Metabolic syndrome components and colorectal adenoma in the CLUE II cohort

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Abstract

Background Metabolic syndrome components have been associated with colorectal cancer in several studies; however, evidence for colorectal adenomas is limited. Thus, we evaluated the association between markers of the metabolic syndrome with colorectal adenoma development in a nested case–control study.

Methods Colorectal adenoma cases ($n = 132$) and matched controls, who had a negative sigmoidoscopy or a colonoscopy ($n = 260$), were identified between baseline in 1989 and 2000 among participants in the CLUE II cohort of Washington County, Maryland. Concentrations of C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured in baseline blood specimens. Body mass index was calculated using baseline height and weight. Use of medications to treat diabetes mellitus was self-reported at baseline. Blood pressure was measured at baseline. Distributional cutpoints of the latter markers were used to define the metabolic syndrome components (hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension) present at baseline.

Results No statistically significant associations with adenomas were observed for the markers of the metabolic syndrome, with the exception of a strong positive association for use of diabetes medications (OR, 8.00; 95% CI, 1.70–37.67), albeit based on small numbers.

Conclusion Our findings do not support that components of the metabolic syndrome influence risk of colorectal adenomas, except possibly for severe diabetes mellitus warranting medical treatment.

Keywords Insulin resistance · Colorectal neoplasia · Prospective study

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Introduction

Dietary and lifestyle exposures typical of Western communities, such as a high-energy diet rich in animal fat and refined carbohydrates, and a low level of physical activity have been consistently associated with both colorectal cancer [1] and insulin resistance [2]. These observations led McKeown-Eyssen [3] and Giovannucci [4] in the early 1990s to independently suggest insulin resistance as the prevailing mechanism for the association of Westernization with colorectal neoplasia. Subsequently, metabolic abnormalities, including hyperinsulinemia, hyperglycemia, excess adiposity, dyslipidemia, and hypertension, which tend to cluster with insulin resistance, have received increased attention for colorectal carcinogenesis [5].

Several prospective studies have evaluated the independent or joint association of this cluster of abnormalities, termed metabolic syndrome, with colorectal cancer. C-peptide, a marker of insulin production, has been statistically significant and positively associated with colorectal cancer [6–9]. Hemoglobin A1c (HbA1c), a time-integrated measure of glucose concentration, has been studied in relation to colorectal cancer, but with inconsistent results [10–15]. Systematic reviews have shown the direct and independent associations of obesity with colorectal cancer [16]. Dyslipidemia, including elevated total cholesterol and triglycerides, reduced high-density lipoprotein cholesterol levels, and colorectal cancer has not been consistently positively associated [17–19]. Hypertension is less well studied in relation to colorectal carcinogenesis [5]. However, the cluster of the metabolic syndrome components has been consistently associated with colorectal cancer [15, 20–24]. In contrast to colorectal cancer, epidemiologic evidence linking metabolic syndrome components to colorectal adenomas, a known colorectal cancer precursor, is limited [25–30]. Statistically significant positive associations between the metabolic syndrome and colorectal adenomas were reported in three case–control studies [31–33].

Given the prior literature and our previous prospective findings in the CLUE II cohort in which use of diabetes medications, obesity, and HbA1c were positively associated with colorectal cancer [11], we sought to address whether metabolic syndrome components contribute to carcinogenesis at an earlier point in the natural history of colorectal neoplasia. We evaluated the association of several markers of metabolic syndrome with colorectal adenomas in a case–control study nested in the CLUE II cohort. We examined plasma concentrations of C-peptide, insulin-like growth factor binding protein 1 (IGFBP-1), glycosylated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides as circulating markers of the metabolic syndrome. We also examined baseline body mass index (BMI), use of medications to treat diabetes mellitus as an indicator for protracted or severe type 2 diabetes, and diastolic and systolic blood pressure as non-circulating markers of the metabolic syndrome.

Materials and methods

Study population

Colorectal adenoma cases and controls were identified among members of the prospective CLUE II cohort, which was established in 1989 to investigate potential serologic risk factors for cancer and heart disease. The cohort population and data collection procedures have been described in detail previously [34]. In brief, the cohort consists of 32,894 residents of Washington County, MD, and neighboring areas. For this analysis, the study population was restricted to 22,887 Washington County residents aged $\geq$18 year old. Participants provided a blood sample and completed a brief medical and lifestyle exposure history at baseline. Seventy-five percent of the participants returned a food frequency questionnaire at baseline. In 1996, 1998, and 2000, questionnaires were mailed to participants to update lifestyle, medical, and family histories, including sigmoidoscopic/colonoscopic procedures and polyp diagnoses. All participants provided informed consent. The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health approved the study.

Selection of colorectal adenoma cases and controls

Participants were eligible to be selected as a case or control if they never had a diagnosis of cancer (except possibly for non-melanoma skin cancer or cervix in situ) or polyps of any type in 1989 or earlier. In 1996, 1998, and 2000, CLUE II members were asked to indicate whether they ever had a polyp diagnosis. After receiving permission from participants, endoscopy and pathology reports were reviewed to confirm a first ever adenoma after 1989 among those who reported a polyp. Only adenomatous polyp cases were studied because these are well-described precursors for colorectal cancer, and risk factors for the development of other polyps (e.g., hyperplastic) may differ. Colorectal adenoma cases were 135 Washington County residents who had a first adenoma detected by endoscopy and pathologically confirmed after 1989 through mid-2000. Of these, 132 were included in the analysis, three were excluded for missing blood marker concentrations. Cases were characterized by site (proximal colon, distal colon, rectum), size ($<$1, $\geq$1 cm), histology (villous, tubulovillous, tubular), and number of adenomas detected on endoscopy (one, multiple).

For each case, two controls matched on age (±1 year), sex, race, date of blood draw (±1 month), and time since last meal (0–1, 2–3, 4–5, 6–7, and ≥8 h) were selected. We matched on time since last meal, because only 37% of our sample had fasted for ≥4 h at baseline. In order to ensure an equal opportunity for the detection of adenomas, which are usually asymptomatic, controls for the 92 distal adenoma cases had to report a negative endoscopic procedure of the colon on the 1996 or 2000 questionnaire, irrespective of whether it was a sigmoidoscopy or colonoscopy; and controls for the 43 proximal adenoma cases had to report a negative colonoscopy on the 2000 questionnaire. Two hundred and seventy controls were selected of which 260 were included in the analysis, six were excluded because their respective cases had missing blood marker concentrations, and another four were excluded due to their missing blood marker concentrations.

Assessment of metabolic syndrome markers

Concentrations of metabolic syndrome markers were measured in archived blood collected in 1989. Plasma concentration of C-peptide, cleaved from pro-insulin and secreted in equimolar amounts with insulin into circulation but with a longer half-life than insulin [35], was measured by ELISA (ALPCO Diagnostics, Windham, NH). Plasma concentration of IGFBP-1, the hepatic secretion of which is reduced by insulin [36], was determined with cell-coated ELISA (Diagnostic Systems Laboratories, Inc., Webster, TX). C-peptide concentration as a marker of insulin production and IGFBP-1 concentration as a marker of insulin action were measured. HbA1c, formed when glucose binds to hemoglobin and is an indicator of glycemia over the prior 6–8 weeks [37], was determined by turbidometric immunoinhibition in red blood cells (Hitachi 917 analyzer, Roche Diagnostics, Indianapolis, IN). Total cholesterol was measured at baseline using an enzymatic assay [38]. HDL-c and triglycerides concentrations were measured simultaneously on a Hitachi 917 analyzer using reagents and calibrators from Roche Diagnostics (Indianapolis, IN). All assays were performed by laboratory personnel blinded to case–control status. Thirty-six quality control samples were arranged in triplets among the cases and the controls. The mean intra-pair coefficients of variation for the embedded quality control samples were: C-peptide, 5.4%; IGFBP-1, 4.1%; HbA1c, 1.6%. For total cholesterol, HDL-c and triglycerides, two levels of quality control for each analyte were run by the laboratory. For total cholesterol at 190 and 90 mg/dl the coefficients of variation were 1.1 and 2.5%, respectively. For HDL-c at 78.6 and 45.5 mg/dl, the coefficients of variation were 2.8 and 1.5%, respectively. For triglycerides at 188 and 89 mg/dl, the coefficients of variation were 1.1 and 3.1%, respectively.

Non-serologic markers of the metabolic syndrome were assessed at baseline. BMI was calculated as self-reported weight in kilograms divided by height in meters squared. Participants were asked whether they had used medications in the 48 h before blood draw; those who reported use of medications to treat diabetes and hypertension were considered to be diabetics and hypertensives, respectively. Sitting blood pressure was taken three times; the third reading was used in the analysis.

No standard definition of the metabolic syndrome has been adopted although most definitions include hyperinsulinemia, hyperglycemia, obesity, dyslipidemia, and hypertension as components [39]. In this study, separate analyses were conducted to evaluate the association of each serologic and non-serologic metabolic syndrome marker (i.e., C-peptide, IGFBP-1, HbA1c, total cholesterol, HDL-c, triglycerides, BMI, use of diabetes medications, and blood pressure), the metabolic syndrome components, and an aggregate score of these components, with colorectal adenomas. In order to evaluate the components that comprise the metabolic syndrome, participants were categorized with respect to: hyperinsulinemia: IGFBP-1 <25th percentile (<4.13 ng/ml) or C-peptide ≥75th percentile (≥1,574 pmol/l); hyperglycemia: use of diabetes medications or HbA1c >6.0%; obesity: BMI ≥75th percentile (≥28.5 kg/m^2); dyslipidemia: total cholesterol (≥237 mg/dl) or triglycerides (≥165 mg/dl) ≥75th percentile or HDL-c <25th percentile (<32.7 mg/dl); hypertension: systolic (≥140 mmHg) or diastolic (≥88 mmHg) blood pressure ≥75th percentile or use of anti-hypertensive medications. Sensitivity analyses were run using clinical cutpoints (BMI ≥30 kg/m^2, triglycerides ≥150 mg/dl, HDL-c <40 or 35 mg/dl in males and <35 or 39 or 50 mg/dl in females, blood pressure ≥130/85 or 140/90 mmHg); inferences were the same.

Covariate assessment

Smoking history (never, current, former) was collected at baseline. Any prescription or over-the-counter medications taken in the past 48 h of blood draw that contained aspirin or other nonsteroidal anti-inflammatory drugs were coded as non-steroidal anti-inflammatory drugs (NSAIDs). Women were asked whether they currently or in the past took oral contraceptives or hormone replacement therapy. Follow-up questionnaires in 1996 and 2000 ascertained whether participants had a first-degree family history of colon or rectal cancer. Intake of alcohol (g/day), energy (kcal/day), saturated fat (g/day), fiber (g/day), folate (μg/day), calcium (mg/day), and red meat (g/day) were estimated from the baseline food frequency questionnaire and were available for 74 and 69% of cases and controls, respectively.

Statistical analysis

In order to compare the distributions of baseline characteristics and metabolic syndrome markers between cases and controls, we used regression models; generalized estimating equations with an exchangeable correlation structure among each matched set and robust estimation of standard errors were used to account for the matched design and the sampling of two controls per case. Highly right skewed variables were natural logarithm transformed.

Matched odds ratios (ORs) of colorectal adenoma and 95% confidence intervals (CIs) were estimated using conditional logistic regression. The continuous markers were modeled using indicator variables for fourths of their distributions among controls. Trends were tested by entering into the model an ordinal term with values corresponding to the median value of each fourth among controls. Several models were run adjusting for known or suspected risk factors for colorectal neoplasia: (i) cigarette smoking status (never, ever), BMI (<25, ≥25 to <30, ≥30 kg/m^2; when BMI was not the exposure of interest), hormone use in women (never, ever), NSAIDs use (yes, no), diabetes medications use (yes, no; when diabetes medication use was not the exposure of interest), and family history of colorectal cancer (yes, no, missing indicator), (ii) as (i) plus indicator variables for the fourths of alcohol, energy, saturated fat, fiber, folate, calcium, and red meat intake, and (iii) as (i) plus indicator variables for the fourths of the other circulating metabolic syndrome markers. Analysis adjusting for the dietary factors was performed among those who completed the food frequency questionnaire (FFQ) (98 cases and 179 matched controls) and among the entire set of cases and controls using a missing FFQ indicator with almost identical results. The findings from models (i)–(iii) were inferentially the same; therefore, only the simple matched model and model (i) were presented in text and tables. Further, we performed analyses according to adenoma location (colon, rectum, proximal colon, distal colon), histology (any villous component, tubular), size (<1, ≥1 cm), and number (1, ≥1).

Analyses were also conducted stratifying by potentially modifying factors (age [<55 vs. ≥55 years], sex, and BMI [<25 vs. ≥25 kg/m^2]). Tests for interaction were performed by using the median value for each marker fourth as a continuous variable, an indicator variable for the potentially modifying factor, and a term for the product of the two variables. In stratified analyses, for factors other than the matching variables we broke the matched sets and performed logistic regression adjusting for the matching variables to preserve power. Analyses were also conducted restricting to participants who did not use diabetes medications or without a family history. In order to evaluate the effect of fasting on the associations, we sequentially increased the minimum time since last meal required for inclusion in the analysis. All p values are from two-sided tests. All analyses were performed using SAS version 9.1 (Cary, NC).

Results

Case–control differences were in the expected directions based on known and suspected risk factors for colorectal adenomas. A greater proportion of cases had a family history of colorectal cancer ($p < 0.01$) and were current or former smokers ($p = 0.06$). Female cases were less likely to have ever used hormones ($p = 0.10$) (Table 1). None of the metabolic syndrome marker levels differed significantly between cases and controls, although cases were more likely to report currently using diabetes medications ($p < 0.01$) (Table 2).

None of the baseline blood markers was statistically significantly associated with colorectal adenoma risk in the matched analysis or after adjustment for lifestyle and medical history risk factors (Table 3). BMI was not associated with adenoma when modeled using quartiles (Table 3) or standard cutpoints (≥30 vs. <25 kg/m^2; OR, 0.70; 95% CI, 0.35–1.38; $P_{trend} = 0.20$). No associations were observed for systolic and diastolic blood pressure (Table 3). The association between diabetes medications use and adenomas was strongly positive and statistically significant, although the number of participants using these medications was small (Table 3). Hyperglycemia (elevated HbA1c or diabetes medication use) was also positively associated with adenomas (OR, 4.69; 95% CI, 1.31–16.7) (Table 4), although the association was explained by use of diabetes medications. No statistically significant associations were observed for hyperinsulinemia, obesity, dyslipidemia, and hypertension (Table 4). The simultaneous presence of more than three metabolic syndrome components was not statistically significantly associated with adenomas, and risk did not change across number of metabolic syndrome components (Table 4). After excluding participants who reported using diabetes medications, the point estimate of the metabolic syndrome score association changed direction (>3 vs. <1 components; OR, 0.84; 95% CI, 0.29–2.45). This exclusion did not materially alter any other association in Tables 3 and 4.

Associations were similar to adenoma location, histology, size and number (data not shown). Associations did not differ by age, sex, and BMI (all $P_{interaction} > 0.15$), with the exception of a possible different association between HDL-c and adenomas by age (highest versus lowest fourth: <55 years; OR, 0.51; 95% CI, 0.20–1.26; ≥55 years; OR, 2.00; 95% CI, 0.80–5.09; $P_{interaction} = 0.06$). Excluding

Table 1 Baseline characteristics of colorectal adenoma cases and matched controls in the CLUE II cohort of Washington County, Maryland, 1989

Characteristic	Cases ($n = 132$)	Controls ($n = 260$)	p[a]
Age (y), mean (SD)	55.2 (10.0)	55.1 (10.0)	Matched
Female (%)	50.0	50.0	Matched
First-degree family history of CRC (%)[b]	22.4	8.3	<0.01
Use (in the past 48 h) of aspirin/NSAIDs (%)	28.0	30.8	0.56
Cigarette smoking status			
Never (%)	42.4	54.2	0.06
Current (%)	16.7	11.9	
Former (%)	40.9	33.9	
Ever use of female hormones (%)[c]	37.9	49.2	0.10
Daily intake, mean (SD)[d]			
Alcohol (g)	7.5 (19.3)	6.7 (16.6)	0.72
Energy (kcal)	1,688 (622)	1,750 (541)	0.18
Saturated fat (g)	24.3 (11.1)	25.3 (11.4)	0.49
Fiber (g)	12.7 (5.7)	13.2 (5.0)	0.22
Folate (μg)	401 (296)	412 (255)	0.49
Calcium (mg)	842 (543)	856 (439)	0.36
Red meat (g)	81.2 (57.0)	85.2 (65.1)	0.59

SD standard deviation, *CRC* colorectal cancer, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] Linear or logistic regression with each characteristic as the response variable, accounting for the matched design using generalized estimating equations with an exchangeable correlation structure and robust estimation of standard errors. Highly skewed characteristics were transformed using the natural logarithm

[b] Among those who returned questionnaires in 1996 and 2000 (125 cases and 242 matched controls)

[c] Use of oral contraceptives or hormone replacement therapy (66 female cases and 130 matched controls)

[d] Among those who completed the food frequency questionnaire (98 cases and 179 matched controls)

Table 2 Distribution of metabolic syndrome markers in colorectal adenoma cases and matched controls in the CLUE II cohort of Washington County, Maryland, 1989

Characteristic	Cases ($n = 132$)	Controls ($n = 260$)	p[a]
C-peptide (pmol/l), median (IQR)	884 (522–1,592)	952 (601–1,574)	0.82
IGFBP-1 (ng/ml), median (IQR)	10.8 (4.9–27.7)	9.2 (4.1–21.1)	0.20
HbA1c (%), mean (SD)	5.2 (0.6)	5.2 (0.6)	0.69
Total cholesterol (mg/dl), mean (SD)	215 (37.4)	215 (36.5)	0.98
HDL-cholesterol (mg/dl), median (IQR)	40.0 (32.4–50.6)	41.2 (32.6–50.7)	0.76
Triglycerides (mg/dl), median (IQR)	110 (79–155)	118 (83–164)	0.37
BMI (kg/m^2), mean (SD)	26.4 (4.5)	26.4 (3.8)	0.98
Use of medication to treat diabetes (%)	6.1	0.8	0.01
Systolic blood pressure (mmHg), mean (SD)[b]	127 (15.9)	127 (15.5)	0.83
Diastolic blood pressure (mmHg), mean (SD)[b]	79.7 (9.2)	80.5 (9.5)	0.44

IGFBP-1 insulin-like growth factor binding protein-1, *IQR* inter-quartile range, *SD* standard deviation, *HDL* high-density lipoprotein, *HbA1c* glycosylated hemoglobin, *BMI* body mass index

[a] Linear or logistic regression with each characteristic as the response variable, accounting for the matched design using generalized estimating equations with an exchangeable correlation structure and robust estimation of standard errors. Highly skewed characteristics were transformed using the natural logarithm

[b] Results based on 131 cases and 260 matched controls

Table 3 Odds ratio (OR) and 95% confidence interval (CI) of colorectal adenoma according to fourths of the distribution of metabolic syndrome markers in the CLUE II cohort of Washington County, Maryland, 1989

	Fourths of the marker distribution				P^{a}_{trend}
	Lowest	Second	Third	Highest	
C-peptide (pmol/l)	<601	602–953	954–1,573	≥1,574	
Cases/controls (*n*)	35/65	34/65	28/66	35/64	
OR (95% CI)[b]	1.00 (ref)	0.95 (0.53–1.72)	0.77 (0.40–1.45)	1.00 (0.52–1.92)	0.95
OR (95% CI)[c]	1.00 (ref)	0.92 (0.47–1.77)	0.79 (0.39–1.60)	1.04 (0.50–2.17)	0.90
IGFBP-1 (ng/ml)	<4.12	4.13–9.22	9.23–21.25	≥21.26	
Cases/controls (*n*)	28/65	30/65	34/65	40/65	
OR (95% CI)[b]	1.00 (ref)	1.14 (0.61–2.14)	1.31 (0.69–2.47)	1.52 (0.82–2.80)	0.18
OR (95% CI)[c]	1.00 (ref)	1.10 (0.54–2.23)	1.29 (0.62–2.67)	1.62 (0.78–3.38)	0.15
HbA1c (%)	<4.92	4.93–5.09	5.10–5.35	≥5.36	
Cases/controls (*n*)	29/64	38/64	28/67	37/65	
OR (95% CI)[b]	1.00 (ref)	1.30 (0.72–2.33)	0.91 (0.47–1.75)	1.36 (0.63–2.90)	0.57
OR (95% CI)[c]	1.00 (ref)	1.26 (0.67–2.40)	0.75 (0.36–1.54)	1.05 (0.45–2.48)	0.93
Total cholesterol (mg/dl)	<190	191–210	211–236	≥237	
Cases/controls (*n*)	34/64	31/66	33/65	34/65	
OR (95% CI)[b]	1.00 (ref)	0.89 (0.49–1.63)	0.96 (0.53–1.71)	0.98 (0.53–1.83)	0.96
OR (95% CI)[c]	1.00 (ref)	0.84 (0.44–1.62)	0.92 (0.49–1.74)	0.97 (0.49–1.94)	0.96
HDL-c (mg/dl)	<32.6	32.7–41.1	41.2–50.6	≥50.7	
Cases/controls (*n*)	34/65	34/64	31/66	33/65	
OR (95% CI)[b]	1.00 (ref)	1.00 (0.56–1.79)	0.89 (0.48–1.64)	0.94 (0.50–1.76)	0.78
OR (95% CI)[c]	1.00 (ref)	1.15 (0.60–2.20)	1.02 (0.51–2.03)	0.92 (0.45–1.90)	0.71
Triglycerides (mg/dl)	<82	83–117	118–164	≥165	
Cases/controls (*n*)	36/65	34/63	35/67	27/65	
OR (95% CI)[b]	1.00 (ref)	0.95 (0.53–1.69)	0.90 (0.50–1.62)	0.73 (0.39–1.37)	0.30
OR (95% CI)[c]	1.00 (ref)	1.04 (0.56–1.94)	1.15 (0.59–2.24)	0.85 (0.40–1.81)	0.65
Total cholesterol/HDL-c	<4.14	4.15–5.20	5.21–6.55	≥6.56	
Cases/controls (*n*)	33/65	31/66	35/64	33/65	
OR (95% CI)[b]	1.00 (ref)	0.95 (0.52–1.75)	1.10 (0.60–2.00)	1.02 (0.54–1.93)	0.86
OR (95% CI)[c]	1.00 (ref)	1.15 (0.60–2.21)	1.22 (0.63–2.37)	1.11 (0.56–2.24)	0.78
Triglycerides/HDL-c	<1.79	1.80–2.83	2.84–4.72	≥4.73	
Cases/controls (*n*)	35/64	38/65	27/66	32/65	
OR (95% CI)[b]	1.00 (ref)	1.05 (0.60–1.84)	0.75 (0.41–1.39)	0.87 (0.46–1.64)	0.58
OR (95% CI)[c]	1.00 (ref)	1.34 (0.73–2.44)	0.91 (0.45–1.84)	0.99 (0.47–2.11)	0.86
BMI (kg/m^2)	<23.6	23.7–26.2	26.3–28.4	≥28.5	
Cases/controls (*n*)	39/65	32/65	25/65	36/65	
OR (95% CI)[b]	1.00 (ref)	0.79 (0.43–1.42)	0.58 (0.30–1.11)	0.88 (0.49–1.59)	0.73
OR (95% CI)[c]	1.00 (ref)	0.74 (0.39–1.40)	0.58 (0.29–1.17)	0.67 (0.35–1.29)	0.24
Diastolic BP (mmHg)	<73	74–79	80–87	≥88	
Cases/controls (*n*)	32/65	27/44	45/89	27/62	
OR (95% CI)[b]	1.00 (ref)	1.22 (0.63–2.35)	0.97 (0.55–1.71)	0.82 (0.43–1.56)	0.55
OR (95% CI)[c]	1.00 (ref)	1.34 (0.65–2.78)	1.00 (0.54–1.88)	0.90 (0.45–1.80)	0.79
Systolic BP (mmHg)	<117	118–126	127–139	≥140	
Cases/controls (*n*)	31/66	41/71	33/59	26/64	
OR (95% CI)[b]	1.00 (ref)	1.18 (0.65–2.17)	1.12 (0.59–2.10)	0.83 (0.42–1.64)	0.60
OR (95% CI)[c]	1.00 (ref)	1.08 (0.55–2.09)	1.11 (0.55–2.23)	0.58 (0.26–1.30)	0.28
Use of diabetes medications	No	Yes			
Cases/controls (*n*)	124/258	8/2			

Table 3 continued

	Fourths of the marker distribution				P^{a}_{trend}
	Lowest	Second	Third	Highest	
OR (95% CI)[b]	1.00 (ref)	8.00 (1.70–37.7)			
OR (95% CI)[c]	1.00 (ref)	11.01 (2.10–57.7)			

IGFBP-1 insulin-like growth factor binding protein-1, *HDL-c* high-density lipoprotein cholesterol, *Cholesterol/HDL-c* ratio of total cholesterol to HDL-c, *Triglycerides/HDL-c* ratio of triglycerides to HDL-c, *HbA1c* glycosylated hemoglobin, *BMI* body mass index, *BP* blood pressure

[a] Entered into the model as a single ordinal variable with values corresponding to the median of each fourth

[b] From a conditional logistic regression model with concentration entered as a series of indicator variables corresponding to fourths among the controls. Cases and controls were matched on age, sex, race, date of blood draw, time since last meal, and type of endoscopy

[c] As ([b]) but further adjusted for ever cigarette smoking, BMI (overweight, obese), ever use of hormones (women), use of aspirin or other non-steroidal anti-inflammatory drugs, use of diabetes medications, and family history of colorectal cancer. The models, where BMI and use of diabetes medications are the exposures, are not adjusted for BMI and use of diabetes medications, respectively

participants who were not fasting did not materially change the reported associations in Tables 3 and 4.

Discussion

In this study, markers of the metabolic syndrome were not statistically significantly associated with risk of colorectal adenomas except for a positive association for use of medications to treat diabetes. We had previously reported a positive association for use of diabetes medications and colorectal cancer risk in this cohort [11].

Despite using different metabolic syndrome risk factors and cutpoints, prior studies have reported statistically significant positive associations between metabolic syndrome and colorectal cancer in five prospective [15, 20–23] and one study that pooled case–control studies [24] and adenoma risk in three case–control studies [31–33]. The associations were stronger for larger, villous, and more dysplastic adenomas [31, 32]. A dose–response association with colorectal cancer [22] or adenomas [33] was observed only in few studies. In most studies, the positive associations for the metabolic syndrome were explained mainly by individual risk factors (e.g., obesity, diabetes, and hyperglycemia). In our study, we did not observe an association between the metabolic syndrome and colorectal adenomas, with the exception of a positive association for treated diabetes. It is likely that some metabolic syndrome components may be associated only with later stages of colorectal tumorigenesis.

A central component of the metabolic syndrome is insulin [5], which is known to stimulate growth of normal colonic and carcinoma cells in vitro [40]. C-peptide and IGFBP-1 were assayed as surrogates of insulin. No statistically significant associations were observed for C-peptide and IGFBP-1 concentrations with adenomas. Although C-peptide has been consistently positively associated with colorectal cancer [6–9], these associations have not been well studied in relation to colorectal adenomas. Some [6, 13], but not all [8, 9, 11, 41], epidemiological studies have shown significant inverse associations between IGFBP-1 and colorectal cancer. The Nurses' Health Study cohort found a statistically significant positive association for C-peptide, but no association for IGFBP-1 and colorectal adenomas [30].

The metabolic syndrome is characterized by increased circulating glucose, which can promote formation of reactive oxygen species, which in turn can cause DNA damage and increase the risk of cancer development [5]. We used circulating concentrations of HbA1c and use of diabetes medications as indicators of glycemia and observed no association for HbA1c and adenoma, but a strong positive association for treated diabetes. At baseline, we did not ask participants to report whether they had a diagnosis of diabetes but we asked them to indicate the medications that they were currently taking. The use of medications to treat diabetes does not capture all the participants who had diabetes at baseline or the usual glucose concentration among diabetics, but should capture the most severe cases that required pharmacologic intervention. These participants are most likely to have protracted hyperglycemia at some point before baseline. However, HbA1c concentration would capture diabetics, irrespective of whether diagnosed and if diagnosed irrespective of whether treated with medication, who are not in good glucose control and thus most likely to have hyperglycemia. Our positive findings for use of diabetes medications and null findings for HbA1c concentration may mean that longer-term diabetics with a longer history of metabolic dysregulation are driving the positive association compared with diabetics not needing medications. In the Nurses' Health Study, a non-significant positive association between HbA1c and adenomas was reported [10, 30]. Epidemiologic evidence for diabetes influencing adenoma risk is scarce [40]. Results for HbA1c and colorectal cancer have not been consistent in prospective studies [11–15],

Table 4 Odds ratio (OR) and 95% confidence interval (CI) of colorectal adenoma by categories of metabolic syndrome components in the CLUE II cohort of Washington County, Maryland, 1989

	Cases/controls	OR (95% CI)[a]	OR (95% CI)[b]
Hyperinsulinemia[c]			
No	80/159	1.00 (ref)	1.00 (ref)
Yes	52/101	1.01 (0.64–1.60)	1.14 (0.67–1.92)
Hyperglycemia[d]			
No	123/255	1.00 (ref)	1.00 (ref)
Yes	9/5	4.17 (1.27–13.65)	4.69 (1.31–16.71)
Obesity[e]			
No	96/195	1.00 (ref)	1.00 (ref)
Yes	36/65	1.14 (0.71–1.84)	0.89 (0.52–1.51)
Dyslipidemia[f]			
No	64/119	1.00 (ref)	1.00 (ref)
Yes	68/141	0.90 (0.59–1.38)	0.88 (0.54–1.43)
Hypertension[g]			
No	73/149	1.00 (ref)	1.00 (ref)
Yes	59/111	1.07 (0.69–1.66)	1.08 (0.66–1.78)
Metabolic syndrome score[h]			
0	26/51	1.00 (ref)	1.00 (ref)
1	45/82	1.08 (0.59–1.97)	1.13 (0.59–2.16)
2	21/61	0.67 (0.33–1.35)	0.71 (0.33–1.50)
3	26/46	1.12 (0.55–2.27)	1.25 (0.59–2.65)
>3	14/20	1.46 (0.59–3.60)	1.22 (0.46–3.20)
P^{i}_{trend}		0.60	0.67

[a] From a conditional logistic regression model with concentration entered as a series of indicator variables corresponding to fourths among the controls. Cases and controls were matched on age, sex, race, date of blood draw, time since last meal, and type of endoscopy

[b] As ([a]) but further adjusted for ever cigarette smoking, ever use of hormones (women), aspirin or other non-steroidal anti-inflammatory drugs, and family history of colorectal cancer. Diabetes medications use, hyperglycemia, hyperinsulinemia, dyslipidemia and hypertension models also adjusted for BMI (overweight, obese). Hyperinsulinemia, obesity, dyslipidemia and hypertension models also adjusted for diabetes medications use

[c] Insulin-like growth factor binding protein-1 <4.13 ng/ml or C-peptide ≥1,574 pmol/l

[d] Use of diabetes medications or glycosylated hemoglobin >6.0%

[e] BMI ≥28.5 kg/m^2

[f] Total cholesterol ≥237 mg/dl or triglycerides ≥165 mg/dl or HDL-c <32.7 mg/dl

[g] Systolic ≥140 mmHg or diastolic blood pressure ≥88 mmHg or blood pressure medication use

[h] Number of metabolic syndrome components: hyperglycemia, hyperinsulinemia, obesity, dyslipidemia, hypertension (as defined above)

[i] Entered into the model as a single ordinal variable

whereas diabetes mellitus has been consistently positively associated with colorectal cancer [42].

Other features of the metabolic syndrome increased adiposity, dyslipidemia, and hypertension. In our study, no association was observed for BMI, total cholesterol, HDL-c, triglycerides, and blood pressure. Obesity has been consistently associated with both colorectal cancer [16], including in our study CLUE II [11], and adenomas [27]. Epidemiological studies of dyslipidemia and colorectal neoplasia have shown inconsistent findings [17–19, 25, 28]. Weak positive but not statistically significant associations were observed for systolic and diastolic blood pressure and colorectal neoplasia [15, 20–24, 31, 32].

In summary, our findings combined with the literature suggest that primarily hyperinsulinemia and hyperglycemia would most likely act as cancer promoters rather than initiators. Several aspects of this study warrant discussion. Participants had to self-report a polyp diagnosis before we sought medical records. All colorectal adenoma cases were pathologically confirmed by medical record review. Controls were required to have an endoscopic examination of their large bowel to ensure an equal opportunity to detect a polyp between cases and controls. As in other cohort studies [30], we did not obtain and review the endoscopy reports for participants who reported a negative endoscopy. Any misclassification of adenoma cases as controls due to

participant misreport is unlikely to be related to the metabolic syndrome markers. Such non-differential misclassification would tend to bias our results toward the null. Our null findings for C-peptide and HbA1c may be explained by this misclassification; however, the positive-looking findings for IGFBP-1 and the inverse-looking findings for BMI are less likely to be explained by this source of misclassification. Although we measured the circulating metabolic syndrome markers at one point in time and C-peptide is not perfectly correlated with fasting insulin concentrations [43], C-peptide and HbA1c are considered better long-term indicators of hyperinsulinemia and hyperglycemia than insulin and glucose concentrations, respectively. The within-person correlation coefficient for C-peptide levels measured 4 years apart has been shown to be reasonably good [7]. Total cholesterol, HDL-c, and triglycerides have been shown to have high intraclass correlation coefficients over a 1-year period [44]. In etiologic studies, use of a single baseline measurement of a biomarker may be preferable to updated measurements over time to minimize the possibility of reverse causation.

A strength of the current study is that the metabolic syndrome markers were assessed before adenoma detection. Adenomas are usually asymptomatic; thus, time of detection may not correlate well with time of development. However, our prospective design is superior to the case–control studies of metabolic syndrome components and colorectal adenoma because the possibility of preclinical disease exerting an effect on the markers is lower than for clinical disease. Our results are unlikely to be explained by the cutpoints chosen for the markers or by the use of primarily non-fasting data because we verified our findings in several sensitivity analyses. Our sample size was small, which increased the probability of chance findings, but the study was powered to detect an OR of 2.00 or higher for adenomas as we previously observed for metabolic syndrome markers and colorectal cancer in this cohort [11]. In conclusion, we observed that only diabetes mellitus warranting medication, but no other component of the metabolic syndrome, is associated with an increased risk of colorectal adenomas.

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