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Association between pre-diagnostic circulating adipokines and colorectal cancer and adenoma in the CLUE II cohort

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Abstract

Objective—Obesity is a known risk factor for colorectal cancer (CRC) and adenoma. Obese individuals have higher circulating concentrations of certain endocrine and immune factors produced by adipocytes thought to partially underlie the association between obesity and colorectal neoplasia. Thus, we evaluated the association of plasma concentrations of adiponectin, leptin, and soluble tumor necrosis factor receptor-2 (sTNFR2) with CRC and adenoma.

Methods—We ascertained 193 CRC cases and 193 matched controls, and 131 colorectal adenoma cases and 131 matched controls who had had an endoscopy nested in the CLUE II cohort of Washington County, MD. Plasma markers were measured using ELISA. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from conditional logistic regression for quartiles of the plasma markers separately for CRC and adenoma.

Results—Adjusting for leptin and adiponectin, sTNFR2 was positively associated with CRC only in men (Q4 vs. Q1: OR = 3.14, 95% CI 1.11–8.86), which was unchanged adjusting for BMI (3.46, 95% CI 1.19–10.06). Leptin and adiponectin were not associated with CRC risk overall or in men or women. Adiponectin, leptin, and sTNFR2 were not associated with adenoma risk overall or in men or women.

Conclusion—In this study, leptin and adiponectin were not associated with colorectal carcinogenesis and thus do not appear to underlie the association between obesity and colorectal carcinogenesis. sTNFR2, which we measured as a correlate of TNF-α, was positively associated with CRC in men adjusting for BMI, suggesting that TNF-α may influence colorectal carcinogenesis independent of adipocyte production.

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Keywords

Adipokines; Adiponectin; Leptin; TNF-α; Colorectal cancer; Adenoma

INTRODUCTION

Evidence supports that obesity is a convincing risk factor for colorectal cancer (CRC) and adenoma [1–3]. The potential mechanisms underlying the association between obesity and colorectal neoplasia include adipose tissue dysfunction leading to metabolic perturbations (e.g., insulin resistance) as well as low-grade inflammation [4]. Adipocytes, which are increased in number or size in obese individuals, produce endocrine factors, such as leptin and adiponectin [4]. These factors in turn influence adipocyte production of inflammatory mediators, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α [5]. Leptin is a peptide hormone that belongs to the cytokine family and controls body weight by modulating energy utilization [6]. Obese individuals may become leptin resistant and exhibit elevated plasma leptin [4, 7]. Leptin also plays a role in the immune response by enhancing adipocyte secretion of TNF-α, which exhibits inflammation-associated activities that may contribute to the progression of a growing colorectal tumor [5]. In an animal model of inflammatory colorectal neoplasia, leptin deficiency was associated with less inflammation and lower production of pro-inflammatory cytokines [8]. Adiponectin is a hormone produced and secreted into circulation by adipocytes and is lower in obese individuals and individuals with diagnosed diabetes [4, 5]. Adiponectin inhibits TNF-α signaling, and thus, lower adiponectin production in obese individuals may contribute to cancer development through increased inflammation [4, 5]. Soluble tumor necrosis factor receptor-2 (sTNFR2), a soluble receptor for TNF-α, has been investigated in epidemiologic studies as a correlate of TNF-α because its role in TNF-α signaling [25] and stability over long periods of time [26].

With respect to the association of adipose tissue-derived adipokines with CRC and colorectal adenoma, results have been inconsistent and whether adipokines have similar associations across the natural history of CRC development remains uncertain. A meta-analysis of cross-sectional studies, case–control studies, and nested case–control studies documented an inverse association between adiponectin and CRC [9], while mixed results have been reported on the association between adiponectin and adenoma risk including an inverse association in a large national case–control study in Japan [10], and a null association in a small hospital-based case–control study [11]. No overall association between leptin and CRC was reported in a 2019 meta-analysis of nine cross-sectional studies, case–control studies, and nested case–control studies with high between-study heterogeneity (I^2 = 74%) [9], while leptin was positively associated with adenoma in four retrospective and nested case–control studies with no heterogeneity [12]. While prior epidemiologic studies have investigated the association between TNF-α polymorphisms, which were positively associated with CRC [14], TNF-α was not associated with CRC risk in women in a case-cohort nested in the Women's Health Initiative [15]. TNF-α was not associated with colorectal adenoma in a meta-analysis of five retrospective and nested case–control studies [13]. Associations between sTNFR2 with CRC risk have been mixed in women [16, 17], and

men [18, 19]. In a nested case–control study, sTNFR2 was not associated with colorectal adenoma risk in women [20]. It is unclear whether associations observed in the prior epidemiologic studies accounted for the mutual influence of other adipokines.

Due to the high correlation among concentrations of adipose tissue-derived factors including leptin, adiponectin, and TNF-α and the pathways through which each marker potentially contributes to colorectal neoplasia, it is necessary to account for the influence of these factors on one another to determine the independent association between each marker and colorectal neoplasia. It is also important to assess when in the natural history of colorectal neoplasia adipokines may influence risk (i.e., early – adenoma, later – adenocarcinoma). Building on our prior work in a nested-case control study in CLUE II investigating the associations of variants in inflammatory genes [21, 22], and circulating IL-6 [23] and C-reactive protein (CRP) [24] with risk of CRC and adenoma, we examined biomarkers of the sequelae of obesity, specifically—circulating concentrations of leptin, adiponectin, and sTNFR2, a stable correlate of circulating TNF-α [25, 26] in relation to CRC and adenoma. Given their biology and prior research, we hypothesized that circulating levels of leptin and sTNFR2 are positively and adiponectin is inversely associated with risk of CRC and adenoma, independent of one another and that they act both early and late in the natural history of colorectal carcinogenesis. We aim to fill gaps in understanding whether adipocyte produced inflammatory and metabolic markers when considered individually and together in CRC carcinogenesis in order to inform whether, in part, they underly the link between obesity and colorectal neoplasia.

METHODS

Study populations

CRC and adenoma cases and controls were identified among participants of CLUE II, a prospective epidemiologic cohort established in 1989 to investigate serologic risk factors for cancer and heart disease. CLUE II includes 32,894 residents of Washington County, MD and neighboring areas aged 13 + years old. For these analyses, the source population was 22,887 Washington County residents only who were ≥ 18 years old. All participants provided a blood sample and completed a brief medical and lifestyle exposure history at baseline. Questionnaires were mailed to participants to update lifestyle, medical, and family histories, including sigmoidoscopic/colonoscopic procedures and polyp diagnoses in 1996, 1998, and 2000. All participants provided informed consent. The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health approved the study.

Selection of CRC cases and controls

We used a nested case–control study that we previously developed [27]. Briefly, participants without a cancer diagnosis (excluding nonmelanoma skin cancer or cervix in situ) in 1989 or earlier were eligible to be selected as a case or control. Cases were identified through linkage with the Washington County Cancer Registry, and since 1992 also with the Maryland Cancer Registry. In this analysis, we included 193 CRC cases diagnosed following the date of blood draw in 1989 through 2003, and who had sufficient plasma volume remaining for all three biomarkers (14 matched pairs were excluded due to insufficient

volume). For each case, we included up to two controls matched on age (± 1 year), sex, race, date of blood draw (± 2 weeks), and time since the last meal (0–1, 2–3, 4–5, 6–7, ≥ 8 h); all controls did not have a cancer diagnosis at blood draw and were known to be alive at the time that the case was diagnosed.

Selection of adenoma cases and controls.

We used a nested case–control study (prospective) that we previously developed [24]. Briefly, participants without a cancer (excluding nonmelanoma skin cancer or cervix in situ) or polyp diagnosis in 1989 or earlier were eligible to be selected as an adenoma case or control. With the participants' permission, endoscopy and pathology reports were reviewed to confirm a first ever adenoma after 1989 among those who reported a polyp. Cases included only participants with a pathologically confirmed colorectal adenomatous polyp because these polys are well-described precursors for CRC, and risk factors for the development of other polyps (e.g., hyperplastic) may differ. Participants with a history of inflammatory bowel disease were excluded because the primary etiology of adenoma in these patients is known (i.e., inflammation). In this analysis, we included 131 cases with a first adenoma detected by colonoscopy or sigmoidoscopy in Washington County from 1990 to 2000 and who had sufficient plasma volume for all three biomarkers (5 matched pairs were excluded due to insufficient volume). For each case, we included 131 controls who reported a prior negative endoscopy and were matched on age (± 1 year), sex, race, date of blood draw (± 2 weeks), and time since the last meal (0–1, 2–3, 4–5, 6–7, ≥ 8 h).

Biomarker measurement

Concentrations of total adiponectin and leptin (R&D Systems, Minneapolis, MN), and sTNFR2 (Genzyme Diagnostics) were measured in plasma collected in 1989 using by enzyme-linked immunoassay (ELISA) in the laboratory of Dr. Rifai at Children's Hospital Boston. Quality control samples derived from pooled plasma and equal to 5% of the samples were interspersed for assessment of intra- and inter-batch variability. Laboratory technicians were masked to case–control status. The inter-batch coefficients of variation from the quality control samples for the CRC and adenoma batches, respectively, were 4.9% and 4.9% for adiponectin, 3.3% and 7.2% for leptin, and 4.9% and 7.3% for sTNFR2.

Other metabolic and inflammatory biomarkers previously measured and used in the current study were: insulin (CRC) or C-peptide (adenoma) [28], insulin-like growth factor binding protein (IGFBP)-1 [28], glycated hemoglobin (HbA1c) [28], total cholesterol [28], HDL cholesterol [28], triglycerides [28], high-sensitivity CRP [24], and IL-6 (CRC only) [23].

Covariate assessment

Self-reported height and weight, weight at age 21, and smoking history (never, current, former) were collected at baseline in 1989. Body mass index (BMI) at baseline was calculated as weight in kilograms divided by height in meters squared and adult weight gain was calculated as the difference in weight at baseline and self-reported weight at age 21. Prescription or over-the-counter medications taken within the past 48 h of blood draw that contained aspirin or other nonsteroidal anti-inflammatory drugs were coded as nonsteroidal anti-inflammatory drugs (NSAIDs). Women reported if they currently or in the

past took oral contraceptives or hormone replacement therapy. Follow-up questionnaires in 1996, 1998, and 2000 ascertained whether participants had a first-degree family history of CRC. Intake of total energy (kcal/day), saturated fat (g/day), fiber (g/day), folate (μg/day), calcium (mg/day), red meat (g/day), and alcohol (g/day) were estimated from the baseline 60-item food frequency questionnaire,[29] which was available for 105 (54%) and 128 (66%) of CRC cases and controls, and 98 (74%) and 179 (69%) of adenoma cases and controls.

Statistical analysis

Analyses were performed separately for CRC and for adenoma. Baseline characteristics were compared between cases and controls overall, in men, and in women. Age-sex-adjusted Spearman correlation coefficients were calculated among adiponectin, leptin, and sTNFR2, and with BMI, adult weight gain, and metabolic and inflammatory markers among CRC controls.

Matched odds ratios (OR) and 95% confidence intervals (CI) for the association of each biomarker with CRC or with adenoma were estimated using conditional logistic regression models overall and stratified by sex. Each biomarker was modeled using quartiles based on the sex-specific distributions among the CRC or adenoma controls with the lowest quartile as the reference group. The median of each biomarker quartile was entered into the model as an ordinal variable, from which we estimated the OR for a 25th to 75th percentile increase in biomarker concentration. The p-trend was based on a single ordinal variable with values corresponding to the biomarker quartile using the Wald test. We first ran the matched model (accounted for the matching factors). Next, to assess the association for each biomarker independent of the other two, we ran the matched model mutually adjusting the three biomarkers entered as quartile indicator variables. To determine whether any biomarker associations with CRC or adenoma are independent of the link between BMI and CRC and adenoma, we ran the matched model for each biomarker adjusting for BMI (continuous).

We additionally adjusted for other known colorectal neoplasia risk factors: cigarette smoking status (current, former, never), alcohol consumption (continuous), NSAID use (yes, no), diabetes medication use (yes, no), hormone replacement therapy use (yes, no, women only), family history of CRC (yes, no); and in a subanalysis, further adjusted for diet-related risk factors: calcium intake (continuous), folate (continuous), fiber (continuous), red meat consumption (continuous), saturated fat consumption (continuous), total energy intake (continuous), and an indicator variable for missing FFQ information.

To determine whether the observed overall association between the three biomarkers (continuous) and CRC varied by strata of BMI (e.g., effect modification), adult weight gain (age 21 to baseline), CRP, IL-6, insulin, HbA1c, NSAID use (yes, no), or smoking status (never, ever), we broke the matching. The Wald test for the joint term between each biomarker and each stratification factor was used to determine statistical interaction. We also assessed associations among participants who did not use diabetes medications. The sample size was too small to evaluate effect modification in adenoma analyses.

SAS version 9.4 (SAS Institute, Inc, Cary, NC) was used for all analyses. All statistical tests were two-sided with $P < 0.05$ considered statistically significant.

RESULTS

CRC

At baseline, participants subsequently diagnosed with CRC (mean of 6.5 years from baseline to CRC diagnosis) were more likely to have a family history of CRC, to use diabetes medications, to be former smokers, and were less likely to take an NSAID, or use HRT (women) (Table 1). CRC cases and controls did not statistically significantly differ on pre-diagnostic inflammatory and metabolic biomarkers except total cholesterol in men and IL-6 in women (Table S1). Median leptin concentrations did not significantly differ between CRC cases and controls in men or in women (Table 2). Among women, median adiponectin concentration was significantly lower in CRC cases compared to controls but similar in men. Among men, median sTNFR2 concentration was significantly higher in cases compared to CRC controls but similar in women. The mean time from baseline to adenoma detection was 6.6 years. Similar patterns of adipokine concentrations were observed among adenoma cases and controls (Table 2).

Adjusting for age and sex, leptin and adiponectin were modestly inversely correlated, leptin and sTNFR2 were modestly positively correlated, and adiponectin and sTNFR2 were not correlated (Table S2). These correlations were consistent in men and in women, although the correlation between leptin and sTNFR2 appeared to be stronger in women. BMI and adult weight gain were moderately positively correlated with leptin and sTNRF2, and modestly inversely correlated with adiponectin overall and in men and in women. With respect to inflammation and metabolic biomarkers, leptin tended to be positively correlated with CRP, IL-6, insulin, and triglycerides, inversely correlated with IGFBP-1 and HDL, but not correlated with HbA1c or total cholesterol. For adiponectin, correlations were in the opposite direction to that for leptin. For sTNFR2, correlation patterns for CRP, IL-6, HDL, and triglycerides were similar to leptin, but were substantially weaker for insulin and IGFBP-1. These patterns were generally similar in men and women.

Higher sTNFR2 concentration was associated with more than a threefold higher CRC risk in men (quartile 4 vs. 1 OR: 3.06; 95% CI: 1.19–7.88) when accounting for matching factors, when mutually adjusting for leptin and adiponectin (quartiles 4 vs. 1 OR: 3.14; 95% CI: 1.11–8.86), and when additionally adjusting for BMI (quartile 4 vs. 1 OR: 3.46; 95% CI: 1.19–10.06) (Table 3). sTNFR2 was not associated with CRC in women (Table 3). Restricting to colon, the pattern of association for sTNFR2 was comparable to CRC in men (70 pairs, per 50^{th} percentile increase: OR: 1.50, 95% CI 1.11–2.04) and in women (79 pairs, OR: 0.97, 95% CI 0.65–1.43). Patterns for sTNFR2 were generally similar to overall when adjusting for non-diet CRC risk factors and when further adjusting for dietary risk factors (Table S3). Adiponectin and leptin were not statistically significantly associated with CRC risk in men or in women when accounting for matching factors, when mutually adjusting leptin, adiponectin and sTNFR2, and when adjusting for BMI (Table 3), and when adjusting for other CRC risk factors, or when further adjusting for dietary risk factors (Table S3). Patterns of associations of sTNFR2, adiponectin, and leptin with CRC were similar within strata of lifestyle, metabolic, and inflammatory factors (Table 4).

To explore whether the positive association between sTNFR2 and CRC risk in men possibly mediates the known positive association between obesity and CRC, we estimated the association between BMI and CRC before and after adjusting for sTNFR2 in men. The OR of CRC per 10 kg/ m^2 of BMI in men of 1.44 was not attenuated by adjusting for sTNFR2 (OR = 1.64).

Colorectal adenoma

As previously described [28], at baseline participants subsequently diagnosed with colorectal adenoma were more likely to have a family history of CRC, to be former smokers, and to use diabetes medications, and were less likely to use oral contraceptives (women) or HRT (women) compared with controls. Mean baseline age of the adenoma cases was 55 years compared to a mean baseline age of 65 years for CRC cases.

Adiponectin, leptin, and sTNFR2 were not associated with adenoma in men or in women when accounting for matching factors, when mutually adjusting leptin, adiponectin, and sTNFR2, and when adjusting for BMI (Table 5). These associations remained null when adjusting for additional colorectal neoplasia risk factors and when further adjusting for dietary factors (Table S4).

DISCUSSION

In these case–control studies nested in a prospective cohort, higher circulating concentration of the inflammatory marker sTNFR2 was associated with a higher CRC risk in men when adjusting for circulating concentrations of leptin and adiponectin, and this association was independent of BMI. Leptin and adiponectin were not associated with CRC in men or women, and none of the 3 biomarkers was associated with adenoma. These findings suggest that leptin and adiponectin do not appear to underlie the association between obesity and colorectal carcinogenesis. The positive association between sTNFR2, which we measured as a correlate of TNF-α, with CRC in men adjusting for BMI suggests that TNF-α may influence CRC independent of adipocyte production. The positive association between BMI and CRC was not attenuated when adjusting for sTNFR2 in men, also suggesting that TNF-α, does not underlie the well-described body fatness-colorectal cancer association. While this could be the true underlying biology, other explanations include potential measurement error in sTNFR2 measured at one point in time and as a surrogate of TNF-α as well as the relative ratio in the source of TNF-α (immune cells vs. fat cells). The potential link between obesity and CRC may be through other features of obesity such as waist circumference or percent body fat not captured by BMI. Further, the positive association for sTNFR2 with CRC, but null association with adenoma suggests that TNF-α may influence colorectal carcinogenesis later in its natural history.

Our finding of a positive association between sTNFR2 and CRC in men in CLUE II is inconsistent with the only two prior prospective studies conducted on this association in men, both of which observed null associations [18, 19]. Our finding that sTNFR2 was not associated with risk of CRC in women in CLUE II is consistent with findings from a prospective analysis in the Women's Health Study (WHS), in which neither TNF-α and sTNFR2 were associated with CRC risk in postmenopausal women [15, 17]. However, our

finding in women is inconsistent with that from a prospective analysis in the Nurses' Health Study (NHS) in which sTNFR2 was previously observed to be associated with a higher CRC risk in women (RR: 1.67; 95% CI: 1.05–2.68) [16].

In the CRC controls and in the adenoma controls in this study in CLUE II, men and women appeared to have similar distributions of sTNFR2, while women had higher levels of both adiponectin and leptin compared to men (Table 2). sTNFR2 was consistently associated with CRC in men and was consistently null in women before and after adjusting for the sex-specific distributions of leptin and adiponectin. Sex-specific differences in the association between adiposity-associated inflammation and CRC align with the pattern of association between obesity and CRC by sex, which is thought to be, in part, a consequence of endogenous sex hormones [30]. For example, estrogen is inversely associated with CRC risk in women, but positively associated with CRC in men [31]. It is possible that the inverse association between estrogen and CRC risk in women may offset the potential positive association of adiposity-associated inflammation. In CLUE II, sTNFR2 was not associated with adenoma, which is consistent with the association between TNF-α and adenoma in a meta-analysis of five studies (1568 cases, 2832 controls) with a summary OR: 1.00 (95% CI: 0.77–1.29; I^2 = 49%) [13]. Our finding is consistent with the null association observed between sTNFR2 and adenoma in a nested case–control study in women in the NHS [20]. However, our finding of a null association between sTNFR2 and CRC in women is not consistent with the positive association observed in the NHS [16].

Higher adiponectin concentration has been hypothesized to be associated with a reduced risk of CRC through improved insulin sensitivity and anti-inflammatory properties [4]. However, adiponectin was not associated with CRC in men or women in the current study. Adiponectin has been found to be inversely associated with CRC in prior epidemiologic studies as indicated in a meta-analysis of cross-sectional studies, retrospective and nested case–control studies [9]. Our results of a null association between adiponectin and CRC in men and women are not consistent with two additional case–control studies nested in larger prospective cohorts where higher adiponectin concentration was inversely associated with CRC risk in men and women [32], and in men only [33]. Our inconsistent findings may be due to differences in the relative abundance of different adiponectin isoforms that may be differentially associated with CRC. In the current study, adiponectin was not associated with adenoma in men or women consistent with our findings for CRC.

In the current study, leptin was not associated with CRC or adenoma. Leptin has been suggested to contribute to carcinogenesis through effects on insulin resistance. Higher soluble leptin receptor (sOB-R) concentration was associated with reduced CRC risk in an EPIC-nested-case control study [34], but sOB-R was not associated with CRC in the HPFS and NHS [33]. In a 2019 meta-analysis of nine studies, higher leptin concentrations was not associated with CRC risk (summary OR: 1.11; 95% CI: 0.67–1.84; I^2 = 74%) [9]. The high between-study heterogeneity in the meta-analysis and the conflicting findings in EPIC [34] and HPFS/NHS [33] suggests leptin may be a risk factor for CRC in certain populations.

A strength of the current analysis is the prospective design with inflammatory and metabolic biomarkers assessed prior to CRC and adenoma diagnosis. This reduces the possibility of

undetected colorectal neoplasia influencing biomarker levels. For adenoma cases, selected controls had to have had a prior large bowel endoscopy to ensure equal opportunity detection between cases and controls. Cases were required to have pathologically confirmed CRC or adenoma diagnosis. Together the methods for selecting cases and controls helped to minimize potential misclassification. The current study is not without some limitations including the small sample size to detect modest associations, thus we cannot rule out the potential chance finding. A single measurement of each biomarker prevented an opportunity to account for changing levels of each biomarker over time in colorectal carcinogenesis.

In conclusion, we observed that independent of obesity, higher circulating sTNFR2 concentration was associated with CRC risk in men, but not women, and that neither leptin nor adiponectin was associated with CRC risk. We also observed null associations between all three biomarkers and adenoma risk. These findings suggest that leptin and adiponectin do not appear to underlie the association between obesity and colorectal carcinogenesis. The positive association between sTNFR2 and CRC in men adjusting for BMI suggests that TNF-α may influence CRC independent of adipocyte production. The association with BMI and CRC was unchanged when adjusting for sTNFR2 in men. Further, the positive association for sTNFR2 with CRC, but null association with adenoma suggests that TNF-α may influence colorectal carcinogenesis later in its natural history. That some, but not all, studies report positive associations for sTNFR2 and CRC, and no study reports a positive association with adenoma, supports further research aiming to understand the role of TNF-α in the progression to CRC for insight into CRC prevention and control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of colorectal cancer cases and matched controls (193 pairs) in CLUE II, 1989

	Overall		Men		Women	
	Case	**Control**	**Case**	**Control**	**Case**	**Control**
N	193	193	89	89	104	104
Mean time from blood draw to cancer diagnosis (years)	6.5		6.5		6.5	
Age (years), median (IQR)	65 (54–71)	65 (54–72)	65 (57–70)	65 (57–70)	65.5 (53–72.5)	65 (53–72)
BMI (kg/m^2), median (IQR)	25.8 (23.2–28.9)	25.7 (23.6–28.5)	26.5 (24.6–29.8)	26.6 (23.7–28.7)	25.5 (22.7–28.4)	24.9 (23.2–27.5)
Female (%)	53.9	53.9			100	100
White (%)	979	97.9	97.8	97.8	98.1	98.1
CRC family history (%)	7.8	2.6	4.5	2.2	10.6	2.9
NSAID use (%)	20.7	26.4	22.5	31.5	19.2	22.1
Diabetes medication use (%)	8.3	4.1	9.0	5.6	7.7	2.9
HRT use (%)					23.1	36.5
Smoking status (%)						
Never	48.7	52.3	32.6	39.3	62.5	63.5
Current	14.0	13.0	10.1	10.1	17.3	15.4
Former	37.3	34.7	57.3	50.6	20.2	21.2
Alcohol intake (g/day) *, median (IQR)	4.73 (1.65–11.52)	5.87 (1.57–16.64)	7.16 (1.57–33.54)	6.33 (1.73–19.52)	4.73 (1.65–10.11)	1.96 (0.84–13.25)

CRC colorectal cancer, *HRT* hormone replacement therapy

* alcohol intake was assessed through FFQ that was available for 105 (54%) and 128 (66%) of CRC cases and controls

Table 2

Median baseline (1989) concentrations of leptin, adiponectin, and sTNFR2 in colorectal cancer cases and matched controls (193 pairs) and adenoma cases and matched controls (131 pairs) nested in CLUE II

	Overall			Men			Women		
Colorectal cancer	**Cases**	**Controls**	**p***	**Cases**	**Controls**	**p***	**Cases**	**Controls**	**p***
Leptin (ng/mL)	10.7	9.7	0.5	6.2	5.3	0.8	16.2	15.6	0.5
Adiponectin (μg/mL)	9.1	9.0	0.1	6.4	6.6	0.7	10.9	12.3	0.04
sTNFR2 (ng/mL)	2.6	2.4	0.06	2.8	2.4	0.01	2.5	2.4	0.8
Adenoma									
Leptin (ng/mL)	8.6	9.1	0.8	5.4	4.6	0.6	15.6	15.7	0.7
Adiponectin (μg/mL)	9.3	8.2	0.5	6.6	6.1	0.2	13.0	11.9	0.9
sTNFR2 (ng/mL)	2.3	2.3	0.9	2.3	2.3	0.3	2.4	2.3	0.2

* from generalized linear model

Table 3

Odds ratio (OR) of colorectal cancer in men and women by sex-specific quartiles of concentration of leptin, adiponectin, and sTNFR2 in the CLUE II cohort

	Case/Control	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
Men							
Adiponectin							
1st Quartile	33/22	1	Ref	1	Ref	1	Ref
2nd Quartile	14/22	0.46	0.19–1.09	0.49	0.19–1.27	0.48	0.19–1.24
3rd Quartile	14/24	0.45	0.19–1.03	0.50	0.20–1.24	0.50	0.20–1.25
4th Quartile	28/21	0.99	0.43–2.29	0.79	0.31–2.01	0.81	0.32–2.08
Per 50th percentile *		0.78	0.28–2.21	0.63	0.20–1.99	0.65	0.08–3.89
p-trend			0.6		0.4		0.5
Leptin							
1st Quartile	26/23	1	Ref	1	Ref	1	Ref
2nd Quartile	11/21	0.40	0.14–1.12	0.45	0.14–1.43	0.39	0.12–1.31
3rd Quartile	31/23	1.19	0.52–2.75	1.50	0.60–3.76	1.25	0.46–3.40
4th Quartile	21/22	0.81	0.34–1.90	0.88	0.34–2.25	0.59	0.16–2.12
Per 50th percentile *		1.18	0.25–5.65	1.48	0.26–8.34	0.98	0.09–10.04
p-trend			0.8		0.7		0.9
sTNFR2							
1st Quartile	16/23	1	Ref	1	Ref	1	Ref
2nd Quartile	14/21	1.07	0.38–3.03	1.08	0.34–3.42	1.16	0.36–3.78
3rd Quartile	19/24	1.40	0.51–3.85	1.21	0.40–3.66	1.34	0.43–4.16
4th Quartile	40/21	3.06	1.19–7.88	3.14	1.11–8.86	3.46	1.19–10.06
Per 50th percentile *		1.37	1.08–1.73	1.38	1.07–1.78	1.41	1.08–1.83
p-trend			0.01		0.01		0.01
Women							
Adiponectin							

	Case/Control	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
1st Quartile	32/26	1	Ref	1	Ref	1	Ref
2nd Quartile	24/27	0.68	0.31–1.51	0.70	0.31–1.60	0.69	0.29–1.62
3rd Quartile	35/25	1.02	0.51–2.02	1.02	0.49–2.13	1.01	0.47–2.14
4th Quartile	13/26	0.34	0.13–0.88	0.34	0.12–0.94	0.33	0.12–0.95
Per 50th percentile *		0.14	0.01–2.09	0.14	0.01–2.71	0.14	0.01–2.85
p-trend			0.2		0.2		0.2
p-interaction			0.02		0.05		0.05
Leptin							
1st Quartile	22/27	1	Ref	1	Ref	1	Ref
2nd Quartile	29/25	1.45	0.67–3.14	1.49	0.66–3.36	1.51	0.66–3.48
3rd Quartile	31/26	1.44	0.69–3.02	1.14	0.50–2.59	1.17	0.48–2.85
4th Quartile	22/26	1.05	0.48–2.26	0.98	0.42–2.29	1.02	0.38–2.76
Per 50th percentile *		1.27	0.03–54.07	0.60	0.01–40.36	0.75	0.01–110.74
p-trend			0.9		0.8		0.9
p-interaction			0.2		0.2		0.2
sTNFR2							
1st Quartile	24/27	1	Ref	1	Ref	1	Ref
2nd Quartile	26/25	1.18	0.54–2.57	1.13	0.50–2.56	1.13	0.50–2.59
3rd Quartile	29/26	1.29	0.57–2.97	1.21	0.49–2.96	1.22	0.49–3.03
4th Quartile	25/26	1.12	0.48–2.64	1.15	0.45–2.90	1.17	0.45–3.02
Per 50th percentile *		1.04	0.77–1.42	1.05	0.75–1.47	1.06	0.75–1.49
p-trend			0.8		0.8		0.7
p-interaction			0.2		0.2		0.2

Model 1 – Matched model (matched on age, race, date of blood draw, and time since last meal)

Model 2 – Model 1 plus mutually adjusted for leptin, adiponectin, and sTNFR2

Model 3 – Model 2 plus further adjusted for BMI (continuous)

* The 25th to 75th percentile delta is based on the biomarker concentration distribution for men and women combined

** The 25th to 75th percentile delta is based on the biomarker concentration distribution separately in men and women

Table 4

Odds ratios of colorectal cancer per 50th percentile increase in concentration of leptin, adiponectin, and sTNFR2 stratified by lifestyle, metabolic, and inflammatory factors in CLUE II

	Cases/ controls	Adiponectin		Leptin		sTNFR2		Cases/ controls	Adiponectin		Leptin		sTNFR2	
		OR*	95%CI	OR*	95%CI	OR*	95%CI		OR*	95%CI	OR*	95%CI	OR*	95%CI
BMI (kg/m^2)														
< 25.7	34/34	1.08	0.31–3.74	0.66	0.05–8.34	1.12	0.84–1.49	55/62	0.10	0.01–2.02	0.42	0.00–90.68	0.94	0.67–1.31
≥ 25.7	55/55	0.72	0.25–2.09	1.27	0.16–10.25	1.20	0.98–1.48	49/42	0.98	0.04–24.27	0.64	0.00–93.21	1.09	0.77–1.54
p-interaction			0.6		0.6		0.8			0.4		0.7		0.6
Adult weight gain (lbs)**														
< 25	34/40	0.96	0.26–3.53	0.15	0.01–3.58	1.53	1.14–2.05	54/54	0.24	0.01–4.16	0.32	0.00–44.10	1.05	0.74–1.50
≥ 25	55/48	0.79	0.26–2.34	1.42	0.20–10.17	0.99	0.79–1.23	49/50	0.75	0.03–18.70	0.31	0.00–81.95	1.07	0.76–1.51
p-interaction			0.6		0.6		0.03			0.5		0.9		0.7
NSAID use														
No	69/61	1.00	0.42–2.40	1.21	0.22–6.76	1.16	0.97–1.39	84/81	0.38	0.03–4.16	0.60	0.01–34.10	0.90	0.69–1.17
Yes	20/28	0.12	0.01–1.31	0.17	0.00–6.89	1.61	0.98–2.65	20/23	0.25	0.00–38.94	0.48	0.00–2428.73	1.56	0.85–2.87
p-interaction			0.2		0.6		0.6			0.9		0.9		0.1
CRP (mg/L)														
< 1.77	20/35	0.90	0.11–7.06	0.96	0.05–19.91	1.49	1.00–2.20	38/44	0.25	0.01–6.73	0.03	0.00–18.25	0.90	0.59–1.36
≥ 1.77	51/35	1.26	0.46–3.45	1.24	0.15–10.06	1.08	0.85–1.36	51/44	0.13	0.00–3.71	0.99	0.01–154.32	1.06	0.76–1.47
p-interaction			0.9		0.6		0.5			0.9		0.5		0.6
IL-6 (pg/mL)														
< 1.773	20/27	1.23	0.20–7.45	0.67	0.03–17.39	1.48	0.90–2.42	32/51	0.15	0.00–7.85	0.00	0.00–4.58	0.95	0.62–1.46
≥ 1.773	51/43	1.04	0.36–2.97	0.78	0.10–6.07	1.11	0.90–1.36	57/36	0.17	0.01–2.81	1.23	0.01–130.53	1.06	0.76–1.46
p-interaction			0.6		0.8		0.3			0.9		0.1		0.2
Insulin (mU/L)														
< 13.544	33/29	1.54	0.38–6.29	1.98	0.16–23.82	1.21	0.92–1.58	46/50	0.33	0.02–6.85	0.27	0.00–54.90	0.90	0.63–1.30
≥ 13.544	37/41	0.80	0.22–2.86	0.57	0.04–7.50	1.19	0.90–1.59	43/38	0.11	0.00–5.40	0.26	0.00–108.25	1.09	0.75–1.60
p-interaction			0.5		0.8		0.7			0.7		0.9		0.8

	Cases/ controls	Adiponectin		Leptin		sTNFR2		Cases/ controls	Adiponectin		Leptin		sTNFR2	
		OR*	95%CI	OR*	95%CI	OR*	95%CI		OR*	95%CI	OR*	95%CI	OR*	95%CI
HbA1c (%)														
< 5.7	42/50	2.56	0.72–9.15	4.01	0.40–40.30	1.18	0.92–1.52	48/59	0.21	0.01–4.79	0.05	0.00–10.19	1.01	0.70–1.44
≥ 5.7	29/20	0.68	0.18–2.55	0.19	0.01–3.74	1.25	0.92–1.70	41/29	0.13	0.00–4.40	1.65	0.00–1013.88	0.99	0.68–1.44
p-interaction			0.1		0.5		0.9			0.7		0.3		0.8
No diabetes medication use	81/84	0.89	0.39–2.03	0.90	0.19–4.19	1.17	0.98–1.38	96/101	0.53	0.06–4.51	0.82	0.02–30.38	1.00	0.78–1.27
Smoking status														
Never	29/35	0.53	0.12–2.34	5.55	0.36–85.39	1.23	0.86–1.76	65/66	0.20	0.01–2.81	0.38	0.00–46.87	1.02	0.76–1.38
Ever	60/54	1.02	0.38–2.75	0.31	0.04–2.46	1.15	0.95–1.39	39/38	0.80	0.02–26.94	0.22	0.00–57.68	1.02	0.70–1.49
p-interaction			0.6		0.1		0.3			0.7		0.9		0.9

*Per 50th percentile increase in biomarker concentration with the 25th to 75th delta based on the distribution for men and women combined estimated using unconditional logistic regression adjusted for the matching factors (age, race, date of blood draw, time since last meal), mutually for leptin, adiponectin, sTNFR2, and for BMI (continuous)

**from age 21 to baseline in 1989

Table 5

Odds ratio of adenoma in men and women by sex-specific quartiles of concentration of leptin, adiponectin, and sTNFR2 in CLUE II

	Case/Control	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
Men							
Adiponectin							
1st Quartile	14/16	1	Ref	1	Ref	1	Ref
2nd Quartile	15/17	1.02	0.36–2.88	1.11	0.38–3.23	1.11	0.38–3.22
3rd Quartile	11/17	0.79	0.24–2.56	0.85	0.25–2.93	0.85	0.25–2.93
4th Quartile	27/17	1.96	0.66–5.82	2.39	0.75–7.64	2.41	0.74–7.78
Per 50th percentile *		2.36	0.65–8.65	2.78	0.71–10.96	2.78	0.69–11.20
p-trend			0.2		0.1		0.2
Leptin							
1st Quartile	12/16	1	Ref	1	Ref	1	Ref
2nd Quartile	16/17	1.25	0.49–3.22	1.12	0.39–3.18	1.10	0.37–3.30
3rd Quartile	23/17	1.84	0.68–4.97	2.09	0.72–6.05	2.03	0.61–6.77
4th Quartile	16/17	1.26	0.46–3.51	1.44	0.46–4.45	1.39	0.37–5.25
Per 50th percentile *		2.09	0.23–18.55	3.26	0.30–35.79	2.82	0.16–48.54
p-trend			0.5		0.3		0.5
sTNFR2							
1st Quartile	16/16	1	Ref	1	Ref	1	Ref
2nd Quartile	18/17	0.97	0.36–2.64	0.85	0.29–2.46	0.85	0.29–2.46
3rd Quartile	21/18	1.12	0.41–3.07	0.78	0.26–2.40	0.78	0.26–2.39
4th Quartile	12/16	0.69	0.21–2.27	0.53	0.14–1.98	0.53	0.14–1.98
Per 50th percentile *		0.91	0.60–1.37	0.81	0.51–1.27	0.80	0.51–1.27
p-trend			0.6		0.4		0.4
Women							
Adiponectin							
1st Quartile	14/16	1	Ref	1	Ref	1	Ref
2nd Quartile	15/16	1.14	0.37–3.50	1.08	0.30–3.81	1.17	0.32–4.23
3rd Quartile	24/16	1.66	0.64–4.30	1.62	0.55–4.77	1.80	0.59–5.54
4th Quartile	11/16	0.71	0.24–2.13	0.57	0.16–1.99	0.61	0.17–2.17
Per 50th percentile *		1.00	0.05–22.09	0.58	0.02–18.92	0.69	0.02–23.91
p-trend			0.9		0.8		0.8
p-interaction			0.1		0.1		0.1
Leptin							
1st Quartile	20/16	1	Ref	1	Ref	1	Ref
2nd Quartile	12/16	0.58	0.21–1.62	0.53	0.17–1.69	0.48	0.14–1.57

	Case/Control	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
3rd Quartile	18/16	0.87	0.31–2.40	0.74	0.22–2.48	0.64	0.18–2.26
4th Quartile	14/16	0.66	0.22–1.94	0.49	0.13–1.84	0.34	0.07–1.68
Per 50th percentile *		0.17	0.00–130.66	0.03	0.00–89.99	0.00	0.00–65.56
p-trend			0.6		0.4		0.8
p-interaction			0.7		0.7		0.7
sTNFR2							
1st Quartile	13/16	1	Ref	1	Ref	1	Ref
2nd Quartile	17/16	1.47	0.43–5.04	1.70	0.44–6.57	1.62	0.41–6.35
3rd Quartile	15/16	1.33	0.39–4.55	1.82	0.42–7.88	1.87	0.43–8.15
4th Quartile	19/16	1.59	0.52–4.84	2.03	0.53–7.75	2.00	0.52–7.65
Per 50th percentile *		1.10	0.84–1.44	1.17	0.84–1.63	1.17	0.84–1.63
p-trend			0.5		0.4		0.3
p-interaction			0.7		0.8		0.8

Model 1 – Matched model (matched on age, race, date of blood draw, and time since last meal)

Model 2 – Model 1 plus mutually adjusted for leptin, adiponectin, and sTNFR2

Model 3 – Model 2 plus further adjusted for BMI (continuous)

*The 25th to 75th percentile delta is based on the biomarker concentration distribution for men and women combined

**The 25th to 75th percentile delta is based on the biomarker concentration distribution separately in men and women