Markers of Insulin Resistance and Colorectal Cancer Mortality

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Abstract

A link between insulin metabolism and colorectal cancer has been hypothesized, supported by a series of potential physiological mechanisms, and confirmed by a number of reports in experimental animals. However, the evidence in humans is limited and mostly indirect.

The aim of the present report is to analyze whether individuals with a cluster of metabolic abnormalities associated with abnormalities in insulin metabolism experience higher mortality for colorectal cancer than those without this cluster of metabolic abnormalities.

A total of 21,311 men and 15,991 women 20–69 years of age were followed-up for an average of 7 years as part of the Risk Factors and Life Expectancy Project, a pooling of a number of epidemiological studies conducted in Italy.

Our analyses indicate that participants with high levels of blood glucose and a cluster of metabolic abnormalities linked to insulin resistance experienced a significant increased risk of colorectal cancer mortality compared with participants without the cluster. For the presence of the cluster of metabolic abnormalities, the calculated hazard ratios and 95% CIs were 2.96 (1.05–8.31) for men, 2.71 (0.59–12.50) for women, and 2.99 (1.27–7.01) when both sexes were combined. These associations were independent from the potential confounding effect of age, drinking of alcoholic beverages, and smoking.

Our findings are supportive of the hypotheses that glucose metabolism hyperinsulinemia, insulin resistance, and metabolic abnormalities associated with it may play a significant role in the etiology of colorectal cancer.

Introduction

Hyperinsulinemic insulin resistance has been hypothesized to play a role in colorectal cancer etiology (1–3). Insulin is a powerful mitogenic agent (4), which is able to stimulate cell proliferation and inhibit apoptosis (5). However, despite strong evidence from experimental studies (6, 7), the epidemiological and clinical evidence linking insulin and markers of insulin metabolism to colon cancer is very limited and comes mostly from retrospective studies (8–11). The present analyses were carried out to evaluate (using a longitudinal study design) the hypotheses that the cluster of metabolic abnormalities associated with alteration in insulin production and sensitivity is a significant risk factor for colorectal cancer mortality.

Materials and Methods

The Risk Factors and Life Expectancy Project represents the pooling of nine different large-scale epidemiological studies conducted in Italy between 1978 and 1987 (12). A total of 62,285 men and women, 20–69 years of age, were included in the original project. All of the studies were conducted under leadership and supervision from the Laboratory of Epidemiology of the Istituto Superiore di Sanita′ and used methods agreed on and standardized by the laboratory. However, not all of the studies measured the same variables. Details on the study are given elsewhere (12).

In six studies (four population-based and two occupational-based), information was gathered on the factors composing Syndrome X, a cluster of metabolic abnormalities associated to insulin resistance (*i.e.,* serum triglycerides, HDL[2] cholesterol, glucose, and blood pressure), and covariates of interest for the present analysis. The population-based studies were all multicenter and recruited from the general population using either electoral rolls (these rolls in Italy include all of the citizens 18 years of age and older) or the local population registry offices. The two occupational studies were single-center studies (13, 14), whereas the four population based studies were all multicenter studies with the number of centers ranging from 4 to 16 (15–18). Some characteristics of the individual studies are reported in the "Appendix." Participation rates in the different studies ranged between 53 and 76.5%. Blood samples were collected after 12 h of fasting. Serum total cholesterol and triglycerides were measured by several automated enzymatic methods. However, all of the laboratories were under the quality control procedures of the WHO Lipid Reference Center in Prague. Serum HDL cholesterol was measured after precipitation with phosphotungstic acid or with heparin or dextran sulfane in different studies; however, comparability among centers was guaranteed by centralized quality control as for total cholesterol. Blood glucose was measured by several automated enzymatic methods, but all of the laboratories were under quality control and standardization of a central laboratory.

Blood pressure was measured according to a standardized

[2] The abbreviations used are: HDL, high-density lipoprotein; ICD-9, International Classification of Disease, 9th Revision; IGF, insulin-like growth factor; CI, confidence interval.

Table 1   The cutpoints of HDL cholesterol triglycerides and glucose for each specific study

	Study #1 Men	Study #2 Women	Study #3		Study #4		Study #5		Study #6	
			Men	Women	Men	Women	Men	Women	Men	Women
HDL-c (mg/dl)[a]	40	49	39	44	40	45	40	46	40	47
TG (mg/dl)	170	106	153	109	167	122	182	148	175	135
Glucose (mg/dl)	103	92	98	94	94	91	100	97	101	96

[a] HDL-c, HDL cholesterol; TG, triglycerides.

protocol by trained observers (13). Systolic and diastolic (fifth phase) levels were recorded. The average of two consecutive measurements (1 min apart) are reported.

Weight and height were measured with participants wearing light clothing, without shoes, according to the procedures described by the WHO manual (19).

The mortality data were collected during an average follow-up period of 7 years (range, 4–12) during which 2.1% of subjects were lost to follow-up. Information on vital status, time, and cause of death in the deceased was collected locally at each center by trained staff. For each individual, a search was conducted through the local Registry Office or in the Emigration Office. For deaths, the cause or causes of death were derived from the official death certificates. Coding of causes of death were performed centrally by a single nosologist using the ICD-9. In cases of multiple causes of death, a hierarchical preference was adopted, with priority given to accidents, cancer, coronary heart disease, and stroke in rank order with other causes reported in the same order as on the death certificate. No validation of death certificates was performed. For the present analysis, causes of death are grouped as follows: (*a*) all cause mortality, ICD-9 codes 140–329; and (*b*) colorectal cancer, ICD-9 codes 153 and 154.

Population for Analysis. In six of the nine studies, information was collected on the variables of interest for the present study for a total of 24,108 men and 19,751 women 20–69 years of age. After exclusion of participants with missing information for any of the variables considered in the analyses, we had a total of 37,302 (21,311 men and 15,991 women) with complete information who are the focus of this report. It should be noted that when participants with complete information were compared with those excluded from the present analysis because of missing variables, there were no substantial differences noted.

Statistical Analyses. For the mortality analyses, hazard ratios as an indication of relative risks were computed using individuals with no metabolic abnormalities as a reference category. Survival analysis using Cox proportional hazard model (20) was our primary mode of analysis and allowed adjustment for age, smoking, and alcohol consumption using participants with no abnormalities as a reference category. The assumption of proportionality of the hazards was tested and found not to be violated.

Definition of Insulin Resistance Syndrome. For the purpose of this analysis, insulin resistance syndrome is defined as having "abnormal" levels of serum total triglycerides, HDL cholesterol, blood glucose, and blood pressure. These markers represent the original factors (alteration in glucose metabolism, increased serum triglycerides, low HDL, hypertension) identified by Reaven (21) as important components of the insulin resistance syndrome. In addition, we have shown recently that this cluster of factors was associated with a significant increase in coronary heart disease mortality in the same cohorts (22). The presence of abnormal values was defined, except for high

blood pressure, based on distribution cutpoints (*i.e.,* values in the highest 25% of the study and sex-specific distribution for glucose and triglycerides and the lowest 25% of the sex-specific distribution for HDL cholesterol or being on medication for diabetes and hyperlipidemia). These distribution-based cutpoints were used because when clinical cutpoints (based on expert and panel recommendations) were used, the prevalence of insulin resistance syndrome was very limited (22). The distribution based cutpoints is appropriate because of the established lack of threshold in the relationship between these markers and mortality/morbidity risk. For hypertension, a cutpoint of systolic pressure ≥140 or a diastolic pressure ≥90 mm Hg or being on antihypertensive treatment was used. For the other variables, to control for the possible confounding effect of differences in laboratory measurements across studies, the population cutpoints were based on each specific study distribution.

The cutpoints of HDL cholesterol triglycerides are glucose for each specific study as seen in Table 1.

Results

Table 2 summarizes the baseline characteristics of the study participants according to whether or not they were alive or died of colorectal cancer or other cancers at the end of the follow-up period.

Table 3 summarizes the result of the Cox proportional hazard model for death from colorectal cancer when the variables comprising the insulin resistance syndrome are analyzed individually. For the purpose of these analyses, variables are dichotomized based on cutpoints described previously. The models include age, alcohol, and smoking as potential covariates. Of all of the individual variables, only glucose is significantly associated with increased risk of death from colorectal cancer. Similar results are reported when the variables are used as continuous variables (data not shown).

The result of the survival analysis for the cluster of metabolic abnormalities and mortality from colorectal cancer is reported in Table 4. In the two sexes separately and in both sexes combined, the presence of the cluster of metabolic abnormalities is associated with an almost 3-fold increase in risk of death from colon cancer; this association reaches statistical significance in men and in both sexes combined. To control for the potential effect of individual studies, we compared the prevalence of insulin resistance syndrome between cases and controls in each individual study and conducted a matched analysis with matching for age, sex, and study. The findings of these analyses confirmed the results presented in Table 4. (Data not shown).

Discussion

Our findings from a large population-based study suggest that glucose and metabolic abnormalities associated with hyperinsulinemia and insulin resistance are associated with increased risk of colorectal cancer mortality in both men and women.

Table 2 Characteristics of participants according to vital status and causes of death at follow-up (x ± SD)

	Men			Women		
	Alive (*n* = 20,903)	Colorectal cancer (*n* = 41)	Other cancers (*n* = 367)	Alive (*n* = 15,895)	Colorectal cancer (*n* = 13)	Other cancers (*n* = 83)
Age (yr)	48.1 ± 11.2	56.7 ± 7.1	57.2 ± 6.8	46.6 ± 11.6	57.1 ± 10.7	54.5 ± 9.6
BMI (kg/m^2)	26.4 ± 3.5	27.6 ± 4.5	26.1 ± 3.4	26.3 ± 4.8	25.6 ± 5.3	27.3 ± 5.1
Serum total cholesterol (mg/dl)	217.9 ± 46.1	225.5 ± 41.9	217.3 ± 48.3	214.5 ± 46.8	223.4 ± 29.9	228.5 ± 42.1
Serum HDL cholesterol (mg/dl)	49.1 ± 13.4	53.6 ± 16.6	47.9 ± 13.4	56.0 ± 13.8	55.0 ± 13.9	55.3 ± 14.4
Serum triglycerides (mg/dl)	145.8 ± 104.9	155.2 ± 91.2	145.2 ± 88.7	110.2 ± 66.0	112.5 ± 50.8	134.5 ± 87.0
Serum glucose (mg/dl)	95.1 ± 24.1	100.3 ± 33.1	98.3 ± 28.1	90.1 ± 19.9	94.2 ± 7.8	94.6 ± 25.6
Systolic blood pressure (mm Hg)	135.3 ± 19.8	143.9 ± 19.8	143.2 ± 21.4	132.7 ± 22.3	144.6 ± 24.7	142.8 ± 23.2
Diastolic blood pressure (mm Hg)	85.2 ± 11.3	86.5 ± 9.7	86.1 ± 11.6	83.2 ± 11.8	86.0 ± 13.5	87.4 ± 14.1
Hypertension (%)	52.7	70.7	65.6	44.8	61.5	63.8
Diabetes (%)	6.1	19.5	10.1	4.6	0.0	9.6
Smoking						
Current smokers (%)	45.5	36.6	59.9	22.2	7.7	14.4
Never smokers (%)	24.5	24.4	8.4	71.1	92.3	74.7
Former smokers (%)	29.9	39.0	31.6	6.7	0.0	10.8
Drinkers (%)	90.1	89.6	90.2	60.1	46.1	68.7
Syndrome X (%)	3.0	9.8	4.1	3.3	15.4	1.2

Table 3 Proportional hazard model for individual metabolic abnormalities comparing insulin resistance syndrome and colorectal cancer (hazard ratios and 95% CI)

Models include: age, smoking, alcohol consumption, and sex (for the model with both sexes combined).

	Low HDL-cholesterol[a]	High triglycerides[b]	Hypertension[c]	High glucose[d]
Men	0.82 (0.38, 1.80)	2.04 (0.84, 1.41)	1.30 (0.90, 1.88)	1.83 (0.99, 3.39)
Women	1.13 (0.34, 3.64)	0.27 (0.06, 1.22)	1.14 (0.61, 2.15)	1.73 (0.58, 5.21)
Total	0.92 (0.48, 1.76)	1.01 (0.83, 1.22)	1.28 (0.93, 1.75)	1.80 (1.05, 3.09)

[a] Low HDL-cholesterol, values in the lowest 25% of the study and sex-specific distribution.
[b] High triglycerides, values in the highest 25% of the study and sex-specific distribution or on lipid-lowering drugs.
[c] Hypertension, SBP ≥140 or DBP ≥90 mm Hg or on antihypertensive drugs.
[d] High glucose, values in the highest 25% of the study and sex-specific distribution or on antidiabetic drugs.

Table 4 Proportional hazard model for insulin resistance syndrome and colorectal cancer mortality (hazard ratios and 95% CI)

Models include: age (yr), smoking (0, no smoking; 1, smoking), alcohol (g/day), and sex (1, men; 2, women) for the model with both sexes combined. Insulin resistance syndrome includes high blood pressure, high serum triglycerides, high blood glucose, and low serum HDL cholesterol based on criteria described in text.

	Men		Women		Total	
	No syndrome (*n* = 20,656)	Yes syndrome (*n* = 655)	No syndrome (*n* = 15,460)	Yes syndrome (*n* = 530)	No syndrome (*n* = 36,116)	Yes syndrome (*n* = 1,185)
Total mortality	880	48	164	9	1044	57
Relative risk	1	1.41	1	.95	1	1.31
95% CI		(1.05, 1.88)		(0.48, 1.86)		(1.00, 1.71)
All cancers	389	19	93	3	482	22
Relative risk	1	1.26	1	0.59	1	1.09
95% CI		(0.64, 1.74)		(0.41, 2.53)		(0.66, 1.61)
Colon cancer	37	4	11	2	48	6
Relative risk	1	2.96	1	2.71	1	2.99
95% CI		(1.05, 8.31)		(0.59, 12.51)		(1.27, 7.02)

A possible link between insulin metabolism and colorectal cancer has been hypothesized (2), and it is supported by experimental studies (5–7). The epidemiological evidence is mostly indirect, coming from studies linking overweight and obesity (an important determinant of hyperinsulinemia and/or insulin resistance) to both colorectal carcinoma and adenomas (23–30) and studies linking single factors influenced by insulin metabolism (*i.e.,* serum triglycerides and plasma glucose/diabetes) to colon cancer (31–34). To date, however, only a few retrospective studies have been presented linking insulin to colorectal cancer (8–11). In our study, whereas we have no direct measurement of insulin, we have attempted to characterize individuals based on a cluster of markers that has been associated to hyperinsulinemia and insulin resistance, *i.e.,* high blood pressure, low levels of HDL, high levels of triglycerides, and blood glucose (21, 35). These abnormalities have been found to be clustered in individuals with increased plasma insulin and/or increased insulin resistance (36). This cluster of metabolic abnormalities has received much attention as a risk factor for cardiovascular disease. Insulin may increase the risk

of colorectal cancer through a number of mechanisms. Insulin has been shown to affect growth of normal and neoplastic colonic epithelial cells and to have mitogenic action *in vitro* (5, 6), and in experimental animals (7) these actions can take place either directly or indirectly through IGF-1 (37, 38). Colon cancer cells have been shown to have both insulin and IGF-1 receptors (5, 39, 40). Insulin, in addition to regulating IGF action through the effect on the availability of IGF-1 binding proteins, may bind to IGF-1 receptors (2, 41). Hyperglycemia, a feature of insulin resistance, may affect colorectal cancer risk through an inhibition of colonic motility (42).

Finally, it is possible that metabolic abnormalities secondary to hyperinsulinemia and/or insulin resistance (*i.e.,* triglycerides and glucose) may act as a powerful source of energy for cancer cell growth (43).

When the individual components of the cluster are analyzed separately, their association with colorectal mortality is inconsistent with only glucose and hypertension, showing consistent findings across gender. The reason for this inconsistency is not apparent. It could be argued that glucose may be the only component of the cluster driving the observed association; however, the hazard ratios for high glucose are clearly lower than those for the presence of the full cluster, indicating that the presence of the other abnormalities has an additive effect on the risk. Glucose may have a stronger role because it may more closely reflect the underlining pathophysiological mechanisms (*i.e.,* insulin resistance) and because, as indicated previously, it may have a direct effect on cancer growth by providing cancerous cells with a source of energy (43). The lack of consistency of the findings for triglycerides (themselves a potential source of energy for cancerous cells) could be the results of their high intra-individual and intra-assay variability.

The present findings together with our previous report from the same population indicating a significant association between this cluster of metabolic abnormalities and cardiovascular disease (22) confirm that insulin resistance and the associated abnormalities may be important risk factors for a number of chronic conditions.

Our findings are most likely an underestimation of the role of insulin in the etiology of colorectal cancer, because it is likely that there are numerous individuals in the population who have various degrees of hyperinsulinemia and/or insulin resistance who do not necessarily present abnormalities in all four of the components of this cluster. Another limitation of our study includes the relatively short follow-up time and our subsequent inability to eliminate early events from the analysis to avoid possible biases attributable to the effect of incipient or underdiagnosed disease on the markers of insulin resistance. The wide CIs of our risk estimates are the result of the limited number of events available for analysis, particularly in women, and are indicative of the instability of our estimates. Finally, the reliance on death certificates and subsequent potential misclassification of causes of death is another important limitation of our study. However, it should be pointed out that this type of error should result in an underestimation of the effect of this cluster of metabolic abnormalities on colorectal cancer mortality risk. The longitudinal design and the population-based nature of the study represent a clear strength of our study and a clear advantage over previous studies published on this topic.

In conclusion, our study indicates that variables associated with increased insulin and/or insulin resistance are associated with a significant increase of risk of death from colorectal cancer. High insulin and insulin resistance are common features of industrialized societies characterized by a large prevalence of overweight and obesity, diet rich in energy intake, and a lifestyle characterized by low calorie expenditure. Evidence is continuing to mount linking this metabolic pattern not only to cardiovascular disease but to other major chronic conditions like cancer and diabetes. Public health efforts aimed at reducing lifestyle patterns and dietary habits associated with this imbalance on insulin metabolism may have profound health benefits on a number of diseases that represent major causes of mortality and morbidity in our societies.

Appendix

Information of individual studies comprising the risk factors and life expectancy project are seen in Table A1.

	Study #1	Study #2	Study #3	Study #4	Study #5	Study #6
Appendix Table 1 Information of individual studies comprising the risk factors and life expectancy project						
N	(13, 2652)	(0, 957)	(4, 3645)	(6, 3578)	(6, 5849)	(25, 20566)
Men[a]/Women[a]	(13/0, 2652/0)	0/957	(3/1, 2212/1433)	(4/2, 1952/1626)	(1/5, 2707/3142)	(20/5, 11747/8819)
Age (mean ± SD)[a]	(57.5 ± 4.8, 55.1 ± 5.2)	40.6 ± 9.6	(52.0 ± 8.6, 42.7 ± 10.2)	(54.0 ± 4.0, 42.6 ± 10.2)	(61.8 ± 5.6, 46.4 ± 13.8)	(57.6 ± 8.2, 48.9 ± 10.7)
Age range[a]	(50–65, 46–66)	25–69	(28–57, 20–60)	(49–59, 20–60)	(53–68, 20–69)	(32–69, 24–69)
Nature of use for samples	Occupational-based	Occupational-based	Population-based	Population-based	Population-based	Population-based
Dates of examination at baseline	1979–1980	1981–1982	1983–1985	1983–1984	1985–1987	1984–1987
Average follow-up (yr)	9.85	8.07	8.16	7.19	7.64	6.06
Participants rate (%)	76.5	75.9	51.5	50.5	53.0	62.1
Study centers[b]	1	1	6	9	4	16
Insulin resistance syndrome (%)[a,c]	(0.0, 2.0)	(0.0, 1.0)	(25.0, 2.7)	(33.3, 5.5)	(16.6, 3.6)	(8.0, 2.9)

[a] Separated into (cases, controls) for each study. Cases are participants deceased with colon or rectal cancer and controls are all other participants.
[b] Study center, numbers of centers involved in the main study.
[c] The cutpoint for variables included in the insulin resistance syndrome are determined specifically for each study.

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