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Colorectal Cancer: Another Complication of Diabetes Mellitus?

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Delayed stool transit and other gastrointestinal abnormalities are commonly observed in persons with diabetes mellitus and are also known to be associated with colorectal cancer. Previous studies of the contribution of diabetes to colorectal cancer incidence and mortality have been limited by small sample sizes and failure to adjust for covariates. With more than 1 million respondents, the 1959–1972 Cancer Prevention Study provided a unique opportunity to explore whether persons with diabetes (n = 15,487) were more likely to develop colorectal cancer during a 13-year follow-up period than were persons without diabetes (n = 850,946). After adjustment for colorectal cancer risk factors, such as race, educational level, body mass index, smoking, alcohol use, dietary intake, aspirin use, physical activity, and family history of colorectal cancer, the incidence density ratio comparing colorectal cancer in those with diabetes and those without diabetes was 1.30 (95% confidence interval 1.03–1.65) for men and 1.16 (95% confidence interval 0.87–1.53) for women. However, diabetes was not associated with greater case fatality. Future studies should explore the possibility of a cancer-promoting gastrointestinal milieu, including delayed stool transit and elevated fecal bile acid concentrations, associated with hyperglycemia and diabetic neuropathy. *Am J Epidemiol* 1998;147:816–25.

colorectal neoplasms; confounding factors (epidemiology); diabetes mellitus; effect modifiers (epidemiology); survival

Constipation is a common complaint of persons with diabetes mellitus (1). Frequent constipation, especially when certain fecal bile acids are present, is believed to contribute to DNA and other cellular damage in the colon and rectum (2). Therefore, we hypothesized that persons with diabetes may be at greater risk of colorectal cancer than would persons without diabetes.

Previous research examining the association between diabetes and colorectal cancer has often been limited by the rarity of these conditions occurring together (3–18). Studies that include 20 or more persons with either diabetes and colon cancer or diabetes and rectal cancer are summarized in table 1. Of those studies that compared the colon cancer experience of a select group of diabetic persons with the expected occurrence in a standard population (19–23), most found that men with diabetes are slightly (but, not statistically significantly) more likely than their counterparts without diabetes to have experienced colon cancer and that the association between diabetes and colorectal cancer among women is generally weaker than that for men (19, 20, 22, 23). The same studies report only weak associations between diabetes and rectal cancer.

Case-control studies have generally found positive associations between diabetes and colorectal cancer for men (range, 1.0–2.9), but again they report only weak associations for women (range, 0.8–1.2) (24–27). Only two case-control studies have accounted for covariates (26, 27). In these, the association between diabetes and colorectal cancer is strengthened by adjustment, especially among men (range, 1.7–2.9). To date, no prospective cohort studies have examined the association between diabetes and colorectal cancer. However, one prospective cohort study has examined postload glucose values for cancer decedents and survivors (28).

Although these previous studies provide a rationale for continuing research on diabetes and colorectal cancer, they are limited by small sample sizes and failure to control for important covariates. To address these limitations, we examined a large prospective cancer incidence study of more than 1 million US citizens, including more than 15,000 eligible participants with diabetes. This study provides estimates of

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Abbreviations: CI, confidence interval; IDR, incidence density ratio.

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TABLE 1. Previous studies* examining the association between diabetes mellitus and colorectal cancer

Author (reference no.)	Colon cancer				Rectal cancer				Description
	Men		Women		Men		Women		
	Estimated effect†	No. of cases of diabetes with cancer	Estimated effect†	No. of cases of diabetes with cancer	Estimated effect†	No. of cases of diabetes with cancer	Estimated effect†	No. of cases of diabetes with cancer	
Wilson and Maher (19)	1.3‡	128	1.2‡	220	1.1	61	0.9	57	Death certificate study. Effect measure equals observed cases with both cancer and diabetes divided by expected cases of both cancer and diabetes.
Bell (20)	1.5§	18	1.2§	14					Autopsy study using data from 1911 to 1954. Excludes cases where cancer preceded diabetes or was concurrent with diabetes. Ages 40 years and older.
Kessler (21)	1.0‡	50	1.2‡	97	0.6	18	1.0	27	Retrospective cohort study of persons with diabetes identified from existing records during 1930–1956 who were followed until 1959 to determine cause of death. Their cancer death rate was compared with the age-standardized cancer death rate in the general population.
Ragozzino et al. (22)	1.4§	12	1.1§	10					Cross-sectional study of observed cancer rates of persons with diabetes (1945–1969) compared with age- and sex-standardized expected rate of cancer in the general population.
O'Mara et al. (24)	1.4	12	1.2	15	1.0	13	1.1	13	Case-control study of patient admissions to a hospital between 1957 and 1965. Age-adjusted estimates.
Kune et al. (25)	1.3§	21	0.8§	12					Case-control study (age- and sex-matched) of colorectal cancer examining prevalence of diabetes in cases and controls.
Levine et al. (28)	1.0¶	23	1.1¶	29	1.0¶	6	0.8¶	4	Prospective cohort study in industrial setting. Comparison of mean age-adjusted plasma glucose loads in cancer decedents and survivors.
Adami et al. (23)	1.2	94	1.0	111	1.3#	73	0.9	47	Hybrid study. Age- and sex-adjusted cancer rates were applied to a diabetes cohort to obtain expected numbers for cancer.
La Vecchia et al. (26)		1.7#,** 55					1.5** 28		Case-control study. Multivariate adjustment included age, sex, area of residence, education, body mass index, and selected indicator foods.
Hardell et al. (27)	2.9#	17	1.0	11					Case-control study of colon cancer. Effect estimate adjusted for age, sex, and occupational physical activity.

* Includes only those studies with 20 or more persons who have colon or rectal cancer.
† For persons with diabetes compared with a control group, except when otherwise noted.
‡ All intestinal cancers combined.
§ For colon and rectal cancers combined.
¶ Mean plasma glucose level among cancer decedents divided by mean plasma glucose levels among survivors.
# Confidence interval does not include 1.0.
** For men and women combined.

the association of diabetes and colorectal cancer adjusted for many important colorectal cancer risk factors.

MATERIALS AND METHODS

Our study involved participants in the first Cancer Prevention Study of the American Cancer Society. This prospective study was designed to assess risk factors for cancer (29). More than 1 million participants aged 30 years and older recruited by volunteers in 25 states between October 1959 and March 1960 completed a baseline questionnaire on personal habits and medical history, including diagnoses of either colorectal cancer or diabetes. Volunteer researchers were to report annually on the vital status of the subjects they enrolled, and several attempts to trace missing subjects were made before a report of "not traced" was accepted. In addition to the annual tracing of subjects, researchers distributed a supplemental questionnaire every other year (1961, 1963, and 1965). This supplement asked about hospitalizations since the completion of the previous questionnaire, diagnoses of cancer and first treatment dates, changes in residence, and current smoking habits.

In October 1972, a final follow-up questionnaire distributed by volunteers included questions on personal habits, medical history of disease, and cancer diagnosis and treatment during the respondent's lifetime. Finally, death certificates used to determine the exact cause of death were coded by a nosologist according to the *International Classification of Diseases*, Seventh Revision (30). The cause of death was determined for 92.2 percent of the study participants who died. Additional details of the study have been published previously (29, 31).

An incident case of colorectal cancer was determined by: 1) a report of colon or rectal cancer on any of the questionnaires completed after baseline, or 2) a death certificate listing colon or rectal cancer as an underlying or contributing cause of death and a review to determine that all previous questionnaires had been completed, indicating no previously diagnosed colon or rectal cancer. For cases, person-years of follow-up were calculated by subtracting the date of the baseline questionnaire from the date of first diagnosis, first treatment, or death. Persons who were alive at first follow-up and failed to complete the first follow-up questionnaire were classified as missing. All other participants were classified as noncases and censored in the analysis. For noncases who were lost to follow-up between the first questionnaire and the 1972 interview, person-years of follow-up were calculated by subtracting the date of the baseline interview from the date of their most recently completed interview. For noncases who died from causes other than colon or rectal cancer, person-years of follow-up were calculated by subtracting the date of the baseline interview from the date of death. For noncases who completed the 1972 interview, person-years of follow-up were calculated by subtracting the date of baseline interview from the date of the 1972 interview.

For this analysis, from the 592,405 women and 455,370 men aged 30 years and older who returned questionnaires at baseline we excluded those who reported a previous diagnosis of any cancer (women, $n = 28{,}206$; men, $n = 17{,}270$). Among those remaining, we then excluded persons who did not fill out their own baseline questionnaire (women, $n = 30{,}279$; men, $n = 70{,}467$) and those who provided no interview information after baseline (women, $n = 23{,}070$; men, $n = 14{,}784$). Hence, the cohort of men and women who were followed from baseline consisted of 510,850 women and 352,849 men, among whom 4,006 women and 3,218 men developed colorectal cancer during the 13 years of follow-up.

Our primary exposure variable, history of diabetes, was determined at baseline by the respondents' selection of diabetes from a checklist of diseases they had ever had (men, $n = 7{,}229$; women, $n = 8{,}258$). We also considered other baseline characteristics potentially related to colorectal cancer: age (continuous), race (white, black and other), body mass index (kg/m^2), educational background (less than high school graduate, high school graduate, some college), current smoker (no, yes), usual level of exercise at work or play (none or slight, moderate, heavy), family history of colon or rectal cancer (none, at least one first-degree relative), eats cereal daily (no, yes), eats meat or poultry daily (no, yes), eats fruit daily (no, yes), eats cooked vegetables daily (no, yes), eats green salads daily (no, yes), eats fried foods daily (no, yes), number of cups of coffee per day (continuous), number of cups of tea per day (continuous), number of cups of milk per day (continuous), number of alcoholic drinks per day (continuous), and often consumes aspirin or buffered aspirin (no, yes). We examined two additional variables: number of pregnancies (none, at least one) for women and pipe or cigar smoking (no, yes) for men.

Proportional hazards analysis was used to estimate the incidence density ratio (IDR) for the association of diabetes history and colorectal cancer incidence while adjusting for other potential risk factors (32, 33). We tested for statistically significant ($p < 0.05$) interactions of diabetes with other variables in the model. In a separate analysis, we eliminated persons younger than age 60 years in an attempt to remove those who died at an early age from heart disease. Since persons

with diabetes are more likely to die early from heart disease than are those without diabetes (34), we believed that this analysis would allow a more equitable comparison of persons with and those without diabetes. Finally, in a third proportional hazards analysis, we estimated, by diabetes status, the likelihood of dying from colorectal cancer for persons who were diagnosed with this disease during the study. For those who died from colorectal cancer and had not reported the disease on any of the questionnaires preceding death, the date of cancer incidence was assumed to be 3.5 years before death. Because three quarters of all colorectal cancer deaths occurred during the 7-year period that elapsed between the last two questionnaires, which were administered in 1965 and 1972, it seemed reasonable that the midpoint would be the best estimate of the date of cancer incidence. Hence, for these cases, we used a survival time of 3.5 years. Reanalysis of the data, using different estimated survival times including 0, 0.5, and 1 year (assuming that cancer was diagnosed during autopsy or at a very late stage), yielded similar results.

Other analyses included testing the proportional hazard assumption for each of the independent variables in the various models. We examined Schoenfeld residuals for all variables in the model and their correlations with time and time squared. We also visually examined plots of the residuals against time and time squared. The proportional hazard assumption was not violated for diabetes, the primary exposure variable. In those instances when the assumption was violated for other variables in the model, we corrected for it by using the strata option in PHREG (32). These corrections did not substantially change the IDR for the diabetes and colorectal cancer association.

RESULTS

Table 2 presents baseline characteristics of the study population by gender and diabetes status. Persons with diabetes were older, more likely to belong to a race other than white, and less likely to have completed high school than persons without diabetes. In general, persons with diabetes appeared to have healthier lifestyles than did persons without diabetes: They were less likely to smoke cigarettes and more likely to consume fruit, vegetables, green salads, and cereal daily than were persons without diabetes. Their average daily consumption of alcohol appeared to be slightly lower than that of persons without diabetes, and their milk consumption appeared to be higher. However, persons with diabetes were more likely to be sedentary than their counterparts without diabetes, and women with diabetes were slightly heavier than women without diabetes.

The age-adjusted IDR for the association of diabetes with colorectal cancer among men was 1.27 (95 percent confidence interval (CI) 1.02–1.58) (table 3). After adjustment for colorectal cancer risk factors (fully adjusted model), the IDR for the association of diabetes mellitus with colorectal cancer was 1.30 (95 percent CI 1.03–1.65) among men. Of all colorectal cancer risk factors examined, family history of colorectal cancer was most strongly related to development of colorectal cancer (IDR = 1.73, 95 percent CI 1.48–2.03). Heavy exercise at work or play was the most protective factor against development of colorectal cancer (IDR = 0.74, CI 0.64–0.86). Other important factors associated with colorectal cancer among men included older age and smoking pipes or cigars. Factors that were significantly, but only weakly, associated with colorectal cancer incidence were a higher body mass index, eating less cereal, drinking fewer glasses of milk daily, drinking more alcohol daily, and never or seldom taking aspirin. We found a significant interaction of diabetes with current cigarette smoking, and stratification by smoking status yielded the following IDRs for the association of diabetes and colorectal cancer incidence: smokers, 0.87 (95 percent CI 0.58–1.31); nonsmokers, 1.72 (95 percent CI 1.28–2.31) (data not shown).

The age-adjusted IDR for the association of diabetes with colorectal cancer among women was 1.06 (95 percent CI 0.84–1.34) (table 4). In the fully adjusted model, the association of diabetes with colorectal cancer was 1.16 (95 percent CI 0.87–1.53). As with men, family history of colorectal cancer most strongly predicted development of colorectal cancer (IDR = 1.71, 95 percent CI 1.48–1.98). Other important predictors of colorectal cancer incidence included older age and consumption of fewer glasses of milk daily. Higher educational level and consumption of cooked vegetables daily were only weakly associated with colorectal cancer incidence. There was a significant interaction of diabetes with daily salad consumption, and stratification by salad consumption resulted in the following IDRs for the association of diabetes with colorectal cancer incidence: no daily salad, 1.48 (95 percent CI 1.07–2.04); and one or more salads every day, 0.67 (95 percent CI 0.38–1.19) (data not shown).

Restriction of the analysis to persons aged 60 years and older at baseline to eliminate persons who died at an early age from heart disease resulted in fully adjusted IDRs for the association of diabetes with colorectal cancer of 1.45 (95 percent CI 1.07–1.97) for men and 0.99 (95 percent CI 0.66–1.49) for women (data not shown).

To determine whether the progression of colorectal cancer was hastened by diabetes, we examined the

TABLE 2. Means and percentages for selected baseline characteristics, by gender and diabetes status in the First Cancer Prevention Study, 1959–1972

Characteristic	Men		Women	
	Diabetes mellitus (n = 7,229)	No diabetes mellitus (n = 345,620)	Diabetes mellitus (n = 8,258)	No diabetes mellitus (n = 502,592)
Age (mean years)	57.4	52.9	57.8	51.7
Colorectal cancer during follow-up				
No	98.8	99.1	99.1	99.2
Yes	1.2	0.9	0.9	0.8
Race				
White	97.4	98.1	95.0	97.6
Black and other	2.6	1.9	5.0	2.3
Education				
Less than high school graduate	46.2	40.9	53.3	35.5
High school graduate	16.0	19.2	19.3	27.2
Some college	37.8	40.9	27.4	37.3
Family history of colorectal cancer				
No	97.0	96.8	96.1	96.3
Yes	3.0	3.2	3.9	3.7
Body mass index (mean kg/m^2)	25.4	25.2	26.2	24.2
History of constipation				
No	87.5	89.9	74.1	76.3
Yes	12.5	10.1	25.9	23.7
Current smoker				
No	45.9	41.0	83.3	71.9
Yes	54.1	59.0	16.7	28.1
Pipe or cigar smoker				
No	76.8	81.5		
Yes	23.2	18.5		
Eats cereal daily				
No	66.0	78.6	75.3	84.1
Yes	34.0	21.4	24.7	15.9

Table continues

association of diabetes with death from colorectal cancer after colorectal cancer diagnosis and found a fully adjusted IDR of 0.98 (95 percent CI 0.70–1.37) for men and 1.07 (95 percent CI 0.71–1.62) for women (data not shown). The two factors most strongly related ($p < 0.01$) to death from colorectal cancer were being from a race other than white (an approximately twofold increase in risk of dying for both men and women) and being older.

DISCUSSION

This study generally confirms previous research findings, including the significance of well-established colorectal cancer risk factors (e.g., family history of colorectal cancer and age) (2), the association between diabetes and colorectal cancer in men and, to a lesser extent, in women (19, 20, 22, 23), and longer survival after colorectal cancer diagnosis for whites compared with races other than white (35).

Our study extends previous colorectal cancer research by providing a more precise estimate of the association between diabetes and colorectal cancer (based on 84 men and 74 women with both diabetes and colorectal cancer). Because of our ability to adjust for important covariates, it probably provides a less-biased estimate of the association than did previous

TABLE 2. Continued

Characteristic	Men		Women	
	Diabetes mellitus (*n* = 7,229)	No diabetes mellitus (*n* = 345,620)	Diabetes mellitus (*n* = 8,258)	No diabetes mellitus (*n* = 502,592)
Eats fruit daily				
No	33.2	44.9	26.8	33.0
Yes	66.8	55.1	73.2	67.0
Eats cooked vegetables daily				
No	35.5	41.2	28.0	29.7
Yes	64.5	58.8	72.0	70.3
Eats green salad daily				
No	65.5	76.2	63.7	68.5
Yes	34.5	23.8	36.3	31.6
Eats fried foods daily				
No	47.9	46.0	66.4	63.0
Yes	52.1	54.0	33.6	37.0
Eats meat or poultry daily				
No	52.0	55.9	51.3	53.1
Yes	48.0	44.1	48.7	46.9
Cups of coffee daily (mean no.)	3.3	3.2	2.9	3.1
Cups of tea daily (mean no.)	0.6	0.6	0.8	0.8
Glasses of milk daily (mean no.)	1.5	1.2	1.2	0.9
Alcohol drinks per day (mean no.)	1.0	1.2	0.5	0.7
Takes aspirin or buffered aspirin				
Never or seldom	87.2	87.7	78.4	78.1
Often	12.8	12.3	21.6	21.9
Exercises at work or play				
None or slight	29.0	22.8	19.2	15.9
Moderate	60.9	63.1	71.5	74.9
Heavy	10.1	14.1	9.3	9.2
Never pregnant			9.3	1.0
At least one pregnancy			90.7	99.0

studies (men = 1.30, women = 1.16). Furthermore, we were able to determine that diabetes did not hasten death from colorectal cancer.

Some factors that might account for the higher colorectal cancer incidence among persons with diabetes mellitus compared with their counterparts without diabetes are 1) slower bowel transit, which contributes to increased exposure to toxic substances; 2) increased production of carcinogenic bile acids; and 3) high insulin levels, which promote colonic tumor development and growth. Delayed stool transit in the presence of carcinogenic agents probably contributes to DNA damage and other damage to cells (2). However, only a few studies have systematically examined actual or reported stool transit times among persons with diabetes and compared the results with those of persons without diabetes. One study reported a 70–80 percent longer mean transit time for persons with diabetes than for those without diabetes (36). Two studies showed that persons with diabetes reported symptoms of constipation more frequently than did persons without diabetes (37, 38), but only one of these studies found the difference to be statistically significant (37). Among persons with diabetes, those who have neuropathy more often report symptoms of constipation than do those without neuropathy (39).

Secondary bile acids may act as carcinogens affecting mainly the large bowel and rectal mucosa (2). A

TABLE 3. Means, percentages, and effect estimators for selected baseline characteristics in relation to incidence of colorectal cancer among men in the First Cancer Prevention Study, 1959–1972

Characteristics	Colorectal cancer (n = 3,218)	No colorectal cancer (n = 349,631)	Age-adjusted rate ratio	95% confidence interval	Fully adjusted rate ratio*	95% confidence interval
Age (mean years)†	57.9	52.9			1.08	1.08–1.09
Diabetes						
No	97.4	98.0	1.00	Referent	1.00	Referent
Yes	2.6	2.0	1.27	1.02–1.58	1.30	1.03–1.65
Race						
White	98.8	98.2	1.00	Referent	1.00	Referent
Black and other	1.2	1.8	0.81	0.59–1.12	0.86	0.58–1.28
Education						
Less than high school	42.1	40.9	1.00	Referent	1.00	Referent
High school graduate	15.6	19.2	1.11	1.00–1.23	1.06	0.95–1.19
Some college	42.3	40.9	1.19	1.11–1.29	1.08	0.99–1.17
Family history of colon cancer						
No	93.9	96.8	1.00	Referent	1.00	Referent
Yes	6.1	3.2	1.73	1.49–2.01	1.73	1.48–2.03
Body mass index (mean kg/m²)	25.4	25.2	1.03	1.02–1.04	1.02	1.01–1.04
Current smoker						
No	46.8	41.1	1.00	Referent	1.00	Referent
Yes	53.2	58.9	0.99	0.93–1.07	0.91	0.83–1.00
Pipe or cigar smoker						
No	77.3	81.5	1.00	Referent	1.00	Referent
Yes	22.7	18.5	1.17	1.07–1.27	1.20	1.08–1.34
Eats cereal daily						
No	76.9	78.2	1.00	Referent	1.00	Referent
Yes	23.1	21.8	0.87	0.80–0.95	0.90	0.82–0.99
Eats fruit daily						
No	41.4	44.6	1.00	Referent	1.00	Referent
Yes	58.6	55.4	1.03	0.96–1.11	1.01	0.93–1.10
Eats cooked vegetables daily						
No	42.0	41.0	1.00	Referent	1.00	Referent
Yes	58.0	59.0	1.03	0.96–1.11	1.06	0.97–1.15
Eats green salad daily						
No	76.2	76.0	1.00	Referent	1.00	Referent
Yes	23.8	24.0	1.04	0.95–1.12	1.00	0.91–1.09
Eats fried foods daily						
No	50.8	46.1	1.00	Referent	1.00	Referent
Yes	49.2	53.9	0.87	0.81–0.93	0.94	0.87–1.02
Eats meat or poultry daily						
No	58.5	55.7	1.00	Referent	1.00	Referent
Yes	41.5	44.3	0.91	0.85–0.98	0.92	0.85–1.00
Cups of coffee daily (mean no.)	3.0	3.2	0.99	0.98–1.01	0.99	0.97–1.01
Cups of tea daily (mean no.)	0.6	0.6	1.00	0.97–1.04	0.99	0.95–1.03
Glasses of milk daily (mean no.)	1.1	1.2	0.95	0.93–0.98	0.96	0.93–0.99
Alcohol drinks per day (mean no.)	1.2	1.2	1.04	1.02–1.06	1.03	1.01–1.05
Takes aspirin or buffered aspirin						
Never or seldom	89.8	87.7	1.00	Referent	1.00	Referent
Often	10.2	12.3	0.86	0.76–0.96	0.82	0.73–0.93
Exercises at work or play						
None or slight	24.1	22.9	1.00	Referent	1.00	Referent
Moderate	65.0	63.1	0.84	0.77–0.91	0.88	0.81–0.97
Heavy	10.9	14.0	0.70	0.62–0.80	0.74	0.64–0.86

* Based on 302,625 men, 2,722 of whom developed colorectal cancer.
† Age-squared term was also included in the model, and it was statistically significant.

TABLE 4. Means, percentages, and effect estimators for selected baseline characteristics in relation to incidence of colorectal cancer among women in the First Cancer Prevention Study, 1959–1972

Characteristics	Colorectal cancer (n = 4,006)	No colorectal cancer (n = 506,844)	Age-adjusted rate ratio	95% confidence interval	Fully adjusted rate ratio*	95% confidence interval
Age (mean years)†	57.6	51.8			1.07	1.06–1.07
Diabetes						
No	98.1	98.4	1.00	Referent	1.00	Referent
Yes	1.9	1.6	1.06	0.84–1.34	1.16	0.87–1.53
Race						
White	98.9	97.8	1.00	Referent	1.00	Referent
Black and other	1.1	2.2	0.64	0.48–0.86	0.73	0.49–1.08
Education						
Less than high school	39.0	35.5	1.00	Referent	1.00	Referent
High school graduate	23.2	27.2	1.13	1.04–1.23	1.13	1.02–1.25
Some college	37.8	37.3	1.12	1.04–1.20	1.11	1.01–1.21
Family history of colon cancer						
No	92.6	96.3	1.00	Referent	1.00	Referent
Yes	7.4	3.7	1.83	1.62–2.06	1.71	1.48–1.98
Body mass index (mean kg/m²)	24.6	24.3	1.00	1.00–1.01	1.01	1.00–1.02
Current smoker						
No	79.4	72.3	1.00	Referent	1.00	Referent
Yes	20.6	27.7	1.03	0.95–1.12	1.01	0.92–1.11
Eats cereal daily						
No	81.6	83.9	1.00	Referent	1.00	Referent
Yes	18.4	16.1	0.94	0.87–1.02	0.94	0.85–1`.04
Eats fruit daily						
No	30.4	32.7	1.00	Referent	1.00	Referent
Yes	69.6	67.3	0.99	0.93–1.06	0.97	0.89–1.06
Eats cooked vegetables daily						
No	29.2	29.5	1.00	Referent	1.00	Referent
Yes	70.8	70.5	1.07	1.00–1.15	1.11	1.02–1.22
Eats green salad daily						
No	68.1	68.3	1.00	Referent	1.00	Referent
Yes	31.9	31.7	1.06	0.99–1.13	1.03	0.95–1.13
Eats fried foods daily						
No	66.4	63.2	1.00	Referent	1.00	Referent
yes	33.6	36.8	0.95	0.89–1.02	0.98	0.91–1.07
Eats meat or poultry daily						
No	52.2	52.9	1.00	Referent	1.00	Referent
Yes	47.8	47.1	1.04	0.97–1.10	1.01	0.93–1.09
Cups of coffee daily (mean no.)	2.8	3.1	0.99	0.97–1.00	0.98	0.96–1.00
Cups of tea daily (mean no.)	0.8	0.8	1.02	1.00–1.05	1.01	0.98–1.05
Glasses of milk daily (mean no.)	0.8	0.9	0.94	0.91–0.97	0.92	0.88–0.96
Alcohol drinks per day (mean no.)	0.7	0.7	1.02	1.00–1.04	1.02	0.99–1.04
Takes aspirin or bufferin aspirin						
Never or seldom	80.1	78.1	1.00	Referent	1.00	Referent
Often	19.9	21.9	0.96	0.89–1.04	0.99	0.91–1.09
Exercises at work or play						
None or slight	15.6	16.0	1.00	Referent	1.00	Referent
Moderate	76.6	74.9	0.94	0.87–1.03	0.94	0.85–1.04
Heavy	7.8	9.1	0.88	0.76–1.01	0.90	0.77–1.06
Never pregnant	11.1	11.0	1.00	Referent	1.00	Referent
At least one pregnancy	88.9	89.0	1.03	0.93–1.14	1.08	0.96–1.22

* Based on 375,796 women, 2,819 of whom developed colorectal cancer.
† Age-squared term was also included in the model, and it was statistically significant.

number of small clinical studies found that fecal bile acids in the colon were generally present in larger amounts in persons with diabetes than in those without diabetes (40–44). Furthermore, among persons with diabetes, those who had worse glucose control had more fecal bile acids than did those with better control (45, 46). Some investigators have observed that insulin therapy normalizes fecal steroid excretion (41, 42), while others have found that it has little impact (40). Therefore, it is not entirely clear whether insulin therapy reduces the concentration of bile acids in the feces of persons with diabetes.

Giovannucci (43) hypothesized that insulin, an important growth factor, may at high serum concentrations increase the risk of colorectal cancer by promoting growth of colon tumors, stimulating insulin-like growth factor receptors, and acting as a cell mitogen. He cautions, however, that diabetes should not be used as an indicator of hyperinsulinemia because hyperglycemia can lower plasma insulin levels in some cases. Because this study and other research on diabetes and colorectal cancer have not measured insulin levels, this intriguing hypothesis awaits further confirmation.

In certain subgroups of men, particularly nonsmokers and older men (aged 60 years or more), the adjusted associations of diabetes mellitus with the incidence of colorectal cancer in our study were generally stronger than those found in most previous studies. Although we found that women with diabetes were no more likely to be diagnosed with colorectal cancer or to die from colorectal cancer than were their female counterparts without diabetes, our study suggests that certain subgroups of women with diabetes may be at higher risk of colorectal cancer. In particular, the association of diabetes and colorectal cancer was higher (IDR = 1.5) among women who did not eat green salads daily. However, the subgroup analyses should be interpreted with caution for two reasons: 1) Only one of 25 possible two-way interactions was significant (a result expected by chance) in each of the sex-specific proportional hazard models; and 2) at present, there are no clear biologic hypotheses to explain the observed subgroup differences.

Although our study is larger than previous studies of diabetes and colorectal cancer, it has several limitations. First, because we relied on self-reported diabetes, we may have misclassified some true cases of diabetes. Previous studies have shown that at any point in time about half of all persons with diabetes are unaware that they have the disease (47). At the time of this study (1959–1960), persons with diabetes may have been less aware of their disease because urine glucose testing, a relatively insensitive test (48), was still being used to screen for diabetes mellitus. One study found that urine glucose testing was less sensitive for women than for men (49). This misclassification of true cases of diabetes may have resulted in a slight underestimate of the magnitude of the association between diabetes and colorectal cancer, especially for women. Second, the diagnosis of colorectal cancer may have been influenced by diabetes status. How this may have affected the magnitude of the association of diabetes with colorectal cancer is unclear. The association could be overestimated if more frequent visits to physicians because of diabetes led to early detection of colorectal cancer. On the other hand, the association could be underestimated if colorectal cancer symptoms (such as altered bowel habits) were attributed to diabetes, thus delaying the diagnosis of colorectal cancer. Third, some residual confounding may have distorted the association of diabetes and the incidence of colorectal cancer. Covariates were assessed by using fairly crude measures; for example, dietary intake was measured using a short food frequency questionnaire, and physical activity was measured using one question. Because this study used large numbers of volunteer lay interviewers to reach over a million persons in a relatively short amount of time, the questionnaire was necessarily simple. Furthermore, the large number of interviewers made it difficult to provide extensive training or to monitor the quality of each completed interview. Realistically, however, a study of this size would have been extremely difficult to complete (because of cost and length of study time) using standard epidemiologic methods (50). Despite the problems noted above, we were encouraged that our findings with regard to established colorectal cancer risk factors did not contradict previous research.

In summary, this large prospective cancer study revealed a moderate association between diabetes and colorectal cancer incidence. It also showed similar colorectal cancer survival times for persons with and those without diabetes. For a clearer understanding of the association of diabetes and the incidence of colorectal cancer, future studies could include biochemical and physiologic measurements such as fecal bile acid composition, stool transit time, glycosylated hemoglobin (or some other measure of blood glucose control), and insulin levels. Investigators should try to understand why factors such as being female may mitigate the association of diabetes and the incidence of colorectal cancer. Most important, future studies should explore the possibility of a cancer-promoting gastrointestinal milieu that may be associated with hyperglycemia or diabetic neuropathy.

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