



## Original Contribution

# A Prospective Study of Anthropometric and Clinical Measurements Associated with Insulin Resistance Syndrome and Colorectal Cancer in Male Smokers

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Type 2 diabetes mellitus shares risk factors for and has shown a positive association with colorectal cancer. Anthropometric measures (height, weight, and body mass index (weight (kg)/height (m)<sup>2</sup>) and metabolic abnormalities associated with insulin resistance syndrome (IRS) (abnormalities in measured blood pressure, high density lipoprotein (HDL) cholesterol, and total cholesterol) were prospectively evaluated for associations with incident colon ( $n = 227$ ), rectal ( $n = 183$ ), and colorectal ( $n = 410$ ) cancers diagnosed between 1985 and 2002 in 28,983 Finnish male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals. In comparison with the lowest quintile, the highest quintile of body mass index was significantly associated with colorectal cancer (hazard ratio (HR) = 1.70, 95% confidence interval (CI): 1.01, 2.85;  $p$ -trend = 0.01), particularly colon cancer. Subjects with a cluster of three IRS-related conditions (hypertension, body mass index  $\geq 25$  kg/m<sup>2</sup>, and HDL cholesterol level  $< 40$  mg/dl ( $< 1.55$  mmol/liter)), compared with those with fewer conditions, had a significantly increased risk of colorectal cancer (HR = 1.40, 95% CI: 1.12, 1.74), particularly colon cancer (HR = 1.58, 95% CI: 1.18, 2.10), but not rectal cancer. These results support the hypothesis that the significant association observed between IRS-defining metabolic abnormalities and colorectal cancer is determined primarily by adiposity.

body mass index; colorectal neoplasms; dyslipidemias; hyperinsulinism; hypertension; insulin resistance; metabolic syndrome X; smoking

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high density lipoprotein; HR, hazard ratio; ICD-9, *International Classification of Diseases*, Ninth Revision; IGF-1, insulin-like growth factor 1; IGF1BP, insulin-like growth factor binding protein; IRS, insulin resistance syndrome.

Colorectal cancer incidence rates in Finland have increased more than twofold since the 1950s (1). Dietary factors and other modifiable risk factors for colorectal cancer are estimated to account for 90 percent of all cases (2). Previous studies in other populations have shown a positive association between type 2 diabetes mellitus and colorectal cancer risk (3–10). Hyperinsulinemia, which occurs in the

early stage of type 2 diabetes as the pancreas secretes increasing amounts of insulin to maintain normoglycemia, has been suggested as an explanation for the association between type 2 diabetes and colorectal cancer (11, 12). Insulin is a growth factor for colon cells and an in-vitro mitogen of colonic carcinoma cells (11). In addition, high insulin levels may stimulate insulin-like growth factor 1 (IGF-1)

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receptors. IGF-1 may further promote carcinogenesis by inhibiting apoptosis (11).

Adult Treatment Panel III of the US National Cholesterol Education Program defines insulin resistance syndrome (IRS), also known as "metabolic syndrome" or "syndrome X," as a prediabetic state that produces compensatory hyperinsulinemia and can be characterized by the presence of three or more of the following five conditions: 1) excess weight around the waist (waist circumference >101.6 cm for men and >88.9 cm for women), 2) high triglyceride levels ( $\geq 150$  mg/dl), 3) low levels of high density lipoprotein (HDL) cholesterol (<40 mg/dl for men and <50 mg/dl for women), 4) high blood pressure ( $\geq 130/85$  mmHg), and 5) high fasting blood glucose levels ( $\geq 110$  mg/dl) (13, 14). Interestingly, several conditions that characterize IRS, namely increased body mass index (BMI; weight (kg)/height (m)<sup>2</sup>) and waist:hip ratio, have been associated with colorectal cancer risk and type 2 diabetes. While many prospective studies have observed a positive association for BMI (15–18) and an inverse association for high cholesterol (7, 18) with regard to colorectal cancer risk, to our knowledge, few studies have investigated an association with hypertension (19). Two studies have shown significant positive associations between IRS and colorectal cancer mortality (19, 20).

The purpose of the present study was to examine associations of anthropometric features, characteristics of IRS, and self-reported medical history of diabetes mellitus with cancers of the colon, the rectum, and the two sites combined in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, a Finnish cohort of middle-aged male smokers.

## MATERIALS AND METHODS

### Study cohort

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was a randomized, double-blind, placebo-controlled primary prevention trial with a two-by-two factorial design. It was conducted to test the effect of alpha-tocopherol and beta-carotene supplementation on incidence of and mortality from lung cancers and other cancers in a high-risk cohort of male smokers (21). Details on the trial have been published elsewhere (21). Between 1985 and 1988, 29,133 male smokers from southwestern Finland were randomized to receive supplements of alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both, or placebo. Participants were excluded if they 1) were smoking fewer than five cigarettes per day; 2) were taking supplements containing vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or beta-carotene (>6 mg/day); 3) had a history of cancer (other than nonmelanoma skin cancer or carcinoma in situ), severe angina upon exertion, chronic renal insufficiency, liver cirrhosis, or alcoholism; 4) were receiving anticoagulant therapy; or 5) had other medical problems that might limit long-term participation, such as a psychiatric disorder or physical disability. The trial ended on April 30, 1993, and for this study, follow-up continued until death or through

April 2002. The study was approved by the institutional review boards of the US National Cancer Institute and the National Public Health Institute of Finland, and written informed consent was obtained from each participant before randomization.

### Baseline characteristics, smoking, and dietary factors

Prior to randomization, at the baseline visit, participants completed questionnaires on background characteristics, including self-reported information on medical, smoking, and dietary history. We had information on three of the five IRS conditions, namely BMI and clinically measured blood pressure and HDL cholesterol (not on triglycerides or glucose). Each participant underwent venipuncture for blood sampling after fasting for 12 hours, from which serum total and HDL cholesterol levels were measured. Trained staff measured height, weight, and blood pressure. BMI was calculated by dividing weight in kilograms by height in meters squared. Blood pressure was measured on the right arm with a mercury sphygmomanometer; the lower of two measurements taken at least 1 minute apart was recorded. Diet was assessed with a self-administered dietary history questionnaire that included 276 food items and mixed dishes and was accompanied by a picture booklet containing 122 pictures of foods and information on portion sizes (21). The questionnaire was developed specifically for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and was tested for validity and reliability (22). The questionnaire was linked to a food composition database of the Finnish National Public Health Institute.

### Case ascertainment

Cases of adenocarcinoma of the colon and rectum (*International Classification of Diseases*, Ninth Revision (ICD-9), codes 153 and 154, respectively) were identified through the Finnish Cancer Registry, which provides almost 100 percent case ascertainment in Finland (23, 24). For this study, we included 227 incident colon cancer cases and 183 rectal cancer cases that occurred between 1985 and April 2002. We also conducted analyses after characterizing colorectal cancers by subsite of origin (proximal tumors (ICD-9 codes 153.0, 153.1, 153.4, 153.6, and 153.7) vs. distal tumors (ICD-9 codes 153.2, 153.3, 154.0, and 154.1)). For the subsite analyses, we included 106 proximal cases and 276 distal cases. The 28 remaining colorectal cancer patients did not specify a subsite, and therefore those cases were not included in the subsite analyses.

### Statistical analysis

Follow-up time was calculated for each participant from the date of randomization to the date of colorectal cancer diagnosis, the date of death, or April 30, 2002. Follow-up totaled 362,084 person-years (median follow-up time, 14.1 years; interquartile range, 10.4–15.4 years). Only subjects with complete data on all relevant factors (medical history; smoking; age; height; weight; BMI; self-reported history of diabetes, myocardial infarction, coronary heart disease, and

**TABLE 1. Baseline characteristics of colon and rectal cancer cases and noncases in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland, 1985–2002**

Characteristic	Noncases (n = 28,573)		Colon cancer cases (n = 227)		Rectal cancer cases (n = 183)	
	Mean or no.	IQR† or %	Mean or no.	IQR or %	Mean or no.	IQR or %
Age (years)	57	53–61	59***	54–62	58*	54–62
Height (cm)	174	169–178	174	170–178	174	170–177
Weight (kg)	78.30	70.50–86.90	80.30	71.10–89.0	80.50	71.3–87.20
Body mass index (kg/m <sup>2</sup> )‡	25.96	23.67–28.50	26.40	24.06–29.58	26.15	24.00–29.01
Body mass index ≥25 kg/m <sup>2</sup>	17,503	61.26	148	65.20	121	66.12
Smoking						
No. of cigarettes smoked per day	20	10–25	15*	10–20	18	10–20
Duration of smoking (years)	36	31–42	39*	31–43	37	30–43
Self-reported disease history						
Diabetes mellitus	1,210	4.23	10	4.41	6	3.28
Myocardial infarction	1,832	6.41	7*	3.08	11	6.01
Coronary heart disease	2,159	7.56	15	6.61	9	4.92
Hypertension	5,413	18.94	43	18.94	33	18.03
Clinical measurements						
HDL† cholesterol level (mmol/liter)	1.15	0.97–1.37	1.13	0.96–1.37	1.13	0.96–1.35
HDL cholesterol level <1.55 mmol/liter	24,855	86.99	204	89.87	155	84.70
Total cholesterol level (mmol/liter)	6.16	5.44–6.94	6.12	5.51–6.84	5.91*	5.19–6.57
Systolic blood pressure (mmHg)	140	128–143	140	130–156	142	128–154
Diastolic blood pressure (mmHg)	88	80–94	88	80–94	90	82–96
Hypertension§	16,677	58.37	135	59.47	122*	66.67
Cluster of three conditions related to insulin resistance¶	6,016	21.05	65**	25.63	43	23.05
Occupational activity						
Nonworking	12,063	42.22	110	48.46	84	45.90
Sedentary	3,924	13.73	36	15.86	28	15.30
Walking	5,208	18.23	39	17.18	35	19.13
Walking/lifting	4,734	16.57	27	11.89	26	14.12
Heavy lifting	2,644	9.25	15	6.61	10	5.46
Leisure activity						
Sedentary	11,943	41.80	98	43.17	71	38.80
Moderate	14,919	52.21	117	51.54	97	53.01
Heavy	1,711	5.99	12	5.29	15	5.20

\*  $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$  (Wilcoxon rank-sum  $p$  value for cases vs. noncases).

† IQR, interquartile range; HDL, high density lipoprotein.

‡ Weight (kg)/height (m)<sup>2</sup>.

§ Stage 1 (systolic blood pressure 140–159 mmHg, diastolic blood pressure 90–99 mmHg) or stage 2 (systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥100 mmHg) hypertension.

¶ Body mass index ≥25.0 kg/m<sup>2</sup>, stage 1 or stage 2 hypertension, and HDL cholesterol level <1.55 mmol/liter (<40 mg/dl).

hypertension; self-reported occupational and leisure-time physical activity; and clinically measured total and HDL cholesterol and systolic and diastolic blood pressure) were included in the analyses ( $n = 28,983$ ). We used the 2003 US National Heart, Lung, and Blood Institute guidelines (25) to define blood pressure in four categories: normal (systolic pressure <120 mmHg/diastolic pressure <80 mmHg), prehypertensive (systolic pressure 120–139 mmHg/diastolic

pressure 80–89 mmHg), stage 1 hypertension (systolic pressure 140–159 mmHg/diastolic pressure 90–99 mmHg), and stage 2 hypertension (systolic pressure ≥160 mmHg/diastolic pressure ≥100 mmHg). We used the US National Cholesterol Education Program guidelines (13) to define an IRS-related cluster of conditions using three characteristics that were available in our data. We defined adiposity as overweight or BMI ≥25.0 kg/m<sup>2</sup> (rather than using waist

circumference); hypertension as systolic and diastolic blood pressures  $\geq 140$  mmHg and  $\geq 90$  mmHg, respectively; and a low HDL cholesterol level as  $< 40$  mg/dl ( $< 1.55$  mmol/liter). We also created a separate IRS cluster using HDL cholesterol adjusted for serum total cholesterol by means of the residual method, since HDL cholesterol and serum total cholesterol levels are highly correlated (results not shown).

We calculated Spearman correlations to determine correspondence between relevant study variables. Wilcoxon's rank-sum test was used to compare the baseline characteristics of cases and noncases. We evaluated the following variables as risk factors for colon cancer, rectal cancer, and colorectal cancer combined, using proportional hazards models to calculate hazard ratios and 95 percent confidence intervals: height; weight; BMI (categorized both by World Health Organization cutpoints (26) (using BMI 18.5–25 kg/m<sup>2</sup> as the reference group) and by the distribution in the cohort (using the lowest quintile as the reference group)); hypertension; HDL cholesterol (BMI, hypertension, and HDL cholesterol were analyzed both by their distribution in the cohort and by the National Cholesterol Education Program guidelines used to generate the three IRS-related conditions (13)); total cholesterol; self-reported history of diabetes mellitus; the cluster of the above three IRS-related conditions; and two-condition clusters including BMI and hypertension, BMI and low HDL cholesterol, and hypertension and low HDL cholesterol. For continuous variables, we created quintiles based on the distribution of the variable within the entire study cohort.

We created multivariate models by adding covariates to the models stepwise. Variables were considered confounders and included in the model if they altered the risk estimate by 10 percent or more and were significantly associated with the disease and exposure. Other potential colorectal cancer risk factors examined as possible confounders included age, height, weight, BMI, HDL cholesterol, total cholesterol, occupational and leisure-time physical activity, education, alcohol drinking, and consumption of dietary fat, carbohydrate, fiber, folate, and red meat. Although number of cigarettes smoked per day did not confound any of the risk estimates, it was added to each multivariate model. The absence of effect modification of IRS by physical activity was determined through the addition of multiplicative interaction terms using categorical trend variables, as well as by stratification. The proportionality of the hazards was tested with a time interaction term, and a lag analysis was performed on variables that showed a significant interaction with time. All *p* values were two-sided, and all statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

The baseline characteristics of colon and rectal cancer cases and noncase subjects are summarized in table 1. Compared with noncases, colon cancer cases were older, smoked fewer cigarettes per day, and had smoked for a longer duration; rectal cancer cases had a lower serum total cholesterol

level and a higher prevalence of hypertension. Colon and rectal cancer cases did not differ significantly from noncases with regard to height, self-reported disease history (diabetes mellitus, myocardial infarction, coronary heart disease, and hypertension), HDL cholesterol, systolic and diastolic blood pressure, and occupational and leisure physical activity. Twenty-one percent of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort had the cluster of three IRS-related conditions.

Tables 2–4 show the age-adjusted and multivariate hazard ratios for colorectal cancer, colon cancer, and rectal cancer, respectively, according to anthropometric characteristics and self-reported history of diabetes. Results from the multivariable hazard models were adjusted for age, smoking, and serum total cholesterol level. In addition, the IRS models adjusted for total cholesterol, the height models adjusted for weight, the weight models adjusted for height and type 2 diabetes mellitus, and the diastolic blood pressure and HDL cholesterol models adjusted for BMI.

For colorectal cancer overall, a significant 70 percent increased risk was observed between the highest and lowest quintiles of BMI, and a significant positive trend was observed for weight. For colon cancer, BMI based on the distribution in the cohort showed a twofold increase in risk, and weight showed a significant positive trend across quintiles. Using the World Health Organization guidelines (26), BMI was significantly associated with colorectal cancer (hazard ratio (HR) = 1.66, 95 percent confidence interval (CI): 1.27, 2.18) and colon cancer (HR = 1.78, 95 percent CI: 1.25, 2.55) and was borderline-significantly associated with rectal cancer (HR = 1.51, 95 percent CI: 0.99, 2.29). Compared with the lowest quintile, the highest quintile of total cholesterol showed a borderline-significant inverse association with colorectal cancer; however, a significant trend across quintiles was observed (HR = 0.75, 95 percent CI: 0.54, 1.02; *p*-trend = 0.02). Reduction in risk with high cholesterol was not observed for colon cancer but was observed for rectal cancer. No significant associations were observed between self-reported type 2 diabetes mellitus at baseline and colorectal, colon, or rectal cancer.

The multivariate results for the two-condition cluster analyses, adjusting for number of cigarettes smoked per day, age, and total cholesterol level, were as follows. For the BMI-hypertension cluster, the hazard ratios were 1.20 (95 percent CI: 0.92, 1.56), 1.39 (95 percent CI: 1.04, 1.86), and 1.28 (95 percent CI: 1.06, 1.56) for colon cancer, rectal cancer, and colorectal cancer, respectively; for the BMI-HDL cholesterol cluster, they were 1.33 (95 percent CI: 1.02, 1.74), 1.21 (95 percent CI: 0.90, 1.63), and 1.28 (95 percent CI: 1.05, 1.56), respectively; and for the HDL cholesterol-hypertension cluster, they were 1.10 (95 percent CI: 0.85, 1.43), 1.18 (95 percent CI: 0.88, 1.58), and 1.13 (95 percent CI: 0.93, 1.38), respectively.

Table 5 summarizes the age- and multivariate-adjusted hazard ratios for BMI, hypertension, and HDL cholesterol based on the National Cholesterol Education Program guidelines used to generate the cluster variable from the three IRS-related conditions (13). BMI  $\geq 25$  kg/m<sup>2</sup> showed a borderline-significant association for colorectal cancer (HR = 1.23, 95 percent CI: 1.01, 1.51), and clinically measured

**TABLE 2. Hazard ratios for colorectal cancer according to anthropometric factors and individual conditions related to insulin resistance syndrome in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland, 1985–2002**

Characteristic and quintile*	No. of cases ( <i>n</i> = 410)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
<b>Height (cm)</b>						
136–168	78	70,326	1.00	Reference	1.00	Reference
169–171	59	61,207	0.91	0.65–1.27	0.87	0.62–1.22
172–175	111	92,220	1.15	0.86–1.53	1.07	0.80–1.44
176–178	82	59,434	1.36	0.99–1.85	1.23	0.89–1.70
179–200	80	78,898	1.05	0.76–1.43	0.90	0.64–1.27
<i>p</i> -trend			0.23		0.17	
<b>Weight (kg)</b>						
36.60–68.50	79	69,889	1.00	Reference	1.00	Reference
68.60–75.20	72	72,456	0.91	0.66–1.26	0.93	0.67–1.28
75.30–81.30	66	73,829	0.83	0.60–1.15	0.85	0.61–1.19
81.40–89.20	100	73,488	1.30	0.97–1.75	1.34	0.98–1.83
89.30–156.20	93	72,422	1.28	0.95–1.73	1.34	0.96–1.86
<i>p</i> -trend			0.01		0.009	
<b>Body mass index (kg/m<sup>2</sup>)‡</b>						
12.97–23.11	75	70,297	1.00	Reference	1.00	Reference
23.12–25.10	68	73,647	1.11	0.86–1.44	1.11	0.86–1.44
25.11–26.88	87	73,656	0.85	0.51–1.42	0.85	0.51–1.42
26.89–29.20	83	73,384	1.23	0.83–1.81	1.24	0.84–1.82
29.21–54.36	97	71,100	1.67	1.00–2.81	1.70	1.01–2.85
<i>p</i> -trend			0.01		0.01	
<b>Body mass index (kg/m<sup>2</sup>)§</b>						
<18.5	3	2,287	1.27	0.40, 3.97	1.25	0.40, 3.93
18.5–25	138	136,909	1.00	Reference	1.00	Reference
25–30	185	168,781	1.11	0.89, 1.39	1.12	0.90, 1.39
>30	84	54,107	1.64	1.25, 2.15	1.66	1.27, 2.18
<b>Diastolic blood pressure (mmHg)</b>						
30–78	72	73,066	1.00	Reference	1.00	Reference
79–84	95	78,015	1.27	0.93–1.72	1.24	0.91–1.68
85–89	49	52,561	0.99	0.69–1.43	0.96	0.67–1.38
90–96	121	91,569	1.41	1.05–1.89	1.32	0.98–1.78
97–148	73	66,873	1.20	0.86–1.66	1.09	0.78–1.53
<i>p</i> -trend			0.21		0.55	

Table continues

hypertension showed an increased risk for rectal cancer (HR = 1.40, 95 percent CI: 1.04, 1.87). None of the other individual characteristics were significantly associated with colorectal cancer, colon cancer, or rectal cancer. Persons with the cluster of three IRS-related conditions had statistically significant 40 percent and 58 percent increased risks of colorectal cancer (95 percent CI: 1.12, 1.74) and colon cancer (95 percent CI: 1.18, 2.10), respectively, while a non-significant 20 percent increased risk was observed for rectal cancer.

Hazard ratios for colorectal cancer categorized by subsite showed slightly different associations than those reported

for colon and rectal cancer. There was a significant positive association between low HDL cholesterol and proximal colon cancer (fifth quintile vs. first: HR = 1.74, 95 percent CI: 0.94, 3.24; *p*-trend = 0.04), as well as a positive association between the cluster of three IRS-related conditions and proximal colon cancer (for persons with three conditions vs. persons with two or fewer conditions, HR = 1.73, 95 percent CI: 1.09, 2.74). There was a significant positive association between weight and distal colorectal cancer (fifth quintile vs. first: HR = 1.38, 95 percent CI: 0.91, 2.11; *p*-trend = 0.04) and a significant inverse association between serum total cholesterol and distal colorectal cancer

TABLE 2. Continued

Characteristic and quintile*	No. of cases ( <i>n</i> = 410)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
Systolic blood pressure (mmHg)						
82–125	73	73,625	1.00	Reference	1.00	Reference
126–135	64	74,649	0.84	0.60–1.18	0.85	0.61–1.19
136–144	92	77,509	1.13	0.83–1.53	1.14	0.84–1.55
145–158	103	72,671	1.30	0.96–1.75	1.30	0.96–1.76
159–270	78	63,630	1.08	0.78, 1.49	1.09	0.79, 1.50
<i>p</i> -trend			0.16		0.15	
HDL‡ cholesterol level (mmol/liter)						
1.44–3.60	86	70,693	1.00	Reference	1.00	Reference
1.23–1.43	94	72,787	0.98	0.72, 1.33	0.94	0.69, 1.28
1.08–1.22	66	73,228	0.79	0.57, 1.09	0.73	0.53, 1.02
0.94–1.07	83	74,119	1.14	0.84, 1.53	1.04	0.76, 1.40
0.20–0.93	81	71,257	1.09	0.80, 1.47	0.96	0.70, 1.31
<i>p</i> -trend			0.48		0.90	
Total cholesterol level (mmol/liter)						
1.94–5.27	89	70,113	1.00	Reference	1.00	Reference
5.28–5.88	95	72,388	1.04	0.78, 1.39	1.04	0.78, 1.39
5.89–6.44	86	73,222	0.94	0.70, 1.26	0.94	0.70, 1.26
6.45–7.14	72	72,758	0.79	0.58, 1.07	0.79	0.58, 1.08
7.15–19.50	68	73,603	0.74	0.54, 1.02	0.75	0.54, 1.02
<i>p</i> -trend			0.02		0.02	
Diabetes#						
No	394	348,858	1.00	Reference	1.00	Reference
Yes	16	13,226	0.91	0.41, 2.06	0.92	0.41, 2.08

\* Actual range within each quantile.

† Results were adjusted for age and number of cigarettes smoked per day. In addition, the HDL cholesterol model controlled for body mass index, the height models adjusted for weight, and the weight models adjusted for height and type 2 diabetes.

‡ Weight (kg)/height (m)<sup>2</sup>.

§ World Health Organization cutpoints.

¶ HDL, high density lipoprotein.

# Self-reported history of diabetes mellitus.

(fifth quintile vs. first: HR = 0.63, 95 percent CI: 0.43, 0.93; *p*-trend = 0.003). BMI (based on the distribution in the cohort) tended to be positively associated with distal colorectal cancer (fifth quintile vs. first: HR = 1.24, 95 percent CI: 0.86, 1.78), as well as increasing diastolic blood pressure (fourth and fifth quintiles vs. first: HR = 1.55 (95 percent CI: 1.07, 2.24) and HR = 1.31 (95 percent CI: 0.87, 1.97), respectively; *p*-trend = 0.06). Other characteristics of IRS were not significantly associated with either proximal or distal colorectal cancer.

The hazards for serum total cholesterol and colorectal and colon cancer and HDL cholesterol and proximal colon cancer were not proportional over time (*p* < 0.05). After deletion of cases diagnosed during the first 2 years of follow-up, the significant inverse association between serum total cholesterol and colorectal cancer was no longer evident. For colon cancer, the null cholesterol association tended to become positive (in 10-year lag analysis, for the

fifth quintile compared with the first, HR = 1.45, 95 percent CI: 0.74, 2.89; *p*-trend = 0.39). The significant positive association between low HDL cholesterol and proximal colon cancer was also no longer evident after deletion of cases diagnosed during the first 2 years of follow-up (fifth quintile vs. first: HR = 1.63, 95 percent CI: 0.85, 3.12; *p*-trend = 0.21). In contrast, the significant protective association with low HDL cholesterol remained for rectal cancer cases diagnosed through approximately the eighth year of follow-up. Physical activity was not found to modify the relation between the IRS cluster and colorectal cancer.

## DISCUSSION

This analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort demonstrated a significant positive association between IRS-related conditions and

**TABLE 3. Hazard ratios for colon cancer according to anthropometric factors and individual conditions related to insulin resistance syndrome in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland, 1985–2002**

Characteristic and quintile*	No. of cases ( <i>n</i> = 227)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
<b>Height (cm)</b>						
136–168	45	70,326	1.00	Reference	1.00	Reference
169–171	33	61,207	0.89	0.56, 1.39	0.84	0.53, 1.32
172–175	60	92,220	1.08	0.74, 1.59	0.99	0.67, 1.38
176–178	46	59,434	1.33	0.88, 2.01	1.18	0.98, 1.78
179–200	43	78,898	0.99	0.65, 1.51	0.82	0.78, 1.53
<i>p</i> -trend			0.50		0.40	
<b>Weight (kg)</b>						
36.60–68.50	44	69,889	1.00	Reference	1.00	Reference
68.60–75.20	42	72,456	0.96	0.63, 1.47	0.97	0.64, 1.49
75.30–81.30	34	73,829	0.78	0.50, 1.21	0.79	0.50, 1.25
81.40–89.20	53	73,488	1.25	0.84, 1.86	1.28	0.84, 1.90
89.30–156.20	54	72,422	1.35	0.91, 2.02	1.40	0.90, 2.18
<i>p</i> -trend			0.05		0.049	
<b>Body mass index (kg/m<sup>2</sup>)‡</b>						
12.97–23.11	37	70,297	1.00	Reference	1.00	Reference
23.12–25.10	44	73,647	1.13	0.86, 1.59	1.13	0.80, 1.60
25.11–26.88	47	73,656	0.76	0.38, 1.53	0.76	0.38, 1.53
26.89–29.20	42	73,384	1.20	0.71, 2.03	1.21	0.71, 2.04
29.21–54.36	57	71,100	2.00	0.98, 4.06	2.03	1.00, 4.13
<i>p</i> -trend			0.03		0.02	
<b>Body mass index (kg/m<sup>2</sup>)§</b>						
<18.5	2	2,287	1.49	0.37, 6.07	1.47	0.36, 5.98
18.5–25	77	136,909	1.00	Reference	1.00	Reference
25–30	98	168,781	1.07	0.79, 1.43	1.07	0.79, 1.44
>30	50	54,107	1.75	1.23, 2.50	1.78	1.25, 2.55
<b>Diastolic blood pressure (mmHg)</b>						
30–78	43	73,066	1.00	Reference	1.00	Reference
79–84	52	78,015	1.17	0.79, 1.75	1.13	0.75, 1.69
85–89	33	52,561	1.12	0.71, 1.77	1.07	0.68, 1.69
90–96	63	91,569	1.23	0.84, 1.82	1.13	0.76, 1.68
97–148	36	66,873	0.99	0.64, 1.55	0.88	0.56, 1.38
<i>p</i> -trend			0.91		0.62	

Table continues

incident colorectal cancer, particularly colon cancer, which showed a 58 percent increased risk. In addition, persons in the highest quintiles of weight and BMI also had increased risks of colorectal and colon cancer. A significant inverse association was observed for serum total cholesterol and colorectal cancer; this relation was strongest for rectal cancer and remained but became nonsignificant in a lag analysis deleting approximately the first 8 years of follow-up.

Although a few studies have examined associations with colorectal cancer mortality, to our knowledge, this is the first prospective study to have examined the relation between a cluster of three characteristics describing IRS and

incident colorectal cancer. In a prospective study, Colangelo et al. (19) reported a significant 67 percent increased risk of colorectal cancer mortality for men with least three of four IRS-related conditions, which included being in the highest quartiles of plasma glucose level, systolic blood pressure, BMI, and resting heart rate. A second prospective study (20) defined IRS as being in the lowest quartile of HDL cholesterol, being in the highest quartiles of serum triglycerides and glucose, and having blood pressure  $\geq 140$  mmHg (systolic)/ $\geq 90$  mmHg (diastolic). In their analyses of 41 colon cancer cases, Trevisan et al. (20) observed an almost threefold increased risk of colorectal

TABLE 3. Continued

Characteristic and quintile*	No. of cases (n = 227)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
Systolic blood pressure (mmHg)						
82–125	41	73,625	1.00	Reference	1.00	Reference
126–135	38	74,649	0.89	0.57, 1.38	0.90	0.58, 1.39
136–144	54	77,509	1.17	0.78, 1.76	1.18	0.79, 1.77
145–158	49	72,671	1.08	0.71, 1.64	1.09	0.72, 1.66
159–270	45	63,630	1.08	0.70, 1.66	1.09	0.71, 1.68
<i>p</i> -trend			0.52		0.49	
HDL‡ cholesterol level (mmol/liter)						
1.44–3.60	49	70,693	1.00	Reference	1.00	Reference
1.23–1.43	48	72,787	0.98	0.65, 1.48	0.93	0.62, 1.41
1.08–1.22	39	73,228	0.84	0.55, 1.28	0.77	0.50, 1.18
0.94–1.07	46	74,119	1.04	0.70, 1.57	0.93	0.61, 1.41
0.20–0.93	45	71,257	1.13	0.74, 1.67	0.95	0.62, 1.46
<i>p</i> -trend			0.64		0.79	
Total cholesterol level (mmol/liter)						
1.94–5.27	38	70,113	1.00	Reference	1.00	Reference
5.28–5.88	56	72,388	1.44	0.95, 2.18	1.44	0.95, 2.18
5.89–6.44	47	73,222	1.21	0.79, 1.85	1.21	0.79, 1.85
6.45–7.14	46	72,758	1.18	0.77, 1.82	1.19	0.77, 1.83
7.15–19.50	46	73,603	1.03	0.66, 1.61	1.03	0.66, 1.61
<i>p</i> -trend			0.71		0.72	
Diabetes#						
No	217	348,858	1.00	Reference	1.00	Reference
Yes	10	13,226	1.08	0.66, 1.78	1.09	0.66, 1.80

\* Actual range within each quantile.

† Results were adjusted for age and number of cigarettes smoked per day. In addition, the HDL cholesterol model controlled for body mass index, the height models adjusted for weight, and the weight models adjusted for height and type 2 diabetes.

‡ Weight (kg)/height (m)<sup>2</sup>.

§ World Health Organization cutpoints.

¶ HDL, high density lipoprotein.

# Self-reported history of diabetes mellitus.

cancer mortality (for men, HR = 2.96, 95 percent CI: 1.05, 8.31). While both previous studies showed significant positive associations, cancer mortality was the endpoint. Several strengths of the present study include the facts that we used incident cases; that our dietary and clinical data were of good quality, with height, weight, and blood pressure being measured by trained nurses and collected before the development of disease (thereby reducing recall and reverse-causation bias); that we had a longer duration of follow-up and therefore more cases; and that we had the ability to evaluate potential effects of latent disease by conducting lag analyses.

Among the three characteristics of IRS examined in our study, BMI showed the strongest association with colorectal cancer, particularly colon cancer, followed by a nonsignificant positive association with hypertension as determined by measured blood pressure. No association with HDL cholesterol was observed. The two-cluster analyses also showed significant associations for the clusters that contained

BMI, whereas the low HDL cholesterol-hypertension cluster showed small, nonsignificant increases in risk for colon cancer, rectal cancer, and colorectal cancer combined. Similar results with BMI have been seen in a number of large prospective studies of men, with relative risks ranging from 1.38 to 2.11 (15–19). The lack of associations between HDL cholesterol and colorectal cancer in particular could be due to the metabolic effect of latent disease. In our study, BMI appeared to be a better predictor than the IRS cluster, and therefore BMI may be the only component needed. The applicability of assessing insulin-related factors, as opposed to a clinical measurement of insulin sensitivity using the hyperinsulinemic clamp (considered the “gold standard”), has been documented (27). In normal subjects and subjects with type 2 diabetes mellitus, BMI showed a direct relation with the clamp results, and in control subjects only, serum cholesterol and systolic and diastolic blood pressures showed an inverse relation with insulin sensitivity (27). It is also possible that factors other than insulin resistance

**TABLE 4. Hazard ratios for rectal cancer according to anthropometric factors and individual conditions related to insulin resistance syndrome in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland, 1985–2002**

Characteristic and quintile*	No. of cases ( <i>n</i> = 183)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
<b>Height (cm)</b>						
136–168	33	70,326	1.00	Reference	1.00	Reference
169–171	26	61,207	0.94	0.56, 1.57	0.91	0.55, 1.53
172–175	51	92,220	1.24	0.80, 1.92	1.18	0.75, 1.85
176–178	36	59,434	1.39	0.86, 2.23	1.30	0.79, 2.13
179–200	37	78,898	1.12	0.79, 1.80	1.02	0.61, 1.70
<i>p</i> -trend			0.30		0.57	
<b>Weight (kg)</b>						
36.60–68.50	35	69,889	1.00	Reference	1.00	Reference
68.60–75.20	30	72,456	0.85	0.52, 1.39	0.87	0.53, 1.42
75.30–81.30	32	73,829	0.90	0.56, 1.45	0.92	0.56, 1.38
81.40–89.20	47	73,488	1.36	0.88, 2.11	1.41	0.89, 2.24
89.30–156.20	39	72,422	1.19	0.75, 1.85	1.25	0.76, 2.07
<i>p</i> -trend			0.14		0.12	
<b>Body mass index (kg/m<sup>2</sup>)‡</b>						
12.97–23.11	38	70,297	1.00	Reference	1.00	Reference
23.12–25.10	24	73,647	1.09	0.74, 1.61	1.09	0.74, 1.61
25.11–26.88	40	73,656	0.96	0.45, 2.01	0.96	0.45, 2.01
26.89–29.20	41	73,384	1.27	0.71, 2.26	1.27	0.71, 2.27
29.21–54.36	40	71,100	1.37	0.64, 2.93	1.38	0.65, 2.96
<i>p</i> -trend			0.22		0.21	
<b>Body mass index (kg/m<sup>2</sup>)§</b>						
<18.5	1	2,287	0.97	0.14, 7.01	0.96	0.13, 6.96
18.5–25	61	136,909	1.00	Reference	1.00	Reference
25–30	87	168,781	1.18	0.85, 1.64	1.18	0.85, 1.64
>30	34	54,107	1.49	0.98, 2.27	1.51	0.99, 2.29
<b>Diastolic blood pressure (mmHg)</b>						
30–78	29	73,066	1.00	Reference	1.00	Reference
79–84	43	78,015	1.42	0.89, 2.28	1.40	0.88, 2.25
85–89	16	52,561	0.80	0.44, 1.48	0.78	0.43, 1.45
90–96	58	91,569	1.67	1.07, 2.61	1.61	1.03, 2.54
97–148	37	66,873	1.50	0.92, 2.44	1.42	0.86, 2.35
<i>p</i> -trend			0.08		0.15	

Table continues

may contribute to the BMI-colorectal cancer association that we observed.

Persons in the highest quintile of total cholesterol level were 25 percent less likely to develop colorectal cancer, primarily because of a 50 percent reduction in risk for rectal cancer and essentially no association with colon cancer. A lag analysis was performed to test whether the observed association with cholesterol resulted from tumor development. While the protective effect of high cholesterol for colorectal cancer disappeared after deletion of cases diagnosed 2 years after baseline, suggesting that the latent form of cancer may depress serum cholesterol levels, the associ-

ation remained for rectal cancer cases diagnosed 8 years after baseline. In previous studies, Eichholzer et al. (28) and Broitman et al. (29) observed low serum cholesterol levels 10 years prior to cancer diagnosis. Additionally, since the latency period for rectal cancer is unknown and may be less than 10 years, we were unable to determine whether the inverse association was due to the disease or a real association.

The significant association that we observed between the three IRS-related conditions and incident colorectal cancer supports the hypothesis that hyperinsulinemia and/or insulin-like growth factor axis proteins may influence colorectal

TABLE 4. Continued

Characteristic and quintile*	No. of cases (n = 183)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
Systolic blood pressure (mmHg)						
82–125	32	73,625	1.00	Reference	1.00	Reference
126–135	26	74,649	0.78	0.47, 1.31	0.79	0.47, 1.32
136–144	38	77,509	1.07	0.67, 1.72	1.08	0.67, 1.73
145–158	54	72,671	1.58	1.02, 2.45	1.59	1.02, 2.46
159–270	33	63,630	1.07	0.65, 1.75	1.08	0.66, 1.76
p-trend			0.17		0.17	
HDL‡ cholesterol level (mmol/liter)						
1.44–3.60	37	70,693	1.00	Reference	1.00	Reference
1.23–1.43	46	72,787	0.98	0.62, 1.55	0.95	0.60, 1.51
1.08–1.22	27	73,228	0.72	0.44, 1.19	0.69	0.41, 1.14
0.94–1.07	37	74,119	1.25	0.81, 1.93	1.17	0.75, 1.83
0.20–0.93	36	71,257	1.05	0.66, 1.66	0.96	0.59, 1.55
p-trend			0.60		0.92	
Total cholesterol level (mmol/liter)						
1.94–5.27	51	70,113	1.00	Reference	1.00	Reference
5.28–5.88	39	72,388	0.74	0.49, 1.13	0.74	0.49, 1.13
5.89–6.44	39	73,222	0.74	0.49, 1.12	0.74	0.49, 1.12
6.45–7.14	26	72,758	0.49	0.31, 0.79	0.49	0.31, 0.79
7.15–19.50	28	73,603	0.53	0.33, 0.84	0.53	0.33, 0.84
p-trend			0.002		0.002	
Diabetes#						
No	177	348,858	1.00	Reference	1.00	Reference
Yes	6	13,226	1.21	0.64, 2.29	1.23	0.65, 2.32

\* Actual range within each quantile.

† Results were adjusted for age and number of cigarettes smoked per day. In addition, the HDL cholesterol model controlled for body mass index, the height models adjusted for weight, and the weight models adjusted for height and type 2 diabetes.

‡ Weight (kg)/height (m)<sup>2</sup>.

§ World Health Organization cutpoints.

¶ HDL, high density lipoprotein.

# Self-reported history of diabetes mellitus.

carcinogenesis. Insulin administration has been shown to stimulate proliferation and reduce apoptosis in colorectal cancer cell lines (30–32). Insulin injection also promotes colorectal tumor growth in animal model systems (33–35). In addition, hyperinsulinemia reduces levels of insulin-like growth factor binding protein (IGFBP), which results in increased levels of free IGF-1. IGFBP proteases degrade IGFBP, which in turn increases levels of free IGF-1 (36). The balance between IGF-1, IGFBPs, and IGFBP proteases may explain the association between characteristics of IRS and colorectal cancer. In support of this, concentrations of circulating insulin, C-peptide, and IGF-1 have been positively associated with colorectal cancer risk in a limited number of human observational studies (37, 38). Additional hypotheses explaining the obesity-colorectal cancer association have been suggested. Preclinical studies have suggested that leptin may play a functional role in obesity-related colorectal cancer risk, and studies have demonstrated colonic cell proliferation and carcinogenesis due to ele-

vated leptin levels in animal models (39). Elevated leptin levels may therefore be an alternative biologic explanation for the BMI-colorectal cancer association observed in the present study.

An additional strength of our study was the ability to examine effects by cancer type (colonic and rectal) and subsite (proximal and distal). Proximal and distal colorectal tumors are known to differ with respect to their population distribution (40, 41), clinicopathologic features (42), and proposed genetic pathways (43, 44). Further investigation of colorectal cancer risk factors by anatomic subsite has been advocated by others (40, 41, 45). Indeed, type 2 diabetes mellitus was found to be a stronger risk factor for proximal colorectal cancer than for distal colorectal cancer among older women (46), suggesting that components of IRS may also exhibit differential associations by colorectal cancer subsite.

This study had several limitations. Contrary to other investigators, we did not observe a significant association

**TABLE 5. Hazard ratios for colorectal cancer, colon cancer, and rectal cancer according to three factors that make up a cluster of IRS\*-related conditions and the cluster of IRS-related conditions in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, Finland, 1985–2002**

Characteristic and quintile	No. of cases (n = 227)	No. of person-years	Age-adjusted hazard ratio	95% confidence interval	Multivariate hazard ratio†	95% confidence interval
<i>Colorectal cancer</i>						
Body mass index (kg/m <sup>2</sup> )‡						
<25	142	139,708	1.00	Reference	1.00	Reference
≥25	268	222,377	1.22	1.00, 1.50	1.23	1.01, 1.51
HDL* cholesterol level (mmol/liter)						
≥1.55	51	46,088	1.00	Reference	1.00	Reference
<1.55	359	315,996	1.02	0.76, 1.36	1.02	0.76, 1.37
Clinically measured hypertension§						
No	254	238,022	1.00	Reference	1.00	Reference
Yes	156	124,062	1.18	0.96, 1.43	1.18	0.96, 1.44
Cluster of IRS-related conditions¶						
No	302	287,354	1.00	Reference	1.00	Reference
Yes	108	74,730	1.39	1.12, 1.73	1.40	1.12, 1.74
<i>Colon cancer</i>						
Body mass index (kg/m <sup>2</sup> )						
<25	80	139,708	1.00	Reference	1.00	Reference
≥25	147	222,377	1.20	0.91, 1.57	1.21	0.92, 1.58
HDL cholesterol level (mmol/liter)						
≥1.55	23	46,088	1.00	Reference	1.00	Reference
<1.55 mmol/liter	204	315,996	1.28	0.83, 1.97	1.29	0.84, 1.98
Clinically measured hypertension						
No	148	238,022	1.00	Reference	1.00	Reference
Yes	79	124,062	1.02	0.77, 1.34	1.02	0.78, 1.34
Cluster of IRS-related conditions						
No	162	287,354	1.00	Reference	1.00	Reference
Yes	65	74,730	1.56	1.10, 2.08	1.58	1.18, 2.10
<i>Rectal cancer</i>						
Body mass index (kg/m <sup>2</sup> )						
<25	62	139,708	1.00	Reference	1.00	Reference
≥25	121	222,377	1.26	0.93, 1.71	1.27	0.93, 1.72
HDL cholesterol level (mmol/liter)						
≥1.55	28	46,088	1.00	Reference	1.00	Reference
<1.55	155	315,996	0.80	0.53, 1.19	0.80	0.54, 1.20
Clinically measured hypertension						
No	106	238,022	1.00	Reference	1.00	Reference
Yes	77	124,062	1.40	1.04, 1.87	1.40	1.04, 1.87
Cluster of IRS-related conditions						
No	140	287,354	1.00	Reference	1.00	Reference
Yes	43	74,730	1.20	0.85, 1.68	1.20	0.85, 1.68

\* IRS, insulin resistance syndrome; HDL, high density lipoprotein.

† Results were adjusted for age and number of cigarettes smoked per day. In addition, the IRS models adjusted for total cholesterol.

‡ Weight (kg)/height (m)<sup>2</sup>.

§ Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg.

¶ Body mass index ≥25.0 kg/m<sup>2</sup>, stage 1 (SBP 140–159 mmHg or DBP 90–99 mmHg) or stage 2 (SBP ≥160 mmHg or DBP ≥100 mmHg) hypertension, and HDL cholesterol level <1.55 mmol/liter (<40 mg/dl).

between history of type 2 diabetes mellitus and colorectal cancer. However, since history of diabetes was self-reported, it is likely that many patients with diabetes were not diagnosed and the true prevalence of diabetes was under-represented, thus attenuating our results. Persons with characteristics of IRS may represent persons with an overall unhealthy lifestyle. One of the most consistent risk factors for colon cancer is lack of physical activity. A reduction in risk with greater physical activity is one of the most consistent associations reported in the literature and has been observed in our cohort (47) as well as in other prospective cohort studies (17, 48, 49). Although physical activity did not confound the risk estimates, it was imprecisely measured, and there may have been residual confounding. Since one of the effects of physical activity is a reduction in glucose levels, it is possible that the protective effects of physical activity are independent of those related to body weight or that physical activity modifies the effect of body weight. Effect modification was not observed in the present study; however, the imprecise measurement of physical activity may account for the lack of association. Finally, our findings in these male smokers may not be generalizable to populations that include nonsmokers, particularly since smoking has metabolic effects on BMI and energy balance (50–52).

In conclusion, we found a relation between a cluster of three IRS-related conditions and increased risk of incident colorectal cancer, particularly colon cancer, in a prospective cohort study of male smokers. Although the cluster including hypertension and HDL cholesterol showed a positive association with colorectal cancer, among the three IRS characteristics associated with colorectal cancer, BMI and weight showed the strongest associations. Since hyperinsulinemia is a clinical manifestation of high BMI and IRS, our results support the hypothesis that hyperinsulinemia may contribute to colorectal carcinogenesis (11, 12). However, it is possible that other mechanistic or confounding factors associated with high BMI may explain our observed associations.

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Conflict of interest: none declared.

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