

BRIEF COMMUNICATIONS

Diabetes Mellitus and Risk of Colorectal Cancer in the Singapore Chinese Health Study

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The incidence of colorectal cancer is highest in populations that consume an energy-dense diet, have low intakes of vegetables and fruit, or lead a sedentary lifestyle. These factors may influence colorectal carcinogenesis via insulin pathways. We examined whether diabetes mellitus was associated with colorectal cancer in Singapore Chinese, whose body type and lifestyle profiles are distinct from those of Western populations. Between April 1993 and December 1998, 63257 Singapore Chinese men and women aged 45 to 74 years were enrolled in a prospective study of diet and cancer. Each subject provided dietary, medical, and lifestyle information through an in-person interview. As of December 31, 2002, 636 incident colorectal cancer cases had been diagnosed. A history of physician-diagnosed diabetes was statistically significantly associated with colorectal cancer risk in both men (relative risk [RR] = 1.5, 95% confidence interval [CI] = 1.2 to 2.1) and women (RR = 1.4, 95% CI = 1.0 to 1.9). In stratified analyses, this association remained statistically significant among the subset of diabetics with high total calorie intake and low physical activity levels. Our results support the hypothesis that hyperinsulinemia may play a role in colorectal carcinogenesis, even in a relatively lean population. [J Natl Cancer Inst 2006;98:135–8]

There is convincing evidence across diverse populations that obesity and diets high in total energy, fat, protein or red

meat, and carbohydrates elevate the risk of colorectal cancer (1–5). Conversely, higher intakes of fruit, vegetables, and an active lifestyle can reduce risk of this malignancy (1–8). Based on both observational and experimental study findings, a unifying hypothesis has been proposed in which insulin and insulin-like growth factors play a central role in colorectal carcinogenesis (9–14). Epidemiologic data suggest that a history of diabetes mellitus, and, in particular, type 2 diabetes (15), and impaired glucose tolerance are risk factors for colorectal cancer (16–22). Individuals with type 2 diabetes have peripheral resistance to insulin and develop hyperinsulinemia as a compensatory response (23,24), and this hyperinsulinemic state is believed to be the mechanism that underlies the association between diabetes and colorectal carcinogenesis (7,25–27).

Ethnic Chinese constitute more than three-quarters of Singapore's population and have experienced dramatic changes in lifestyle over the past few decades as a consequence of the country's rapid industrialization and rising affluence. Among these changes is a marked increase in total calorie and meat consumption (28) and a rise in obesity rates (29). The population-based estimate of the prevalence of diabetes mellitus among Singapore Chinese was 8.0% in 1998 (29), compared with global prevalence estimates of 6% in developed countries and 3.3% in developing countries (30). Between 1970 and 2000, age-standardized colon cancer incidence rates (per 100000) increased from 11.6 to 26.6 in men and from 9.5 to 20.9 in women. Similar increases have been observed for rectal cancer in this population (31). We assessed whether a history of diabetes was associated with colorectal cancer in Singapore Chinese and investigated whether this association was modified by other factors possibly involved in the putative insulin–colorectal cancer pathway in a prospective study, the Singapore Chinese Health Study.

The Singapore Chinese Health Study is a population-based prospective cohort study of ethnic Chinese men and women, aged 45–74 years at baseline, who belong to either the Hokkien or the Cantonese dialect groups and live in government housing estates (which house 86% of all residents in Singapore) (32). A total of 63257 individuals gave informed written consent and enrolled between April

1993 and December 1998. For the present analysis, we excluded 1937 individuals with a history of any invasive cancer (except nonmelanoma skin cancer) or in situ bladder cancer. The study was approved by the Institutional Review Boards of the University of Southern California and the National University of Singapore.

At recruitment, each participant completed an in-person interview using a structured questionnaire that requested information about demographic characteristics, height and weight, use of tobacco, usual physical activity, medical history, and family history of cancer. The questionnaire included a validated semiquantitative food frequency section listing 165 food items commonly consumed in the study population, from which we were able to derive average daily intake of calories and other nutrients using the Singapore Food Composition Database (32).

For each subject, person-years of follow-up were counted from the date of enrollment to the date of diagnosis of colorectal cancer, date of death, or December 31, 2002, whichever occurred first. We identified incident colorectal cancer cases through the Singapore Cancer Registry and deaths through the Singapore Registry of Births and Deaths. We used Cox proportional hazards modeling (33) to examine the association between diabetes mellitus and the risk of developing colorectal cancer. The proportionality assumption was tested using the method of Lin et al. (34) and found to be satisfied ($P = .13$). All models were adjusted for age at enrollment, year of enrollment, dialect group, and known risk factors for colorectal cancer (see footnote to Table 2). We also examined the association between diabetes and colorectal cancer in subjects stratified by

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sex, body mass index (BMI; <20 kg/m², 20–23.9, 24–27.9, ≥ 28), total calorie intake (below and above the median level of 1458.04 kcal/day), and vigorous work or strenuous physical activity (yes or no). Statistical analysis was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC) and Epilog for Windows version 1.0 (Epicenter Software, Pasadena, CA). All *P* values are two-sided.

Of the 61 320 cohort members who were free of cancer at baseline, 5469 (8.9%) reported a history of any physician-diagnosed diabetes mellitus. Diabetics and nondiabetics were similar in distribution by gender and familial history of colorectal cancer (Table 1). Compared with nondiabetics, diabetics were statistically significantly older and had slightly higher BMI levels, had less formal education, and engaged in less physical activity (Table 1). Diabetics also reported lower alcohol and total calorie consumption at baseline than nondiabetics (Table 1).

As of December 31, 2002 (mean follow-up time = 7.1 years), 636 subjects (284 women and 352 men) had developed colorectal cancer (391 colon and 245 rectal cancers), 97% of which were histopathologically confirmed. The mean age at diagnosis was 66.6 years, and the mean interval between entry into the study and cancer diagnosis was 4.4 years (range = <1 month to 9.5 years). The incidence rate of colorectal cancer was 208.9 per 100 000 person-years (90 cases) in diabetics and 140.2 per 100 000 person-years (546 cases) in nondiabetics, after adjustment for age and sex. Compared with control subjects, case patients were statistically significantly older, more likely to be male or to be smokers, had less formal education, and reported lower consumption of calories, less physical activity, and higher intake of alcohol at baseline (Table 1).

The risk of colorectal cancer after adjustment for age, sex, dialect group, and year of interview was 50% higher among diabetics than among nondiabetics (relative risk [RR] = 1.5, 95% confidence interval [CI] = 1.2 to 1.9). Further adjustment for level of education, BMI, cigarette smoking, alcohol consumption, physical activity, and familial history of colorectal cancer did not change the association (Table 2). The risk elevation was seen in both men (RR = 1.5, 95% CI = 1.2 to 2.1) and women (RR = 1.4, 95% CI = 1.0 to 1.9). The relative risk

Table 1. Baseline characteristics of cohort members (mean ± standard deviation or %) of the Singapore Chinese Health Study (1993–2002) by history of diabetes and incident colorectal cancer case status

	Diabetes		Colorectal cancer	
	No (n = 55 851)	Yes (n = 5469)	No (n = 60 684)	Yes (n = 636)
Age (y) at recruitment	56.0 ± 7.9	60.0 ± 7.7*	56.3 ± 8.0	61.7 ± 7.6†
Body mass index (kg/m ²)	23.0 ± 3.2	24.1 ± 3.3*	23.1 ± 3.3	23.2 ± 3.3
Total calories (kcal/day)	1566.3 ± 567.7	1458.3 ± 540.8*	1557.1 ± 566.6	1509.6 ± 527.5†
Sex				
Males	44.7	43.2*	44.4	55.4†
Females	55.4	56.9	55.6	44.7
Dialect				
Cantonese	46.3	45.6	46.2	41.4†
Hokkien	53.8	54.4	53.8	58.7
Level of education				
No formal education	26.4	35.0*	27.1	34.1†
Primary school (1–6 years)	44.4	44.1	44.4	45.0
Secondary school and above	29.2	21.0	28.5	20.9
Smoking history‡				
Nonsmokers	69.6	67.8*	69.5	60.4†
Light smoker	26.7	28.3	26.7	33.0
Heavy smoker	3.7	3.9	3.7	6.6
No. of alcoholic drinks per day				
Nondrinkers	80.2	88.6*	81.0	78.9†
<1	14.9	8.5	14.3	13.1
1+	4.9	2.9	4.7	8.0
Family history of colorectal cancer				
No	97.8	97.8	97.8	97.3
Yes	2.2	2.2	2.2	2.7
Vigorous work/strenuous physical activity§				
No	85.7	91.8*	86.2	91.8†
Yes	14.3	8.2	13.8	8.2

*Differences between diabetics and nondiabetics were statistically significant at *P* < .05.

†Differences between colorectal cancer patients and control subjects were statistically significant at *P* < .05.

‡Light smoker = fewer than 13 cigarettes a day or started smoking after 15 years of age. Heavy smoker = 13 or more cigarettes a day and started smoking before the age of 15.

§Vigorous activity included: work (e.g., moving heavy furniture, loading or unloading trucks, or shoveling) or strenuous sports (e.g., jogging, bicycling on hills, tennis, squash, swimming laps, or aerobics) for at least 30 minutes a week, on average.

estimates were similar for both colon cancer (RR = 1.5, 95% CI = 1.1 to 2.0) and rectal cancer (RR = 1.5, 95% CI = 1.0 to 2.1). To account for prevalent cases that may have been undetected at the time of recruitment, we repeated the analysis but restricted it to those diagnosed 2 or more years after entry into the cohort; this restriction did not materially affect the relative risk estimates (data not shown).

When cancer patients and control subjects were stratified by BMI (Table 2), diabetics had a 70% higher risk of developing colorectal cancer (*P* < .001) than nondiabetics among subjects with a BMI between 20 and 24 kg/m². There was no trend suggesting increasing risk of colorectal cancer among diabetics in the higher BMI categories. A statistically significantly elevated relative risk of colorectal cancer among diabetics compared with nondiabetics was also observed

among subjects with higher total caloric intake (RR = 1.8, 95% CI = 1.3 to 2.4; *P*_{interaction} = .10). When subjects were stratified by physical activity, an elevated risk of colorectal cancer among diabetics versus nondiabetics was observed only in those subjects with lower levels of physical activity (RR = 1.5, 95% CI = 1.2 to 1.9; *P*_{interaction} = .16).

Our results are consistent with the growing body of epidemiologic evidence that links a history of diabetes mellitus (primarily type 2) with colorectal cancer risk (16). In two large U.S. prospective cohorts (17,18), investigators reported risk ratios of approximately 1.3 for colon cancer mortality among men and women with diabetes. In the Nurses' Health Study, a history of type 2 diabetes was associated with a statistically significant 43% increase in colorectal cancer risk (19). A statistically significant 60%

Table 2. Risk of colorectal cancer and history of diabetes mellitus in the Singapore Chinese Health Study (1993–2003)

Stratifying variables	Nondiabetics			Diabetics		
	Person-years	Cases	RR (95% CI)*	Person-years	Cases	RR (95% CI)
All	401 189	546	1.0 (referent)	35 840	90	1.5 (1.2 to 1.8)†
Sex						
Male	175 976	305	1.0 (referent)	14 811	47	1.5 (1.2 to 2.1)
Female	225 213	241	1.0 (referent)	21 029	43	1.4 (1.0 to 1.9)
						<i>P</i> _{interaction} = .62
Body mass index (kg/m ²)						
<20	62 392	90	1.0 (referent)	2 697	8	1.6 (0.8 to 3.4)
20–23.9	219 922	276	1.0 (referent)	18 320	49	1.7 (1.3 to 2.3)
24–27.9	91 825	145	1.0 (referent)	10 677	23	1.1 (0.7 to 1.7)
≥28	27 050	35	1.0 (referent)	4 147	10	1.5 (0.7 to 3.1)
						<i>P</i> _{interaction} = .38
Total calorie intake						
< Median	199 469	280	1.0 (referent)	20 210	43	1.2 (0.9 to 1.7)
> Median	201 720	266	1.0 (referent)	15 630	47	1.8 (1.3 to 2.4)
						<i>P</i> _{interaction} = .10
Vigorous work/strenuous physical activity						
No	345 645	496	1.0 (referent)	32 829	88	1.5 (1.2 to 1.9)
Yes	55 543	50	1.0 (referent)	3 011	2	0.6 (0.1 to 2.4)
						<i>P</i> _{interaction} = .16

*RR = risk ratio; CI = confidence interval.

†Adjusted for age at enrollment, year of enrollment, sex, dialect group (Hokkien or Cantonese), level of education (no formal education, primary school, or secondary or higher education), body mass index (<20, 20–23.9, 24–27.9, or ≥28 kg/m²), cigarette smoking (nonsmoker, light smokers, and heavy smokers), alcohol consumption (0, <1, or ≥1 drinks/day), and familial history of colorectal cancer (no or yes), and vigorous work/strenuous physical activity (no or yes).

elevation in colorectal cancer risk was associated with self-reported diabetes among Norwegian women but not men (20). In the EPIC-Norfolk study, diabetes was associated with a twofold increase in colorectal cancer risk in both males and females (21). More recently, Jee et al. (22) reported that mortality from colorectal cancer in a large Korean prospective cohort was increased by 30% among men with diabetes but was not elevated among women with diabetes and that risk of incident colorectal cancers was only slightly elevated among diabetics (RR = 1.11, 95% CI = 1.00 to 1.24 in men and RR = 1.17, 95% CI = 0.98 to 1.40 in women).

In stratified analyses we observed a statistically significant association between diabetes and colorectal cancer risk among individuals with higher calorie intake and lower levels of physical activity. This finding is consistent with higher levels of insulin resistance among these individuals (35–39), and this interaction requires further evaluation in other large studies. In addition, the association between diabetes and colorectal cancer risk was present even among individuals with BMI levels that are considerably lower than the average values in Western populations. In the Korean cohort (22), the association between fasting serum glucose and overall cancer mortality was consistent across BMI categories, and the association was most marked in those

with BMI of 20–22.9 kg/m². Both Asian populations (i.e., Koreans and Singapore Chinese) are generally lean, with the average BMI being about 23 kg/m². By comparison, the average BMI in U.S. adults is 28 kg/m² (40). Therefore, our data suggest that high BMI per se does not drive the diabetes–colorectal cancer association. It is conceivable that other aspects of adiposity that were not measured in this study, such as waist-to-hip ratio (a surrogate for visceral adipose tissue) are more important determinants of insulin resistance, as has been observed in other populations (41–43).

A limitation of this analysis is the use of self-report for physician-diagnosed diabetes. The proportion of cohort members who reported a history of diabetes (8.9%) is substantially lower than estimates of the prevalence in the general population (18.2% and 22.0% among male and female Singapore Chinese aged 50–59 years, respectively) based on an oral glucose tolerance test (29). However, this form of underreporting would attenuate a true association between diabetes and colorectal cancer. Also, the questionnaire was administered only once, at baseline, and any changes in physical activity or diet during follow-up were not captured. Detection bias is another concern, because it may be argued that diabetics would be under closer surveillance and more likely to have cancer

detected than nondiabetics. However, the small size of Singapore and the even distribution of health care facilities that promote access by all segments of the population make this bias unlikely (44). In addition, all cases were ascertained through the population-based Cancer Registry, which maintains excellent coverage and has a “death certificate–only” rate of less than 1% (31).

In summary, we observed that diabetes mellitus was a risk factor for colorectal cancer in Singapore Chinese and that this association was statistically significant among those with high intake of total calories and lower levels of physical activity, both of which are independent predictors of high insulin levels. Our results provide support for an association between hyperinsulinemia and colorectal cancer, even in a relatively lean population.

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NOTES

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