Increased Blood Glucose and Insulin, Body Size, and Incident Colorectal Cancer

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Background: **Abdominal obesity—an elevated level of visceral adipose tissue—has been linked to colorectal cancer. Furthermore, elevated levels of visceral adipose tissue have been associated with hyperinsulinemia, and insulin is a growth factor in the colon. We assessed whether waist circumference, a surrogate measure of visceral adipose tissue, and metabolic parameters associated with visceral adipose tissue were related to colorectal cancer.** ***Methods:*** **In the Cardiovascular Health Study cohort, we examined the relationship of baseline measurements of body size, glucose, insulin, and lipoproteins to incident colorectal cancer. All *P* values are two-sided.** ***Results:*** **Among 5849 participants, 102 incident cases of colorectal cancer were identified. Individuals in the highest quartile of fasting glucose had a nearly twofold increased risk of colorectal cancer (relative risk [RR] = 1.8; 95% confidence interval [CI] = 1.0–3.1), and the linear trend RR (LT RR = 1.2; 95% CI = 1.0–1.5) for fasting glucose level was statistically significant (*P* = .02). Glucose and insulin levels 2 hours after oral glucose challenge also exhibited statistically significant associations with colorectal cancer (2-hour glucose levels: RR = 2.4 [95% CI = 1.2–4.7]/LT RR = 1.3 [95% CI = 1.0–1.6; *P* = .02]; 2-hour insulin levels: RR = 2.0 [95% CI = 1.0–3.8]/LT RR = 1.2 [95% CI = 1.0–1.5; *P* = .04]). Analysis of fasting insulin levels suggested a threshold effect, with values above the median associated with colorectal cancer (RR = 1.6; 95% CI = 1.1–2.4; *P* = .02). Higher levels of waist circumference were also statistically significantly associated with colorectal cancer (RR = 1.9; 95% CI = 1.1–3.3; *P* = .02).** ***Conclusions:*** **These data provide, to our knowledge, the first direct evidence of an association between elevated visceral adipose tissue level, its associated metabolic effects, and colorectal cancer. [J Natl Cancer Inst 1999; 91:1147–54]**

Many studies *(1–3)* have demonstrated a relationship between body mass index (BMI) and increased risk for colorectal cancer, especially in men. Additional data *(4)* suggest that adipose tissue distribution may be an important mediating factor in the association between BMI and colorectal cancer. In the Health Professionals Follow-up Cohort Study of more than 31 000 men *(4)*, waist-to-hip ratio, a surrogate measure of intra-abdominal fat or visceral adipose tissue (VAT), demonstrated a strong relationship with the subsequent development of colorectal cancer (relative risk [RR] = 3.4 for those in the highest versus the lowest quintile). An elevated waist-to-hip ratio was also associated with incident colorectal adenomas of at least 1 cm in size, which are considered at high risk for subsequent development of colorectal cancer, but not with small adenomas, which are less likely to progress *(5)*.

A biologic rationale for the association of abdominal obesity with colorectal cancer has emerged as an elevated VAT level has been shown to be associated with hyperinsulinemia *(6–8)*, and insulin and insulin-like growth factors (IGFs) are mitogens for the colonic mucosa and for colon carcinoma cell lines *(9–11)*. These findings have spawned an "insulin hypothesis" of colorectal cancer pathogenesis *(9)*.

Risk factors associated with colorectal cancer can be integrated into a causative model centering on the relationship between VAT, insulin, and colorectal cancer. For example, epidemiologic evidence supports a protective role for physical activity against colorectal cancer *(4,12–15)*. Physical activity can result in preferential loss of VAT relative to subcutaneous adipose tissue *(16)*, with a concomitant improvement in the metabolic profile *(17–19)*. The effect of physical activity on VAT may be a means by which physical activity mediates decreased risk for colorectal cancer. Similarly, hypertriglyceridemia has been linked to colorectal cancer risk *(20)*, and increased amounts of VAT, because of its more active lipolytic responsiveness, result in elevated triglyceride levels and increased free fatty acid production *(7)*.

We hypothesized that waist circumference, as a surrogate measure of VAT, and the metabolic parameters associated with VAT, including insulin, glucose, triglycerides, and high-density lipoprotein (HDL), would be associated with incident colorectal cancer. To our knowledge, no previous studies have prospectively measured these parameters for their relationship to incident colorectal cancer.

METHODS

Population

The Cardiovascular Health Study (CHS) is an observational, population-based, cohort study of risk factors for coronary heart disease and stroke in individuals 65 years old and older *(21)*. The design, rationale, and recruitment of subjects in the CHS have been detailed elsewhere *(21,22)*. The CHS cohort was recruited in two phases from four communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. After recruitment of a first cohort (n = 5201; 5.3% members of minority groups) in 1989–1990, a second cohort with 687 minority subjects (97.8% African-American) was enrolled in 1992–1993. Community samples were identified from the Medicare enrollment lists of the Health Care Financing Administration (HCFA), Baltimore, MD.

Testing

Subjects underwent comprehensive psychosocial, medical, and physical assessments with the use of questionnaires, blood measurements, and noninvasive testing that included electrocardiography, carotid ultrasonography, and echocardiography *(21)*. Dietary intake was assessed by use of a modified version of the food-frequency questionnaire of Block et al. *(23)*. Physical activity was determined with the modified Minnesota Leisure Time Activities *(24)* and Paffenbarger et al. *(25)* questionnaires, by use of a weighted average of regular and leisure activities.

Anthropometric measurements were performed in a standardized fashion and included waist and hip circumferences. BMI was calculated as weight in kilograms/height in meters squared. Fasting venipuncture was performed with aliquots of plasma and

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See "Notes" following "References."

serum frozen at −70 °C and shipped to a central blood analysis laboratory. Serum insulin was measured by solid-phase radioimmunoassay with the use of serum-based standards (Diagnostic Products Corp., Los Angeles, CA). In the initial cohort, all participants, except diabetics treated with insulin or oral hypoglycemic agents, drank a 75-g oral glucose load and underwent 2-hour post-challenge measurement of glucose and insulin levels. Impaired glucose tolerance was defined as a fasting glucose level of less than 140 mg/dL (7.8 mmol/L) and a 2-hour glucose value between 140 and 199 mg/dL. Diabetes was defined as a fasting glucose level of greater than 140 mg/dL (7.8 mmol/L) or a 2-hour glucose value of at least 200 mg/dL (11.1 mmol/L), in accordance with World Health Organization guidelines *(26)*, or a medical history of diabetes. Glucose and insulin measurements at 2 hours after glucose challenge and food-frequency questionnaires were not administered to the second cohort at their baseline examination.

Lipid analyses were performed according to the standards of the Centers for Disease Control and Prevention. Low-density lipoprotein (LDL) cholesterol was calculated according to the equation of Friedewald et al. *(27)*. Blind replicate blood samples were drawn from 5% of the participants, and reliability and reproducibility estimates have been published *(28)*.

End Points

The participants were followed semiannually by alternating phone calls and clinic visits and underwent a second extensive clinical examination 3 years after enrollment. Between contacts, participants and their physicians were encouraged to report hospitalizations and major illnesses. Periodic searches of the HCFA Medicare utilization (MEDPAR) files were performed to identify hospitalizations not otherwise ascertained, but these accounted for only 7% of hospital ascertainment *(29)*.

Although the CHS was designed to investigate cardiovascular end points, the abstraction of medical records on all hospitalizations for all diagnoses allowed assessments of incident colorectal cancer that led to hospitalization. ICD-9 (International Classification of Diseases, 9th revision) codes for colon (153.0–153.4 and 153.6–153.9) and rectal (154.0, 154.1, and 154.8) cancers were ascertained for each case of colorectal cancer. Incident cancers that did not lead to hospitalization were not available for study. Events received at the CHS coordinating center as of June 30, 1996, were used in these analyses.

Analysis and Statistical Methods

To evaluate the association of baseline characteristics with incident colorectal cancer, categorical and continuous variables were included in univariate Cox models (Table 1). Continuous variables were categorized into quartiles, separately by sex, and Cox regression models adjusted for age, sex, and physical activity were fit for the sample as a whole and by sex. Hazard ratios for time-to-cancer diagnosis were estimated for each of the upper three quartiles (Q2, Q3, and Q4) of each covariate examined relative to Q1. A test for linear trend was performed to assess for a monotonically increasing or decreasing relationship to incident colorectal cancer. If the *P* value was >.10 for the linear test, this was considered supportive of a linear relationship, and a linear model was fit. If a linear relationship did not fit the data, appropriate categorization of the quartiles for general trends was performed. All *P* values were two-sided and were considered statistically significant for a *P* value less than .05. The proportional hazards assumption was tested and was found to be reasonable for each model, with the possible exception of the model for triglycerides.

Table 1. Baseline characteristics of subjects by incident colorectal cancer*

Covariate	Colorectal cancer (n = 102)	No colorectal cancer (n = 5747)	Hazard ratio	*P*†
Sex, % male	57.8	42.1	2.0	<.001
Race, % black	12.8	15.7	1.2	.52
Mean age, y (SD)	73.9 (5.5)	72.8 (5.6)	1.2‡	.01
% income ⩾$25 000/y	29.5	38.4	0.6	.04
% married	62.8	66.2	0.8	.25
% current smoker	13.0	12.0	1.1	.69
No. of alcoholic drinks consumed per wk§ (SD)	3.6 (8.9)	2.4 (6.2)	1.1	.23
% current aspirin use‖	31.4	33.8	0.9	.64
Total kilocalories of physical activity (SD)§	1458 (1759)	1727 (2044)	1.0	.24
Time to walk 15 feet in seconds (SD)§	5.7 (1.6)	5.8 (2.3)	1.1	.85
Mean % of diet that is fat¶ (SD)	34.5 (6.7)	33.8 (7.2)	1.0	.26
Mean No. of vegetable servings per wk¶,# (SD)	9.2 (5.4)	9.1 (5.6)	1.0	.95
Mean No. of fruit servings per wk¶,# (SD)	10.1 (7.4)	9.5 (6.9)	1.2	.43

*SD = standard deviation.
†All *P* values are two-sided; if <.05, *P* values are considered statistically significant.
‡Relative risk for an increase of 5 years.
§Square root transformation was used in proportional hazards model.
‖Defined as aspirin used ⩾3 days in the previous 2 weeks.
¶Available for the majority of the first cohort only.
#Modeled as ">7 servings per week" relative to "⩽7 servings per week."

Results

Baseline Characteristics

Over a median follow-up of 77 months (79 months for cohort 1 [range, 73–84 months] and 38 months for cohort 2 [range, 36–43 months]) among 5849 participants (excluding 39 individuals with self-reported diagnosis of colorectal cancer prior to entry in the cohort), 102 incident cases of colorectal cancer were identified. Ninety-three of the cases were diagnosed in cohort 1, and nine were diagnosed in cohort 2. Characteristics of the subjects with incident colorectal cancer compared with those without are presented in Table 1. Subjects with colorectal cancer were more likely to be male, 57.8% versus 42.1% (*P*<.001); to be older, 73.9 versus 72.8 years (*P* = .01); and to have lower yearly household incomes, 29.5% of the cancer patients having an income of at least $25 000/year versus 38.4% of the subjects without colorectal cancer (*P* = .04). Patients with colorectal cancer did not differ from those without colorectal cancer in terms of smoking, current use of aspirin, alcoholic drinks consumed per week, percent of fat calories in diet, or mean number of vegetable or fruit servings per week (Table 1). Median follow-up time was 78.9 months among case patients and 77.4 months among non-case subjects.

Although mean physical activity levels were lower in case patients (Table 1), this did not reach statistical significance. Individuals in the highest quartile of physical activity (measured as total kilocalories of physical activity) compared with those in the lowest quartile were at decreased risk for incident colorectal cancer (RR = 0.8; 95% confidence interval [CI] = 0.4–1.4), but none of the quartiles of physical activity were statistically significantly different from quartile 1 (*P* = .08; 3 *df*). Regardless, physical activity was adjusted for in the subsequent analysis.

Associations With Incident Colorectal Cancer

The relationships between baseline glucose, insulin, anthropometric measures, lipid levels, and incident colorectal cancer in men and women in Cox proportional hazards models adjusted for age, sex, and physical activity are presented in Table 2. For each of the covariates, the sex-specific range of values of the quartiles is listed.

Individuals in the highest quartile of fasting glucose were at 80% higher risk of developing incident colorectal cancer compared with those in the lowest quartile (RR = 1.8; 95% CI = 1.0–3.1; *P* = .04). A monotonic increase in risk by quartile was demonstrated (linear trend [LT] RR = 1.2; 95% CI = 1.0–1.5; *P* =

Table 2. Relative risk of incident colorectal cancer in the Cardiovascular Health Study*

Factor	Q1	Q2	Q3	Q4	Linear model†
Fasting glucose, mg/dL					
Range					
Men	61–96	97–103	104–115	116–448	
Women	53–93	94–99	100–110	111–657	
No. of case patients/total No. of subjects	22/1591	18/1352	29/1433	32/1393	
Relative risk	1.0 (referent)	0.9	1.4	1.8	1.2
95% CI		0.5–1.8	0.8–2.4	1.0–3.1	1.0–1.5
					$P = .02$
2-h glucose,‡,§ mg/dL					
Range					
Men	41–108	109–134	135–170	171–660	
Women	38–110	111–137	138–173	174–691	
No. of case patients/total No. of subjects	12/1155	22/1162	19/1126	29/1130	
Relative risk	1.0 (referent)	1.8	1.6	2.4	1.3
95% CI		0.9–3.6	0.8–3.3	1.2–4.7	1.0–1.6
					$P = .02$
Fasting insulin, IU/mL					
Range					
Men	4–10	11–13	14–18	19–400	
Women	3–9	10–13	14–18	19–400	
No. of case patients/total No. of subjects	29/1661	17/1538	29/1232	26/1297	
Relative risk	1.0 (referent)	0.6	1.4	1.2	NA‖
95% CI		0.3–1.1	0.8–2.3	0.7–2.1	
2-h insulin‡,§					
Range					
Men	5–38	39–65	66–101	102–400	
Women	5–45	46–70	71–109	110–500	
No. of case patients/total No. of subjects	14/1163	21/1139	21/1094	27/1117	
Relative risk	1.0 (referent)	1.5	1.6	2.0	1.2
95% CI		0.8–2.9	0.8–3.1	1.0–3.8	1.0–1.5
					$P = .04$
Waist circumference, cm					
Range					
Men	69–91	91.1–97	97.1–104	104.1–145.5	
Women	32.5–82	82.1–91.5	91.6–101.1	101.2–167	
No. of case patients/total No. of subjects	16/1517	31/1411	21/1461	30/1422	
Relative risk	1.0 (referent)	2.2	1.4	2.2	NA‖
95% CI		1.2–4.0	0.7–2.7	1.2–4.1	
Body mass index¶					
Range					
Men	15.6–23.9	23.91–26.1	26.11–28.5	28.51–46.2	
Women	14.6–23.2	23.21–26.1	26.11–29.6	29.61–58.8	
No. of case patients/total No. of subjects	22/1456	25/1458	26/1460	27/1456	
Relative risk	1.0 (referent)	1.2	1.2	1.4	1.1
95% CI		0.7–2.1	0.7–2.2	0.8–2.5	0.9–1.3
					$P = .26$
Waist-to-hip ratio					
Range					
Men	0.61–0.93	0.931–0.97	0.971–1.00	1.01–2.33	
Women	0.61–0.83	0.831–0.90	0.91–0.96	0.961–2.06	
No. of case patients/total No. of subjects	14/1454	34/1445	16/1482	34/1427	
Relative risk	1.0 (referent)	2.5	1.2	2.6	NA‖
95% CI		1.3–4.6	0.6–2.4	1.4–4.8	
High-density lipoprotein, mg/dL					
Range					
Men	18–39	40–46	47–54	55–125	
Women	15–48	49–57	58–68	69–149	
No. of case patients/total No. of subjects	29/1608	34/1424	22/1333	16/1419	
Relative risk	1.0 (referent)	1.3	0.9	0.6	0.9
95% CI		0.8–2.2	0.5–1.6	0.3–1.2	0.7–1.0
					$P = .09$
Low-density lipoprotein, mg/dL					
Range					
Men	26.8–100.8	101.0–122	122.8–143.8	144–336.8	
Women	24.8–109.8	110–132	132.8–157.8	158–314.8	
No. of case patients/total No. of subjects	35/1447	26/1416	23/1467	16/1386	
Relative risk	1.0 (referent)	0.8	0.6	0.5	0.8
95% CI		0.5–1.3	0.4–1.1	0.3–0.9	0.7–0.9
					$P = .01$

(Table continues)

Table 2 (continued). Relative risk of incident colorectal cancer in the Cardiovascular Health Study*

Factor	Q1	Q2	Q3	Q4	Linear model†
Triglycerides, mg/dL					
Range					
Men	35–90	91–118	119–162	163–1323	
Women	24–93	94–121	122–166	167–1216	
No. of patients/total No. of subjects	20/1466	28/1438	26/1469	27/1420	
Relative risk	1.0 (referent)	1.4	1.3	1.4	1.1
95% CI		0.8–2.5	0.7–2.3	0.8–2.5	0.9–1.3
					$P = .34$

*Cox proportional hazard models adjusted for age, sex, and physical activity. Q = quartile; RR = relative risk; 95% CI = 95% confidence interval.
†All *P* values are two-sided; if <.05, they are considered statistically significant.
‡First cohort only.
§Does not include diabetics.
‖NA = not applicable because a linear relationship was not indicated by the data.
¶Body mass index = weight in kg/height in m^2.

.02), with a 20% increase in risk for each successive quartile. Glucose and insulin levels 2 hours after oral glucose challenge were also significantly related to colorectal cancer. For 2-hour glucose levels (Q4 versus Q1), there was a 2.4-fold increased risk (95% CI = 1.2–4.7); for 2-hour insulin levels (Q4 versus Q1), the risk was increased 2.0-fold (95% CI = 1.0–3.8). Both 2-hour glucose (LT RR = 1.3; 95% CI = 1.0–1.6; $P = .02$) and 2-hour insulin (LT RR = 1.2; 95% CI = 1.0–1.5; $P = .04$) were linearly related to increased risk (Table 2), with a 30% and 20% increased risk, respectively, for each successive quartile. Quartile analysis of fasting insulin levels suggested a threshold effect, with an adjusted RR of 1.6 (95% CI = 1.1–2.4; $P = .02$) for insulin levels above versus below the median (Q1 + Q2 versus Q3 + Q4) (Table 2).

BMI was not statistically significantly associated with colorectal cancer incidence, but waist circumference was (RR = 2.2; 95% CI = 1.2–4.1; $P = .01$) for Q4 compared with Q1. A linear relationship across quartiles was not evident, but risk appeared to rise at Q2. A model comparing participants in Q2 through Q4 with those in Q1 showed that the adjusted RR for a higher level of waist circumference was 1.9 (95% CI = 1.1–3.3; $P = .02$).

Repeating these analyses with adjustment for diabetes or by exclusion of diabetics did not change the RR estimates.

Triglyceride and HDL levels were not statistically significantly associated with colorectal cancer (Table 2). Higher levels of LDL (Q4 versus Q1) were strongly linked to lower risk of colorectal cancer (RR = 0.5; 95% CI = 0.3–0.9), and a linear decreasing relationship was observed (LT RR = 0.8; 95% CI = 0.7–0.9; $P = .01$).

An exploratory subset analysis of risk by sex was performed. There were 59 colorectal cancers among 2476 men and 43 cancers among 3373 women. The results suggested that the relationship between 2-hour insulin and waist circumference and colorectal cancer is largely accounted for by the results in men.

The relationship between those with glucose intolerance or diabetes (defined by baseline blood glucose, medication history, and the results of the oral glucose load) and incident colorectal cancer are presented in Table 3. Neither those with glucose intolerance (RR = 1.5; 95% CI = 0.9–2.4; $P = .09$) nor those classified as diabetic (RR = 1.4; 95% CI = 0.8–2.4; $P = .20$) were at significantly increased risk, nor were there apparent differences by sex (Table 3).

To determine if the results were affected by alterations in covariate levels due to prevalent cancer that had not yet reached clinical attention, we repeated the analysis, excluding 22 patients who had been diagnosed in the 1st year of follow-up. The point estimates for RR did not change. The mean risk-factor levels by year of diagnosis were also examined. There was no evidence of a temporal pattern to suggest an effect due to subclinical disease (Table 4).

Discussion

In this prospective cohort study in elderly U.S. men and women, fasting glucose and 2-hour glucose and insulin levels after a glucose challenge were associated with an approximately twofold increased risk for incident colorectal cancer. A threshold effect for fasting insulin was also suggested, with individuals above the median level being at a 60% increased risk for incident colorectal cancer. Increased waist circumference also was as-

Table 3. Relationship of diabetes and glucose intolerance to incident colorectal cancer*

	Normal	Glucose intolerant	Diabetic
Men + women			
No. of case patients/total No. of subjects	38/2576	32/1425	23/1161
Relative risk	1.0 (referent)	1.5	1.4
95% CI		0.9–2.4	0.8–2.4
P		.09	.20
Men only			
No. of case patients/total No. of subjects	21/1085	17/604	15/531
Relative risk	1.0 (referent)	1.5	1.6
95% CI		0.8–2.8	0.8–3.1
P		.24	.16
Women only			
No. of case patients/total No. of subjects	17/1491	15/821	8/630
Relative risk	1.0 (referent)	1.6	1.1
95% CI		0.8–3.1	0.5–2.6
P		.21	.82

*First cohort only. All *P* values are two-sided and are considered statistically significant for $P<.05$. 95% CI = 95% confidence interval.

Table 4. Mean risk factor levels by year of diagnosis for patients with colorectal cancer

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7*
No. of case patients†	22	13	19	16	16	10	6
Risk factor‡							
Fasting glucose	104.4 (10.3)	117.7 (41.7)	125.0 (60.5)	118.6 (40.7)	115.4 (27.5)	122.9 (35.5)	101.8 (14.0)
Fasting insulin	12.9 (6.0)	14.7 (7.3)	28.5 (30.9)	15.3 (7.1)	18.8 (11.4)	13.1 (5.8)	15.3 (7.6)
Low-density lipoprotein	116.7 (32.3)	127.4 (31.5)	131.6 (36.6)	113.2 (34.3)	130.6 (36.5)	102.3 (34.3)	106.9 (18.4)
High-density lipoprotein	48.3 (12.4)	47.3 (12.8)	49.3 (14.7)	49.3 (13.2)	51.8 (9.9)	48.5 (7.1)	43.7 (9.3)
Triglycerides	127.3 (45.6)	174.1 (86.1)	147.7 (81.4)	155.8 (90.1)	125.8 (43.0)	130.6 (37.5)	197.2 (119.4)
Body mass index§	26.1 (3.6)	28.4 (3.6)	27.7 (6.0)	27.4 (6.5)	26.7 (4.2)	27.0 (3.4)	26.7 (2.7)
Waist circumference	94.0 (9.7)	99.7 (11.1)	100.6 (16.2)	97.7 (14.8)	97.7 (14.6)	101.1 (8.9)	96.1 (9.1)
Waist-to-hip ratio	0.94 (.08)	0.95 (.06)	0.97 (.11)	0.93 (.07)	0.95 (.07)	0.98 (.06)	0.96 (.09)
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
No. of case patients (cohort 1 only)	19	11	15	16	16	10	6
Risk factor‡							
2-h glucose	173.4 (42.4)	155.5 (61.9)	143.4 (31.4)	151.0 (66.6)	152.3 (69.3)	154.4 (45.5)	145.5 (38.3)
2-h insulin	92.9 (54.4)	77.9 (48.7)	101.9 (72.9)	80.2 (36.6)	101.8 (97.7)	71.3 (26.3)	163.2 (139.2)

*Year 7 has median follow-up duration for 7 months; hence, the number of cases for this interval is smaller.

†The minority cohort contributes cases for 3 years and 2 months of year 4, since their median follow-up is 38 months.

‡Data are presented as mean (standard deviation).

§Body mass index = weight in kg/height in m^2.

sociated with an approximately twofold increased risk for colorectal cancer. The level of increased risk observed with these variables is substantial and equals or exceeds that of other recognized risk factors for colorectal cancer, such as having a first-degree relative with colorectal cancer *(30)* or consuming a high-fat or low-fiber diet *(31–34)*. The demonstration of a relationship between waist circumference and metabolic parameters associated with VAT and colorectal cancer supports a link between VAT and colorectal cancer.

Abdominal obesity has been linked to cardiovascular disease *(35–37)*, diabetes *(38,39)*, and overall mortality *(40)*. Data suggest that abdominal obesity may also be associated with breast *(41)*, colon *(4)*, and prostate *(42)* neoplasia. While epidemiologic studies have shown an association between waist circumference and waist-to-hip ratio and colorectal cancer *(4)*, to our knowledge this study is the first to demonstrate an association between measures of insulin exposure and colorectal cancer. These data directly support *in vitro* biologic studies that show a growth-promoting effect of insulin on colorectal cancer *(9–11)*.

Our findings of a relationship between fasting glucose and insulin levels as well as glucose and insulin levels 2 hours after glucose challenge and colorectal cancer are consistent with data linking diabetes to colorectal cancer risk. Recent cohort and case–control studies *(43,44)*, population-based studies of hospital discharges *(45)*, and population-based studies via national cancer registries *(46)* confirm a 10%–40% increase in colorectal cancer in subjects with diabetes mellitus. While some studies have not shown a statistically significant association between diabetes and colorectal cancer *(47–49)*, small sample size and an inability to account for important covariates may have limited those investigations. A recent report *(50)* from a prospective cancer mortality study of more than 1 million U.S. citizens confirms an increased risk of colorectal cancer in diabetics, especially in men. Although a significant relationship between glucose intolerance, diabetes, and colorectal cancer was not demonstrated in this study, the point estimates (RR = 1.5 for glucose intolerance; RR = 1.4 for diabetes) support the hypothesis of an increased risk. The inability to show statistical significance may be secondary to a lack of power due to the small number of case subjects and the low level of increased risk.

The increased risk of colorectal cancer observed with higher fasting insulin as well as higher insulin levels 2 hours after glucose challenge in this cohort is consistent with the increased risk of colorectal cancer seen with non-insulin-dependent diabetes because most individuals with this type of diabetes tend to be insulin resistant and to have higher levels of circulating insulin *(51)*. The association with 2-hour stimulated glucose and insulin levels in this elderly population is of interest, because post-prandial glucose and insulin levels rise to higher levels and remain elevated for a longer period in the elderly *(52)*. Some studies *(53,54)* have shown a relationship between dietary glucose intake and colorectal cancer, but the biologic basis for this relationship is unknown.

It should be emphasized that our results relating measures of insulin, glucose, and waist circumference to colorectal cancer risk were independent of the presence of diabetes. Thus, nondiabetics appear to have an elevated risk of colorectal cancer as their fasting insulin and glucose rise, even if glucose levels do not reach levels defined as consistent with diabetes.

Hyperinsulinemia is thought to be a

consequence of insulin resistance. Although our results suggest an association between insulin and colorectal cancer, it is not known whether the mechanism that renders individuals insulin resistant also attenuates the insulin effect on colorectal cancer.

The hypothesized causative model relating VAT, insulin, and colorectal cancer benefits from integrating a variety of risk factors for colorectal cancer into a coherent scheme. For example, VAT accumulates with increased age *(55–57)*, and this parallels the increased incidence in colorectal cancer that occurs with aging. Men have more VAT than women, even when controlling for BMI *(55–58);* thus, VAT may explain the stronger association observed in epidemiologic investigations in men between BMI and colorectal cancer *(1)*. Although this study was not adequately powered to investigate the independent associations within each sex, our study is suggestive of a stronger relationship between VAT and colorectal cancer in men than in women. The link between physical activity and colorectal cancer risk can also be accounted for by invoking a role for VAT.

Surprisingly, a strong association between increased LDL levels and decreased risk of colorectal cancer was identified. The explanation for this finding is unclear. There was no relationship between subclinical evidence of atherosclerotic disease, such as carotid artery stenosis, and colorectal cancer (data not shown), although subclinical atherosclerotic disease is associated with increased LDL *(59)*. LDL levels are generally associated with VAT, though not as strongly as triglycerides or as negatively as HDL cholesterol *(60)*. Excluding colorectal cancer diagnosed in the 1st year of observation did not alter the relationship, nor was there a pattern of low LDL levels in the first few years of follow-up to suggest subclinical prevalent disease as the cause of the observed association (Table 4). Further research on this unexpected finding is required.

The link between VAT, as estimated by waist circumference, may be stronger than that observed because waist circumference only approximates VAT. For example, in studies using computerized tomographic measurement as a gold standard assessment of VAT, the VAT value estimated by anthropometric variables, such as sagittal diameter or BMI, varied by as much as a factor of 3 in both men and women *(61)*. Thus, inaccuracies in the estimation of VAT by using waist circumference as a surrogate measure may attenuate the actual association.

Although these data are consistent, we did not demonstrate, as one might expect, an association between triglyceride levels and colorectal cancer because triglyceride levels increase with increased amounts of VAT. Similarly, although HDL levels, which are inversely related to VAT, were somewhat lower in patients with colorectal cancer, this did not reach statistical significance. The small number of case patients and the limited follow-up in this cohort may have diminished our ability to demonstrate these associations.

IGFs are acknowledged as potentially important mitogens for many types of malignancy *(62–64)*, including colorectal cancer *(10,65)*. The relationship of obesity, and in particular abdominal obesity, to the IGF family of peptides, binding proteins, and receptors is not well established. A recent nested case–control study *(65)* found a statistically significant association between IGF-1 and colorectal cancer. Several studies *(66–69)*, mostly in children, suggest that obesity is associated with a decrease in IGF-binding protein-1 and an increase in free and bioavailable IGF-1. Future studies to elucidate the relationship of adipose tissue distribution, insulin, and IGF and IGF-binding proteins to colorectal cancer are anticipated.

Several limitations of this investigation should be acknowledged. The results of this inquiry are based on a relatively small number of colorectal cancer cases ($n = 102$). The limited number of end points precludes accurate estimation of risk within subsets, such as by sex. Similarly, some of the statistically significant or inconsistent results may be due to the multiple statistical tests and comparisons performed. Because of the high degree of association between glucose, insulin, and waist circumference, multivariate testing would likely only identify predictors with the least amount of measurement error, not necessarily those that were most biologically influential. As a result, multivariate testing was not employed, and the independent effects of waist circumference, insulin, or glucose on colorectal cancer risk could not be assessed. Secondly, because the CHS was not designed to acquire cancer end points, case ascertainment may be incomplete. For example, early colorectal cancers removed by endoscopic polypectomy that did not require hospitalization were not counted. Similarly, histologic confirmation of cases was not performed, and the results cannot be analyzed in relation to cancer stage.

In conclusion, prospective data from the CHS show an approximately twofold increased risk of colorectal cancer in individuals with higher levels of fasting glucose and insulin, with higher levels of glucose and insulin 2 hours after oral glucose challenge, and with increased waist circumference. To our knowledge, these data provide the first direct evidence of an association between VAT and its associated metabolic effects and colorectal cancer.

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NOTES

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