SSAT/TAT (%)[c]	35(23)	43(25)	0.2048	34(20)	30(8)	0.5828	0.1341	**<.0001***
DSAT/TAT (%)	24(13)	30(12)	**0.0121***	25(12)	25(12)	0.1797	0.9471	**0.0294***

*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.

7.2.2. Multiple Regression Analysis Stratified by Race/Ethnicity

The results for the multiple regression analysis for AA then NHW groups are presented followed by highlights of similarities and differences. As previously noted matching criteria for this study (age, gender, BMI and race/ethnicity) are not included in these models.

7.2.2.1. Predictors of Body Composition for AA

Significant predictors for each of the body composition variables **within AA** using multiple linear regression are displayed on Tables XII. Significant predictors of VAT in AA included waist, IMAT, reported history of weight loss and CRC (yes/no) and smoker. Approximately, 63% of the variance in VAT (F =42.61, p<0.0001, R^2=0.6475, Adjusted R^2=0.6323) was predicted by this model. Significant predictors of SAT in AA were waist and IMAT and predicted approximately 63% of the SAT variance (F =77.03, p<0.0001, R^2=0.6534, Adjusted R^2=0.6620). Significant predictors of SSAT were waist, VAT and IMAT which predicted 55% of its variance (F =58.79, p<0.0001, R^2=0.5610, Adjusted R^2=0.5515). Significant predictors of IMAT in AA included SAT, VAT and current smoker and predicted 45% of the IMAT variance (F = 33.80, p<0.0001, R^2=0.4622, Adjusted R^2=0.4485). Significant predictors of SM in AA were waist, SSAT, IMAT, diabetes and alcohol which predicted 48% of the variance (F =23.50, p<0.0001, R^2=0.5032, Adjusted R^2=0.4818).

TABLE XI

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION BY RACE/ETHNICITY OF FEMALE CASES AND CONTROLS

	AA Female Cases (n=37)	**AA Female Controls (n=37)**	**AA Females Cases vs Controls**	**NHW Female Cases (n=12)**	**NHW Female Controls (n=12)**	**NHW Females Cases vs Controls**	**AA Female Cases vs NHW Female Cases**	**AA Female Controls vs NHW Female Controls**
Demographics and Anthropometrics	**Median (IQ)**	**Median (IQ)**	**[a]p- value**	**Median (IQ)**	**Median (IQ)**	**[a]p- value**	**[b]p value**	**[b]p value**
Age (yrs)	60(9)	60(9)	0.4816	63(11)	62(13)	0.9380	0.2450	0.2989
Height (cm)	163(10)	162(8)	0.4188	157(6)	164(12)	**0.0016***	**0.0371***	0.8345
Weight (kg)	68(29)	70(22)	0.7528	68(16)	72(15)	0.0870	0.4330	0.8896
BMI (kg/m^2)	27(9)	26(8)	0.7544	27(8)	27(8)	0.3729	0.7725	0.7280
WC (cm)	95(11)	99(16)	0.4297	102(11)	103(14)	0.3814	0.3616	0.4783
Abdominal Depots								
TAT (cm^2)	298(171)	320(217)	0.0551	353(222)	337(211)	0.9104	0.4264	0.9908
SAT (cm^2)	229(141)	197(182)	0.1888	207(117)	209(117)	0.6114	0.8805	0.7903
SSAT (cm^2)	140(71)	141(86)	0.6153	132(33)	161(43)	0.2794	0.9851	0.4668
DSAT (cm^2)	83(57)	90(77)	0.1593	105(50)	99(66)	0.8644	0.1464	0.7903
VAT (cm^2)	64(48)	85(58)	0.0931	113(125)	90(96)	0.9151	0.1178	0.4961
IMAT (cm^2)	11(10)	17(8)	0.0569	18(16)	18(14)	0.7861	0.0526	0.7029
SM (cm^2)	111(31)	115(16)	0.1037	109(13)	111(30)	0.1609	0.4198	0.7029
VAT / TAT (%)	21(18)	22(11)	0.4101	30(19)	24(11)	0.9783	0.1030	0.1660
VAT / SAT (%)	28(18)	29(22)	0.3877	47(39)	34(24)	0.9935	0.0897	0.1231
SAT/TAT (%)	75(12)	71(10)	0.2893	64(20)	69(10)	0.9822	0.0611	0.1660
SSAT/TAT (%)	53(12)	48(19)	0.5653	50(21)	49(13)	0.5460	0.2577	0.8077
DSAT/TAT (%)	28(11)	30(10)	0.5124	32(7)	28(10)	0.8501	0.3395	0.6033

*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 = 26 for AA and 9 NHW per group.

TABLE XII

PREDICTORS OF BODY COMPOSITION FOR AA CASES AND CONTROLS

	Body Composition Variables					
Variable	**VAT**	**SAT**	**SSAT**	**DSAT**	**IMAT**	**SM**
Intercept	-12.65**	-8.53**	-207.03**	-6.40**	0.84**	5.01**
WC	0.20**	0.18**	3.14**			0.13**
VAT			-2.93**		0.09**	
SAT					0.14**	
SSAT						-0.42**
DSAT						
IMAT	0.61**	0.87**	10.58**	0.43**		-0.40**
Smoker (yes/no)	-0.96	-0.72			0.46*	
Aspirin (yes/no)						
Alcohol (yes/no)						
Hypertension (yes/no)						0.46*
Diabetes (yes/no)						-0.76**
Reported Weight Loss (yes/no)	-1.82**					
CRC (yes/no)	1.19*					
N	122	122	122	122	122	122
R^2	0.6475	0.662	0.561	0.7132	0.4622	0.5032
Adjusted R^2	0.6323	0.6534	0.5515	0.709	0.4485	0.4818

*Significant p-value <0.05.

**Significant p-value <0.01.

7.2.2.2. Multiple Regression Analysis within NHW

Significant predictors for each of the body composition variables **within NHW** using multiple linear regression are displayed on Table XIII. Significant predictors of VAT included waist, SSAT, IMAT and current smoker and predicted 71% of the VAT variance (F =4, p<0.0001, R^2=0.7352, Adjusted R^2=0.7111). Both DSAT and SSAT included IMAT and VAT as significant predictors, however aspirin was a significant predictor for SSAT whereas WC was a significant predictor of DSAT. The model for DSAT predicted approximately 69% of the variance (F =32.91, p<0.0001,

R^2=0.6869, Adjusted R^2=0.6660); the model for SSAT predicted 52% of the variance (*F* =16.48, p<0.0001, R^2=0.5234, Adjusted R^2=0.4917). Significant predictors of IMAT within NHW included only VAT and DSAT. This model predicted about 38% of the variance in IMAT (*F* =15.94, p<0.0001, R^2=0.4093, Adjusted R^2=0.3836). Significant predictors for SM included VAT, IMAT, diabetes and aspirin and predicted 41% of the variance in SM (*F* =42.61, p<0.0001, R^2=0.4063, Adjusted R^2=0.3525).

TABLE XIII

PREDICTORS OF BODY COMPOSITION FOR NHW CASES AND CONTROLS

	Body Composition Variables					
Variable	**VAT**	**SAT**	**SSAT**	**DSAT**	**IMAT**	**SM**
Intercept	-17.74**	-5.88*	-274.85**	-9.29**	1.35*	11.03**
WC	0.31**	0.16**	4.55**	0.18**		
VAT			-6.92**	-0.15*	0.11**	0.23**
SAT					0.17*	
SSAT	-0.56**					
DSAT						
IMAT	0.58	0.45		0.42*		-0.47*
Smoker (yes/no)	-1.37					
Aspirin (yes/no)			-19.08			0.93*
Alcohol (yes/no)						
Hypertension (yes/no)						
Diabetes (yes/no)						-1.08*
Unintentional Weight Loss (yes/no)						
CRC (yes/no)						
N	49	49	49	49	49	49
R^2	0.7352	0.5485	0.5234	0.6869	0.4093	0.4063
Adjusted R^2	0.7111	0.5289	0.4917	0.666	0.3836	0.3523

*Significant p-value <0.05.

**Significant p-value <0.01.

7.2.2.3. Similarities and Differences of Multiple Regression Results: AA vs. NHW

WC and IMAT were common predictors of VAT for both race/ethnic groups. VAT was a significant predictor of SSAT, DSAT, IMAT and SM in NHW, however for AA, VAT only predicted SSAT and IMAT. SM was significantly associated with many variables for both NHW and AA groups, however, the only predictors of SM that were common to both were IMAT and diabetes. Current smoking was a common predictor for VAT, SAT and IMAT in AA but only for VAT in NHW. Reported weight loss did not enter any of the models in the NHW group, however it was a significant predictor of VAT in AA.

7.2.3. Unadjusted and Adjusted Conditional Logistic Regression by Race/Ethnicity

Unadjusted and adjusted conditional logistic regression models assessing the association between selected variables and CRC are presented in this section first for AA then NHW. As will multiple linear regression matching variables (age, gender, BMI and race/ethnicity) are excluded from the models. The section concludes with highlights of similarities and differences between these two race/ethnic groups.

7.2.3.1. Unadjusted and Adjusted Conditional Logistic Regression within AA

Unadjusted conditional logistic regression of median split variables previously defined for abdominal adipose tissues are displayed on Table XIV for AA group. Within AA, only median WC and median SSAT had statistically significant OR estimates. Significant crude OR for median WC was 0.35 (p=0.0283) and for median SSAT was 0.37 (p=0.0239). Trends for significance were noted for median VAT/SAT ratio (Crude OR=1.007, p=0.0641) and for median SAT/VAT ratio (Crude OR 0.978, p=0.0780).

Unadjusted conditional logistic regression models (Table XIV) of demographic variables (independent) and group (dependent, where Event = 1) revealed weight loss history (Crude OR = 4.5, p=0.0009) and aspirin use (Crude OR = 3.1, p=0.0083) as statistically significant predictors

for disease in AA. A trend for significance was observed for alcohol (Crude OR = 0.50, p = 0.0605). In support of previous findings, unintended weight loss was reported in cases and suggesting AA cases were at greater odds (4 times more likely) of experiencing weight loss compared to AA controls.

TABLE XIV

UNADJUSTED CONDITIONAL LOGISTIC REGRESSION FOR MEDIAN SPLITS OF BODY COMPOSITION VARIABLES AND CRC IN AA

			CRC (yes/no)		
Variables[a]	**B**	**OR**	**Lower CI**	**Upper CI**	**p-value**
Median WC	-1.04	0.35	0.139	0.895	**0.0283***
Median VAT	-0.44	0.65	0.303	1.381	0.2606
Median IMAT	-0.26	0.77	0.410	1.455	0.4246
Median SAT	-0.56	0.57	0.281	1.161	0.1220
Median SSAT	-0.53	0.37	0.155	0.876	**0.0239***
Median DSAT	-1	0.59	0.298	1.173	0.1326
Median VAT/TAT	0.02	1.02	0.996	1.046	0.1069
Median VAT/SAT	0.01	1.01	1.000	1.015	0.0641
Median SAT/TAT	-0.02	0.98	0.954	1.003	*0.0780*
Median SSAT/TAT	-0.01	0.99	0.978	1.007	0.2844
Median DSAT/TAT	-0.02	0.98	0.950	1.007	0.1379
Smoker (yes/no)	-0.45	0.64	0.326	1.244	0.1862
Aspirin (yes/no)	1.15	3.14	1.343	7.357	**0.0083***
Alcohol (yes/no)	-0.69	0.50	0.242	1.031	*0.0605*
Hypertension (yes/no)	-0.05	0.95	0.497	1.805	0.8694
Diabetes (yes/no)	-0.06	0.94	0.464	1.896	0.8575
Unintentional Weight Loss (yes/no)	-0.06	4.50	1.858	10.90	**0.0009***

*Significant p-value <0.05.

[a]Median splits defined as: WC = 101.4cm; VAT = 94.2cm^2; IMAT = 14.5cm^2; SAT = 172.9cm^2; SSAT = 109.9cm^2; DSAT = 80.7 cm^2; VAT/TAT = 32.5%; VAT/SAT = 52.1%; SAT/TAT = 61.4%; DSAT/TAT = 27.8%; SSAT/TAT = 42.2%.

Adjusted conditional logistic regression using stepwise selection methods determined a main effects model (Table XV) which included SSAT, aspirin use and history of unintentional weight loss within AA. The odds of reporting daily aspirin use (Adjusted OR = 3.6, p=0.0156) was 4 times greater controlling for median SSAT and reported weight loss among AA cases compared to AA controls. Reported unintentional weight loss (Adjusted OR = 5.8, p=0.0156) was almost 6 times higher controlling for aspirin use and median SSAT among AA cases compared to AA controls. AA cases were more likely to have lower SSAT (Adjusted OR = 0.22, p=0.0236) than AA controls which may indicate the consequences of higher weight loss reported within AA cases.

TABLE XV

ADJUSTED CONDITIONAL LOGISTIC REGRESSION OF SIGNIFICANT PREDICTORS OF CRC IN AA

	CRC (yes/no)				
Model	B	OR	Lower CI	Upper CI	p-value
Median SSAT[a]	-1.52	0.24	0.070	0.852	**0.0270***
Aspirin	1.27	4.42	1.782	10.976	**0.0013***
Unintentional Weight Loss	1.76	7.91	2.559	24.438	**0.0003***

*p<0.05;

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

7.2.3.2. Unadjusted and Adjusted Conditional Logistic Regression within NHW

Unadjusted conditional logistic regression of median split variables previously defined for abdominal adipose tissues are displayed on Table XVI for the NHW group. Among NHW only

median SSAT significantly (Crude OR = 0.13, p=0.0499) predicted disease. Unadjusted conditional logistic regression models (Table XVI) of demographic variables (independent) and group (dependent, where Event = 1) for NHW revealed that aspirin as the only significant predictor of disease (Crude OR = 3.7, p-value = 0.0461). A trend towards significance was observed for weight loss history (Crude OR = 3.3, p=0.0674), current smoker (Crude OR = 2.8, p=0.0832) and current use of alcohol (Crude OR = 3.0, p-value = 0.0571).

Adjusted conditional logistic regression using stepwise selection method determined a main effects model (Table XVII) for NHW included only alcohol as a significant predictor of disease. The odds of current alcohol use (Adjusted OR = 5.0, p=0.0377) was 5 times greater among NHW cases compared to NHW controls.

TABLE XVI

UNADJUSTED CONDITIONAL LOGISTIC REGRESSION FOR MEDIAN SPLITS OF BODY COMPOSITION VARIABLES AND CRC IN NHW

			CRC (yes/no)		
Variables[a]	**B**	**OR**	**Lower CI**	**Upper CI**	**p-value**
Median WC	-1.61	0.20	0.023	1.712	0.1418
Median VAT	1.00	1.20	0.351	2.851	0.9999
Median IMAT	0.41	1.50	0.534	4.214	0.4417
Median SAT	-0.98	0.38	0.099	1.414	0.1474
Median SSAT	-2.08	0.13	0.016	0.999	**0.0499***
Median DSAT	-0.98	0.38	0.099	1.414	0.1474
Median VAT/TAT	-0.01	0.99	0.96	1.025	0.6126
Median VAT/SAT	0.00	1.00	0.996	1.007	0.6200
Median SAT/TAT	0.00	1.00	0.971	1.037	0.8371
Median SSAT/TAT	0.01	1.01	0.984	1.028	0.5797
Median DSAT/TAT	0.01	1.01	0.968	1.047	0.7244
Smoker	1.01	2.75	0.876	8.636	*0.0832*
Aspirin	1.30	3.67	1.023	13.143	**0.0461**
Alcohol	1.10	3.00	0.968	9.302	*0.0571*
Hypertension	0.41	1.50	0.423	5.315	0.5299
Diabetes	0.15	1.17	0.392	3.471	0.7817
Unintentional Weight Loss	1.20	3.33	0.917	12.112	*0.0674*

*Significant p-value <0.05.

[a]Median splits defined as: WC = 101.4cm; VAT = 94.2cm^2; IMAT = 14.5cm^2; SAT = 172.9cm^2; SSAT = 109.9cm^2; DSAT = 80.7 cm^2; VAT/TAT = 32.5%; VAT/SAT = 52.1%; SAT/TAT = 61.4%; DSAT/TAT = 27.8%; SSAT/TAT = 42.2%.

TABLE XVII

ADJUSTED CONDITIONAL LOGISTIC REGRESSION OF SIGNIFICANT PREDICTORS OF CRC IN NHW

	Group Assignment (Case/Control)				
Model	B	OR	Lower CI	Upper CI	p-value
Alcohol	1.6094	5.00	1.096	22.82	**0.0377***

*Significant p-value <0.05.

7.2.3.3. Similarities and Differences of Conditional Logistic Regression: AA vs. NHW

Median SSAT was a common predictor of unadjusted conditional logistic models for both race/ethnic groups. Median WC was only significant predictor in AA group. No other abdominal adipose tissue parameters predicted the odds of disease for either race/ethnic group. Reported weight loss was a significant predictor for the AA group trended significant in the NHW group. These findings support a higher percentage of AA cases in our sample experienced recent weight loss attributable to CRC disease process compared to NHW. The adjusted main effects model for AA included median SSAT, aspirin and reported weight loss. This is consistent to findings of the unadjusted models in AA. However, for NHW, previously determined significant predictor, median SSAT in the unadjusted model did not enter the final adjusted model with alcohol.

7.2.3.4. Subset Analysis of Weight Stable Group for AA Group

Reported history of unintentional weight loss entered into the model for AA but not the NHW. A subset analysis of AA with and without weight loss was examined to determine if differences in body composition phenotype between cases and controls who reported weight loss existed. Stratified analysis was performed for cases and controls with or without weight loss. Table XVIII shows that within AA cases, the positive weight loss group compared to negative for weight loss had significantly lower BMI, WC, TAT, SAT, IMAT, SM, DSAT, VAT/TAT and VAT/SAT

ratios. Within controls, AA with weight loss also had significantly less TAT, SAT, SSAT, VAT, VAT/TAT, VAT/SAT, SAT/TAT and SSAT/TAT than AA without weight loss.

Overall, AA cases compared to AA controls in the weight loss positive group were not significantly different in any body adipose depot or SM with the exception of trend for difference of SSAT(p=0.0524). Chi-square analysis comparing higher cancer stage (Stage II-III, n=55) versus lower cancer stage (Stage 0-II, n=22) with reported weight loss (n = 26) versus no reported weight loss (n = 51) also showed no association between higher stage and higher reporting of unintentional weight loss (p-value = 0.2867).

TABLE XVIII

DEMOGRAPHICS, ANTHROPOMETRICS AND BODY COMPOSITION FOR AA CASES AND CONTROLS WITH AND WITHOUT WEIGHT LOSS

	Weight Loss Positive			**Weight Loss Negative**			**Cases**	**Controls**
	Cases (n=29)	Controls (n=79)	Cases vs Controls	Cases (n=59)	Controls (n=79)	Cases vs Controls	**Positive vs Negative Loss**	**Positive vs Negative Loss**
Variables[a]	**Median (IQ)**	**Median (IQ)**	**p-value**	**Median (IQ)**	**Median (IQ)**	**p-value**	**p-value**[c]	**p-value**[c]
Age (yrs)	62(10)	61(13)	0.3898	60(12)	62(10)	0.3622	0.3572	0.2591
BMI (kg/m^2)	24(7)	26(4)	0.6991	27(6)	28(8)	0.1309	**0.0010***	0.2781
WC (cm)	94(7)	96(29)	0.8039	102(18)	101(14)	0.7317	**0.0012***	*0.0613*
TAT (cm^2)	173(189)	206(212)	0.6992	329(284)	313(177)	0.7131	**0.0019***	**0.0175***
SAT (cm^2)	118(132)	140(134)	0.7825	182(190)	168(114)	0.3136	**0.0012***	**0.0039***
SSAT (cm^2)	78(62)	83(98)	0.0524	121(83)	112(58)	0.7789	0.2506	**0.0039***
DSAT (cm^2)	54(68)	71(58)	0.9559	86(81)	78(40)	0.8428	**0.0055***	0.1585
VAT (cm^2)	55(43)	72(80)	0.6041	90(129)	105(134)	0.6511	0.1925	**0.0469***
IMAT (cm^2)	9(12)	5(11)	NS[b]	15(13)	13(11)	0.8743	**0.0056***	0.1319
SM (cm^2)	132(53)	119(51)	NS[b]	162(62)	155(55)	0.7373	**0.0189***	0.1659
VAT / TAT (%)	23(14)	13(16)	0.1999	29(24)	37(31)	0.1137	**0.0231***	**0.0199***
VAT / SAT (%)	32(26)	16(28)	0.1647	44(58)	65(87)	0.1285	**0.0353***	**0.0199***
SAT/TAT (%)	71(18)	84(19)	0.1089	67(22)	57(33)	0.1720	0.0574	**0.0138***
SSAT/TAT (%)	51(19)	69(61)	0.0772	44(21)	36(28)	**0.0325***	**0.0066***	**0.0019***
DSAT/TAT (%)	32(16)	42(23)	0.2867	30(11)	25(11)	**0.0129***	0.1114	0.1143

*Significant p-value <0.05.

[a]Sample size for WC, SSAT and SSAT/TAT = 46 for AA cases without weight loss; 64 for AA controls without weight loss; 22 for AA cases with weight loss and 7 AA controls with weight loss.

[b]NS=not significant.

[c]Wilcoxon-rank test used for within cases or controls.

7.3. Specific Aim 3. What are the associations among cases between abdominal adipose depots and serum biomarkers of CRC risk? Are these associations modified by race/ethnicity?

This section presents data on the analysis of the associations between abdominal adipose depots and serum biomarkers with CRC for a subset of cases (n=59). No serum data was available for controls. A brief description of the characteristics and demographic variables introduce the section. Frequencies (%/n) and medians with interquartiles(IQ) as indicated are presented in each section that follows for overall sample, then stratification by gender and where possible by race/ethnicity. Further stratifications based on cancer stage, obesity status and weight loss status are presented when feasible. Additional stratification tables based on diabetes and hypertension are include in the appendix. This section concludes with regression analysis exploring associations between the serum biomarkers and abdominal adipose depots.

7.3.1. Characteristics of Subset Sample (n = 59, cases)

Only a small subset of cases had serum available to address our questions in Specific Aim 3. The major demographics and characteristics of the participants with and without serum samples are presented in Table XIX. Participants with serum were more likely to be males (73%) and AA (71%) compared to those without serum; all other variables were not significantly different between these groups. Among the female cases only 16 had serum and all but 2 were AA thus further exploration for race/ethnicity difference in this group is uninformative and thus not presented. The effect of gender has been included in the regression analysis.

About 27% (16/59) of the sample had a normal BMI, 42% were overweight (25/59) and 31% obese (18/59). Most of the patients (64%) were in Cancer Stage II or III. Most were non-smokers (83%), although 68% (40/59) reported regular alcohol use. Approximately, 27% (16/59) of this subsample also self-reported history of unintentional weight loss.

TABLE XIX

DEMOGRAPHICS AND CHARACTERISTICS FOR CASES WITH SERUM (N=59)

Characteristics	**Cases with Serum (n=59) %(n)**	**Cases without Serum (n=69) %(n)**	**p-value[a]**
Male	72.9(43)	52.2(36)	**0.0186***
Female	27.1(16)	47.8(33)	
African Americans	71.2(42)	66.7(46)	0.5824
Non-Hispanic Whites	28.8(17)	33.3(23)	
Normal weight, BMI (18.5-25)	27.1(16)	33.3(23)	0.7473
Overweight, BMI (25-30)	42.4(25)	39.1(27)	
Obese, BMI (≥30)	30.5(18)	27.5(19)	
Cancer Stages 0-I	25.4(15)	27.3(18)	0.9923
Cancer Stage 2 (II, IIA, IIB, IIC)	32.2(19)	36.4(24)	
Cancer Stage 3 (III,IIIA, IIIB, IIIC)	32.219)	36.4(24)	
Married, yes	33.9(20)	21.2(15)	0.1080
High school of higher, yes	88.1(52)	49.3(34)	0.2532
Current smoker, yes	17.0(10)	63.6(42)	0.9693
Alcohol consumption, yes	67.8(40)	43.5(30)	0.1399
Diabetes, yes	23.7(14)	24.6(17)	0.8367
Hypertension, yes	67.8(40)	60.9(42)	0.7085
Unintentional weight loss, yes (within 6 months)	27.1(16)	33.3(23)	0.3222

*Significant p-value < 0.05.

[a]Chi-Square test used for these categorical variables.

7.3.2. Comparisons of Serum Biomarkers with Reference Values by Gender

The median values and interquartile (IQ) range for serum biomarkers and the reference values for these variables are provided in Table XX. Among males glucose and insulin variables were within the reference range except testosterone (lower), and IGFBP3 (below) while glucose, TNF-α, IL-6, leptin and estradiol were above reference ranges as published in respective ELISA assays (see Methods section). For females, TNF-α, IL-6, leptin and testosterone were above reference ranges and IGFBP3 and IGF-1 were lower than.

7.3.3. Correlation Analysis of Body Composition and Serum Biomarkers for Cases (n=59)

Correlation analyses was used to examine the relationship between body composition, various demographic variables and serum biomarkers. Tables for these relationships are provided in the supplemental tables in the Appendix Section (APPENDIX A). In brief, APN was negatively associated with waist (r=-0.38, p=0.0089, n=47), SM (r=-0.29, p=0.026, n=59) and with TAT (r=-0.27, p=0.040, n =59 and positively associated with TNF-α (r=0.35, p=0.007, n=59) and testosterone (r=0.33, p=0.013, n=58). IL-6 was inversely associated with IGF-1 (r=-0.27, p=0.039, n=59). Leptin was highly correlated with many body composition parameters including BMI (r=0.69, p=<0.001, n=59), waist (r=0.35, p=0.016, n=47), VAT (r=0.29, p=0.028, n=59), SAT (r=0.80, p<0.001, n=59), TAT (r=0.646, p<0.001, n=59) and IL-6(r=0.27, p=0.04, n=59). Insulin was positively related to IMAT (r=0.30, p=0.02, n=59), SAT(r=0.37, p=0.004, n=59), TAT(r=0.32, p=0.004, n=59) and leptin (r=0.34, p=0.008, n-59). IGFBP-3 is positively related with IMAT (r=0.29, p=0.026), DSAT (r=0.29, p=0.026, n=59) and IGF-1 (r=0.45, p=0.001, n=59) and negatively with race (r=-0.39, p=002, n=59) and SM(r=-0.28, p=0.032, n=59).

TABLE XX

COMPARISON OF SERUM BIOMARKERS WITH REFERENCE VALUES OF HEALTHY POPULATION BY GENDER

	MALES[a] (n=43)				**FEMALES[b] (n=16)**			
Serum Biomarkers	**Median (SD)**	**Lower 95% CI**	**Upper 95% CI**	**Reference Standards Healthy Population[c]**	**Median (SD)**	**Lower 95% CI**	**Upper 95% CI**	**Reference Standards Healthy Population[c]**
APN (µg/mL)	9.5(9.1)	8.81	14.11	0.87-21.42 µg/mL	10.9(11.3)	8.27	18.81	0.87-21.42 µg/mL
TNF-α (pg/mL)	10.9(13.4)	8.93	14.68	1.6-15.6 pg/mL	7.8(12.4)	4.03	12.53	1.6-15.6 pg/mL
IL-6 (pg/mL)	3.4(6.2)	4.15	8.23	0.45-9.96 pg/mL	4.4(18.9)	4.16	22.42	0.48-9.96 pg/mL
LEPTIN (pg/mL)	4.7(8.3)	5.30	12.45	2.21-11.2pg/mL	17.6(21.2)	13.60	28.69	3.88-77.27pg/mL
Estradiol (pg/mL)	57.5(31.3)	55.31	74.30	15-100pg/mL	32.9(13.6)	28.16	48.44	15-90pg/mL postmenopausal women
Testosterone (pg/mL)	5.12(47.8)	14.32	34.05	0.01-34.1pg/mL	1.20(28.8)	4.05	23.53	0.01-34.1pg/mL
Insulin (uU/mL)	4.9(2.7)	5.25	8.55	5-35µIU/mL	5.6(13.4)	4.96	17.27	5-35µIU/mL
Glucose (mg/dL)	104(26)	99.73	118.79	<100mg/dL	88(34)	84.25	113.14	<100mg/dL
IGFBP-3 (ng/mL)	2.03(0.77)	1.75	2.12	0.835-3.778µg/mL	2.19(0.80)	2.03	2.65	0.835-3.778µg/mL
IGF-1 (ng/mL)	46.6(21.5)	43.46	55.89	40-258ng/mL	53.2(26.9)	45.41	65.23	40-258ng/mL

[a]For males n = 39 for glucose and n = 42 for testosterone.

[b]For females n = 13 for glucose.

[c]Reference standards based on assays (ELISA kits) used in study.

7.3.4. Predictors of Serum Biomarkers using Multiple Regression Analysis

The matching requirements that were adhered to for Specific Aims 1 and 2 are not necessary for the subset of participants with serum measurements. Therefore, age, race and gender were included in the models. Additionally, smoking status and self-reported weight loss, waist, diabetes, cancer stage and alcohol consumption were covariates included in model building process. In lieu of HTN, diastolic and systolic blood pressure were entered individually. Stepwise selection method determined significant predictors which were then evaluated for biological significance. Variables related at $r^2 = 0.8$ or below were entered into the models with VIF, an indicator of multi-collinearity, was calculated for each variable to confirm that collinearity was not violated. A VIF level of 4 was used as a maximum value for allowable level of inclusion for a variable in the model. No value of VIF greater than 3 for any variable was detected.

Significant predictors of selected serum biomarkers associated with CRC for are provided in Table XXI. Significant predictors of APN included IMAT, race/ethnicity, TNF-α and diabetes (F =10.70, p<0.0001, R^2=0.5045, Adjusted R^2=0.4577). Significant predictors of TNF- α were age and testosterone only (F =23.33, p<0.0001, R^2=0.4590, Adjusted R^2=0.4393). Significant predictors of IL-6 were race/ethnicity, TNF-α, leptin, IGF-1 and diastole (F =7.85, p<0.0001, R^2=0.4254, Adjusted R^2=0.3711). Significant predictors of leptin included SAT, IMAT, gender, APN, testosterone and IGF-1 (F =25.25, p<0.0001, R^2=0.8048, Adjusted R^2=0.7729). Significant predictors of estradiol were age, gender, APN, TNF-α and IGF-1 (F =12.44, p<0.0001, R^2=0.4795, Adjusted R^2=0.4410). For testosterone, only IMAT, SM and TNF-α were significant predictors (F =18.38, p<0.0001, R^2=0.5052, Adjusted R^2=0.4777). Predictors of IGFBP-3 included age, race/ethnicity, gender, testosterone, IGF-1, smoking status, IMAT and SM (F = 9.85, p<0.0001, R^2=0.6165, Adjusted R^2=0.5539).

TABLE XXI

PREDICTORS OF SERUM BIOMARKERS FOR CASES WITH SERUM SAMPLES (N=59)

	Predictors of Serum Biomarkers[a]										
Variables	**logAPN**	**TNF-α**	**logIL-6**	**logLeptin**	**logER**	**logTST**	**Insulin**	**logGlu**	**HOMA-IR**	**IGFBP-3**	**IGF-1**
Intercept	2.886*	-9.48*	15.140*	1.192*	4.14*	-0.351*	1.867*	5.914*	-0.770*	3556.294*	194.109*
sqVAT	-0.102*										
sqSAT				0.005*							
sqIMAT	0.191*			0.028*		-0.234*				133.808*	
SM						0.012*				-5.514*	0.117*
Age		0.225*			-0.021*					-21.621*	-0.593*
Race	-0.573*		0.497*							-379.367*	12.603*
Gender				-1.464*	0.427*					-287.116	
logAPN (µg/mL)				-0.424*	-0.139*			-0.089*			
TNF-α (pg/mL)	0.018*		0.028*		0.014*	0.119*					
logIL-6 (pg/mL)							1.867*		0.483*		-4.362*
logLEPTIN (ng/mL)			0.229*				2.186*		0.180*		
logER (pg/mL)								0.186*			
logTST(pg/mL)		3.30*		0.243*						79.431*	
Insulin (uU/mL)											
logGlu (mg/dL)											
HOMA-IR											
IGFBP-3 (ng/mL)								0.0001*			0.016*
IGF-1 (ng/mL)			-0.019*	0.010*						11.451*	
logSystole (mmHg)											
logDiastole (mmHg)			-3.187*					-0.474*			-36.768*
Smoker (yes/no)										-301.921*	
Diabetes (yes/no)	-0.338*										
N	59	58	59	58	59	58	52	52	51	58	59
R^2	0.5045	0.4590	0.4254	0.8048	0.4730	0.5052	0.2201	0.2891	0.2379	0.6165	0.4506
Adjusted R^2	0.4577	0.4393	0.3711	0.7729	0.4340	0.4777	0.1882	0.2286	0.2061	0.5539	0.3872

*Significant p-value <0.05.

[a]Abbreviations for variables: sqVAT=square root of VAT; sqSAT = square root of SAT; sqIMAT = square root of IMAT; logAPN = log of adiponectin; logIL-6 = log of IL-6; logLEPTIN = log of leptin; logER = log of estradiol; logTST = log of testosterone; logGlu = log of glucose; logSystole = log of systolic blood pressure; logDiastole = log of diastolic blood pressure.

7.3.5. Correlations of Serum Biomarkers with Body Composition by Male Gender (n=43)

Correlation analysis was used to examine the associations of serum data with body composition and various demographic variables (age, race, weight loss history) in sample of males with serum data. The most significant correlations for various biomarkers will be briefly summarized. APN was inversely correlated with waist (r=-0.34, p=0.04) and VAT/TAT ratio (r=-0.37, p=0.02). Leptin was significantly associated with all body composition variables (BMI r=0.71, p<0.0001; waist r=0.50, p=0.002; VAT r=0.58, p<0.001; IMAT r=0.44, p=0.003; SAT r = 0.88, p<0.0001; TAT r=0.81, p<0.0001; DSAT r=0.79 p<0.0001; and SM r=0.38 p=0.01). Estradiol was negatively associated only with age (r=-0.37, p=0.02). Testosterone was only positively associated with TNF-α (r=0.73, p<0.0001). IGFBP-3 was positively associated with various body composition depots (VAT r=0.30, p=0.05; IMAT r=0.37, p=0.01; DSAT r=0.30, p=0.05) and negatively associated with age (r=-0.48, p=0.001), race (r=-0.58, p<0.0001) and IL-6 (r=-0.27, p= 0.07). Weight loss history was negatively associated with SAT (r=-0.38, p=0.01) and SSAT (r=-0.39, p=0.02).

7.3.6 Correlations of Serum Biomarkers with Body Composition by Race/ethnicity for Male Gender

Tables XXII and XXIII provide the correlation matrices by race/ethnicity for major body composition parameters and various serum biomarkers for males. APN was negatively correlated with BMI (r=-0.48, p=0.009), waist (r=-0.68, p=0.0002), VAT (r=-0.55, p=0.002), SAT (r=-0.39, p=0.039), DSAT (r=-.47, p=0.020) and TAT (r=-0.51, p=0.005) for AA but not for NHW males. Leptin was positively associated with most body composition parameters including WC (r=0.82, p<0.0001) and VAT (r=0.63, p=0.0003) in AA but not for NHW (WC r= 0.34, p = 0.272; VAT r=0.43, p=0.106

TABLE XXII

PEARSON CORRELATIONS OF BODY COMPOSITION AND SERUM BIOMARKERS OF CRC RISK IN AA MALES[a]

	BMI	WAIST	TAT	SAT	VAT	IMAT	SSAT	DSAT	SM	APN	TNFA	LEPTIN	IGFBP3	IGF1
BMI	1.00	0.91	0.86	0.86	0.74	0.45	0.71	0.72	0.60	-0.45	-0.03	0.82	-0.10	0.09
		<.0001	<.0001	<.0001	<.0001	0.02	0.00	<.0001	0.00	0.02	0.88	<.0001	0.60	0.66
WC	0.91	1.00	0.92	0.81	0.87	0.67	0.74	0.86	0.41	-0.65	0.01	0.83	0.11	0.25
	<.0001		<.0001	<.0001	<.0001	0.00	<.0001	<.0001	0.05	0.00	0.97	<.0001	0.60	0.25
TAT	0.86	0.92	1.00	0.90	0.94	0.58	0.74	0.76	0.51	-0.59	-0.11	0.72	0.02	0.13
	<.0001	<.0001		<.0001	<.0001	0.00	<.0001	<.0001	0.01	0.00	0.56	<.0001	0.91	0.51
SAT	0.86	0.81	0.90	1.00	0.71	0.54	0.92	0.83	0.54	-0.46	-0.08	0.80	-0.10	0.04
	<.0001	<.0001	<.0001		<.0001	0.00	<.0001	<.0001	0.00	0.01	0.68	<.0001	0.62	0.85
VAT	0.74	0.87	0.94	0.71	1.00	0.49	0.53	0.57	0.42	-0.63	-0.14	0.57	0.11	0.18
	<.0001	<.0001	<.0001	<.0001		0.01	0.01	0.00	0.03	0.00	0.46	0.00	0.59	0.35
IMAT	0.45	0.67	0.58	0.54	0.49	1.00	0.59	0.74	0.37	-0.23	-0.04	0.39	0.06	-0.04
	0.02	0.00	0.00	0.00	0.01		0.00	<.0001	0.05	0.25	0.82	0.04	0.76	0.83
SSAT	0.71	0.74	0.74	0.92	0.53	0.59	1.00	0.88	0.30	-0.51	-0.10	0.63	-0.13	0.05
	0.00	<.0001	<.0001	<.0001	0.01	0.00		<.0001	0.15	0.01	0.66	0.00	0.53	0.82
DSAT	0.72	0.86	0.76	0.83	0.57	0.74	0.88	1.00	0.52	-0.40	-0.01	0.66	-0.08	-0.02
	<.0001	<.0001	<.0001	<.0001	0.00	<.0001	<.0001		0.01	0.03	0.96	0.00	0.68	0.93
SM	0.60	0.41	0.51	0.54	0.42	0.37	0.30	0.52	1.00	-0.43	-0.21	0.64	-0.01	0.21
	0.00	0.05	0.01	0.00	0.03	0.05	0.15	0.01		0.02	0.27	0.00	0.96	0.29
APN	-0.45	-0.65	-0.59	-0.46	-0.63	-0.23	-0.51	-0.40	-0.43	1.00	0.20	-0.36	0.06	-0.18
	0.02	0.00	0.00	0.01	0.00	0.25	0.01	0.03	0.02		0.32	0.06	0.75	0.35
TNFA	-0.03	0.01	-0.11	-0.08	-0.14	-0.04	-0.10	-0.01	-0.21	0.20	1.00	-0.05	-0.16	-0.07
	0.88	0.97	0.56	0.68	0.46	0.82	0.66	0.96	0.27	0.32		0.81	0.41	0.71
LEPTIN	0.82	0.83	0.72	0.80	0.57	0.39	0.63	0.66	0.64	-0.36	-0.05	1.00	-0.13	0.04
	<.0001	<.0001	<.0001	<.0001	0.00	0.04	0.00	0.00	0.00	0.06	0.81		0.52	0.86
IGFBP3	-0.10	0.11	0.02	-0.10	0.11	0.06	-0.13	-0.08	-0.01	0.06	-0.16	-0.13	1.00	0.57
	0.60	0.60	0.91	0.62	0.59	0.76	0.53	0.68	0.96	0.75	0.41	0.52		0.00
IGF1	0.09	0.25	0.13	0.04	0.18	-0.04	0.05	-0.02	0.21	-0.18	-0.07	0.04	0.57	1.00
	0.66	0.25	0.51	0.85	0.35	0.83	0.82	0.93	0.29	0.35	0.71	0.86	0.00	

*Significant p-value < 0.05.

[a]Transformed variables used in analysis.

TABLE XXIII

PEARSON CORRELATIONS OF BODY COMPOSITION AND SERUM BIOMARKERS OF CRC RISK IN NHW MALES[a]

	BMI	WAIST	TAT	SAT	VAT	IMAT	SSAT	DSAT	SM	APN	TNFA	LEPTIN	IGFBP3	IGF1
BMI	1.00	0.54	0.51	0.66	0.26	0.33	0.51	0.67	0.70	0.12	-0.06	0.55	0.29	0.47
		0.07	0.05	0.01	0.35	0.23	0.09	0.01	0.00	0.68	0.83	0.03	0.30	0.07
WC	0.54	1.00	0.87	0.78	0.82	0.74	0.53	0.78	0.57	-0.32	0.06	0.34	0.04	0.27
	0.07		0.00	0.00	0.00	0.01	0.08	0.00	0.05	0.32	0.85	0.27	0.91	0.40
TAT	0.51	0.87	1.00	0.89	0.90	0.76	0.43	0.87	0.52	-0.14	0.14	0.68	0.32	0.09
	0.05	0.00		<.0001	<.0001	0.00	0.16	<.0001	0.05	0.63	0.63	0.01	0.24	0.76
SAT	0.66	0.78	0.89	1.00	0.61	0.55	0.62	0.99	0.51	-0.05	0.17	0.81	0.43	0.18
	0.01	0.00	<.0001		0.01	0.03	0.03	<.0001	0.05	0.85	0.55	0.00	0.11	0.51
VAT	0.26	0.82	0.90	0.61	1.00	0.74	0.17	0.60	0.45	-0.23	0.10	0.41	0.12	-0.06
	0.35	0.00	<.0001	0.01		0.00	0.60	0.02	0.09	0.40	0.71	0.13	0.67	0.83
IMAT	0.33	0.74	0.76	0.55	0.74	1.00	0.36	0.48	0.23	0.22	0.03	0.46	0.19	0.26
	0.23	0.01	0.00	0.03	0.00		0.25	0.07	0.42	0.42	0.93	0.08	0.49	0.35
SSAT	0.51	0.53	0.43	0.62	0.17	0.36	1.00	0.56	0.17	-0.03	0.13	0.52	0.46	0.06
	0.09	0.08	0.16	0.03	0.60	0.25		0.06	0.60	0.92	0.69	0.08	0.14	0.86
DSAT	0.67	0.78	0.87	0.99	0.60	0.48	0.56	1.00	0.52	-0.12	0.10	0.79	0.41	0.19
	0.01	0.00	<.0001	<.0001	0.02	0.07	0.06		0.04	0.66	0.72	0.00	0.13	0.50
SM	0.70	0.57	0.52	0.51	0.45	0.23	0.17	0.52	1.00	0.02	0.30	0.31	0.27	0.29
	0.00	0.05	0.05	0.05	0.09	0.42	0.60	0.04		0.95	0.27	0.26	0.33	0.30
APN	0.12	-0.32	-0.14	-0.05	-0.23	0.22	-0.03	-0.12	0.02	1.00	0.50	0.21	0.18	0.12
	0.68	0.32	0.63	0.85	0.40	0.42	0.92	0.66	0.95		0.06	0.45	0.53	0.68
TNFA	-0.06	0.06	0.14	0.17	0.10	0.03	0.13	0.10	0.30	0.50	1.00	0.26	0.26	-0.20
	0.83	0.85	0.63	0.55	0.71	0.93	0.69	0.72	0.27	0.06		0.35	0.35	0.47
LEPTIN	0.55	0.34	0.68	0.81	0.41	0.46	0.52	0.79	0.31	0.21	0.26	1.00	0.70	0.23
	0.03	0.27	0.01	0.00	0.13	0.08	0.08	0.00	0.26	0.45	0.35		0.00	0.40
IGFBP3	0.29	0.04	0.32	0.43	0.12	0.19	0.46	0.41	0.27	0.18	0.26	0.70	1.00	0.20
	0.30	0.91	0.24	0.11	0.67	0.49	0.14	0.13	0.33	0.53	0.35	0.00		0.47
IGF1	0.47	0.27	0.09	0.18	-0.06	0.26	0.06	0.19	0.29	0.12	-0.20	0.23	0.20	1.00
	0.07	0.40	0.76	0.51	0.83	0.35	0.86	0.50	0.30	0.68	0.47	0.40	0.47	

*Significant p-value < 0.05.

[a]Transformed variables used in analysis.

7.3.7. Comparisons of Anthropometric, Body composition and Serum Biomarkers by Race/ethnicity and Male Gender

The anthropometric, body composition and serum biomarker data stratified by race for male cases in subset are presented in Table XXIV. As stated earlier analysis of females was not possible due to small sample size for NHW females (n = 2). AA men with CRC had significantly lower waist, VAT, IMAT and trend for lower DSAT than their NHW counterparts. The only serum biomarker that varied between race/ethnicity was IGFBP-3 (significantly lower in AA vs NHW). A trend for lower insulin (p-value = 0.0531), lower APN (p-value = 0.0817) and lower HOMA-IR (p-value = 0.0831) was noted for men reporting with vs without weight loss.

The body composition and serum biomarkers of male cases with lower CRC Stage (0-I) are compared to those with advanced CRC Stage (II-III) and presented in Table XXV. Both VAT (p-value=0.0684) and SM (p=0.0613) trended lower in CRC Stages II-III vs I. Diastolic blood pressure was significantly lower in advanced stages compared to lower stages (p-value = 0.0046) and insulin and HOMA-IR were significantly higher in lower stages compared to advanced stages.

Body composition and serum biomarkers of stratified by obesity status are presented in Table XXVI for the subset of males with serum. As expected, obese cases had significantly greater SSAT and SAT than their lean counterparts, however no other difference for any other depots were observed. Leptin was higher in obese than non-obese cases (p=0.0433) while trend for slightly higher in non-obese cases (p=0.0815) compared to obese cases.

The impact of self-reported unintentional weight loss on serum biomarkers are presented in Table XXVII for the subset of males with serum samples. No significant differences were observed in cases with and without weight loss of serum biomarkers. Trends for higher APN (n=0.0817) and lower HOMA-IR (p=0.0831) and insulin (p=0.0531) were observed.

TABLE XIV

BODY COMPOSITION AND SERUM BIOMARKERS BY RACE/ETHNICITY FOR SUBSET OF MALE CASES WITH SERUM

Variables	AA Male Cases (n=28) Median (IQ)	NHW Male Cases (n=15) Median(IQ)	p-value
BMI (kg/m^2)	26(7)	28(5)	0.2328
WC (cm)[a]	100.7(17.1)	115(18)	**0.0311***
TAT (cm^2)	254(298)	450(228)	**0.0162***
SAT (cm^2)	122(76)	166(102)	0.0976
SSAT (cm^2)[a]	85(46)	87(63)	0.7429
DSAT (cm^2)	59(45)	89(69)	0.0680
VAT (cm^2)	93(199)	241(76)	**0.0232***
IMAT (cm^2)	10.7(11.6)	22(24)	**0.0049***
SM (cm^2)	170(40)	148(45)	**0.0508***
VAT/TAT(%)	43(38)	53(26)	0.1370
VAT/SAT(%)	85(129)	119(144)	0.1131
SAT/TAT(%)	50(33)	40(29)	0.0700
SSAT/TAT(%)[a]	35(30)	25(16)	**0.0402**
DSAT/TAT(%)	23(21)	24(12)	0.5867
Systole (mmHg)	137(26)	132(30)	0.5472
Diastole (mmHg)	78(18)	71(17)	0.7347
APN (µg/mL)	8(8)	11(12)	0.0684
TNF-α (pg/mL)	16(5)	18(7)	0.5481
IL-6 (pg/mL)	4(7)	3(3)	0.4873
LEPTIN (ng/mL)[b]	5(6)	8(15)	0.2396
Estradiol (pg/mL)[b]	56(13)	51(41)	0.5644
Testosterone(pg/mL)[c]	3(3)	3(3)	0.4139
Insulin (uU/mL)	5(3)	5(3)	0.9990
Glucose (mg/dL)[d]	104(26)	104(18)	0.9420
IGFBP-3 (ng/mL)	1.8(0.7)	2.4(0.7)	**0.0001***
IGF-1 (ng/mL)	45(24)	49(17)	0.9159
HOMA-IR[d]	1.2(1.0)	1.5(0.7)	0.4956

*Significant p-value < 0.05.

[a]Sample size for WC, SSAT and SSAT/TAT: n=28 for AA, n=12 for NHW.

[b]Sample size for leptin and estradiol n = 24 for AA and n = 14 for NHW.

[c]Sample size for testosterone: n=26 for AA, n = 15 NHW.

[d]Sample size for glucose and HOMA-IR: n=25 for AA, n=14 for NHW.

TABLE XXV

BODY COMPOSITION AND SERUM BIOMARKERS STRATIFIED BY CRC CANCER STAGES FOR SUBSET OF MALE CASES WITH SERUM

Variables	Cancer Stages 0-I (N=12) Median(IQ)	Cancer Stages II-III (N= 28) Median(IQ)	p-value
BMI (kg/m^2)	29(4)	26(6)	0.1329
WC (cm)[a]	104(5)	103(23)	0.4007
TAT (cm^2)	421(189)	302(320)	0.1636
SAT (cm^2)	158(93)	122(91)	0.1871
SSAT (cm^2)[a]	93(38)	85(63)	0.6157
DSAT (cm^2)	63(56)	66(47)	0.5106
VAT (cm^2)	230(83)	129(213)	0.0684
IMAT (cm^2)	17(10)	14(18)	0.4389
SM (cm^2)	178(37)	154(42)	0.0613
VAT/TAT(%)	53(21)	46(34)	0.0684
VAT/SAT(%)	126(110)	95(118)	0.0977
SAT/TAT(%)	42(18)	49(32)	0.1047
SSAT/TAT(%)[a]	24(10)	34(28)	0.1114
DSAT/TAT(%)	20(10)	25(20)	0.1688
Systole (mmHg)	147(31)	131(25)	0.0552
Diastole (mmHg)	89(20)	74(12)	**0.0046***
APN (µg/mL)	9(6)	12(10)	0.2195
TNF-α (pg/mL)	15(3)	19(6)	0.0732
IL-6 (pg/mL)	5(6)	7(7)	0.3012
LEPTIN (ng/mL)[b]	11(11)	10(13)	0.1972
Estradiol (pg/mL)[c]	56(15)	60(22)	0.7392
Testosterone (pg/mL)[d]	4(3)	3(2)	0.5338
Insulin (uU/mL)	8(6)	7(5)	**0.0387***
Glucose (mg/dL)[e]	112(25)	108(33)	0.4267
IGFBP-3 (ng/mL)	2.06(0.6)	1.9(0.6)	0.4083
IGF-1 (ng/mL)	52(28)	47(17)	0.5903
HOMA-IR[e]	2.6(1.8)	1.8(1.8)	**0.0381***

*Significant p-value < 0.05.

[a]Sample size for WC, SSAT, SSAT/TAT: n=24 for Stage II-III, n=9 for Stage 0-I.

[b]Sample for leptin: n=25 for Stage 0-I.

[c]Sample size for estradiol: n=10 for Stage 0-I, n=27 for Stage II-III

[d]Sample for testosterone: n=26 for Stage II-III.

[e]Sample size for glucose, HOMA-IR: n= 27 for Stage II-III, n=9 for Stage 0-I.

TABLE XXVI

BODY COMPOSITION AND SERUM BIOMARKERS BY OBESITY STATUS OF MALE CASES WITH SERUM

Variables	Obese (n=11) Median (IQ)	Non-Obese (n=32) Median (IQ)	p-value
BMI (kg/m^2)	33(3.8)	26(5)	**<.0001***
Waist (cm) [a]	121(11)	102(15)	**0.0006***
TAT (cm^2)	503(382)	263(267)	**0.0003***
SAT (cm^2)	202(324)	116(76)	**0.0067***
SSAT (cm^2) [a]	125(54)	79(48)	**0.0552***
DSAT (cm^2)	100(84)	59(37)	**0.0043***
VAT (cm^2)	241(106)	108(223)	**0.0136***
IMAT (cm^2)	21(17)	11(12)	**0.0029***
SM (cm^2)	192(63)	160(29)	**0.0020***
VAT/TAT(%)	48(24)	49(39)	0.5345
VAT/SAT(%)	113(115)	109(135)	0.3988
SAT/TAT(%)	45(25)	45(32)	0.4483
SSAT/TAT(%)[a]	27(10)	36(32)	0.1957
DSAT/TAT(%)	20(15)	24(20)	0.3564
Systole (mmHg)	140(18)	134(28)	0.8212
Diastole (mmHg)	78(17)	74(16)	0.4100
APN (µg/mL)	9(8)	10(10)	0.6287
TNF-α (pg/mL)	17(4)	18(6)	0.4127
IL-6 (pg/mL)	3(3)	3(6)	0.4007
LEPTIN (ng/mL)	10(36)	5(6)	**0.0433***
Estradiol (pg/mL)	44(25)	59(22)	**0.0815***
Testosterone(pg/mL)[b]	2(3)	3(2)	0.1835
Insulin (uU/mL)	7(11)	5(2)	0.0285
Glucose (mg/dL)[c]	104(25)	104(28)	0.8354
IGFBP-3 (ng/mL)	1.9(1.5)	2(0.7)	0.8464
IGF-1 (ng/mL)	53(30)	44(17)	0.8735
HOMA-IR[c]	1.6(3.1)	1.2(0.8)	0.1605

*Significant p-value < 0.05.

[a]Sample size for WC, SSAT and SSAT/TAT: n=29 for non-obese, n=7 for obese.

[b]Sample size for testosterone = 30 for non-obese.

[c]Sample size for glucose and HOMA-IR: n= 29 for non-obese, n=10 for obese.

TABLE XXVII

BODY COMPOSITION AND SERUM BIOMARKERS STRATIFIED BY SELF-REPORTED UNINTENTIONAL WEIGHT LOSS FOR MALE CASES WITH SERUM

Variables	Weight Loss Positive (n=12) Median(IQ)	Weight Loss Negative (n=31) Median(IQ)	p-value
BMI (kg/m^2)	28(5)	26(7)	0.1548
WC (cm)[a]	108(19)	98(20)	0.1054
TAT (cm^2)	353(270)	161(289)	0.2878
SAT (cm^2)	157(88)	97(47)	**0.0185***
SSAT (cm^2)[a]	95(54)	79(28)	**0.0096***
DSAT (cm^2)	78(44)	54(19)	0.0790
VAT (cm^2)	198(182)	54(236)	0.2791
IMAT (cm^2)	15(14)	13(22)	0.6381
SM (cm^2)	162(44)	165(42)	0.7101
VAT/TAT(%)	50(27)	30(44)	0.6381
VAT/SAT(%)	113(110)	52(168)	0.6966
SAT/TAT(%)	44(23)	57(43)	0.6053
SSAT/TAT(%)[a]	29(20)	51(37)	0.4481
DSAT/TAT(%)	23(11)	36(33)	0.5457
Systole (mmHg)	140(34)	133(22)	0.2438
Diastole (mmHg)	77(19)	74(19)	0.6598
APN (µg/mL)	13(11)	8(8)	0.0817
TNF-α(pg/mL)	18(4)	17(5)	0.5955
IL-6 (pg/mL)	3(10)	3(4)	0.8611
LEPTIN (ng/mL)[b]	3(11)	5(6)	0.1206
Estradiol (pg/mL)[b]	53(23)	58(27)	0.6252
Testosterone (pg/mL)[c]	3(4)	3(3)	0.2660
Insulin (uU/mL)	4(2)	5(3)	0.0531
Glucose (mg/dL)[d]	104(29)	104(26)	0.7057
IGFBP-3 (ng/mL)	1.8(0.8)	2.1(0.8)	0.8908
IGF-1 (ng/mL)	44(27)	49(21)	0.9142
HOMA-IR[d]	1.0(0.7)	1.5(0.9)	0.0831

*Significant p-value < 0.05.

[a]Sample size for WC, SSAT and SSAT/TAT: n=27 for no weight loss group, n=9 for weight loss group.

[b]Sample size for leptin and estradiol: n=9 for obese group.

[c]Sample size for testosterone: n=29 for no weight loss group.

[d]Sample size for glucose and HOMA-IR: n=27 for no weight loss group.

7.4. Specific Aim 4. What is the feasibility of using two techniques for assessment of HFC in cases and controls? How many patients classify as having hepatic steatosis according to these two methods?

The results hereinto include rationale for changes to methodology of HFC assessment, a description of the demographics for cases and controls with CE or NCE images, results of the CE protocol, results of the NCE protocol and a brief description of cases and controls classifying with hepatic steatosis according to NCE CT criterion.

Our original intention was to acquire non-contrast enhanced (NCE) CT images for HF analysis as this is the preferred method of analysis[118]. Unfortunately, we found most CT scans performed in a majority of cases were contrast-enhanced (CE) scans, despite the radiology data base label of 'with and without contrast'. The literature was searched for solutions and two publications describing methods to use CE CT images for HF analysis were found[116,230]. These stipulate standardized CE CT scanning procedures required standard injection rate of contrast (3ml/s) and CT image acquisition at 75 seconds after contrast injection for estimating HFC[116]. The use of diagnostic CT scans, retrospectively in our investigation prevented CT acquisition standardization, however published guidelines for the standardization seemed worth efforts to assess if the CE protocol could yield accurate HFC assessment. Exploration of these parameters used at each institution revealed very different injection rates (ranging from 2-4mL/s depending on needle gauge) and CT acquisition intervals that varied wildly (70 vs 45-60 vs 60 seconds). Identification and measurement of the three anatomical features of aorta, main portal vein and liver, the protocol for CE images[230] with radiologist oversight was applied to evaluated results.

A total of 177 images were analyzed for HFC of these 119 were analyzed using the CE protocol and 58 using the NCE protocol after removal of 4 outliers. A number of patients (n=75) did not have a T12L1 image where aorta, MPV and liver for CE protocol or spleen and liver for NCE protocol were visible. Most of the sample eligible for HFC was AA (68%, 120/177) and male gender (60%, 107/177) for HFC. The mean and (SD) for hepatic attenuation (n=119) at CE CT

was 85.9HU (27.2) with a range of -5 to 147HU. The mean and (SD) for hepatic attenuation (n=58) at NCE CT was 54.5(11.5) with a range of 20.29 to 70.3 HU and for spleen was 45.7(9.5) with a range of 8.3-64.6HU at CE CT. Tables XXVIII shows the basic demographic and clinical characteristics of cases and controls with CE images.

TABLE XXVIII

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF CASES AND CONTROLS WITH CONTRAST ENHANCED (CE) IMAGES

Characteristics	**Cases with CE Images (n=87) %(n)**	**Controls with CE Images (n=32) %(n)**
Male	60.9(53)	59.4(19)
Female	39.1(34)	40.6(13)
African Americans	64.4(56)	69.0(22)
Non-Hispanic Whites	35.6(31)	31.3(10)
Normal BMI (18.5-25)	25.3(22)	31.3(10)
Overweight BMI (25-30)	42.5(37)	43.8(14)
Obese BMI (≥30)	32.2(28)	25.0(8)
Cancer Stage 0-I	29.5(23)	----
Cancer Stage 2 (II, IIA, IIB, IIC)	32.1(25)	----
Cancer Stage 3 (III,IIIA, IIIB, IIIC)	38.5(30)	----
Current Smoker, yes	28.7(25)	28.1(9)
Alcohol consumption, yes	42.4(36)	35.5(11)
Diabetes, yes	20.0(20)	28.1(9)
Hypertension, yes	64.0(55)	71.9(23)
Unintentional Weight loss (within 6 months), yes	27.9(24)	12.5(4)

Using the CE protocol by Monjardim et al[230] revealed that 78% (68/87) of cases and 81% (26/32) of controls had hepatic steatosis of greater than 5%. In our study, we found that 88% (132/150) CE images met the criteria for hepatic steatosis of greater than 5% (Table XXIX).

TABLE XXIX

HEPATIC STEATOSIS IN CASES AND CONTROLS ACCORDING TO CONTRAST-ENHANCED CT IMAGE CRITERIA

Hepatic Fat Content Criteria (Kim et al 2010)	**Cases (n=87) %(n)**	**Controls (n=32) %(n)**
Hepatic Attenuation < 104 HU	78.2(68)	81.3(26)

Table XXX shows the characteristics of those with and without NCE images. Results of the NCE protocol using two definitions for evaluation of HFC are found in Table XXXI. The first definition uses hepatic attenuation less than or equal to 40HU[118] (HFC greater than 30%) as indicator of moderate-to-severe hepatic steatosis. This definition indicated 13% (6/47) of cases were categorizes as moderate-to-severe hepatic steatosis; no controls were included in this category. The second definition is a ratio based on the liver to spleen attenuation values less than or equal to 1.1 which indicates moderate hepatic steatosis[117]. This definition indicated overall 32% (16/58) of participants had moderate hepatic steatosis representing 30% (3/10) of cases and 27.1% (13/48) of controls were classified as having a liver to fat ratio consistent with moderate hepatic steatosis. All six participants identified with the first definition were included in the control group (Table 25). A total of 5 patients classified with hepatic steatosis under both definitions; 1 of 16 classified with liver HU criteria (Definition 1) whereas 11 of 16 classified with liver to spleen ratio criteria (Definition 2).

TABLE XXX

DEMOGRAPHICS OF CASES AND CONTROLS WITH NON-CONTRAST ENHANCED (NCE) CT IMAGES

Characteristics	**Cases with NCE Images (n=10) %(n)**	**Controls with NCE Images (n=48) %(n)**
Male	80.0(8)	56.3(27)
Female	20.0(2)	43.8(21)
African Americans	80.0(8)	70.8(34)
Non-Hispanic Whites	14.3(2)	29.2(14)
Normal BMI (18.5-25)	50.0(5)	22.9(11)
Overweight BMI (25-30)	50.0(5)	41.7(20)
Obese BMI (≥30)	0(0)	35.4(17)
Cancer Stage 0-I	40.0(4)	----
Cancer Stage 2 (II, IIA, IIB, IIC)	30.0(3)	----
Cancer Stage 3 (III,IIIA, IIIB, IIIC)	30.0(3)	----
Current Smoker, yes	10.0(1)	27.7(13)
Alcohol consumption, yes	20.0(2)	42.6(20)
Diabetes, yes	20.0(2)	27.1(13)
Hypertension, yes	70.0(7)	56.3(27)
Unintentional Weight loss (within 6 months), yes	30.0(3)	8.3(4)

TABLE XXXI

HEPATIC STEATOSIS IN CASES AND CONTROLS ACCORDING TO NON-CONTRAST ENHANCED CT IMAGE PROTOCOL

NCE Hepatic Attenuation Criteria	**Overall (n=58) %(n)**	**Cases (n=10) %(n)**	**Controls (n=48) %(n)**
Hepatic attenuation ≤ 40 (Definition 1)	10.3 (6)	0(0)	12.5(6)
Liver to Spleen Ratio ≤ 1.1 (Definition 2)	31.6 (16)	30.0(3)	27.1(13)

Characteristics of cases and controls defined with hepatic steatosis according to two criteria are described in Table XXXII. The median and interquartile (IQ) for BMI and VAT of participants classified with definition 1 was 31.5 kg/m^2 (7kg/m^2) and 282 cm^2 (107.6cm^2), respectively. The median and IQ for BMI and VAT for cases using definition 2 was 25.7 kg/m^2 (4.9kg/m^2) and 154.4 cm^2 (158.5cm^2), respectively. The median and IQ for BMI and VAT for controls using definition 2 was 30.0 kg/m^2 (6kg/m^2) and 159.6 cm^2 (107cm^2), respectively.

TABLE XXXII

CHARACTERISTICS OF CASES AND CONTROLS CLASSIFIED WITH HEPATIC STEATOSIS

	Hepatic Attenuation Criteria		
	Hepatic attenuation ≤ 40 (Definition 1)	**Liver to Spleen Ratio ≤ 1.1 (Definition 2)**	
Characteristics	**Controls (n=6)**	**Cases (n=3)**	**Controls (n=13)**
Age, Median(IQ)	57(7)	81.0(18)	59(5)
Male Gender, %(n)	50(3)	100(3)	46.2(6)
African American, %(n)	50(3)	66.7(2)	76.9(10)
BMI, Median(IQ)[a]	31.5(7)	25.7(4.9)	30(6)
VAT*, Median(IQ)	282(107.6)	154.4(158.5)	159.6(107)

[a]BMI unit = kg/m^2.

[b]VAT unit = cm^2.

7.5. Summary of Major Findings

In summary, the major findings for Specific Aim 1 was that no VAT-related CRC phenotype was observed in cases such that no significant differences were observed between cases and controls. However, SSAT in particular was significantly higher in controls and adjusted conditional logistic regression determined that SSAT reduced the odds of CRC for AA but not for NHW. The major finding for Specific Aim 2 was that AA cases and controls had lower VAT areas compared to NHW cases and controls. These differences in lower VAT remained for AA males compared to NHW males. The major findings for Specific Aim 3 were significant race/ethnic differences in serum biomarkers APN and IGFBP-3. And finally, for Specific Aim 4 both techniques were applied for evaluation of HFC and these revealed that the NCE protocol for HFC showed lower prevalence of hepatic steatosis compared to the CE protocol for overall sample.

VIII. Discussion

This chapter is divided into five main sections. The first four present the significance and implications of major finding for each of the Specific Aims. Section five presents the limitations and strengths of our investigation and the overall findings.

8.0. Specific Aim 1: Hypothesis - Is there a CRC body composition phenotype?

8.0.1. Visceral Adipose Tissue and Colorectal Cancer

Counter to our hypothesis we did not find excess VAT impacted the risk for CRC in our participants. Only six studies using CT image data have been reported in this area; two[102,232,233] found no association and three reported positive relationship between greater VAT area and CRC risks[1,99,234]. Our findings support and extend the case control study by Choe et al[232] and two cross sectional studies by Erarslan et al.[102,233] Choe et al[232] compared age and gender matched healthy Korean participants (N=557), with patients with adenomas (n=554) matched and to early stage (Stage 0-I) CRC (N=153) group that were not matched for age and gender and found similar VAT areas between these groups. Measures of adiposity (i.e. BMI or WC) between groups were significantly different (23.8±2.5 for controls vs. 24.3±2.6 for adenomas vs. 24.3±2.5kg/m^2 for cases, p=0.01) and were not controlled. Erarslan et al[233] conducted a cross-sectional study of VAT volume (cm^3) in Turkish patients with incident CRC (N=21), adenoma (N=27) and controls (N=30) and found lower VAT in adenoma group but similar amounts in CRC group and controls. An earlier smaller study by this group in healthy Turkish adults (N= 54) vs. patients with incident CRC with (N=23) and patients with adenomas (N=31) also found similar VAT volume (cm^3) between the groups, however participants were not matched for any parameters and included 82% fewer cases than our investigation. Further, body composition of healthy Asian Americans and East Asians (China, Korea, Japan) differ from healthy NHW, Europeans and AA[235-238] and are more similar to those reported by Chou et al. Additionally, the variation of obesity status

(reported mean BMI for Korean study: 23-25kg/m^2, Turkish study: 24-29kg/m^2, current study: 27kg/m^2) between these studies further limits generalizability.

Three other investigations, all conducted in Asian populations, have reported greater VAT area in participants with CRC compared to their healthy counterparts. Lee et al[234] found increasing VAT (tertiles) was positively associated with CRC in Korean postmenopausal female pairs (N=191) with and without prevalent CRC that were propensity score matched for age, BMI, smoking status, alcohol consumption and exercise habits[234]. As participants were Korean women comparisons with our predominantly male, AA and NHW participants from the United States are limited. Yamamoto et al[1] compared Japanese patients enrolled over a 4-yr interval with (N=22) and without CRC (N=66) matched on age, sex and year of examination and found VAT was significantly higher in CRC patients. Results from logistic models adjusting for BMI indicated VAT remained a significant predictor of CRC, supporting suggesting a direct relationship with CRC, independent of BMI. Oh et al[99] also reported higher VAT in unmatched Korean patients with CRC (N=53) and greater odds of CRC risk for VAT greater than 136.61cm^2 compared to controls (N= 147) selected from a pool of patients (N=200) undergoing colonoscopies and routine CT scans. The multivariable analysis were adjusted for age, gender, smoking status and family history; BMI and WC were not significant predictors. There is a steeper increase in VAT for every 1kg/m^2 increase in BMI among Asians compared to AA and NHW[237]. Additionally, AA have lower VAT for a given BMI or WC than NHW as well as Asian's while their risks for CRC are higher. To our knowledge the current study is the only investigation that has controlled for BMI at recruitment, enabling robust comparisons based on estimates of adiposity between groups.

Variations in findings of the studies in cited above may reflect overestimations of VAT due to failure to eliminate all fat within the kidneys and intestines and the location of the CT scans (i.e. L3, vs L4 vs L4-5 etc.). Quantifying VAT using suggested threshold (-150, -50 HU) captures fat within the intra-abdominal cavity (VAT) *and* within the kidneys and intestines. Improper imaging analysis produces unreliable, overestimated VAT data. Removing the fat within the kidneys and

intestines from the VAT area is possible with the Slice-O-matic software, but not with NIH ImageJ. The VAT area reported in this study reflects CT body composition imaging analysis training provided by Dr. Vickie Baracos and her lab at the University of Alberta (Canada) using their Slice-O-matic training manual. Among the six VAT-CRC studies[1,99,102,232-234] none mentioned removal of extra fat from their VAT estimates. Anatomical features within the intra-abdominal cavity on a CT image vary between individuals at the same anatomical landmark (L3, L4, L4-L5). Therefore a CT image will not always show fat within the kidneys and intestines at the same anatomical landmark. Our rigorous design coupled with accurate body composition analysis indicates the adipose depots of individuals with CRC do not differ from cancer-free controls of similar age, BMI and gender.

8.0.1.0. Implications of finding no association between VAT and CRC

We believe there are at least three major reasons the association between larger VAT depots and CRC was not observed. First, it may be that VAT is not related to CRC, despite its established heightened risks from inflammation and IR. Second, it may be that VAT impacts CRC risks earlier in the carcinogenic pathway. Finally, bias from various aspects of our study design may have limited our ability to detect this relationship.

The VAT areas of cases were similar to that of controls. As described in the background section greater VAT area has been significantly related to various insulin resistant, pro-inflammatory conditions, including metabolic syndrome, diabetes, CVD and certain obesity-related cancers, including CRC.[239] Further, chronic inflammation (elevated CRP, IL-6) and up-regulation of insulin resistance pathways have been associated directly with increased VAT and CRC.[55,57,240] Despite this established relationship the exact mechanisms underlying the association are not known. It is speculated that inflammation within the adipocyte and adipose tissue, and systemically, is upregulated by expanding SAT depots eventually becoming dysfunctional (i.e. unable to expand by hyperplasia). This results in ectopic fat accumulation intra-

abdominally (VAT) and within other tissues, including the liver (which under normal conditions are devoid of fat) creating an environment conducive to CRC (upregulation of PIK3/AKT, IGF axis).[109,241]

The lack of an independent role for greater VAT assessed at CRC diagnosis in increasing disease risks, coupled with the large body of data supporting the impact of VAT on IR and inflammation which are established risk factors suggests VAT may exert its impact earlier in the pathogenic process. It may be that exposure to greater VAT area, between the normal colonic environment and increases the development of adenomas and this relationship dissipates with disease progression. In contrast to the sparse and inconsistent data for enhanced risks for CRC from greater VAT, there is strong, consistent evidence supporting heightened risks for adenomatous polyps from larger VAT depots. CR adenomas (adenomatous polyps) are precursors for CRC[11] and if left untreated have a 70-90% chance of converting to CRC.[242] Excess VAT is a strong independent predictor of CR adenomas and both the size and number of adenomas increase with increasing VAT.[37,109,243-246] Various meta-analyses provide strong evidence for the association between VAT and adenoma risk. The meta-analysis by Keum et al[243] reported a 13% increase in adenoma risk for every 25cm^2 increase in VAT (OR 1.13, CI 1.04-5-1.21). In another meta-analysis, Hu et al[245] reported a 67% increase in adenoma risk when comparing lowest to highest VAT tertiles (OR: 1.67, CI 1.29-2.16). Thus, It is likely the time interval between having CRC and being diagnosed with this disease ranges from months to years, particularly in uninsured populations that are not routinely screened or in patients that are asymptomatic. It may be that excess VAT stimulates the progression of adenomas to CRC and once cancer has developed changes in metabolism and overall adipose depots occur. If this is the situation, CRC case-control studies would not detect associations between the disease and these depots measured at CRC diagnosis. Detection would require a prospective design with baseline colonoscopies and CT scans of cancer free status at enrollment followed by sequential

colonoscopies (every 10 years) and body composition analysis. This study would require a large population monitored over a long time interval and would be very expensive.

Weight loss is a common symptom of many malignant conditions, including CRC. Loss of appetite and dramatic weight change are red flags for this complication[15] and unplanned weight loss contributes to body compositional changes.[35,247] Adjustment for weight loss is needed when evaluating abdominal adipose tissues in cross sectional studies, particularly VAT in males as it is very sensitive to weight change.[247] To address the impact of weight loss participants (both cases and controls) with self-reported unintentional weight loss history within 6 months of their CT scan were removed from this analysis. No association between VAT and CRC was found, however this weight stable group included only 78 cases and 78 controls and was inadequately powered (β=0.63). Further, as "weight loss" was obtained from self-reported information recorded in the medical records it may have reflected biased data collection. If random misclassification of weight loss was present the impact on our overall associations would likely have been small. However, if this bias was systematic (e.g. if one facility probed less frequently or differently or if probing rates varied by insurance or race/ethnicity status) it would have biased our findings toward the null. Although our design precludes discerning if this occurred, as weight loss was obtained identically in both cases and controls it is unlikely this resulted in significant bias of our findings concerned.

There is sustained interest in detailing the mechanisms by which VAT acts as a mediator between generalized obesity and metabolic disease. Hypothesized models have conceptualized VAT (an ectopic fat) as an intermediary in the metabolic pathway between obesity and CRC via its suggested pro-inflammatory and pro-insulin resistant capabilities.[239] Due to limitations in ours and other studies in this area coupled with the potential to tailor interventions and/or medications to modify/change these ectopic adipose depots supports further exploration.

8.0.2. Subcutaneous Adipose Tissue Subtypes and CRC

Having a higher SAT to VAT body fat distribution is considered less pathogenic.[57,248,249] It is postulated that insulin-sensitive 'healthy' functioning SAT (functional adipogenesis) provides a depot where excess fat can be safely stored without inducing inflammation and IR.[55,250] Individuals with greater SAT than VAT have lower risks for IR and inflammation[55,65] however contradictory findings have been reported in males and patients with T2DM.[251,252] Emerging evidence on subtypes of SAT in diabetes and cardiovascular research implicates DSAT as more 'pathogenic' than SSAT due to its metabolic resemblance to VAT.[253] Among male participants, the adjusted logistic regression predictors of CRC included IMAT (OR=2.8, 95%CI 1.1-7.0), SSAT (OR=0.2, 95%CI 0.1-0.7) and weight loss history (OR=3.9, 1.4-10.7). For the complete sample, we found SSAT but not SAT reduced the odds for CRC (Adjusted OR: 0.19, CI 0.06-0.64) and was the only depot that significantly predicted CRC (adjusting for aspirin and reported weight loss). No previous data exploring a role of DSAT or SSAT in CRC is available for comparison. Higher SSAT has been associated with protective metabolic effects such as better glycemic control and cardiovascular parameters (better blood pressure and heart rates) in patients with T2DM.[249] Furthermore, biopsy studies have determined that SSAT has a lower saturated fatty acid to monounsaturated fatty acid content[248] and higher expression of pro-inflammatory genes[254] than DSAT. Additionally, SSAT has been described as 'protective storage', 'a sink' or 'a buffer' due to its affinity for accumulating and storing fatty acids.[248] This protective relationship between SSAT and CRC was not apparent when SAT rather than its two components (superficial and deep SAT) was analyzed. Our findings provide the first quantification of these depots controlling for BMIin a CRC population and provide intriguing hypothesis generation for future areas of investigation.

8.0.3. Intermuscular Adipose Tissue and Colorectal Cancer

The connection between IMAT and CRC has not been previously described. Our linear regression models indicated IMAT significantly predicted other abdominal adipose depots: VAT, SAT, SSAT and DSAT, confirming the interrelationships that has been reported in healthy populations, but it was not associated with CRC. Unadjusted logistic analysis indicated IMAT was significantly related to CRC but this disappeared when other variables were added to the models. The discrepancies between these two multivariable techniques likely reflects the loss of power from dichotomizing IMAT in the logistic models. Although excess IMAT has been closely associated with IR [255-257] and inflammatory markers (C-reactive protein),[255,258] our results suggests it is not related to CRC risk. Excess abdominal IMAT has been associated with muscle dysfunction[259] and aging[255,260] and mid-thigh IMAT has been associated with T2DM.[251] Aging and T2DM are both risk factors for CRC. It is possible the contribution of IMAT to the pathogenesis of CRC is via similar inflammatory and insulin resistance pathways. Abdominal IMAT remains a vastly understudied adipose tissue, particularly in chronic disease conditions such as CVD and CRC. This emerging area of research holds promise for clarifying the link between ectopic fat and CRC.

8.0.4. Gender differences of Body Composition Parameters

Gender differences of body composition parameters have been established[55,78,82] however, little information has been reported on gender specific body composition in patients with CRC. In agreement with established literature for the age of our participants, female cases and controls (median age 62.5, n=98) retained a lower VAT and higher SAT body composition phenotype than males. Although we could not generate gender specific incidence rates of CRC the participant inclusion reflected the availability of cases accrued between 2009 and 2014 and, not surprisingly, also reflected the gender specific national incidence rates in the United States (57.2% men, 42.1%

women) for CRC.[24] Our SAT and VAT estimates for cases and controls were similar to those reported for gender-specific healthy populations[55,78] further corroborating our earlier findings for a lack of relationship.

Body composition in women change from low VAT and high SAT prior to menopause to higher VAT and lower SAT after menopause.[52,55,81] The average age of menopause is 51 years of age[261] and the average age women are diagnosis with CRC is 73.[24] Our female cases and controls were 63 years old and their VAT and SAT depots reflected those of pre-menopausal rather than postmenopausal women. These findings suggest we may not have captured the age range consistent with the expected postmenopausal body composition phenotype associated with increased CRC risk in women. This further suggests that other factors associated with obesity may be increasing CRC risk in mid-age women such as estrogen and its interaction with the estrogen receptor-α which has been implicated in CRC[216] but remains inconclusive.

8.1. Specific Aim 2: Hypothesis – Is there a race/ethnic influence on body composition that impacts colorectal cancer risks?

In agreement with our hypothesis, we found the same race/ethnic variations in body composition reported in the literature within and between our AA and NHW cases and controls, with the exception of IMAT. Unadjusted stratified analysis showed AA cases and controls had significantly lower VAT and similar SAT areas as their NHW counterparts. The race/ethnic variation of VAT between NHW and AA is well established for males[7,200-202,262,263] but less conclusive for females.[81,205,263]

Race/ethnic differences in abdominal IMAT is less studied and we are the first to identify a difference between AA and NHW cases *and* controls in unadjusted stratified analysis. The few available studies in this arear have assessed mid-thigh rather than abdominal IMAT in healthy populations. We found significantly lower abdominal IMAT in AA cases/controls compared to NHW cases/controls which is contrary to the literature. Beasley et al examined inter and

intramuscular mid-thigh fat in AA and NHW older men and women (>70 years of age) and determined that AA (males and females) had higher thigh-IMAT than NHW counterparts.[258] Similarly Ryan et al found higher mid-thigh IMAT in AA vs NHW postmenopausal women.[264] Collectively these results suggest AA have less abdominal IMAT and more mid-thigh IMAT accumulation compared to NHW and may reflect their tendency for peripherally driven insulin resistance.[257,264] There may be other factors influencing deposition of IMAT preferentially in mid-thigh for AA but this remains speculative. More research disentangling the relationships between mid-thigh and abdominal IMAT are needed with specific emphasis on race/ethnicity.

It is possible that the race/ethnic differences we observed were due to weight loss in our AA group however several findings suggest it was not responsible for the differences observed. First, IMAT was not statistically different between cases and controls ***within*** each of the race ethnic groups. Additionally, weight loss history was not a significant predictor of IMAT for either race/ethnic group.

Our unadjusted stratified analysis indicated AA cases and controls had significantly lower VAT and similar SAT area than their NHW counterparts, however in adjusted logistic regression the only remaining significant predictor for CRC was SSAT (adjusting for aspirin and weight loss history). Results of Specific Aim 1 indicated SSAT was the only abdominal adipose depot that predicted CRC (adjusted logistic regression, OR: 0.19, 95% CI 0.06-0.65). Additionally, stratified tables for AIM 2 showed that AA cases and NHW cases had significantly lower SSAT compared to controls and the only depot that was statistically significant for AA (adjusting for aspirin and weight loss history) but not for NHW. No other investigations exploring race/ethnicity and SSAT in CRC have been reported and only one study in healthy postmenopausal women has explored the race/ethnic differences of SSAT in AA and NHW. They found SSAT was significantly higher in AA compared to NHW after adjusting for total body fat and age.[265] Our findings indicate that higher SSAT is protective in relation to CRC for AA. It may be AA with lower VAT and SSAT have a body composition that is particularly protective for CRC. These findings are provocative

and require further study with larger samples of both race/ethnic groups to make conclusive statements.

8.2. Specific Aim 3. Hypothesis - What are the associations between abdominal adipose depots and serum biomarkers of colorectal cancer risk? Are these associations modified by race/ethnicity?

This discussion for Specific Aim 3 is divided into two sections. First the implications of our significant results in the subgroup of male cases with serum biomarker data will be discussed. The second section describes the significant major findings using the complete sample (males and females) with serum data.

8.2.1. Significant Findings between Body Composition and Serum Biomarkers in Male Cases with Serum Samples

We found race/ethnicity, VAT, diabetes, TNF-α, and IMAT were independent predictors of APN. Inverse associations with VAT and diabetes and positive associations with TNF-α and IMAT were observed. The inverse associations with VAT and diabetes are expected since the protective role of APN diminishes as these conditions manifest.[223,266] The positive association between APN and TNF-α and IMAT possibly indicates its potential dual role as a pro-inflammatory cytokine as has been described in several cancers including CRC.[148,155,223] The race/ethnic differences of APN are well established[267-269] and our findings confirm this association in men with CRC. VAT is negatively related with APN[270] however this association is not as pronounced for AA males who have low levels of VAT and low APN levels compared to other race groups.[271] Our findings of diabetes as an independent predictor of APN in cases is consistent with its role as insulin-sensitizing adipokine and in diabetes circulating levels are lower.[151,266,272] It is also well established that TNF-α inhibits APN. It is reported that TNF-α is a major regulator of many metabolic pathways including insulin signaling pathways, adipocyte metabolism and APN synthesis[147,151] and with increased adipose tissue (especially VAT origin) secretion of TNF-α is increased.[147] Increased TNF-α secretion represses APN synthesis.[147] Also, TNF-α is a potent

pro-inflammatory cytokine associated mechanistically to CRC via activation of oncogenic transcription factors nuclear factor kappa-B (NFkB) and signal transducer and activator of transcriptor 3 (STAT3).[273-275] In turn activation of NFkB and STAT3 reduces apoptosis of pre-tumor and tumor cells and increases proliferation.[142,275] Therefore, TNF-α is implicated in every stage of tumor development from initiation to metastasis.[275] High levels of circulating TNF-α are observed in patients with CR adenomas[276] and mRNA expression is elevated in VAT biopsies of CRC patients[277]

We found that IMAT predicted APN in our men with CRC. The relationship between IMAT, APN and CRC has not previously been reported. This is supported by the findings by Register et al[278] in AA patients with T2DM where APN was positively associated with IMAT. Previous studies have found AA populations have low VAT and high thigh IMAT and greater IR.[208,264] These findings may indicate that thigh IMAT is involved with IR whereas abdominal IMAT may not.[208] We assessed IMAT at the L3 region rather than mid-thigh and found AA men had low IMAT and VAT and low APN. This suggests that abdominal IMAT at L3 may not impact insulin sensitivity similarly as mid-thigh IMAT particularly in males. Further studies quantifying simultaneous measures of IMAT in both of these regions are needed to clarify these relationships.

Stratified analysis indicated only APN and IGFBP-3 varied between AA and NHW male cases, despite the AA men having significant lower VAT. Race/ethnic differences in APN have been reported but not specifically for CRC limiting the ability to directly compare our findings with others. An et al[154] reported CRC cases had lower APN levels than CR adenomas or healthy controls. While we could not compare serum level in our cases to controls we did find significantly lower APN levels in our AA males compared to NHW males which has been previously reported in healthy populations.[266-268] Lower levels of APN have also been associated with increased CRC risk in males in the Health Professionals Study.[279] Our findings are consistent with race/ethnic variations observed in healthy populations, even within our limited sample size for NHW (N=15). These findings suggest although AA have lower VAT compared to NHW, their lower circulating

levels of APN may override the “low VAT benefits” and contribute to their increased CRC risk. More studies exploring the race/ethnic variations of APN are needed to determine which mechanisms are involved.

Mean IGFBP-3 levels for AA were significantly lower than for NHW males while IGF-1 did not differ between the groups. This finding is consistent with a healthy representative sample of the US population which found that AA had lower serum levels of IGFBP-3 than NHW but IGF-1 was similar between race/ethnic groups.[280] The role of IGFBP-3 and IGF-1 in CRC is not fully understood and there is conflicting evidence on their importance. A nested case-control study of CRC in a large European cohort compared did not find any associations between IGFBP-3 and CRC risk, while a moderate association for IGF-1 with CRC was found.[228] The role of IGFBP-3 in CRC remains inconclusive and whether race/ethnic differences of IGFBP-3 observed between AA and NHW are biologically important need to be determined.

Although our serum biomarker analysis was restricted to a small sample of cases, significant race/ethnic differences of known biomarkers associated with CRC risk were found, particularly APN and IGFBP-3. We were also able to describe associations between serum biomarkers of CRC risk and body composition in AA and NHW in patients with non-metastatic CRC. Our male AA cases had significantly less APN and IGFBP-3 than NHW cases. Furthermore we postulate a connection between VAT, abdominal IMAT and mid-thigh IMAT with APN in AA that needs further examination. Our findings indicate that certain serum biomarkers in our cases (APN) resembled levels associated with chronic conditions (T2DM) while others resembled levels observed in healthy populations. We observed similar race/ethnic differences in APN and IGFBP-3 in our participants as previously reported in healthy populations.

8.3. Specific Aim 4. Hypothesis - What is the feasibility of using two techniques for assessment of hepatic fat contents in patients with and without colorectal cancer and how many patients classify as having hepatic steatosis according to these two methods?

The discussion presented in this section briefly summarizes the feasibility of using a CE and NCE techniques for HFC in our study. This is followed with the implications of our results of the CE and NCE protocols and future directions.

We found an unexpectedly high number of patients with CE CT images, despite scans being labeled as 'with and without contrast'. In an effort meet the aims proposed of HFC analysis, the literature was explored and two studies were identified[116,230] that described techniques for calculating HFC from CE images. The first method was developed by Kim et al[116] and required the average of multiple circular regions of liver (8 measurements), spleen (3 measurements), aorta (3 measurements) and main portal vein (3 measurements). Monjardim et al[230] simplified this approach to three circular measurements (1 measurement each for aorta, main portal vein and liver). They compared this approach to those obtained with the Kim et al[116] protocol found good agreement between the two methods (kappa =0.84, p=0.001).

The CE technique by Monjardim et al[230] was applied for the HFC calculation. As presented in Specific Aim 4 results, 78%(68/87) of cases and 81%(26/32) of controls were classified as having hepatic steatosis. These findings are similar to those reported by Monjardim et al[230] (88%; 132/150) in their retrospective study of cancer-free patients 18 years. Although our findings are consistent with Monjardim et al caution is warranted in accepting their validity. Variations in techniques between the three hospitals in our study likely influenced the calculations. Furthermore, we are the first to apply these techniques in a non-validation format for hepatic steatosis diagnosis. The use of these techniques is in its infancy and this is an exciting and emerging area for future studies especially in CRC where CE CT scans are a norm.

Our NCE CT image criterion of HFC yielded prevalence rates closer to what has been reported by other studies in healthy populations. Lawrence et al[281] reported 7.6% (38/500) of patients 18 years and older with CT scans completed between 2007 - 2010 completed for multiple

health reasons (hepatocellular carcinoma screening, abnormal liver tests, pancreatic cancer metastatic evaluation) had hepatic steatosis. Differences of HFC by race/ethnic in healthy populations has been reported by two publications derived from the prospective cohort Dallas Heart Study.[206,210] Browning et al[210] reported (n=2,287, 24% AA vs 33% NHW vs 45% Hispanics)[210] significantly lower HFC in AA males compared to NHW males (23 vs 42%, $p<0.05$). Guerrero et al[206] found in 22% AA (474/1007) of and 41% NHW (364/1007) men had hepatic steatosis ($p<0.05$). Among women 23% of AA (584/1136) and 24% of NHW (355/1136) had hepatic steatosis.[206] Overall 10 % of our patients with available scans were categorized has having HCF defined as hepatic attenuation less than or equal to 40HU. This rate is very similar to than those reported by Lawrence et al but much lower than Browning et al and Guerrero et al. Unfortunately, our small sample prohibited race/ethnic exploration of HFC. Interestingly we found that 100% of the patients that classified with hepatic steatosis were controls using the 40HU. This finding is paradoxical considering hepatic steatosis is a risk factor for CRC.[123] Our findings suggest the HFC of cases is not greater than controls, however due to the tiny numbers explored further studies are needed before conclusions can be made.

In depth analysis of hepatic steatosis was not possible in this study due to small sample size, problems with CT acquisition and common use of CE scans for CRC metastatic evaluation. Additionally, our study demonstrated that using one landmark (T12L1) for HFC excludes a large number of possible participants. Hepatic steatosis is a risk factor for CRC and other factors related to CRC such as MetS and T2DM.[126,282,283] However, exact mechanisms are not well understood and require further investigations especially in minority populations. We suggest that future studies apply standardized CT techniques especially if using CE scans (injection rate and image acquisition), use flexible landmarks to ensure that important anatomical features are visible and whenever possible implement the NCE technique for HFC analysis which is more accurate than the CE technique. The CE techniques initially proposed by Kim et al[116] and modified by

Monjardim et al[230] hold great promise for analyzing CE images in clinical settings when these are more readily available than NCE CT images.

8.4. Limitations and Strengths

Our study, though rigorous in design has several limitations that should be considered. First resources were extremely limited. Cases were selected from medical records of individuals with good quality CT images that included the L3 region of newly diagnosed CRC at three urban medical centers. Controls were selected from patients hospitalized with good quality CT images of L3 region at the same medical centers and during the same time interval (2009 - 2014) as the cases. A superior design would have selected both cases and controls from the pool of individuals seeking colonoscopies at the same centers. Unfortunately CT imaging is not the standard of care for disease free patients seeking CRC screening colonoscopies in the US. Selecting controls as described would require payment for the subsequent CT rather than exploitation of their diagnostic images. Additional limitations of our controls include the lack of serum biomarker data thus their inflammatory status was not known.

Because our controls were hospitalized patients with various chronic and acute illnesses they may have greater VAT and had higher inflammatory status than our cases. Individuals with medical histories of obesity-related diseases (diabetes, HTN) were included in our cohort. Hypertension was present in ~65% of our subjects (64 % of cases and 66 % of controls) and larger VAT depots occur in patients with HTN, especially in AA males.[240,284,285] VAT is postulated to increase blood pressure by activation of the-sympathetic nervous system or by increasing the free fatty acids delivery into the portal circulation which increases insulin resistance or by stimulating the renin-angiotensin system[240]. Thus, HTN is in the causal pathway between VAT and CRC. In our study, the prevalence of diabetes and HTN was not statistically different between cases and controls and our VAT areas reflected those reported in healthy populations, thus it is unlikely that these clinical conditions impacted VAT estimates.

Although we excluded controls with CRC, patients with undiagnosed CRC may have been unintentionally included. Adenomas CRC develops over 10-20 years[24] and patients may have polyps or undiagnosed disease for months or years, particularly in underserved populations not routinely screened with various health access disparities and not receiving regular medical evaluations. Thus exposure to the effects of the VAT-inflammation-IR pathways may be present months or years prior to manifestation of the disease.

Overmatching was a significant concern however, ultimately matching on BMI, age and race was employed to ensure adequate numbers within each category to enable comparisons. This did result in small numbers for some categories but it provided preliminary data for assessment of variability and power analysis for sample size requirements in future investigations. We also did not have information on dietary and exercise habits of subjects in our study and these are important risk factors that have been associated with CRC. Our participants represented a diverse race/ethnically recruited from an urban city with and without CRC and therefore are not generalizable to other populations. Finally, median splits rather than lower and upper quartiles were used in our logistic models, potentially limiting the ability to detect differences between groups.

Our study has several important strengths. First, it is the first study to explore the relationship between CRC and race/ethnicity and body composition of a US population. Our findings contribute important, much needed data on body composition in AA and NHW adults with and without CRC. Additionally, we are the first to rigorously match on age, BMI, gender and race/ethnicity to explore the relationship between VAT and CRC. We explored abdominal adipose depots including SSAT and DSAT which are depots that have received less attention in the literature. We analyzed the CT images using detailed, standardized body composition analysis protocols, including accurate measurements of VAT. We obtained information about weight loss in both our cases and controls identically, thus likely controlling for this potential confounder. We explored the relationship of nine biomarkers associated with CRC in some of our patients and

examined the race/ethnic differences in this sample. And finally, both the NCE and CE CT imaging protocol were used for HFC analysis in our sample enabling their feasibility, however in depth analysis was not possible due to small sample size and differences in CT acquisition. Therefore results of HFC interpreted cautiously and recommendations for future studies based on our findings were provided.

IX. CONCLUSIONS

Our findings indicate cases and controls had similar amounts of VAT and excess VAT did not increase risks for CRC. Additionally, race/ethnic differences in body composition between cases and controls were not found other than from those established in the literature in healthy populations. The AA group (cases and controls) had significantly lower VAT stores than their NHW countertops and these differences remained after exploring a weight stable contingent. The SAT subtype, SSAT was protective particularly for AA males. This depot has been studied much less than VAT and our findings support exploration of its contribution to CRC, particularly as it is a readily accessible for tissue acquisition. Our study also confirmed that AA males tended to have lower levels of APN compared to NHW males. This association warrants further study as lowered APN levels are associated with increased CRC risks and AA males in particular even in healthy populations have a tendency for lower APN this may be a contributing factor to their increased CRC risk. Our serum data results also supports the theory that APN plays a significant role.

X. APPENDICES

1. APPENDIX A

PEARSON CORRELATION MATRIX OF BODY COMPOSITION DEPOTS AND SERUM BIOMARKERS IN MALES

	BMI	WC	TAT	SAT	SSAT	DSAT	VAT	IMAT	APN	TNFα	IL6	LEPTIN	IGFBP3	IGF1
BMI	1.00	0.79	0.72	0.68	0.55	0.59	0.66	0.46	-0.31	-0.06	-0.11	0.62	0.15	0.25
		<.0001	<.0001	<.0001	0.00	<.0001	<.0001	0.00	0.04	0.73	0.50	<.0001	0.34	0.11
WC	0.79	1.00	0.92	0.81	0.61	0.84	0.85	0.72	-0.36	0.05	-0.08	0.72	0.23	0.21
	<.0001		<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.03	0.77	0.63	<.0001	0.17	0.21
TAT	0.72	0.92	1.00	0.85	0.55	0.75	0.93	0.74	-0.28	-0.04	-0.03	0.80	0.35	0.11
	<.0001	<.0001		<.0001	0.00	<.0001	<.0001	<.0001	0.07	0.79	0.83	<.0001	0.02	0.47
SAT	0.68	0.81	0.85	1.00	0.74	0.87	0.69	0.59	-0.29	0.02	-0.05	0.73	0.23	0.10
	<.0001	<.0001	<.0001		<.0001	<.0001	<.0001	<.0001	0.06	0.90	0.73	<.0001	0.14	0.53
SSAT	0.55	0.61	0.55	0.74	1.00	0.66	0.34	0.40	-0.28	0.11	-0.06	0.50	0.08	0.06
	0.00	<.0001	0.00	<.0001		<.0001	0.04	0.02	0.10	0.52	0.73	0.00	0.66	0.72
DSAT	0.59	0.84	0.75	0.87	0.66	1.00	0.59	0.67	-0.21	0.05	0.11	0.69	0.17	-0.06
	<.0001	<.0001	<.0001	<.0001	<.0001		<.0001	<.0001	0.17	0.75	0.47	<.0001	0.26	0.72
VAT	0.66	0.85	0.93	0.69	0.34	0.59	1.00	0.64	-0.37	-0.08	-0.04	0.73	0.29	0.10
	<.0001	<.0001	<.0001	<.0001	0.04	<.0001		<.0001	0.02	0.63	0.79	<.0001	0.06	0.51
IMAT	0.46	0.72	0.74	0.59	0.40	0.67	0.64	1.00	0.06	0.04	-0.06	0.62	0.33	-0.04
	0.00	<.0001	<.0001	<.0001	0.02	<.0001	<.0001		0.72	0.79	0.70	<.0001	0.03	0.79
APN	-0.31	-0.36	-0.28	-0.29	-0.28	-0.21	-0.37	0.06	1.00	0.22	-0.19	-0.33	0.23	-0.09
	0.04	0.03	0.07	0.06	0.10	0.17	0.02	0.72		0.16	0.21	0.03	0.14	0.56
TNFα	-0.06	0.05	-0.04	0.02	0.11	0.05	-0.08	0.04	0.22	1.00	0.32	0.24	0.07	-0.14
	0.73	0.77	0.79	0.90	0.52	0.75	0.63	0.79	0.16		0.03	0.12	0.66	0.39
IL6	-0.11	-0.08	-0.03	-0.05	-0.06	0.11	-0.04	-0.06	-0.19	0.32	1.00	0.16	-0.24	-0.34
	0.50	0.63	0.83	0.73	0.73	0.47	0.79	0.70	0.21	0.03		0.31	0.12	0.03
LEPTIN	0.62	0.72	0.80	0.73	0.50	0.69	0.73	0.62	-0.33	0.24	0.16	1.00	0.35	0.12
	<.0001	<.0001	<.0001	<.0001	0.00	<.0001	<.0001	<.0001	0.03	0.12	0.31		0.02	0.43
IGFBP3	0.15	0.23	0.35	0.23	0.08	0.17	0.29	0.33	0.23	0.07	-0.24	0.35	1.00	0.42
	0.34	0.17	0.02	0.14	0.66	0.26	0.06	0.03	0.14	0.66	0.12	0.02		0.01
IGF1	0.25	0.21	0.11	0.10	0.06	-0.06	0.10	-0.04	-0.09	-0.14	-0.34	0.12	0.42	1.00
	0.11	0.21	0.47	0.53	0.72	0.72	0.51	0.79	0.56	0.39	0.03	0.43	0.01	

2. APPENDIX B

CT SCAN Checklist

Subject ID:	**CT Scan Date:**
Date of Procedure:	**Landmarks:** L3 T12L1 Other:
Good Quality Image: YES NO If no, explain:	**Scanner Location:** UIHHSS JHS RUMC
Slice Format:	**Scanner Manufacturer:** **Model:**
Type of Scanner: Conventional Helical Other	**CT Scan Protocol:**
IV Contrast: YES NO	**Scan Time (s):**
Image Resolution Matrix: ☐ 512X512 Other:	**Slice Thickness (mm):** 3mm 5mm Other:
Table Position (mm):	**Table Height (mm):**
Gantry/Tilt:	**Tube Voltage (kV):**
Tube Current (mA):	**Field of View (FOV, mm):**
Review all scans and answer questions for each.	
1. Is L3 or L4-L5 identifiable? YES NO If no, explain:	**2. Is T12-L1 identifiable?** YES NO If no, explain:
3. Is visceral cavity identifiable? YES NO If no, explain:	**4. Is subcutaneous cavity identifiable?** YES NO If no, explain:
5. Is there any other problem with scan?	

Standard Hounsfield Unit Ranges for use during analysis:

- ☐ Adipose Tissue -190 to -30 HU
- ☐ Visceral Adipose Tissue -150 to -50 HU
- ☐ Muscle -29 to 150 HU

Reviewer Initials:_____

Date when CT Scan Checklist collected:_____

3. APPENDIX C

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review – Expedited Review

September 19, 2014

Sandra L. Gomez-Perez, MS, RD
Department of Kinesiology and Nutrition
1919 W. Taylor Street
Room 650, M/C 517
Chicago, IL 60612
Phone: (312) 413-9896 / Fax: (312) 413-0319

RE: Protocol # 2014-0837
"Body composition and biomarkers of colorectal cancer risk in African Americans and Non-Hispanic Whites"

Dear Ms. Gomez-Perez:

Members of Institutional Review Board (IRB) #3 reviewed and approved your research protocol under expedited review procedures [45 CFR 46.110(b)(1)] on September 19, 2014. You may now begin your research.

Your research meets the requirements for approval under the following Expedited Review [45 CFR 46.110(b)(1)] Category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

Please note the following information about your approved research protocol:

1. **OPRS records indicate that investigator training for Dr. Xavier Llor expired on 9/6/2014; additionally, OPRS has no training record for Liam McKeever. Dr. Llor must complete 2 hours of Investigator Continuing Education, and Mr. McKeever must complete both the Initial and HIPAA Investigator Training requirements prior to any participation in this research. Please provide an amendment to notify OPRS and update the training records once the training requirements have been met.**

2. **Provide documentation of IRB approval from Rush upon availability, as well as documentation of training for Dr. Joy Sclamberg. Such documentation must be submitted to OPRS via an amendment, and must be approved by the UIC IRB before any research-related activities occur at the Rush site.**

Protocol Approval Period: September 19, 2014 - September 19, 2015
Approved Subject Enrollment #: 256 (100 at UIC; 156 from other sites)
Performance Sites: UIC; John H. Stroger, Jr. Hospital of Cook County; Rush University Medical Center
Sponsor: None
Research Protocol:

a) Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites; Version 2, June 16, 2014

Informed Consent:

a) Waiver of Informed Consent granted, [45 CFR 46.116(d)]

HIPAA Authorization:

a) Waiver of Authorization granted, [45 CFR 164.512(i)(1)(i)]

Additional Determinations for Research Involving Minors:
These determinations have not been made for this study since it has not been approved for enrollment of minors.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
09/04/2014	Initial Review	Expedited	09/19/2014	Approved

Please remember to:

→ Use your **research protocol number** (#2014-0837) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS office at (312) 996-1711 or me at (312) 413-3202. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Teresa D. Johnston, B.S., C.I.P.
Assistant Director
Office for the Protection of Research Subjects

Enclosures:

1. **UIC Investigator Responsibilities, Protection of Human Research Subjects**
2. **HIPAA Authorization:**
   a) Certificate of Waiver of Authorization

cc: Carol Braunschweig, Faculty Sponsor, Kinesiology and Nutrition, M/C 517
Charles B. Walter, Department of Kinesiology and Nutrition, M/C 517
Meha Singh, Cancer Center, 318 MCA, MC 700
Privacy Office, Health Information Management Department, M/C 772

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval of Request for Waiver or Alteration of Individual Authorization For Disclosure of Protected Health Information

The University of Illinois at Chicago Institutional Review Board (IRB) #3 hereby approves a waiver or alteration of the requirements for individual authorization for the use or disclosure of protected health information regarding:

UIC Protocol Number: **2014-0837**

Research Protocol Title: **Body composition and biomarkers of colorectal cancer risk in African Americans and Non-Hispanic Whites**

Principal Investigator: **Sandra L. Gomez-Perez, MS, RD**

The IRB has determined that the request for a waiver of authorization satisfies the criteria for a waiver of authorization in accordance with 45 CFR Part 164.512, such that:

1) The use or disclosure of protected health information involves no more than minimal risk to the individuals;
   a) There is an adequate plan to protect the identifiers from improper use and disclosure;
   b) There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law;
   c) There are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted;
2) The research could not practicably be conducted without the alteration or waiver; and
3) The research could not practicably be conducted without access to and use of the protected health information.

The type of protected health information (PHI) to be used in the research includes: Date of birth, date of CT scan and CT scan results, date of admission, medical record number, anthropometrics, demographics, medical history.

Additionally, the IRB has determined that the requested PHI is the minimum necessary for the investigator to reasonably conduct the research.

This waiver of authorization has been reviewed under Expedited review procedures on September 19, 2014.

Paul Heckerling, MD
Chair, IRB #3

9/23/14
Date

Cook County Health & Hospitals System
Research Affairs
627 S. Wood St, Rm 218
Chicago, IL 60612
(312) 864-0716

John Jay Shannon, MD
Chief of Clinical Integration

Lynda Brodsky
Director, Research Affairs

June 9, 2014
Vivek Chaudhry MD
Surgery
1900 W. Polk, #407
Chicago IL 60612

RE: Our Study #14-053 **Meeting Date:** 5/20/2014

Dear Dr. Chaudhry:

Protocol Title:

Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites

This is to inform you that the above referenced Study has been presented to the Institutional Review Board was approved subject to the conditions and explanation below. **You must obtain a stamped consent form before you can begin.**

Expiration Date: 5/19/2015
Approved: New protocol, by expedited review.

Please note the expiration date. **Unless you have a waiver of consent, use a current stamped consent form when enrolling subjects.** If you plan to continue any aspect of your protocol beyond this date, please submit a progress report six weeks prior to the expiration. **Submission of a progress report is your responsibility. The protocol will be suspended and ultimately closed if it is not renewed.**

Your study may be audited by a member of the Institutional Review Board. These random visits are to assure compliance and address questions that may arise.

If you change your protocol in any way or if you add participant, provider or recruitment materials to the protocol, you must submit these for review and approval before initiation. Additionally, you must report any adverse events whether they are local or off site in a timely manner. **Subsequent approvals for modifications do not change your expiration date.**

Sincerely,

Funeka M. Sihlali, MJ, R.N.
IRB Quality Assurance Officer

RUSH UNIVERSITY MEDICAL CENTER
1653 WEST CONGRESS PARKWAY, CHICAGO, ILLINOIS, 60612-3833
RUSH UNIVERSITY

RUSH UNIVERSITY MEDICAL CENTER

Full Accreditation

RESEARCH AND CLINICAL TRIALS ADMINISTRATION OFFICE
312.942.5498
312.942.2874 (FAX)

Institutional Review Board #1
FWA #: 00000482

Notification of Amendment Approval

The following amendment has been reviewed and approved by the Institutional Review Board at Rush University Medical Center in accordance with the Common Rule (45CFR46, December 13, 2001) and any other governing regulations or subparts. Our Institutional Federalwide Assurance Number is FWA00000482.

ORA Number: 10031003-IRB01-AM12
Principal Investigator: Ece Mutlu
Project Title: Chicago Colorectal Cancer Consortium: Colorectal Cancer in African Americans
Date of approval: 4/30/2014
Due for continuing/annual review: 4/30/2015
Date Amendment Approved: 10/2/2014

Description of Amendment: The following will be added to the protocol: A single cross-sectional slice from diagnostic CT scans of male patients of varying race/ethnicities (>40 years) with colorectal cancer (CRC) enrolled in the Chicago Colon Cancer Consortium will be quantified for liver fat content, visceral, subcutaneous (deep and superficial), intramuscular. Suspected or proven CRC requires a chest/abdominal/pelvic CT as part of the routine care/ work-up prior to CRC surgery. CT images will be exploited for this study for assessment of various

body composition depots. The electronic medical record will be reviewed to document dates of diagnostic abdominal CT scans. A radiology resident will pull the scan and locate a single axial CT slice located at the midpoints of the L3 region for abdominal depots and T12-L1 intervertebral space for liver fat content will be isolated, using PACS. A DICOM image will be created, this image will not contain any patient identifying information. Dicom images will be uploaded and analyzed using Slice-O-matic software V4.3 (Tomovision) and IMAGEJ (NIH). This software permits specific tissue demarcation for abdominal adipose tissue by using Hounsfield unit (HU) thresholds of -29- to 150 for skeletal muscles (SK) (psoas, erector spinae, quadrates lumborum, transverses abdominus, external and internal obliques, and rectus abdominus) 9, -150 to -50 for visceral adipose tissue (VAT) and -190 to -30 for subcutaneous (SCAT) and intermuscular (IMAT) adipose tissue. Cross-sectional area (cm2) will be computed for each of these tissues by summing tissue pixels and multiplying by the pixel surface area. A line will be drawn around the liver to calculate its attenuation in HU following protocol by Davidson et al, 2008.

- Expedited
-
-

{The below is a representation of an electronic record that was signed electronically and is the manifestation of the electronic signature.}

Stephanie Pittman
10/3/2014 2:10 PM
Signing for Mary Jane Welch

Mary Jane Welch, DNP, APRN, BC
Director, Human Subjects Protection
Research and Clinical Trials Administration Office

UNIVERSITY OF ILLINOIS
Hospital & Health Sciences System
Cancer Center
PROTOCOL REVIEW COMMITTEE

914 S. Wood St. (M/C 700)
Room 318 MCA

Robert Molokie, MD, Chair
Meha Singh, MS, Quality Assurance

March 28, 2014

Carol Braunschweig, Ph.D., R.D.
Associate Professor
Department of Kinesiology and Nutrition

RE: PRC # 2014-0011

Decision: Approved

Dear Dr. Braunschweig:

This letter is to inform you that the University of Illinois Cancer Center Protocol Review Committee (CC-PRC) approved your protocol titled, "**BCCRC2014: Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites**" at the March 27, 2014 meeting.

A copy of the reviews is attached.

If you have not already done so, you may now submit this protocol to the UIC Institutional Review Board (IRB). Please enclose a copy of this letter and the reviewer forms.

Thank you for your attention to this letter. Please feel free to contact Meha Singh at 312-355-3046, if you have questions.

Sincerely,

Robert Molokie, M.D.
Chair
University of Illinois Cancer Center
Protocol Review Committee

UIC

Phone (312) 355-4226 Fax (312) 355-1085

UNIVERSITY OF ILLINOIS
Hospital & Health Sciences System
Cancer Center
PROTOCOL REVIEW COMMITTEE

Protocol Review Committee (CC-PRC)
Reviewer Form

Please do not exceed spaces provided.

CC-PRC # 2014-0011	**IRB #**
Principle Investigator: C. Braunschweig	
Protocol Title: Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites	
Name of Sponsor: depart	**No. of Patients to be Enrolled at UIC**: 256
Phase: n/a	**Type of Study**: observational

Brief Summary (Please include rationale, study design, any duplications of existing studies, progress in accrual and study goals, etc):
The purpose of this study is to determine if there is a unique abdominal and hepatic fat distribution phenotype in patients with colorectal cancer. To discern if patients with it retain the racial variation in body fat depots that exists in healthy populations. To discern the associations between abdominal adipose depots and hepatic fat content on biomarkers of colorectal cancer risk in serum and non-tumor tissues and explore if these relationships are modified by race/ethnicity.

Explanations/Comments:

Does the protocol have adequate safety monitoring?	☐No ☐Yes xNot Applicable	
Has the protocol been peer reviewed by NIH/NCI	xNo ☐Yes	(if yes, explain)
Does the research have feasibility?	☐No xYes	(if no, explain)
Are there foreseeable risks not acknowledged in the submission?	xNo ☐Yes	(if yes, explain)
Does the research have scientific merit?	☐No xYes	(if no, explain)
Is there a conflict of interest?	xNo ☐Yes	(if yes, explain)
Is/Are the investigator(s) qualified to conduct the research?	☐No xYes	(if no, explain)

Recommendation:
xApprove ☐Modify ☐Defer Due to Overlap ☐Defer Due to Scientific Reason ☐Disapprove

For Office Use Only:
PRC Meeting Date: 3/27/2014
Agenda # 4.1-1

REV 2/2013
Version 3.0

UNIVERSITY OF ILLINOIS
Hospital & Health Sciences System
Cancer Center
PROTOCOL REVIEW COMMITTEE

Protocol Review Committee (CC-PRC)
Reviewer Form

Please do not exceed spaces provided.

CC-PRC # 2014-0011	**IRB #**
Principle Investigator: Braunschweig, Carol	
Protocol Title: Body Composition and Biomarkers of Colorectal Cancer Risk in African Americans and Non-Hispanic Whites	
Name of Sponsor: NA	**No. of Patients to be Enrolled at UIC**:
Phase: NA	**Type of Study**: Observational

Brief Summary (Please include rationale, study design, any duplications of existing studies, progress in accrual and study goals, etc): The goal is to determine relations between abdominal adiposity, hepatic fat content, and colorectal cancer (CRC) using CT scans in cases and controls, and to assess relations of adiposity to inflammation, insulin resistance and biomarkers within non-tumor tissue from cases.

Explanations/Comments:

Does the protocol have adequate safety monitoring?	☐No ☒Yes ☐Not Applicable	
Has the protocol been peer reviewed by NIH/NCI	☒No ☐Yes	(if yes, explain)
Does the research have feasibility?	☐No ☒Yes	(if no, explain)
Are there foreseeable risks not acknowledged in the submission?	☒No ☐Yes	(if yes, explain)
Does the research have scientific merit?	☐No ☒Yes	(if no, explain)
Is there a conflict of interest?	☒No ☐Yes	(if yes, explain)
Is/Are the investigator(s) qualified to conduct the research?	☐No ☒Yes	(if no, explain)

Recommendation:
☒Approve ☐Modify ☐Defer Due to Overlap ☐Defer Due to Scientific Reason ☐Disapprove

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Agenda # 4.1-2

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XI. CITED LITERATURE

1. Yamamoto S, Nakagawa T, Matsushita Y, et al. Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. Diabetes care 2010;33:184-9.
2. Yamaji T, Iwasaki M, Sasazuki S, et al. Visceral fat volume and the prevalence of colorectal adenoma. American Journal of Epidemiology 2009;170:1502-11.
3. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Annals of Internal Medicine 1995;122:327-34.
4. Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253-63.
5. Lee IM, Manson JE, Ajani U, Paffenbarger RS, Jr., Hennekens CH, Buring JE. Physical activity and risk of colon cancer: the Physicians' Health Study (United States). Cancer Causes Control 1997;8:568-74.
6. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013.
7. Katzmarzyk PT, Bray GA, Greenway FL, et al. Racial differences in abdominal depot-specific adiposity in white and African American adults. The American Journal of Clinical Nutrition 2010;91:7-15.
8. Katzmarzyk PT, Heymsfield SB, Bouchard C. Clinical utility of visceral adipose tissue for the identification of cardiometabolic risk in white and African American adults. Am J Clin Nutr 2013;97:480-6.
9. Lund EK, Belshaw NJ, Elliott GO, Johnson IT. Recent advances in understanding the role of diet and obesity in the development of colorectal cancer. The Proceedings of the Nutrition Society 2011;70:194-204.
10. Burke CA. Colonic complications of obesity. Gastroenterology clinics of North America 2010;39:47-55.
11. Tanaka T. Colorectal carcinogenesis: Review of human and experimental animal studies. Journal of carcinogenesis 2009;8:5.
12. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: a cancer journal for clinicians 2010;60:277-300.
13. Chang S, Masse LC, Moser RP, et al. State ranks of incident cancer burden due to overweight and obesity in the United States, 2003. Obesity (Silver Spring, Md) 2008;16:1636-50.
14. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians 2011;61:69-90.
15. American Cancer S. Colorectal Cancer Facts & Figures 2011-2013. Atlanta, Ga. American Cancer Society 2011.
16. Irby K, Anderson WF, Henson DE, Devesa SS. Emerging and widening colorectal carcinoma disparities between Blacks and Whites in the United States (1975-2002). Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2006;15:792-7.
17. Society AC. Cancer Facts and Figures 2011. Atlanta. American Cancer Society2011.
18. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancerJournal international du cancer 2010;127:2893-917.
19. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet 2011;378:815-25.
20. Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, Konig HH. Economic costs of overweight and obesity. Best practice & research Clinical endocrinology & metabolism 2013;27:105-15.
21. Wick EC, Hirose K, Shore AD, et al. Surgical site infections and cost in obese patients undergoing colorectal surgery. Archives of surgery (Chicago, Ill : 1960) 2011;146:1068-72.
22. Nomura A, Heilbrun LK, Stemmermann GN. Body mass index as a predictor of cancer in men. J Natl Cancer Inst 1985;74:319-23.

23. Huang XF, Chen JZ. Obesity, the PI3K/Akt signal pathway and colon cancer. Obesity reviews : an official journal of the International Association for the Study of Obesity 2009;10:610-6.
24. Society AC. Colorectal Cancer Facts & Figures 2014-2016. Atlanta: . American Cancer Society2014.
25. Le Marchand L, Wilkens LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. Cancer causes & control : CCC 1992;3:349-54.
26. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. The New England journal of medicine 2003;348:1625-38.
27. Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women. International journal of cancerJournal international du cancer 2008;123:1892-6.
28. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni JF, Jr. Obesity and cancer risk among white and black United States veterans. Cancer causes & control : CCC 2004;15:35-43.
29. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007;16:2533-47.
30. Campbell PT, Jacobs ET, Ulrich CM, et al. Case-control study of overweight, obesity, and colorectal cancer risk, overall and by tumor microsatellite instability status. Journal of the National Cancer Institute 2010;102:391-400.
31. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. The American Journal of Clinical Nutrition 2007;86:556-65.
32. Laake I, Thune I, Selmer R, Tretli S, Slattery ML, Veierod MB. A prospective study of body mass index, weight change, and risk of cancer in the proximal and distal colon. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2010;19:1511-22.
33. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. Diabetology & metabolic syndrome 2011;3:12.
34. Shen W, Punyanitya M, Chen J, et al. Visceral adipose tissue: relationships between single slice areas at different locations and obesity-related health risks. International journal of obesity (2005) 2007;31:763-9.
35. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes 1999;48:839-47.
36. Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 2004;28:559-67.
37. Nam SY, Kim BC, Han KS, et al. Abdominal visceral adipose tissue predicts risk of colorectal adenoma in both sexes. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2010;8:443-50.e1-2.
38. Balentine CJ, Marshall C, Robinson C, et al. Validating quantitative obesity measurements in colorectal cancer patients. The Journal of surgical research 2010;164:18-22.
39. Dehal A, Garrett T, Tedders SH, Arroyo C, Afriyie-Gyawu E, Zhang J. Body Mass Index and Death Rate of Colorectal Cancer Among a National Cohort of U.S. Adults. Nutrition and cancer 2011.
40. Meyerhardt JA, Catalano PJ, Haller DG, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. Cancer 2003;98:484-95.
41. Doria-Rose VP, Newcomb PA, Morimoto LM, Hampton JM, Trentham-Dietz A. Body mass index and the risk of death following the diagnosis of colorectal cancer in postmenopausal women (United States). Cancer causes & control : CCC 2006;17:63-70.
42. Healy LA, Ryan AM, Sutton E, et al. Impact of obesity on surgical and oncological outcomes in the management of colorectal cancer. International journal of colorectal disease 2010;25:1293-9.

43. Prizment AE, Flood A, Anderson KE, Folsom AR. Survival of women with colon cancer in relation to precancer anthropometric characteristics: the Iowa Women's Health Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2010;19:2229-37.
44. Sakai T, Maekawa T, Mikami K, Kuramochi H, Noda S. Visceral fat volume and surgical outcomes of colorectal resection. International surgery 2009;94:370-2.
45. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 2006;98:920-31.
46. Shen W, Wang Z, Punyanita M, et al. Adipose tissue quantification by imaging methods: a proposed classification. Obes Res 2003;11:5-16.
47. Bjorndal B, Burri L, Staalesen V, Skorve J, Berge RK. Different adipose depots: their role in the development of metabolic syndrome and mitochondrial response to hypolipidemic agents. Journal of obesity 2011;2011:490650.
48. Tokunaga K, Matsuzawa Y, Ishikawa K, Tarui S. A novel technique for the determination of body fat by computed tomography. International journal of obesity 1983;7:437-45.
49. Bjorntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis (Dallas, Tex) 1990;10:493-6.
50. Bjorntorp P. Abdominal obesity and the metabolic syndrome. Annals of medicine 1992;24:465-8.
51. Bjorntorp P. Visceral obesity: a "civilization syndrome". Obesity research 1993;1:206-22.
52. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. Am J Clin Nutr 1993;58:463-7.
53. Despres JP. Abdominal obesity as important component of insulin-resistance syndrome. Nutrition 1993;9:452-9.
54. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983;72:1150-62.
55. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiological reviews 2013;93:359-404.
56. Despres JP, Couillard C, Gagnon J, et al. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. Arterioscler Thromb Vasc Biol 2000;20:1932-8.
57. Bays HE, Gonzalez-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert review of cardiovascular therapy 2008;6:343-68.
58. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obesity reviews : an official journal of the International Association for the Study of Obesity 2010;11:11-8.
59. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. The American journal of cardiology 1994;73:460-8.
60. Ford ES, Mokdad AH, Giles WH. Trends in waist circumference among U.S. adults. Obes Res 2003;11:1223-31.
61. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2008;33:997-1006.
62. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM, Baracos VE. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. The American Journal of Clinical Nutrition 2009;89:1173-9.

63. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. The lancet oncology 2008;9:629-35.
64. Staiano AE, Katzmarzyk PT. Ethnic and sex differences in body fat and visceral and subcutaneous adiposity in children and adolescents. Int J Obes (Lond) 2012;36:1261-9.
65. Bjorntorp P. The regulation of adipose tissue distribution in humans. Int J Obes Relat Metab Disord 1996;20:291-302.
66. Lafontan M, Girard J. Impact of visceral adipose tissue on liver metabolism. Part I: heterogeneity of adipose tissue and functional properties of visceral adipose tissue. Diabetes & metabolism 2008;34:317-27.
67. Liu KH, Chan YL, Chan WB, Chan JC, Chu CW. Mesenteric fat thickness is an independent determinant of metabolic syndrome and identifies subjects with increased carotid intima-media thickness. Diabetes care 2006;29:379-84.
68. Liu KH, Chan YL, Chan WB, Kong WL, Kong MO, Chan JC. Sonographic measurement of mesenteric fat thickness is a good correlate with cardiovascular risk factors: comparison with subcutaneous and preperitoneal fat thickness, magnetic resonance imaging and anthropometric indexes. Int J Obes Relat Metab Disord 2003;27:1267-73.
69. Komiya H, Mori Y, Yokose T, Kurokawa N, Horie N, Tajima N. Effect of intramuscular fat difference on glucose and insulin reaction in oral glucose tolerance test. J Atheroscler Thromb 2006;13:136-42.
70. Goodpaster BH, Wolf D. Skeletal muscle lipid accumulation in obesity, insulin resistance, and type 2 diabetes. Pediatric diabetes 2004;5:219-26.
71. Therkelsen KE, Pedley A, Speliotes EK, et al. Intramuscular fat and associations with metabolic risk factors in the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2013;33:863-70.
72. Muoio DM. Intramuscular triacylglycerol and insulin resistance: guilty as charged or wrongly accused? Biochim Biophys Acta 2010;1801:281-8.
73. Muoio DM. Revisiting the connection between intramyocellular lipids and insulin resistance: a long and winding road. Diabetologia 2012;55:2551-4.
74. Malis C, Rasmussen EL, Poulsen P, et al. Total and regional fat distribution is strongly influenced by genetic factors in young and elderly twins. Obes Res 2005;13:2139-45.
75. Direk K, Cecelja M, Astle W, et al. The relationship between DXA-based and anthropometric measures of visceral fat and morbidity in women. BMC cardiovascular disorders 2013;13:25.
76. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing research reviews 2009;8:339-48.
77. Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism 1995;44:369-73.
78. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gender medicine 2009;6 Suppl 1:60-75.
79. Lee MJ, Wu Y, Fried SK. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. Molecular aspects of medicine 2013;34:1-11.
80. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Menopause-related changes in body fat distribution. Ann N Y Acad Sci 2000;904:502-6.
81. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 2008;32:949-58.
82. Tchoukalova YD, Koutsari C, Votruba SB, et al. Sex- and depot-dependent differences in adipogenesis in normal-weight humans. Obesity (Silver Spring) 2010;18:1875-80.
83. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. Biology of sex differences 2012;3:13.
84. Eisner BH, Zargooshi J, Berger AD, et al. Gender differences in subcutaneous and perirenal fat distribution. Surg Radiol Anat 2010;32:879-82.

85. Tchoukalova YD, Koutsari C, Karpyak MV, Votruba SB, Wendland E, Jensen MD. Subcutaneous adipocyte size and body fat distribution. Am J Clin Nutr 2008;87:56-63.
86. Greer JB, O'Keefe SJ. Microbial induction of immunity, inflammation, and cancer. Frontiers in physiology 2011;1:168.
87. Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F. Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. The American Journal of Clinical Nutrition 1986;44:739-46.
88. Bjorntorp P. Hormonal control of regional fat distribution. Human reproduction (Oxford, England) 1997;12 Suppl 1:21-5.
89. Demerath EW, Rogers NL, Reed D, et al. Significant associations of age, menopausal status and lifestyle factors with visceral adiposity in African-American and European-American women. Annals of human biology 2011;38:247-56.
90. Stanforth PR, Jackson AS, Green JS, et al. Generalized abdominal visceral fat prediction models for black and white adults aged 17-65 y: the HERITAGE Family Study. Int J Obes Relat Metab Disord 2004;28:925-32.
91. Molenaar EA, Massaro JM, Jacques PF, et al. Association of lifestyle factors with abdominal subcutaneous and visceral adiposity: the Framingham Heart Study. Diabetes Care 2009;32:505-10.
92. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. Physiological reviews 2012;92:157-91.
93. Trussardi Fayh AP, Lopes AL, Fernandes PR, Reischak-Oliveira A, Friedman R. Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese individuals: a randomised clinical trial. Br J Nutr 2013;110:486-92.
94. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. PLoS One 2013;8:e56415.
95. Clair C, Chiolero A, Faeh D, et al. Dose-dependent positive association between cigarette smoking, abdominal obesity and body fat: cross-sectional data from a population-based survey. BMC Public Health 2011;11:23.
96. Kim JH, Shim KW, Yoon YS, Lee SY, Kim SS, Oh SW. Cigarette smoking increases abdominal and visceral obesity but not overall fatness: an observational study. PLoS One 2012;7:e45815.
97. Otake S, Takeda H, Suzuki Y, et al. Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clinical cancer research : an official journal of the American Association for Cancer Research 2005;11:3642-6.
98. Sass DA, Schoen RE, Weissfeld JL, et al. Relationship of visceral adipose tissue to recurrence of adenomatous polyps. The American Journal of Gastroenterology 2004;99:687-93.
99. Oh TH, Byeon JS, Myung SJ, et al. Visceral obesity as a risk factor for colorectal neoplasm. Journal of gastroenterology and hepatology 2008;23:411-7.
100. Kang HW, Kim D, Kim HJ, et al. Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. The American Journal of Gastroenterology 2010;105:178-87.
101. Alexander DD, Waterbor J, Hughes T, Funkhouser E, Grizzle W, Manne U. African-American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review. Cancer biomarkers : section A of Disease markers 2007;3:301-13.
102. Erarslan E, Turkay C, Koktener A, Koca C, Uz B, Bavbek N. Association of visceral fat accumulation and adiponectin levels with colorectal neoplasia. Digestive diseases and sciences 2009;54:862-8.
103. Wree A, Kahraman A, Gerken G, Canbay A. Obesity affects the liver - the link between adipocytes and hepatocytes. Digestion 2011;83:124-33.
104. Hwang ST, Cho YK, Park JH, et al. Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. Journal of gastroenterology and hepatology 2010;25:562-7.

105. Ma X, Holalkere NS, Kambadakone RA, Mino-Kenudson M, Hahn PF, Sahani DV. Imaging-based quantification of hepatic fat: methods and clinical applications. Radiographics : a review publication of the Radiological Society of North America, Inc 2009;29:1253-77.
106. Milic S, Stimac D. Nonalcoholic fatty liver disease/steatohepatitis: epidemiology, pathogenesis, clinical presentation and treatment. Digestive diseases (Basel, Switzerland) 2012;30:158-62.
107. Speliotes EK, Massaro JM, Hoffmann U, et al. Liver fat is reproducibly measured using computed tomography in the Framingham Heart Study. Journal of gastroenterology and hepatology 2008;23:894-9.
108. Kim S, Keku TO, Martin C, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer research 2008;68:323-8.
109. Muhidin SO, Magan AA, Osman KA, Syed S, Ahmed MH. The relationship between nonalcoholic fatty liver disease and colorectal cancer: the future challenges and outcomes of the metabolic syndrome. Journal of obesity 2012;2012:637538.
110. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. Journal of hepatology 2009;51:433-45.
111. Mehta SR, Thomas EL, Bell JD, Johnston DG, Taylor-Robinson SD. Non-invasive means of measuring hepatic fat content. World journal of gastroenterology : WJG 2008;14:3476-83.
112. Shores NJ, Link K, Fernandez A, et al. Non-contrasted computed tomography for the accurate measurement of liver steatosis in obese patients. Digestive diseases and sciences 2011;56:2145-51.
113. Fabbrini E, Conte C, Magkos F. Methods for assessing intrahepatic fat content and steatosis. Current opinion in clinical nutrition and metabolic care 2009;12:474-81.
114. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of nonalcoholic Fatty liver disease in the United States: the third national health and nutrition examination survey, 1988-1994. Am J Epidemiol 2013;178:38-45.
115. Davidson LE, Kuk JL, Church TS, Ross R. Protocol for measurement of liver fat by computed tomography. Journal of applied physiology (Bethesda, Md: 1985) 2006;100:864-8.
116. Kim DY, Park SH, Lee SS, et al. Contrast-enhanced computed tomography for the diagnosis of fatty liver: prospective study with same-day biopsy used as the reference standard. European radiology 2010;20:359-66.
117. Boyce CJ, Pickhardt PJ, Kim DH, et al. Hepatic steatosis (fatty liver disease) in asymptomatic adults identified by unenhanced low-dose CT. AJR American journal of roentgenology 2010;194:623-8.
118. Kodama Y, Ng CS, Wu TT, et al. Comparison of CT methods for determining the fat content of the liver. AJRAmerican journal of roentgenology 2007;188:1307-12.
119. Bydder GM, Chapman RW, Harry D, Bassan L, Sherlock S, Kreel L. Computed tomography attenuation values in fatty liver. The Journal of computed tomography 1981;5:33-5.
120. Stephens DH, Sheedy PF, Hattery RR, MacCarty RL. Computed tomography of the liver. AJR American journal of roentgenology 1977;128:579-90.
121. Zeb I, Li D, Nasir K, Katz R, Larijani VN, Budoff MJ. Computed tomography scans in the evaluation of fatty liver disease in a population based study: the multi-ethnic study of atherosclerosis. Acad Radiol 2012;19:811-8.
122. Lee YI, Lim YS, Park HS. Colorectal neoplasms in relation to non-alcoholic fatty liver disease in Korean women: a retrospective cohort study. Journal of gastroenterology and hepatology 2012;27:91-5.
123. Stadlmayr A, Aigner E, Steger B, et al. Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. Journal of internal medicine 2011;270:41-9.
124. Wong VW, Wong GL, Tsang SW, et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut 2011;60:829-36.
125. Touzin NT, Bush KN, Williams CD, Harrison SA. Prevalence of colonic adenomas in patients with nonalcoholic fatty liver disease. Therapeutic advances in gastroenterology 2011;4:169-76.
126. Armstrong MJ, Adams LA, Canbay A, Syn WK. Extra-hepatic complications of nonalcoholic fatty liver disease. Hepatology 2013.

127. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Archives of medical science : AMS 2013;9:191-200.
128. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation 2012;126:1301-13.
129. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. The New England journal of medicine 1988;319:525-32.
130. Powell SM, Zilz N, Beazer-Barclay Y, et al. APC mutations occur early during colorectal tumorigenesis. Nature 1992;359:235-7.
131. Takahashi M, Wakabayashi K. Gene mutations and altered gene expression in azoxymethane-induced colon carcinogenesis in rodents. Cancer science 2004;95:475-80.
132. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. The American Journal of the Medical Sciences 2005;330:280-9.
133. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. Journal of the American Society of Nephrology : JASN 2004;15:2792-800.
134. Trayhurn P, Wood IS. Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochemical Society transactions 2005;33:1078-81.
135. Cancello R, Clement K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. BJOG : an international journal of obstetrics and gynaecology 2006;113:1141-7.
136. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Cleveland Clinic journal of medicine 2008;75:721-8.
137. Maachi M, Pieroni L, Bruckert E, et al. Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 2004;28:993-7.
138. Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Japanese journal of cancer research : Gann 1989;80:51-8.
139. Housa D, Housova J, Vernerova Z, Haluzik M. Adipocytokines and cancer. Physiological Research / Academia Scientiarum Bohemoslovaca 2006;55:233-44.
140. Siegel EM, Ulrich CM, Poole EM, Holmes RS, Jacobsen PB, Shibata D. The effects of obesity and obesity-related conditions on colorectal cancer prognosis. Cancer control : journal of the Moffitt Cancer Center 2010;17:52-7.
141. Sethi G, Shanmugam MK, Ramachandran L, Kumar AP, Tergaonkar V. Multifaceted link between cancer and inflammation. Bioscience reports 2012;32:1-15.
142. Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010;138:2101-14.e5.
143. Vazzana N, Riondino S, Toto V, et al. Obesity-driven inflammation and colorectal cancer. Current medicinal chemistry 2012;19:5837-53.
144. Bollrath J, Greten FR. IKK/NF-kappaB and STAT3 pathways: central signalling hubs in inflammation-mediated tumour promotion and metastasis. EMBO reports 2009;10:1314-9.
145. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. The American Journal of Clinical Nutrition 2011;93:234-42.
146. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. European cytokine network 2006;17:4-12.
147. Arner P. The adipocyte in insulin resistance: key molecules and the impact of the thiazolidinediones. Trends in endocrinology and metabolism: TEM 2003;14:137-45.
148. Byeon JS, Jeong JY, Kim MJ, et al. Adiponectin and adiponectin receptor in relation to colorectal cancer progression. International journal of cancerJournal international du cancer 2010;127:2758-67.
149. Barb D, Pazaitou-Panayiotou K, Mantzoros CS. Adiponectin: a link between obesity and cancer. Expert opinion on investigational drugs 2006;15:917-31.

150. Hammes TO, Costa Cdos S, Rohden F, et al. Parallel Down-Regulation of FOXO1, PPARgamma and Adiponectin mRNA Expression in Visceral Adipose Tissue of Class III Obese Individuals. Obesity facts 2012;5:452-9.
151. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. The American Journal of Clinical Nutrition 2007;86:s858-66.
152. Nishizawa H, Shimomura I, Kishida K, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002;51:2734-41.
153. Sugiyama M, Takahashi H, Hosono K, et al. Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. International journal of oncology 2009;34:339-44.
154. An W, Bai Y, Deng SX, et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2012;21:126-33.
155. Gialamas SP, Petridou ET, Tseleni-Balafouta S, et al. Serum adiponectin levels and tissue expression of adiponectin receptors are associated with risk, stage, and grade of colorectal cancer. Metabolism: clinical and experimental 2011;60:1530-8.
156. Fisher G, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Markers of Inflammation and Fat Distribution Following Weight Loss in African-American and White Women. Obesity (Silver Spring, Md) 2011.
157. Varady KA, Tussing L, Bhutani S, Braunschweig CL. Degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women. Metabolism: clinical and experimental 2009;58:1096-101.
158. Chang CK, Ulrich CM. Hyperinsulinaemia and hyperglycaemia: possible risk factors of colorectal cancer among diabetic patients. Diabetologia 2003;46:595-607.
159. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S, Japan Public Health Center-based Prospective Study G. Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. International journal of cancerJournal international du cancer 2007;120:2007-12.
160. Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2003;12:412-8.
161. Gonullu G, Kahraman H, Bedir A, Bektas A, Yucel I. Association between adiponectin, resistin, insulin resistance, and colorectal tumors. International journal of colorectal disease 2010;25:205-12.
162. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. Journal of the National Cancer Institute 1999;91:1147-54.
163. Ortiz AP, Thompson CL, Chak A, Berger NA, Li L. Insulin resistance, central obesity, and risk of colorectal adenomas. Cancer 2011.
164. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006;107:28-36.
165. Pelucchi C, Negri E, Talamini R, et al. Metabolic syndrome is associated with colorectal cancer in men. European journal of cancer (Oxford, England : 1990) 2010;46:1866-72.
166. Aleksandrova K, Boeing H, Jenab M, et al. Metabolic Syndrome and Risks of Colon and Rectal Cancer: the European Prospective Investigation into Cancer and Nutrition Study. Cancer prevention research (Philadelphia, Pa) 2011.
167. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. The Proceedings of the Nutrition Society 2011:1-9.
168. Jenab M, Riboli E, Cleveland RJ, et al. Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. International journal of cancerJournal international du cancer 2007;121:368-76.

169. Keku TO, Sandler RS, Simmons JG, et al. Local IGFBP-3 mRNA expression, apoptosis and risk of colorectal adenomas. BMC Cancer 2008;8:143.
170. Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Experimental diabetes research 2012;2012:789174.
171. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. The Journal of clinical investigation 2003;112:1821-30.
172. Becker S, Dossus L, Kaaks R. Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. Archives of Physiology and Biochemistry 2009;115:86-96.
173. Ewing GP, Goff LW. The insulin-like growth factor signaling pathway as a target for treatment of colorectal carcinoma. Clinical colorectal cancer 2010;9:219-23.
174. Jenkins PJ, Khalaf S, Ogunkolade W, et al. Differential expression of IGF-binding protein-3 in normal and malignant colon and its influence on apoptosis. Endocr Relat Cancer 2005;12:891-901.
175. Williams AC, Smartt H, AM HZ, Macfarlane M, Paraskeva C, Collard TJ. Insulin-like growth factor binding protein 3 (IGFBP-3) potentiates TRAIL-induced apoptosis of human colorectal carcinoma cells through inhibition of NF-kappaB. Cell death and differentiation 2007;14:137-45.
176. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. Journal of chronic diseases 1979;32:563-76.
177. Abotchie PN, Vernon SW, Du XL. Gender differences in colorectal cancer incidence in the United States, 1975-2006. Journal of women's health (2002) 2012;21:393-400.
178. Park JY, Mitrou PN, Keogh RH, Luben RN, Wareham NJ, Khaw KT. Self-reported and measured anthropometric data and risk of colorectal cancer in the EPIC-Norfolk study. International journal of obesity (2005) 2012;36:107-18.
179. Russo A, Franceschi S, La Vecchia C, et al. Body size and colorectal-cancer risk. International journal of cancerJournal international du cancer 1998;78:161-5.
180. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. International journal of cancer Journal international du cancer 2004;108:433-42.
181. Sturmer T, Buring JE, Lee IM, Gaziano JM, Glynn RJ. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2006;15:2391-7.
182. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
183. Slattery ML, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD. Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). Cancer Causes Control 2003;14:75-84.
184. Simon MS, Chlebowski RT, Wactawski-Wende J, et al. Estrogen plus progestin and colorectal cancer incidence and mortality. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:3983-90.
185. Barone M, Lofano K, De Tullio N, Licinio R, Albano F, Di Leo A. Dietary, endocrine, and metabolic factors in the development of colorectal cancer. J Gastrointest Cancer 2012;43:13-9.
186. Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M. The role of androgens and estrogens on healthy aging and longevity. The journals of gerontology Series A, Biological sciences and medical sciences 2012;67:1140-52.
187. Koo JH, Leong RW. Sex differences in epidemiological, clinical and pathological characteristics of colorectal cancer. J Gastroenterol Hepatol 2010;25:33-42.
188. Witte D, Chirala M, Younes A, Li Y, Younes M. Estrogen receptor beta is expressed in human colorectal adenocarcinoma. Human pathology 2001;32:940-4.
189. Tchernof A, Despres JP. Sex steroid hormones, sex hormone-binding globulin, and obesity in men and women. Horm Metab Res 2000;32:526-36.

190. Wu AH, Siegmund KD, Long TI, et al. Hormone therapy, DNA methylation and colon cancer. Carcinogenesis 2010;31:1060-7.
191. Lin JH, Zhang SM, Rexrode KM, et al. Association between sex hormones and colorectal cancer risk in men and women. Clin Gastroenterol Hepatol 2013;11:419-24 e1.
192. Gates MA, Mekary RA, Chiu GR, Ding EL, Wittert GA, Araujo AB. Sex steroid hormone levels and body composition in men. J Clin Endocrinol Metab 2013;98:2442-50.
193. Trabert B, Graubard BI, Nyante SJ, et al. Relationship of sex steroid hormones with body size and with body composition measured by dual-energy X-ray absorptiometry in US men. Cancer Causes Control 2012;23:1881-91.
194. Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. Clinical endocrinology 2005;63:239-50.
195. Marin P, Krotkiewski M, Bjorntorp P. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. The European journal of medicine 1992;1:329-36.
196. Halpern MT, Pavluck AL, Ko CY, Ward EM. Factors associated with colon cancer stage at diagnosis. Digestive diseases and sciences 2009;54:2680-93.
197. Berry J, Bumpers K, Ogunlade V, et al. Examining racial disparities in colorectal cancer care. Journal of Psychosocial Oncology 2009;27:59-83.
198. Kirby JB, Liang L, Chen HJ, Wang Y. Race, Place, and Obesity: The Complex Relationships Among Community Racial/Ethnic Composition, Individual Race/Ethnicity, and Obesity in the United States. American Journal of Public Health 2012.
199. Barreira TV, Staiano AE, Harrington DM, et al. Anthropometric correlates of total body fat, abdominal adiposity, and cardiovascular disease risk factors in a biracial sample of men and women. Mayo Clinic proceedings Mayo Clinic 2012;87:452-60.
200. Camhi SM, Bray GA, Bouchard C, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity (Silver Spring, Md) 2011;19:402-8.
201. Carroll JF, Chiapa AL, Rodriquez M, et al. Visceral fat, waist circumference, and BMI: impact of race/ethnicity. Obesity (Silver Spring, Md) 2008;16:600-7.
202. Demerath EW, Sun SS, Rogers N, et al. Anatomical patterning of visceral adipose tissue: race, sex, and age variation. Obesity (Silver Spring, Md) 2007;15:2984-93.
203. Kanaley JA, Giannopoulou I, Tillapaugh-Fay G, Nappi JS, Ploutz-Snyder LL. Racial differences in subcutaneous and visceral fat distribution in postmenopausal black and white women. Metabolism 2003;52:186-91.
204. Thompson CL, Berger NA, Chak A, Li L. Racial differences in measures of obesity and risk of colon adenoma. Obesity (Silver Spring, Md) 2012;20:673-7.
205. Hoffman DJ, Wang Z, Gallagher D, Heymsfield SB. Comparison of visceral adipose tissue mass in adult African Americans and whites. Obesity research 2005;13:66-74.
206. Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? Hepatology (Baltimore, Md) 2009;49:791-801.
207. D'Adamo E, Northrup V, Weiss R, et al. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. The American Journal of Clinical Nutrition 2010;92:500-8.
208. Miljkovic I, Cauley JA, Petit MA, et al. Greater adipose tissue infiltration in skeletal muscle among older men of African ancestry. The Journal of clinical endocrinology and metabolism 2009;94:2735-42.
209. Cardel M, Higgins PB, Willig AL, et al. African genetic admixture is associated with body composition and fat distribution in a cross-sectional study of children. International journal of obesity (2005) 2010.
210. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology (Baltimore, Md) 2004;40:1387-95.
211. Weston SR, Leyden W, Murphy R, et al. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology (Baltimore, Md) 2005;41:372-9.

212. Pusatcioglu CK, Nemeth E, Fantuzzi G, et al. Systemic and tumor level iron regulation in men with colorectal cancer: a case control study. Nutr Metab (Lond) 2014;11:21.
213. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998;6 Suppl 2:51s-209s.
214. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194-202.
215. Kabat GC, Kim MY, Strickler HD, et al. A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. Br J Cancer 2012;106:227-32.
216. Chen J, Iverson D. Estrogen in obesity-associated colon cancer: friend or foe? Protecting postmenopausal women but promoting late-stage colon cancer. Cancer Causes Control 2012;23:1767-73.
217. Sikalidis AK, Varamini B. Roles of Hormones and Signaling Molecules in Describing the Relationship Between Obesity and Colon cancer. Pathology oncology research : POR 2011.
218. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. Cancer Res 2008;68:329-37.
219. Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M. Testosterone concentrations in women aged 25-50 years: associations with lifestyle, body composition, and ovarian status. Am J Epidemiol 2001;153:256-64.
220. Wang C, Jackson G, Jones TH, et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care 2011;34:1669-75.
221. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. Journal of endocrinological investigation 1999;22:110-6.
222. Guffey CR, Fan D, Singh UP, Murphy EA. Linking obesity to colorectal cancer: recent insights into plausible biological mechanisms. Curr Opin Clin Nutr Metab Care 2013.
223. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. The Journal of allergy and clinical immunology 2008;121:326-30.
224. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nature reviewsImmunology 2006;6:772-83.
225. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
226. Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. Trends in endocrinology and metabolism: TEM 2010;21:610-8.
227. Erarslan E, Coskun Y, Turkay C, Koktener A, Aydogan T. IGF-I levels and visceral fat accumulation in colonic neoplasia. Clinics and research in hepatology and gastroenterology 2013.
228. Rinaldi S, Cleveland R, Norat T, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. International journal of cancer Journal international du cancer 2010;126:1702-15.
229. Sande EP, Martinsen AC, Hole EO, Olerud HM. Interphantom and interscanner variations for Hounsfield units--establishment of reference values for HU in a commercial QA phantom. Physics in medicine and biology 2010;55:5123-35.
230. Monjardim RdF, Costa DMC, Romano RFT, et al. Diagnosis of hepatic steatosis by contrast-enhanced abdominal computed tomography. Radiologia Brasileira 2013;46:134-8.
231. Pan Y, Jackson RT. Ethnic difference in the relationship between acute inflammation and serum ferritin in US adult males. Epidemiology and infection 2008;136:421-31.
232. Choe EK, Kim D, Kim HJ, Park KJ. Association of visceral obesity and early colorectal neoplasia. World J Gastroenterol 2013;19:8349-56.
233. Erarslan E, Coskun Y, Turkay C, Koktener A, Aydogan T. IGF-I levels and visceral fat accumulation in colonic neoplasia. Clinics and research in hepatology and gastroenterology 2014;38:99-105.

234. Lee JY, Lee HS, Lee DC, et al. Visceral fat accumulation is associated with colorectal cancer in postmenopausal women. PLoS One 2014;9:e110587.
235. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). The American Journal of Clinical Nutrition 2007;86:353-9.
236. Tanaka S, Horimai C, Katsukawa F. Ethnic differences in abdominal visceral fat accumulation between Japanese, African-Americans, and Caucasians: a meta-analysis. Acta Diabetol 2003;40 Suppl 1:S302-4.
237. Nazare JA, Smith JD, Borel AL, et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the International Study of Prediction of Intra-Abdominal Adiposity and Its Relationship With Cardiometabolic Risk/Intra-Abdominal Adiposity. The American Journal of Clinical Nutrition 2012;96:714-26.
238. Kohli S, Sniderman AD, Tchernof A, Lear SA. Ethnic-specific differences in abdominal subcutaneous adipose tissue compartments. Obesity (Silver Spring, Md) 2010;18:2177-83.
239. Riondino S, Roselli M, Palmirotta R, Della-Morte D, Ferroni P, Guadagni F. Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. World J Gastroenterol 2014;20:5177-90.
240. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39-48.
241. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet 2010;375:2267-77.
242. Rudy DR, Zdon MJ. Update on colorectal cancer. American family physician 2000;61:1759-70, 73-4.
243. Keum N, Lee DH, Kim R, Greenwood DC, Giovannucci EL. Visceral adiposity and colorectal adenomas: dose-response meta-analysis of observational studies. Ann Oncol 2015;26:1101-9.
244. Nagata N, Sakamoto K, Arai T, et al. Visceral abdominal fat measured by computed tomography is associated with an increased risk of colorectal adenoma. International journal of cancer Journal international du cancer 2014;135:2273-81.
245. Hu H, Cai Y, Huang J, Zhang J, Deng Y. Visceral adipose tissue and the risk of colorectal adenomas: a meta-analysis of observational studies. Eur J Cancer Prev 2014.
246. Hong S, Cai Q, Chen D, Zhu W, Huang W, Li Z. Abdominal obesity and the risk of colorectal adenoma: a meta-analysis of observational studies. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2012.
247. Doucet E, St-Pierre S, Almeras N, et al. Reduction of visceral adipose tissue during weight loss. European journal of clinical nutrition 2002;56:297-304.
248. Lundbom J, Hakkarainen A, Lundbom N, Taskinen MR. Deep subcutaneous adipose tissue is more saturated than superficial subcutaneous adipose tissue. Int J Obes (Lond) 2013;37:620-2.
249. Golan R, Shelef I, Rudich A, et al. Abdominal superficial subcutaneous fat: a putative distinct protective fat subdepot in type 2 diabetes. Diabetes care 2012;35:640-7.
250. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881-7.
251. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes 1997;46:1579-85.
252. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest 1995;96:88-98.
253. Walker GE, Verti B, Marzullo P, et al. Deep subcutaneous adipose tissue: a distinct abdominal adipose depot. Obesity (Silver Spring, Md) 2007;15:1933-43.
254. Marinou K, Hodson L, Vasan SK, et al. Structural and functional properties of deep abdominal subcutaneous adipose tissue explain its association with insulin resistance and cardiovascular risk in men. Diabetes Care 2014;37:821-9.
255. Zoico E, Rossi A, Di Francesco V, et al. Adipose tissue infiltration in skeletal muscle of healthy elderly men: relationships with body composition, insulin resistance, and inflammation at the systemic

and tissue level. The journals of gerontology Series A, Biological sciences and medical sciences 2010;65:295-9.
256. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. Journal of applied physiology (Bethesda, Md: 1985) 2000;89:104-10.
257. Albu JB, Kovera AJ, Allen L, et al. Independent association of insulin resistance with larger amounts of intermuscular adipose tissue and a greater acute insulin response to glucose in African American than in white nondiabetic women. The American Journal of Clinical Nutrition 2005;82:1210-7.
258. Beasley LE, Koster A, Newman AB, et al. Inflammation and race and gender differences in computerized tomography-measured adipose depots. Obesity (Silver Spring, Md) 2009;17:1062-9.
259. Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. Int J Endocrinol 2014;2014:309570.
260. Gallagher D, Kuznia P, Heshka S, et al. Adipose tissue in muscle: a novel depot similar in size to visceral adipose tissue. Am J Clin Nutr 2005;81:903-10.
261. Al-Azzawi F, Palacios S. Hormonal changes during menopause. Maturitas 2009;63:135-7.
262. Carroll JF, Fulda KG, Chiapa AL, et al. Impact of race/ethnicity on the relationship between visceral fat and inflammatory biomarkers. Obesity (Silver Spring, Md) 2009;17:1420-7.
263. Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. The American Journal of Clinical Nutrition 1999;69:381-7.
264. Ryan AS, Nicklas BJ, Berman DM. Racial differences in insulin resistance and mid-thigh fat deposition in postmenopausal women. Obesity research 2002;10:336-44.
265. Lovejoy JC, Smith SR, Rood JC. Comparison of regional fat distribution and health risk factors in middle-aged white and African American women: The Healthy Transitions Study. Obesity research 2001;9:10-6.
266. Hanley AJ, Wagenknecht LE, Norris JM, et al. Adiponectin and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. Diabetes Care 2011;34:2231-6.
267. Bush NC, Darnell BE, Oster RA, Goran MI, Gower BA. Adiponectin is lower among African Americans and is independently related to insulin sensitivity in children and adolescents. Diabetes 2005;54:2772-8.
268. Hulver MW, Saleh O, MacDonald KG, Pories WJ, Barakat HA. Ethnic differences in adiponectin levels. Metabolism: clinical and experimental 2004;53:1-3.
269. Gardener H, Crisby M, Sjoberg C, et al. Serum adiponectin in relation to race-ethnicity and vascular risk factors in the northern Manhattan study. Metab Syndr Relat Disord 2013;11:46-55.
270. Considine RV, Premkumar A, Reynolds JC, Sebring NG, Ricks M, Sumner AE. Adiponectin and leptin in African Americans. Obesity (Silver Spring) 2008;16:428-34.
271. Bidulescu A, Liu J, Hickson DA, et al. Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in African Americans: the Jackson Heart Study. BMC cardiovascular disorders 2013;13:9.
272. Hanley AJ, Bowden D, Wagenknecht LE, et al. Associations of adiponectin with body fat distribution and insulin sensitivity in nondiabetic Hispanics and African-Americans. The Journal of clinical endocrinology and metabolism 2007;92:2665-71.
273. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochemical pharmacology 2006;72:1605-21.
274. Aggarwal BB. Nuclear factor-kappaB: the enemy within. Cancer cell 2004;6:203-8.
275. Grivennikov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. Annals of the Rheumatic Diseases 2011;70 Suppl 1:i104-8.
276. Kim BC, Shin A, Hong CW, et al. Association of colorectal adenoma with components of metabolic syndrome. Cancer causes & control : CCC 2012.

277. Catalan V, Gomez-Ambrosi J, Rodriguez A, et al. Up-regulation of the novel proinflammatory adipokines lipocalin-2, chitinase-3 like-1 and osteopontin as well as angiogenic-related factors in visceral adipose tissue of patients with colon cancer. The Journal of nutritional biochemistry 2011;22:634-41.
278. Register TC, Divers J, Bowden DW, et al. Relationships between serum adiponectin and bone density, adiposity and calcified atherosclerotic plaque in the African American-Diabetes Heart Study. J Clin Endocrinol Metab 2013;98:1916-22.
279. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst 2005;97:1688-94.
280. Berrigan D, Potischman N, Dodd KW, et al. Race/ethnic variation in serum levels of IGF-I and IGFBP-3 in US adults. Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society 2009;19:146-55.
281. Lawrence DA, Oliva IB, Israel GM. Detection of hepatic steatosis on contrast-enhanced CT images: diagnostic accuracy of identification of areas of presumed focal fatty sparing. AJR American journal of roentgenology 2012;199:44-7.
282. Greenfield V, Cheung O, Sanyal AJ. Recent advances in nonalcholic fatty liver disease. Current opinion in gastroenterology 2008;24:320-7.
283. Karagozian R, Derdak Z, Baffy G. Obesity-associated mechanisms of hepatocarcinogenesis. Metabolism 2014.
284. Ding J, Visser M, Kritchevsky SB, et al. The association of regional fat depots with hypertension in older persons of white and African American ethnicity. Am J Hypertens 2004;17:971-6.
285. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.

XII. VITA

Curriculum Vitae

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EDUCATION

2015 PhD, University of Illinois at Chicago, *Human Nutrition*
Dissertation: Body composition and biomarkers of colorectal cancer risk in African Americans and Non-Hispanic Whites

1999 MS, University of Illinois at Chicago, *Human Nutrition*
Thesis: Metabolic consequences of pregnancy in African American and Latino teenagers
Advisor: Carol Braunschweig, PhD, Co-Advisor: Rebecca Lipton, PhD

1995 BS, University of Illinois at Chicago, *Nutrition and Medical Dietetics*

PROFESSIONAL EXPERIENCE

2013- Research Assistant, University of Illinois at Chicago, Kinesiology and Nutrition
1998-2013 Senior Research Specialist, University of Illinois at Chicago, Kinesiology and Nutrition
2008-2011 Clinical Trial Study Coordinator, University of Illinois at Chicago, Pediatric Surgery
2004-2008 Foodservice Manager/School Dietitian, Sonia Shankman Orthogenic School, Chicago, IL
1995-1998 Clinical Dietitian Graduate Assistant, University of Illinois Hospital, Chicago, IL

PROFESSIONAL TRAINING AND DEVELOPMENT

2012- Pre-Doctoral Fellow, NIH R25T Cancer Education and Career Development Program

PROFESSIONAL BOARD CERTIFICATION AND LICENSURE

1996- Registered Dietitian, Commission on Dietetic Registration #819031
1996- Licensed Dietitian Nutritionist, State of Illinois, License No. 164.001730

RESEARCH INTERESTS

The pathology, prevention and treatment of obesity specific to its influence on cardiovascular disease, colorectal cancer and other epithelial cancers, body composition assessment, nutritional assessment, imaging technologies, racial/ethnic disparities, insulin resistance and inflammation.

PUBLICATIONS

Published Peer-Reviewed Manuscripts

1. Braunschweig CA, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Lateef O, Gurka D, Fantuzzi G. Intensive Nutrition in Acute Lung Injury: A Clinical trial (INTACT). JPEN J Parenter Enteral Nutr. 2014 Apr 9. PMID: 24722769

2. Sheean PM, Peterson SJ, **Gomez-Perez S**, Troy KL, Patel A, Sclamber JS, Ajanaku FC, Braunschweig CA. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. JPEN JParenteral Enteral Nutr 2013 Aug 26. 38(7):873-9 PMID: 23980135

3. Braunschweig CB, Sheean P, Peterson S, **Perez SG**, Freels S, Troy KL, Ajanaku FC, Patel A, Sclamber JS, Wang Z. Exploitation of diagnostic computed tomography scans to assess the impact

of nutritional support on body composition changes in respiratory failure patients. JPEN J Parenteral Enteral Nutrition 2014 Sep; 38(7):880-5. Epub 2013 Aug 23. PMID: 23976767

4. Fitzgibbon ML, Stolley MR, Schiffer L, Kong A, Braunschweig CL, **Gomez-Perez SL**, Odoms-Young A, Van Horn L, Christoffel KK, Dyer AR. Family-based hip-hop to health: outcome results. Obesity (Silver Spring). 2013 Feb;21 (2):274-83. doi: 10.1002/oby.20269. PubMed PMID: 23532990.

5. Lown DA, Fitzgibbon ML, Dyer A, Schiffer L, **Gomez S**, Braunschweig CL. Effect of variable energy served on 24-hour energy intake in 16 preschools, Chicago, Illinois, 2007. Prev Chronic Dis. 2011 May;8(3):A58. Epub 2011 Apr 15.

6. Fitzgibbon ML, Stolley MR, Schiffer LA, Braunschweig CL, **Gomez SL**, Van Horn L, Dyer AR. Hip-Hop to Health Jr. Obesity Prevention Effectiveness Trial: Post-intervention results. Obesity (Silver Spring). 2011 May;19 (5):994-1003. Epub 2010 Dec 30.

7. Fitzgibbon ML, Stolley MR, Schiffer LA, Braunschweig CL, **Gomez SL**, Van Horn L, Dyer AR. Hip-Hop to Health Jr. Obesity Prevention Effectiveness Trial: Postintervention Results. Obesity (Silver Spring). 2010 Dec 30.

8. Holterman AX, Browne A, Tussing L, **Gomez S**, Phipps A, Browne N, Stahl C, Holterman MJ. A prospective trial for laparoscopic adjustable gastric banding in morbidly obese adolescents: an interim report of weight loss, metabolic and quality of life outcomes. J Pediatr Surg. 2010 Jan;45(1):74-8; discussion 78-9.

9. Braunschweig CL, **Gomez S**, Liang H, Tomey K, Doerfler B, Wang Y, Beebe C, Lipton R. Obesity and risk factors for the metabolic syndrome among low-income, urban, African American schoolchildren: the rule rather than the exception? Am J Clin Nutr. 2005 May;81(5):970-5.

10. Braunschweig C, **Gomez S**, Sheean P. Nutritional status and risk factors for chronic disease in urban-dwelling adults with Down syndrome. Am J Ment Retard. 2004 Mar; 109(2):186-93.

Manuscripts in Press

1. McKeever, Liam; Nguyen, Van; Peterson, Sarah; **Gomez-Perez, Sandra**; Braunschweig, Carol. Demystifying the Search Button: A Comprehensive PubMed Search Strategy for Performing an Exhaustive Literature Review. Journal of Parenteral and Enteral Nutrition
2. Kong A, Kim Y, Schiffer L, Van Horn L, Stolley A, **Gomez-Perez SL**, Buscemi J, Blumstein L, Fitzgibbon M. Hip Hop to Health Jr. Obesity Prevention Effectiveness Trial: 1-year post-intervention findings. Preventative Medicine.
3. Gomez-Perez SL, Haus J, Troy K, Sheean T, McKeever L, C Braunschweig. Tutorial on measuring abdominal circumference and skeletal muscle from a single cross-sectional CT image: a step-by-step guide for clinicians using NIH IMAGEJ. Journal of Parenteral and Enteral Nutrition.

Manuscripts in Review

1. Lown D, **Gomez-Perez S**, Agarwal P, Beaudoin C, Braunschweig CA. Body image satisfaction and misreporting of total energy intake in midlife African American women. Journal of Black Psychology.

Manuscripts in Preparation

1. **Gomez-Perez SL** and Braunschweig CB. Body Composition and Biomarkers of Colorectal Cancer in African – Americans and Non-Hispanic White Males: A Case-Control Study.

Book Chapters

1. Sheean P, **Gomez-Perez SL**, Aggarwal P and Braunschweig CB (Submitted). Obesity and Colon and Postmenopausal Breast Cancer. In: Fantuzzi G, Mazzone T editors. Adipose Tissue & Adipokines in Health and Disease, Vol 2.

CONFERENCE PRESENTATIONS AND PUBLISHED ABSTRACTS

International

1. **Gomez-Perez SL**, Chaudhry V, Mar W, Patel B, Sclamberg J, Mutlu E, Llor X and Braunschweig C. Abdominal adiposity in African American and Non-Hispanic White men with and without colorectal cancer: a case-control study. 10th Scientific and Annual Meeting of European Society of Coloproctology (ESCP), Dublin, Ireland, September 23-25, 2015; accepted for oral poster.

National

1. **Gomez-Perez SL**, Llor X, Patel B, Pusatcioglu CK, Braunschweig C. Correlations of various abdominal adipose depots with serum and colonic tumor tissue biomarkers in newly diagnosed men with colorectal cancer (CRC). American Institute for Cancer Research (AICR), Bethesda MD, November 7-8, 2013; poster.

2. Rhodes DH, Nguyen V, Sullivan MM, **Gomez Perez S**, Braunschweig C, Fantuzzi, G. Modulation of the IL-6 System and STAT-3 Activation in Lymphocytes of Lean and Obese Women. The Obesity Society 30th Annual Scientific Meeting, San Antonio, TX, Sept 20-24, 2012; poster.

3. PM Sheean, SJ Peterson, S Freels, **S Gomez**, K Troy, J Sclamberg, A Patel, O Lateef, CA Braunschweig . Computed tomography fails to validate Subjective Global Assessment measures of malnutrition in critically ill patients. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), Orlando, FL, January 21-24, 2012; oral presentation.

4. Braunschweig C, Sheean PM, Peterson S, Freels S, Troy K, Sclambert J, Patel A, Lateef O, **Gomez S**. Use of computed tomography image analysis in critically ill patients to evaluate the impact of nutrition support. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), Orlando, FL, January 21-24, 2012; oral presentation.

5. H Hollandsworth, Y Nieves, **S Gomez**, C Beaudoin, D Lown. Anthropometric, dietary and psychosocial characteristics of under-reporters of energy: a study among middle-class African American women. The Obesity Society 29th Annual Scientific Meeting, Orlando, FL, October 03, 2011; poster.

6. Braunschweig C, **Gomez S**, Liang H, Tomey K, Wang QJ, Hedeker D, Flay B. Obesity and related risk factors among low-socioeconomic status (SES) minority students in Chicago? The North American Association for the Study of Obesity (NAASO) 2004 Annual Meeting, Las Vegas, Nov 14-17, 2004; oral presentation.

7. Liang H, **Gomez S**, Doerfler B, Beebe C, Lipton R, Braunschweig C. Overweight and chronic disease risk factors in African American school children is unrelated to traditional risk factors. The 2003 North American Association for the Study of Obesity (NAASO) Annual Meeting, Ft. Lauderdale, Florida, October 2003; poster.

8. Braunschweig C, **Gomez S**, Liang H, Tomey K, Wang QJ, Hedeker D, Flay B. Obesity and related risk factors among low-socioeconomic status (SES) minority students in Chicago? The North

American Association for the Study of Obesity (NAASO) 2004 Annual Meeting, Las Vegas, Nov 14-17, 2004; oral presentation.

9. Liang H, **Gomez S**, Doerfler B, Beebe C, Lipton R, Braunschweig C. Overweight and chronic disease risk factors in African American school children is unrelated to traditional risk factors. The 2003 North American Association for the Study of Obesity (NAASO) Annual Meeting, Ft. Lauderdale, Florida, October 2003; poster.

CONFERENCE PRESENTATIONS AND PUBLISHED ABSTRACTS

Regional

1. **Gomez-Perez, Sandra L**; Llor X, Mar W, Sclamberg J, Haus J, Chaudhry V, Peterson S, Mutlu E, Muňoz-Xicola R, Jung B, Yang, J and Braunschweig C. Relationship between Colorectal Cancer, Body Composition and Race/ethnicity. 5th Annual UIC KN Recognition for Achievement, Research and Excellence (RARE). University of Illinois at Chicago, IL; April 20, 2015; oral presentation.

2. **Gomez-Perez, Sandra L**; Chaudhry V; Haus J; Mar W; Patel B; Jung B; Muňoz-Xicola R; Llor X; Braunschweig C. Body Composition Differences between African American and Non-Hispanic White Men with Colorectal Cancer. SPH Research and Practice Awards Day, University of Illinois at Chicago, Chicago, Illinois; April 07, 2015; poster.

3. **Gomez-Perez, Sandra L**; Llor X, Mar W, Sclamberg J, Haus J, Chaudhry V, Peterson S, Mutlu E, Muňoz-Xicola R, Jung B, Yang, J and Braunschweig C. Relationship between Colorectal Cancer, Body Composition and Race/ethnicity: A Case-Control Study. UIC Student Research Forum, University of Illinois at Chicago, Chicago, Illinois; April 02, 2015; poster.

4. **Gomez-Perez, Sandra L**; Llor, Xavier; Mar, Winnie; Patel, Bimal; Chaudhry, Vivek; Haus, Jacob; Fantuzzi, Giamila; Freels, Sally; Tussing-Humphreys, Lisa; Jung, Barbara; and Braunschweig, Carol. Body Composition and Biomarkers of Colorectal Cancer in African – American and Non-Hispanic Whites: Imaging Analysis and Pilot Study Findings. Department of Kinesiology and Nutrition from Cells to Community Research Day, University of Illinois at Chicago, Chicago, Illinois; September 26, 2014; poster presentation.

5. **Gomez-Perez, Sandra L**; Llor, Xavier; Mar, Winnie; Patel, Bimal; Chaudhry, Vivek; Haus, Jacob; Fantuzzi, Giamila; Freels, Sally; Tussing-Humphreys, Lisa; Jung, Barbara; and Braunschweig, Carol. Body Composition and Biomarkers of Colorectal Cancer in African – American and Non-Hispanic Whites: Imaging Analysis and Pilot Study Findings. Department of Medicine Scholarly Activities Day, University of Illinois at Chicago, Chicago, Illinois, June 12, 2014; oral presentation.

6. **Gomez-Perez, Sandra L**; Llor, Xavier; Mar, Winnie; Patel, Bimal; Chaudhry, Vivek; Haus, Jacob; Fantuzzi, Giamila; Freels, Sally; Tussing-Humphreys, Lisa; and Braunschweig, Carol. Correlations of Body Composition, Inflammation, Insulin Resistance and Iron in Colorectal Cancer (CRC): A Pilot Study. Cancer Center Research Forum & Poster Prize Competition, University of Illinois at Chicago, Chicago, Illinois, April 22, 2014; poster.

7. **Gomez-Perez, Sandra L**; Llor, Xavier; Mar, Winnie; Patel, Bimal; Chaudhry, Vivek; Haus, Jacob; Fantuzzi, Giamila; Freels, Sally; Tussing-Humphreys, Lisa; and Braunschweig, Carol. Correlations of Body Composition, Inflammation, Insulin Resistance and Iron in Colorectal Cancer (CRC): A Pilot Study. UIC Student Research Forum, University of Illinois at Chicago, Chicago, Illinois, April 08, 2014; poster.

RESEARCH FUNDING

Previous Grant Support

UIC Chancellors Graduate Research Fellowship Gomez-Perez, S (PI) 1/15/2014-6/15/2015
This award supports research-related expenses for up to 2 years and was awarded by the UIC Chancellors Graduate Research Program. Successful recipients demonstrate creativity in their fields of interest and plan a research project that is multidisciplinary in nature.

TEACHING EXPERIENCE

Courses

2002-2003 Foodservice Preceptor, HN332 Quantity Food Production, Coordinated Program, Human Nutrition and Medical Dietetics, University of Illinois at Chicago
2002-2003 Clinical Fieldwork Coordinator, HN355/455 Supervised Practice I/II, Coordinated Program, Human Nutrition and Medical Dietetics, University of Illinois at Chicago
2000-2002 Instructor, HN202 Culture and Food, Coordinated Program, Human Nutrition and Medical Dietetics, University of Illinois at Chicago
2000-2002 Instructor, HN313 Intro to Community Nutrition, Coordinated Program, Human Nutrition and Medical Dietetics, University of Illinois at Chicago

Guest Lectures & Laboratory Teaching Assistant Opportunities

2013 Guest Lecturer, *24-Hour Recall Mock Interview Process and Demonstration*, HN 532 University of Illinois at Chicago, Kinesiology and Nutrition
2008-2012 Guest Lecturer, *Anthropometrics Demonstration and Training*, HN200 and HN532, University of Illinois at Chicago, Kinesiology and Nutrition
2008-2012 Lab Teaching Assistant, *Nutrition Assessment,* HN200, University of Illinois at Chicago

HONORS AND AWARDS

Professional

2009 UIC Certificate of Recognition, Division of Pediatric Surgery, University of Illinois at Chicago
2003 5 Years of Service, Board of Trustees of the University of Illinois at Chicago

Academic

2015 UIC KN Recognition for Achievement, Research and Excellence in Graduate Student Research
2015 UIC Student Research Forum, Third Place Poster Winner
2014 UIC Cancer Center Research Forum Poster Prize Competition Winner
1996 American Diabetes Association Student Award
1995 University of Illinois at Chicago, Martin Luther King, Jr. Scholarship

PROFESSIONAL SERVICE

2014- UIC Interdisciplinary Undergraduate Research Journal (IURJ)

PROFESSIONAL MEMBERSHIP

Academy of Nutrition and Dietetics
American Association for Cancer Research
American Society of Preventive Oncology
American Society of Clinical Oncology
The Obesity Society