Colorectal Cancer Mortality and Factors Related to the Insulin Resistance Syndrome[1]

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Abstract

It has been proposed that hyperinsulinemia is involved in colon carcinogenesis. An association between post-load plasma glucose (PLG) levels and risk of colorectal cancer mortality would be consistent with this hypothesis. We used data from the Chicago Heart Association Detection Project in Industry to examine the associations of nonfasting PLG and other variables related to the insulin resistance syndrome (*i.e.*, systolic blood pressure, body mass index, uric acid, and resting heart rate) with colorectal cancer mortality. After excluding participants reporting a history of diabetes, 191 and 126 colorectal cancer deaths occurred among 20,433 men and 15,149 women, respectively. In multivariate Cox regression analysis, there was a positive relationship between PLG levels and colorectal cancer mortality for women (*P* for trend = 0.08) but not for men. When men and women were combined, a trend (*P* = 0.05) for PLG remained. Examination of clustering of insulin resistance syndrome-related risk factors revealed that men with at least 3 of 4 risk factors (*i.e.*, in the highest quartile of the sex-specific distribution for PLG, systolic blood pressure, body mass index, or resting heart rate) had a relative risk (RR) of 1.67 [95% confidence interval (CI), 1.04–2.70] as compared with men who were not in the upper quartile for any of these factors. For women, the RR was 1.29 (95% CI, 0.70–2.37). For men and women combined, the RR was 1.50 (95% CI, 1.03–2.19). These findings provide evidence for a modest association of PLG and insulin resistance syndrome with colorectal cancer mortality and support the insulin hypothesis.

Introduction

It has been proposed that insulin and insulin-like growth factors may be involved in colon carcinogenesis (1, 2). Recent studies in CRC[3] epidemiology have focused on risk factors associated with hyperinsulinemia, such as increased plasma insulin and plasma glucose (3), glucose intolerance (4), BMI (5–7), and physical activity (5, 6, 8). Some of these risk factors, such as physical activity and BMI, have undergone extensive examination in epidemiological studies. In general, there appears to be a consistent inverse association of CRC risk with physical activity and a positive association with BMI. Other risk factors, such as plasma insulin, plasma glucose, and serum C-peptide have been examined in only a few studies (3, 4, 9–11). Plasma glucose, in particular, has largely been limited to examination in men. One study that did include women (3) did not present risk estimates separately by gender but reported a strong positive association between PLG level and CRC incidence. In short, the relationship of plasma glucose to risk of CRC has not been examined thoroughly.

An association between PLG and risk of CRC would be consistent with the hypothesis that hyperinsulinemia is involved in colon carcinogenesis. In the present study, we examined the associations of PLG and other variables that are components of, or strongly related to, the insulin resistance syndrome, BMI, SBP, resting heart rate, and serum uric acid, as well as other risk factors identified previously, to CRC. Participants without diagnosed diabetes were the focus of this report because, as noted by Giovannucci (2), risk of CRC may depend on the type and stage of development of diabetes, and these data were not available.

Materials and Methods

Study Population. In the CHA Detection Project in Industry, nearly 75,000 employees from 84 cooperating companies and organizations were invited to participate in a large screening program of cardiovascular disease risk from late 1967 through early 1973. The number of participants who had baseline screening assessments was 39,522. Details of the recruitment of participants and standardized methods have been described previously (12, 13).

Because PLG is the risk factor of primary interest in individuals who did not have diagnosed diabetes, we excluded 674 men and 370 women who reported a diagnosis of diabetes at baseline or did not answer the question on personal history of diabetes. We also excluded 1220 men and 1518 women who did not receive a glucose load, were missing glucose data, or had blood drawn >65 min after the glucose load or whose time of blood draw was unknown. Additionally, 38 men and 43 women were excluded who were missing data for height, weight, smoking, or education. Finally, 45 men and 42 women were excluded who were missing vital status. This left 20,433

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[3] The abbreviations used are: CRC, colorectal cancer; BMI, body mass index; PLG, post-load plasma glucose; SBP, systolic blood pressure; CHA, Chicago Heart Association; RR, relative risk; CI, confidence interval.

men and 15,149 women remaining in the cohort used for analysis.

Risk Factors. Baseline data recorded on the self-administered questionnaire included age, gender, race, education, cigarette smoking history and number of cigarettes smoked per day, brief medical history, and history of treatment for diabetes or hypertension. Height and weight were measured, and BMI was computed as weight in kilograms divided by height in meters squared. A single casual supine blood pressure reading was obtained, and a resting electrocardiogram was obtained. During the initial years of the examinations, resting heart rate was determined to the nearest beat/min by measuring the interval between R-waves for three consecutive QRS complexes on the electrocardiogram. During the later years of the examinations, a heart rate meter attached to skin electrodes performed the same measurement electronically and provided a digital reading. Heart rate was not systematically measured during a brief middle period and, consequently, is missing for 4,420 men and women in the analysis cohort. Venipuncture was performed on each individual, and biochemical tests included plasma glucose 1 h after a nonfasting 50 g of oral glucose load. Serum uric acid was measured after March 1970. Therefore, a total of 25,748 men and women from the cohort of 35,582 had serum uric acid measured.

Determination of Vital Status. From the baseline examination until 1979, vital status was ascertained annually through direct mailings to individuals, submission of records to the Social Security Administration, mailings to employers, direct telephone or neighborhood contact. After 1979, the National Death Index was used. Underlying cause of death was classified from death certificates and coded using the Eighth Revision of the International Classification of Diseases, adapted for use in the United States (ICD-8). Colorectal cancer deaths were defined by ICD-8 codes 153 (colon) and 154 (rectum). For 98% of the cohort, follow-up continued until the date of death or until December 31, 1997.

Data Analysis. The association of baseline risk factors with CRC mortality was assessed using Cox proportional hazards regression. SAS statistical software (PROC PHREG) was used for the analysis (version 8.0; SAS Institute, Inc., Cary, NC). Risk factors assessed in age adjusted and in multivariable adjusted models included age, the variables associated with the insulin resistance syndrome (*i.e.,* PLG concentration, BMI, SBP, heart rate, and serum uric acid concentration), height, education, cigarette smoking, and race. Height was included because previous studies (6, 14) have found it to be positively associated with risk of colorectal cancer. Although BMI may be an adequate measure of body composition or adiposity, it may not fully capture information on body size independent of obesity (15). The risk factors, except for race, were considered both as continuous and as categorical variables. Four categories were used for age ($\leq$39, 40–49, 50–59, and $\geq$60 years) and for PLG ($\leq$ 119, 120–159, 160–199, and $\geq$200 mg/dl). The categories for PLG were selected for comparability with previous reports from the CHA cohort (16). For BMI, SBP, heart rate, uric acid, and height, cutpoints for quartiles were used to define categories. Large numbers of ties resulted in unequal quartile sizes for some variables. Education was classified as less than high school graduate, high school graduate, some college, or college graduate. Four categories were used for cigarette smoking: never smoked, past smoker, currently smoke 1–20 cigarettes/day, and currently smoke >20 cigarettes/day. Race was classified as African American and white/other (other included Hispanic and Asian). Tests for trend were performed by assigning to each individual the mean value of a risk factor in its category and modeling this as a continuous variable.

Clustering on four insulin resistance syndrome (17–22) related risk factors was examined by creating three dummy variables that represented degrees of clustering on the four risk factors: upper quartile of the sex-specific distribution for PLG, SBP, BMI, and heart rate. The reference level was defined as having 0 of the four risk factors in the upper quartile of the sex-specific distribution. The second and third levels were defined as having one risk factor and two risk factors, respectively, of the four risk factors in the upper quartile of the sex-specific distribution. Finally, the fourth level was defined as having at least three of the four risk factors in the upper quartile of the sex-specific distribution. We also examined clustering on insulin resistance related risk factors by including uric acid as a fifth risk factor and defining the highest level as having at least three of the five risk factors in the upper quartile of the sex-specific distribution.

Age-adjusted and multivariable-adjusted RRs and their 95% CIs were obtained. On the basis of significance in the age-adjusted analysis or significance in previous studies, risk factors selected for evaluation in multivariable models included age, heart rate, smoking categories, height, SBP, BMI, PLG, education, and race. Risk factors were eliminated from consideration when they were neither significant nor marginally significant ($P < 0.10$) in any models and their exclusion from a model did not materially alter the risk ratios of other risk factors retained in the model. Risk factors were considered as continuous covariates when evaluation for influential data points using dfbeta residuals (23) indicated there were no notably influential data points. Analyses were conducted separately for each sex, and multivariable models were also obtained with men and women combined, with adjustment for sex. The final multivariate models were rerun with colon cancer mortality alone as the end point and censoring the rectal cancer deaths to determine whether RRs become stronger. The final multivariate models for men and women combined were also rerun limiting follow-up to 15 years to determine whether risk was more closely associated with risk factors assessed more closely in time to the outcome.

Results

Baseline Characteristics. During 866,926 person-years of follow-up, there were 317 colorectal cancer deaths, 191 (160 colon, 31 rectum) among 20,433 men and 126 (108 colon, 18 rectum) among 15,149 women. Median follow-up was 26.2 years. Characteristics of the cohort on risk factors are shown in Table 1. Average age of men and women was ~40 years. A higher proportion of men than women were college educated, and women were more likely to report never smoking. Although the cohort was primarily white, the proportion of African-Americans was greater among women than among men.

Correlations among insulin resistance syndrome-related risk factors (Table 2) were notable in many cases for both men and women, being at least 0.10 in magnitude. Correlations were highest for BMI with SBP and serum uric acid for both men and women and for PLG with SBP for women, all being nearly 0.30 or above in magnitude.

Associations with CRC Mortality. Table 3 shows sex-specific, age-adjusted RRs for insulin resistance syndrome-related risk factors, height, and demographic risk factors. PLG was positively associated with CRC mortality in women. For men, BMI, SBP, and height showed evidence of a positive trend with risk of CRC over the quartile categories ($P = 0.08$,

Table 1 Baseline characteristics of men and women in the CHA Detection Project in Industry

	Men (n = 20,433)	Women (n = 15,149)
Age, mean (SD), yr	40.0 (12.45)	39.8 (14.10)
Plasma glucose, mean (SD), mg/dl	134.2 (44.84)	129.5 (42.28)
BMI, mean (SD), kg/m^2	26.6 (3.66)	24.0 (4.38)
SBP, mean (SD), mm Hg	138.7 (18.56)	131.3 (19.34)
Heart rate, mean (SD), beats/min	75.8 (12.14)	77.8 (12.01)
Serum uric acid, mean (SD), mg/dl	6.2 (1.28)	4.5 (1.14)
Height, mean (SD), cm	175.8 (7.24)	163.3 (6.60)
Education, %		
Less than high school	19.6	21.0
High school graduate	30.9	49.8
Some college	19.2	17.3
College graduate	30.3	11.8
Smoking, %		
Never smoked	26.5	44.7
Past smoker	29.8	15.8
Smoke 1–20 cigs/day	28.7	32.2
Smoke >20 cigs/day	15.1	7.2
Race, %		
White	90.3	84.1
African-American	6.6	13.3
Other	3.1	2.6

Table 2 Correlation coefficients of baseline insulin resistance syndrome-related risk factors by sex in the CHA Detection Project in Industry

	Men				Women			
	BMI, kg/m^2	SBP, mm Hg	Heart rate, beats/min	Serum uric acid, mg/dl	BMI kg/m^2	SBP, mm Hg	Heart rate, beats/min	Serum uric acid, mg/dl
PLG, mg/dl	0.187[a]	0.262[a]	0.128[a]	0.105[a]	0.182[a]	0.297[a]	0.058[a]	0.231[a]
BMI, kg/m^2		0.295[a]	0.040[a]	0.308[a]		0.358[a]	−0.031[a]	0.361[a]
SBP, mm Hg			0.267[a]	0.170[a]			0.167[a]	0.264[a]
Heart rate, beats/min				0.073[a]				−0.003

[a] $P < 0.001$.

$P = 0.07$, and $P = 0.03$, respectively). However, for women, neither BMI, SBP, nor height was associated with CRC mortality. Insulin resistance clustering also exhibited a weak association with CRC mortality for men but not for women. Men in the upper quartile of the distribution on at least three of four insulin resistance syndrome risk factors had a 67% higher risk as compared with men who were not in the upper quartile of any of the four risk factors. When uric acid was included in the definition of insulin resistance clustering, the association with CRC mortality was still positive but nonsignificant (RR for having at least three of five risk factors in the upper quartile of the distribution, 1.46; 95% CI, 0.89–2.38).

Results for the final multivariable models, which comprised the risk factors age, race, education, PLG, BMI, and height, are shown in Table 4 (model 1). For women, the relation between PLG and risk of CRC was not confounded by other factors. For men, the RRs for BMI increased in a graded manner over the quartiles (P for trend, 0.07). Height was statistically significant for men ($P = 0.004$) with a difference of 7 additional cm in height associated with a RR of 1.24 (95% CI, 1.07–1.43) for colorectal cancer mortality. When men and women were combined in the analysis, PLG had a marginally significant test for trend ($P = 0.05$), but BMI did not have a significant relationship with risk for CRC.

When BMI was excluded from model 1 in Table 4, the RRs for PLG for men became slightly stronger (RRs, 1.10, 0.87, 1.54; P for trend = 0.19), those for women were changed minimally (RRs, 1.75, 1.34, 1.93; P for trend = 0.08), and those for men and women combined increased slightly (RRs, 1.03, 1.25, 1.24; P for trend = 0.18). When PLG was excluded from model 1, only the RR for the highest quartile of BMI for men and for women changed (for men RR = 1.44 and P for trend = 0.06; for women RR = 0.94 and P for trend = 0.86). For men and women combined, the RRs increased slightly (RRs, 1.03, 1.25, 1.24; P for trend = 0.18).

In the assessment of insulin resistance clustering (Table 4, model 2), categories exhibited graded increases in RRs for both men and women separately, but the associations were only significant for men. When uric acid was added to the definition of insulin resistance clustering, the association with CRC mortality again became nonsignificant (data not shown). In the analysis combining men and women, the graded increases over the categories were statistically significant (Table 4, model 2).

When the final multivariate models shown in Table 4 were rerun using colon cancer mortality alone as the end point, the RRs for PLG were not materially altered. For insulin resistance clustering, the RRs for men became weaker (0.95, 1.59, and 1.50 for one of four, two of four, and ≥ three of four components, respectively), the RRs for women became stronger (1.16, 1.41, and 1.44, for their respective categories), and they changed slightly for men and women combined (1.03, 1.50, and 1.45 for their respective categories).

When the final multivariate models with men and women combined shown in Table 4 were rerun restricting follow-up to 15 years, magnitudes for the highest categories of PLG and of

Table 3 Age-adjusted relative risk of CRC mortality associated with potential risk factors in the CHA Detection Project in Industry

Risk factor	Men				Women			
	No. of deaths	Total person-years	Age-adjusted RR	95% CI	No. of deaths	Total person-years	Age-adjusted RR	95% CI
PLG, mg/dl								
≤19	56	221,085	1.00		31	185,374	1.00	
120–159	71	163,649	1.10	0.77–1.57	56	118,352	1.74	1.11–2.72
160–199	33	72,952	0.86	0.55–1.33	23	50,212	1.32	0.76–2.30
≥200	31	33,307	1.51	0.96–2.40	16	21,994	1.86	1.00–3.45
P for trend			0.22				0.10	
Quartiles of BMI,[a] kg/m^2								
Q1	33	125,420	1.00		19	95,163	1.00	
Q2	41	124,038	1.07	0.68–1.69	26	95,562	0.92	0.51–1.67
Q3	56	123,046	1.27	0.82–1.96	41	93,868	1.11	0.64–1.93
Q4	61	118,489	1.40	0.91–2.14	40	91,339	0.94	0.54–1.65
P for trend			0.08				0.86	
Quartiles of SBP,[b] mm Hg								
Q1	35	126,959	1.00		14	83,448	1.00	
Q2	37	120,775	1.00	0.63–1.58	20	88,873	1.06	0.53–2.09
Q3	39	115,470	0.98	0.62–1.55	46	128,682	1.18	0.64–2.17
Q4	80	127,572	1.36	0.91–2.05	46	74,610	1.24	0.66–2.31
P for trend			0.07				0.47	
Quartiles of heart rate,[c] beats/min								
Q1	41	104,529	1.00		30	78,870	1.00	
Q2	44	105,384	1.04	0.68–1.60	33	90,811	1.07	0.65–1.75
Q3	33	105,228	0.84	0.53–1.32	32	82,944	1.33	0.80–2.19
Q4	51	102,488	1.32	0.88–2.00	22	85,100	1.03	0.59–1.79
P for trend			0.23				0.74	
Quartiles of uric acid,[d] mg/dl								
Q1	35	86,588	1.00		16	79,560	1.00	
Q2	30	73,028	1.04	0.64–1.70	23	70,569	1.26	0.66–2.39
Q3	30	87,553	0.87	0.53–1.41	25	66,817	1.20	0.64–2.26
Q4	31	76,325	1.00	0.62–1.62	39	73,285	1.31	0.72–2.38
P for trend			0.86				0.44	
Quartiles for height,[e] m								
Q1	55	126,914	1.00		42	87,287	1.00	
Q2	45	132,858	0.92	0.62–1.37	36	109,310	0.84	0.54–1.32
Q3	51	126,886	1.34	0.91–1.97	30	104,098	0.86	0.54–1.38
Q4	40	104,335	1.50	0.99–2.28	18	75,238	0.92	0.52–1.61
P for trend			0.03				0.72	
Education								
Less than high school	46	88,223	1.00		33	76,233	1.00	
High school graduate	75	150,900	1.37	0.94–1.99	69	189,244	1.50	0.98–2.29
Some college or trade	25	95,276	0.80	0.49–1.30	20	65,379	1.47	0.84–2.59
College graduate	45	156,594	0.93	0.61–1.41	4	45,077	0.44	0.16–1.26
P for trend			0.31				0.75	
Smoking								
Never smoked	53	134,577	1.00		62	169,372	1.00	
Past smoker	68	147,099	0.97	0.68–1.39	15	60,105	0.83	0.47–1.46
Smoke 1–20 cigs[f]/day	40	139,531	0.91	0.60–1.38	41	119,964	1.39	0.93–2.08
Smoke >20 cigs/day	30	69,787	1.36	0.86–2.13	8	26,491	1.40	0.66–2.94
Race								
White/other	182	459,302	1.00		117	324,321	1.00	
African-American	9	31,691	0.95	0.49–1.86	9	51,611	1.33	0.66–2.70
Insulin resistance clustering: in the upper quartile of the distribution on PLG, SBP, BMI, or heart rate								
0 of 4 components	43	167,780	1.00		29	136,083	1.00	
1 of 4 components	47	136,321	1.00	0.66–1.52	40	116,437	1.11	0.68–1.80
2 of 4 components	48	75,151	1.50	0.99–2.29	30	57,738	1.21	0.72–2.04
≥3 of 4 components	31	38,213	1.67	1.04–2.68	18	27,310	1.25	0.68–2.29

[a] Cutpoints for quartiles of BMI (kg/m^2) for men were ≤24.13, 24.14–26.29, 26.30–28.63, and ≥28.65; for women, ≤20.97, 20.98–23.23, 23.24–26.17, and ≥26.22.
[b] Cutpoints for SBP (mm HG) for men were ≤128, 130–138, 140–148, and ≥150; for women, ≤118, 120–129, 130–140, and ≥142.
[c] Cutpoints for heart rate (beats/min) for men were ≤67, 68–74, 75–83, and ≥84; for women, ≤69, 70–76, 77–85, ≥86.
[d] Cutpoints for uric acid (mg/dl) for men were ≤5.3, 5.4–6.0, 6.1–6.9, ≥7.0; for women, ≤3.7, 3.8–4.3, 4.4–5.0, ≥5.1.
[e] Cutpoints for height (cm) for men were ≤170.2, 172.7–175.3, 177.7–180.3, and ≥182.9; for women, ≤157.5, 160.0–162.6, 165.1–167.6, and ≥170.2.
[f] cigs, cigarettes.

Table 4 Multivariable adjusted RR of CRC mortality

	Men		Women		Men and women	
	RR	95% CI	RR	95% CI	RR	95% CI
Model 1[c]						
PLG, mg/dl						
≤119	1.00		1.00		1.00	
120–159	1.08	0.76–1.55	1.76	1.13–2.76	1.31	0.99–1.73
160–199	0.84	0.54–1.31	1.35	0.77–2.35	1.01	0.71–1.42
≥200	1.48	0.93–2.35	1.94	1.04–3.60	1.64	1.13–2.37
P for trend	0.26		0.08		0.05	
Quartiles of BMI, kg/m^2						
Q1	1.00		1.00		1.00	
Q2	1.08	0.68–1.71	0.92	0.50–1.66	1.02	0.71–1.47
Q3	1.31	0.85–2.02	1.09	0.63–1.90	1.24	0.88–1.75
Q4	1.42	0.92–2.19	0.91	0.52–1.61	1.22	0.87–1.72
P for trend	0.07		0.76		0.22	
Height[b]	1.24	1.07–1.43	0.95	0.79–1.16	1.13	1.01–1.27
Model 2[c]						
Insulin resistance clustering: in the upper quartile of the distribution on PLG, SBP, BMI, or heart rate						
0 of 4 components	1.00		1.00		1.00	
1 of 4 components	1.00	0.66–1.52	1.12	0.69–1.81	1.05	0.76–1.44
2 of 4 components	1.53	1.00–2.34	1.22	0.72–2.07	1.39	1.00–1.93
≥3 of 4 components	1.67	1.04–2.70	1.29	0.70–2.37	1.50	1.03–2.19

[a] Under Model 1, RR, adjusted for categories of age, race (African-American versus other), categories of education, and each of the other factors listed. Model for men and women combined includes a covariate for sex.
[b] RRs are for an increase of 7 cm in height.
[c] Under Model 2, RR, adjusted for categories of age, race (African-American versus other), categories of education, and height. Model for men and women combined includes a covariate for sex.

insulin resistance clustering were increased (RRs of 1.33, 0.80, and 1.96 for PLG and RRs of 0.96, 1.20, and 1.60 for insulin resistance syndrome clustering).

Discussion

In this study, 1-h PLG levels were associated with CRC mortality in women, the risk being nearly 2-fold higher for women with glucose levels of 200 mg/dl or higher compared with women with levels of 119 mg/dl or lower. The clustering of insulin resistance syndrome risk factors was related to CRC mortality in men; those who had at least three of four risk factors in the upper quartile of the risk factors' distributions had a nearly 70% increase in risk of fatal CRC.

Few studies have examined the relation between PLG and risk of CRC, its precursor lesion, colorectal adenomas, or CRC mortality. Recently Schoen *et al.* (3) reported a statistically significant RR of 2.4 for the highest quartile *versus* the lowest quartile of glucose levels 2 h after oral glucose challenge associated with CRC incidence. In that cohort study, there were a relatively small number of cases (59 men and 43 women), and RR estimates were not presented separately by sex. In a second study (4), glucose intolerance (as determined by a 75-g oral glucose tolerance test) was positively related to prevalence of distal colon adenomas. Although that study was restricted to men, their analysis was adjusted for multiple potential confounders: BMI, cigarette smoking, alcohol use, Self Defense Forces rank, and hospital. Two earlier examinations of plasma glucose in relation to CRC mortality came from the Whitehall study and the CHA. In the Whitehall Study (9), also restricted to men, no association was found between PLG concentration and colon cancer mortality or rectal cancer mortality in normoglycemic men. The analysis was adjusted for age only and no other potential confounders. In an earlier report from the CHA study (10) which included 52 colon cancer deaths and 10 rectal cancer deaths, higher mean concentrations of PLG were found among colon cancer decedents than among survivors. Overall, the present study provides stronger evidence of an association between plasma glucose and CRC mortality in men and women combined and in women in particular. Similar to two of the recent studies (3, 4), this study had the ability to adjust for multiple potential confounders.

McKeown-Eyssen (1) hypothesized that plasma glucose and triglycerides would be associated with risk of CRC and proposed several mechanisms underlying the associations. One mechanism suggests that insulin plays a key role in carcinogenesis because it might act as a growth factor, and insulin receptors are present in normal and malignant colorectal cells. The association between CRC and blood glucose then arises through the action of elevated plasma glucose increasing the secretion of insulin. Giovannucci (2) expanded on the insulin hypothesis citing evidence that insulin is a mitogen of colonic carcinoma cells *in vitro* (24–26). Excess insulin could also affect development of CRC, as well as other cancers, indirectly by down-regulating insulin-like growth factor binding protein 1 (27, 28). Reduced concentrations of insulin-like growth factor binding protein 1 could result in an increase in the bioavailable fraction of insulin-like growth factor-I, leading to increase in cell proliferation, inhibition of apoptosis, and promotion of tumor growth.

Hyperinsulinemia is a metabolic consequence of insulin resistance. Although data on hyperinsulinemia were not available in this study, we did have several of the variables that either comprise, or are closely related to, the insulin resistance syndrome, the cluster of risk factors for heart disease associated with insulin resistance, including elevated BMI, SBP, heart rate, plasma glucose, and uric acid (17–22). Hypertension and hyperglycemia constitute two of the original six factors proposed by Reaven (17) as those comprising the insulin resistance

syndrome. Obesity and hyperuricaemia were added subsequently (18, 29). Although elevated heart rate has not been formally adopted as a component of insulin resistance syndrome, it has been associated with insulin resistance syndrome and with insulin insensitivity (19–21). Our finding that having at least three of elevated BMI, SBP, heart rate, or plasma glucose was related to increased risk of CRC mortality in men without self-reported diabetes is consistent with the insulin hypothesis. It is likely that these men had concurrent elevated plasma insulin at baseline. Although the separate components of the insulin resistance syndrome may only be weakly correlated with plasma insulin levels (30, 31), when taken in combination they have been found more strongly associated with hyperinsulinemia (32, 33). Among nondiabetics, linear associations between measures of insulin resistance and plasma insulin concentration have been reported as reviewed by Reaven (18).

We found a weak association for BMI in men but not in women. Numerous studies have examined BMI in relation to CRC. Most recently, Murphy *et al.* (7) examined the BMI and colon cancer mortality association in detail in a cohort of 496,239 women and 379,167 men. Similar to our findings, risk increased from the lowest to the highest BMI levels in men, and the relation was weaker in women. Among men, risk ratios reported from a multivariable-adjusted model were 1.23, 1.20, 1.40, 1.55, and 1.90 for the BMI categories 25.0–25.9, 26.0–27.4, 27.5–29.9, 30.0–32.4, and $\geq$32.5 kg/m^2, respectively. Among women, the RRs in the highest BMI categories (*i.e.*, 25.0–27.4, 27.5–29.9, 30.0–32.4, and $\geq$32.5 kg/m^2) were 1.07, 1.26, 1.37, and 1.23, respectively. Our point estimates for men, although not statistically significant, are consistent with these previous findings. Reasons for the absence of an association between BMI and CRC mortality in women are not apparent. Murphy *et al.* (7) suggested that the weaker BMI-colon cancer mortality association observed in their study might be attributable to the protective effects of higher estrogen levels, which are associated with obesity, counteracting the adverse effects of elevated BMI. However, further complicating this matter is the finding that higher estrogen levels are also associated with reduced risk of microsatellite instability-positive CRC in women (34). Recent studies indicate that microsatellite instability in CRC is associated with a survival advantage as compared with microsatellite stability (35). This would imply that women with elevated BMI should have higher risk of CRC mortality.

Some limitations of this study must be mentioned: (*a*) we did not have available all components of the insulin resistance syndrome. Missing were plasma insulin, high density lipoprotein cholesterol, and triglycerides. Also, the smaller sample size for uric acid limited its utility; (*b*) RR estimates are based on only single measurements of baseline risk factors. Using single measurements in the presence of notable intraindividual variation may lead to the attenuation of the RR estimates (36, 37); (*c*) we examined CRC mortality rather than incidence as the end point. Because elevated postload plasma glucose and clustering of risk factors for insulin resistance syndrome are strong risk factors for cardiovascular disease mortality (38), participants who had both CRC and either of these risk factors may have died of cardiovascular disease rather than CRC, resulting in an underestimate of the association between these risk factors and CRC; (*d*) during the 26-year follow-up, it is likely that some individuals with higher PLG levels, as well as some with lower PLG levels, would become diabetic. It has been proposed that during later-stage diabetes, there will be β-cell failure, resulting in reduced insulin secretion (39); thus, long-term follow-up could lead to potential misclassification of exposure because of change in insulin secretion. However, this misclassification would likely attenuate estimates of association toward the null. Indeed, we found stronger associations of PLG and insulin resistance syndrome clustering when analysis was restricted to the first 15 years of follow-up. A particular strength of this study is the availability of risk factor information on a large cohort of women.

In summary, our findings of significant associations of plasma glucose and insulin resistance syndrome risk factor clustering with risk of CRC are in support of the hypothesis that hyperinsulinemia is involved in colon carcinogenesis. Bruce *et al.* (40) suggest that the hypothesized insulin resistance mechanism begins with excess dietary energy. They have also discussed the complexities of the relationship of dietary factors with colon cancer risk and suggest that these complexities might account for the negative results of recent clinical trials (41–43) examining the effect of dietary factors on colorectal adenoma recurrence. They propose some considerations for future intervention studies. One consideration suggests that interventions should be focused on reducing insulin resistance and incorporate more than simply modifications of dietary fat and fiber intake (40). If future studies can establish a causal relation between insulin resistance and CRC, this may have implications for public health. For example, obesity has become a national epidemic (44), and public health efforts to reduce the prevalence of obesity may impact insulin resistance and consequently the incidence of CRC, which ranks second among cancer deaths in the United States.

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