Prospective Study of Adult Onset Diabetes Mellitus (Type 2) and Risk of Colorectal Cancer in Women

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Background: **The remarkable similarity of lifestyle and environmental risk factors for type 2 (non-insulin-dependent) diabetes mellitus and colon cancer has led to the hypothesis that diabetes may increase the risk of this cancer. We prospectively examined the relationship between diabetes and risk of colorectal cancer in a cohort of 118 403 women aged 30 through 55 years who were without previously diagnosed cancer at baseline in 1976.** ***Methods:*** **The women, who were enrolled in the Nurses' Health Study, were assessed for history of diabetes at baseline and during follow-up by use of biennial questionnaires. Self-reported diabetes was validated by information obtained from a supplemental questionnaire on symptoms and treatment and was confirmed by medical record review in a sample of the participants. Incident cases of colorectal cancer were ascertained through medical record review. All reported *P* values are two-sided.** ***Results:*** **During 18 years of follow-up (2 001 061 person-years), we documented 892 new cases of colorectal cancer. After adjustment for age, body mass index (weight in kg/height in m^2), physical activity, and other covariates, relative risks (RRs) were 1.43 (95% confidence interval [CI] = 1.10–1.87; *P* = .009) for colorectal cancer, 1.49 (95% CI = 1.09–2.06; *P* = .01) for colon cancer, 1.11 (95% CI = 0.56–2.21; *P* = .76) for rectal cancer, 1.56 (95% CI = 1.07–2.28; *P* = .02) for advanced colorectal cancer, and 2.39 (95% CI = 1.46–3.92; *P* = .0005) for fatal colorectal cancer.** ***Conclusion:*** **Our data provide support for the hypothesis that diabetes is associated with an increased risk of colorectal cancer in women. [J Natl Cancer Inst 1999;91:542–7]**

The remarkable similarity of lifestyle and environmental risk factors for type 2 (non-insulin-dependent) diabetes mellitus and colon cancer, such as high body mass index, increased central obesity, physical inactivity, and higher intake of refined carbohydrates, has led to the hypothesis that type 2 diabetes itself is a risk factor for colon cancer *(1)*. This hypothesis is spawned from a more general hypothesis that hyperinsulinemia (excessively high blood insulin levels) increases the risk of colon cancer by directly promoting colon carcinogenesis and stimulating insulin-like growth factor-I (IGF-I) receptors *(1,2)*. The expected relationship between type 2 diabetes and colon cancer based on the insulin–colon cancer hypothesis, however, is complex because hyperinsulinemia exists at an early stage of insulin resistance but, as glucose intolerance worsens, intensified hyperglycemia and depletion of β cells may lead to a hypoinsulinemic response. Thus, it is important to consider both the duration and severity of diabetes when examining the relationship of type 2 diabetes with colon cancer.

Epidemiologic data on the association between diabetes and risk of colon cancer are sparse and inconclusive. When compared with the age-standardized cancer rates in the general populations, diabetics appear to have slightly elevated rates of colorectal cancer *(3–5)*. However, these results are difficult to interpret because individuals in the cohorts may differ in many aspects (especially body mass index) from external comparison populations. A positive association between history of diabetes and colorectal cancer has been reported in several case–control studies *(6–9)*, but not in all *(10)*. Also, the positive association tended to be stronger for men than for women *(6,7,10)*. However, the small number of colon cancer cases among diabetics *(6–10)*, potential recall bias *(6,7,10)*, lack of control for important confounders such as obesity and physical activity *(7,10)*, and failure to consider the type or duration of diabetes *(6,7,10)* have hampered the interpretation of the findings. Recently, a prospective study *(11)* with 13 years of follow-up found a significant positive association between diabetes and incidence of colorectal cancer in men (relative risk [RR] = 1.30; 95% confidence interval [CI] = 1.03–1.65) and a weaker nonsignificant positive association in women (RR = 1.16; 95% CI = 0.87–1.53). However, diabetes was not associated with an increased risk of fatal colon cancer. This finding raises the question of detection or diagnostic bias because earlier and less aggressive cancers are typically more prone to heightened detection and surveillance that may occur among individuals with diabetes.

The present study, with 18 years of follow-up, examines the relationship of diabetes with the incidence of colorectal cancers among women enrolled in the Nurses' Health Study. We specifically examine this relationship by years since the diagnosis of diabetes because insulin levels may differ depending on earlier or later stage of type 2 diabetes.

Subjects and Methods

Subjects

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses 30–55 years of age completed a mailed questionnaire on their medical histories and lifestyles. Every 2 years, follow-up questionnaires are sent to obtain updated information on risk factors and to identify newly diagnosed diseases. The validity of the biennial questionnaire on medical history and lifestyle factors has been described in detail previously *(12)*. Beginning in 1980, validated food-frequency questionnaires have been used to assess dietary intakes at 2- to 4-year cycles *(13)*. The participants in the present study included women who were free of diagnosed cancer at baseline in 1976 (n = 118 403). This study was approved by the Human Research Committee at the Brigham and Women's Hospital.

Assessment of Diabetes Mellitus

On the baseline and subsequent biennial questionnaires, we asked the participants if and when they

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had ever been diagnosed with diabetes (either insulin-dependent or non-insulin-dependent). At baseline, 2095 women reported a previous diagnosis of diabetes. During follow-up (1976–1992), an additional 5305 women reported a diagnosis. We excluded women who had diabetes before age 30 years because they were most likely to have type 1 diabetes (n = 331).

Self-reported diabetes was validated by a supplementary questionnaire regarding symptoms, diagnostic tests, and treatment of diabetes and confirmed by medical record review in a sample *(14)*. We obtained medical records in a random sample of 84 participants who reported a diagnosis of diabetes. Of the 84 women, 71 provided permission for medical record review; medical records could be obtained for 62. An endocrinologist who was blinded to the information reported on the supplementary questionnaire reviewed the available records using the National Diabetes Data Group Criteria *(15)*. The diagnosis of type 2 diabetes was confirmed by medical record review in 61 (98.4%) of the 62 women *(14)*.

Identification of Cases of Colorectal Cancer

We identified cases of colorectal cancer through biennial questionnaires and medical record review *(16)*. On each follow-up questionnaire, we asked whether cancer of the colon or rectum has been diagnosed during the previous 2 years. In addition to reports from next of kin, we also used the National Death Index and the U.S. Postal Service to identify fatalities; we estimate that more than 98% of deaths were ascertained *(17)*. When a participant (or the next of kin for decedents) reported a diagnosis of cancer of the colon or rectum on our follow-up questionnaire, we asked her (or the next of kin) for permission to obtain hospital records and pathology reports pertaining to this diagnosis. A study physician blinded to the exposure information reviewed the medical records to extract information on the histologic type, the anatomic location, and the stage of the cancer. Proximal colon cancers were defined as those from the cecum to and including the splenic flexure, and distal colon cancers were defined as those in the descending and sigmoid colon. Advanced cancers were defined as those with evidence of metastasis (to regional lymph nodes or to distant organs) at diagnosis. Fatal cancers were defined as those diagnosed since 1976 but fatal by the end of the follow-up (June 1, 1994).

Statistical Analysis

Person-time for each participant was calculated from the date of return of the 1976 questionnaire to the date of colorectal cancer diagnosis, death from any cause, or June 1, 1994, whichever came first. Diagnosis of diabetes was reported at baseline and updated every 2 years. For incident diabetic cases (diabetes occurring during follow-up), diabetic person-years were calculated from the diagnosis of the diabetes. For prevalent diabetic cases (diabetes at baseline), diabetic person-years were calculated from the beginning of the study (1976). Women who reported cancer on previous questionnaires were excluded from subsequent analyses. We calculated incidence rates of colorectal cancer for women diagnosed with diabetes by dividing the number of incident cases by the number of person-years of follow-up. The RR was computed as the rate among women with diabetes divided by the rate among nondiabetics, with adjustment for 5-year age categories. Years since diagnosis of diabetes was determined by questionnaire at baseline and updated every 2 years. We classified years since diagnosis into four categories based on the frequency distribution (no diabetes, ⩽10 years, 11–15 years, and >15 years).

We used pooled logistic regression across the nine 2-year intervals (June 1976–June 1978 and similar time periods in the following years: 1978–1980, 1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, and 1992–1994) *(18)*, which is asymptotically equivalent to time-varying Cox regression, to adjust simultaneously for potential confounding variables, including age (age groups: <49, 50–54, 55–59, 60–64, ⩾65 years old); body mass index (10 categories); and menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement). These variables were first assessed in 1976 and updated every 2 years. We also adjusted for multivitamin use (yes or no); alcohol consumption (0, >0–4, 5–14, or ⩾15 g/day); aspirin use (yes or no); and average hours per week of moderate or vigorous activity (<1, 1–1.9, 2–3.9, 4–6.9, or ⩾7). These variables were first assessed in 1980 and updated every 2 to 4 years. We also adjusted for intake of red meat (including beef as a main dish, beef in a sandwich or mixed dish, hamburger, hot dog, processed meat, and bacon), which was assessed in 1980, 1984, 1986, and 1990. To best represent long-term diet and reduce measurement error, we adjusted for cumulative averages of red meat intake in the pooled logistic model *(19)*. For example, 1980 meat intake was related to incident colorectal cancer from 1980 through 1984 and the average of 1980 and 1984 intakes was related to incident cases from 1984 through 1986. For variables that were initially assessed in 1980, we replaced missing values in 1976 with the values from 1980. In addition, we controlled for pack-years of smoking before age 30 because it was more predictive of colon cancer than was current or lifetime smoking *(20)*. We also controlled for parental history of colorectal cancer. All reported *P* values were derived from the two-sided Wald test.

Results

During 18 years of follow-up (2 001 061 person-years), we documented 892 new cases of colorectal cancer, including 607 colon cancers and 176 rectal cancers (subsite information was unavailable for 109 cases). Of these cancers, 414 were defined as advanced colorectal cancers (metastasis at diagnosis or fatal by June 1994), and 177 were fatal colorectal cancers by June 1994.

Table 1 shows baseline characteristics for all self-reported diabetics (n = 7069) and nondiabetics (n = 111,003) up to 1992. Smoking rate, parental history of colorectal cancer, aspirin use, multivitamin supplement use, and intakes of red meat, dietary fats, and folate were similar between diabetics and nondiabetics. Diabetic women were slightly less active and substantially heavier. Utilization of colonoscopy or sigmoidoscopy by 1992 was comparable among diabetic and nondiabetic women.

After adjustment for age, history of diabetes was significantly associated with increased risk of colorectal cancer (Table 2). The age-adjusted RR was 1.53 (95% CI = 1.18–1.99; $P = .001$). After adjustment for body mass index, smoking, alcohol use, menopause and estrogen use, family history of colorectal cancer, aspirin use, physical activity, and red meat

Table 1. Age-standardized characteristics of study subjects at baseline by status of diabetes up to 1992

	History of diabetes mellitus	
	No: 111 003 women	Yes: 7069 women
Women, %		
Current smoking	33	32
Parental history of colorectal cancer	6	7
Aspirin use*	38	40
Vigorous exercise at least once/wk*	37	31
Multivitamin supplement use*	28	27
History of colonoscopy or sigmoidoscopy by 1992	26	28
Mean values		
Age, y	42	45
Body mass index, weight in kg/height in m^2	24	28
Alcohol use, g/day	7	4
Red meat,† servings/day	1.1	1.2
Saturated fat, % energy	16	16
Monounsaturated fat, % energy	16	16
Polyunsaturated fat, % energy	5	5
Folate, μg/day	353	363

*These variables and all dietary variables were assessed in 1980.

†A composite score of the following foods: beef as a main dish, beef in a sandwich or mixed dish, hamburger, hot dog, processed meat, and bacon.

Table 2. History of diabetes and relative risks (RRs) and 95% confidence intervals (CIs) of colorectal cancer in the Nurses' Health Study, 1976–1994

	History of diabetes		
	No	Yes	Two-sided *P**
Colorectal cancer			
No. of case patients	830	62	
Person-years	1 938 221	62 840	
Age-adjusted RR (95% CI)	1.0 (referent)	1.53 (1.18–1.99)	.001
Multivariate RR† (95% CI)	1.0 (referent)	1.43 (1.10–1.87)	.009
Colon cancer			
No. of cases	564	43	
Age-adjusted RR (95% CI)	1.0 (referent)	1.60 (1.17–2.18)	.003
Multivariate RR† (95% CI)	1.0 (referent)	1.49 (1.09–2.06)	.01
Proximal colon cancer‡			
No. of cases	254	21	
Age-adjusted RR (95% CI)	1.0 (referent)	1.62 (1.03–2.53)	.04
Multivariate RR† (95% CI)	1.0 (referent)	1.64 (1.04–2.60)	.03
Distal colon cancer‡			
No. of cases	310	22	
Age-adjusted RR (95% CI)	1.0 (referent)	1.57 (1.01–2.44)	.04
Multivariate RR† (95% CI)	1.0 (referent)	1.38 (0.88–2.15)	.16
Rectal cancer‡			
No. of cases	167	9	
Age-adjusted RR (95% CI)	1.0 (referent)	1.13 (0.58–2.23)	.72
Multivariate RR† (95% CI)	1.0 (referent)	1.11 (0.56–2.21)	.76
Advanced colorectal cancer			
No. of cases	383	31	
Age-adjusted RR (95% CI)	1.0 (referent)	1.67 (1.16–2.42)	.006
Multivariate RR† (95% CI)	1.0 (referent)	1.56 (1.07–2.28)	.02
Fatal colorectal cancer			
No. of cases	158	19	
Age-adjusted RR (95% CI)	1.0 (referent)	2.57 (1.59–4.17)	.0001
Multivariate RR† (95% CI)	1.0 (referent)	2.39 (1.46–3.92)	.0005

*Two-sided *P* values by Wald test.

†Models included age (age groups: <49, 50–54, 55–59, 60–64, and ⩾65 years); time periods (June 1976–June 1978 and similar time periods in the following years: 1978–1980, 1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, and 1992–1994); body mass index (weight in kg/height in m^2) (<20.0, 20.0–20.9, 21.0–21.9, 22.0–22.9, 23.0–23.9, 24.0–24.9, 25.0–25.9, 26.0–27.9, 28.0–30.9, and ⩾31.0); pack-years of cigarette smoking before age 30 (pack-years = number of packs per day × years of smoking; continuous variable); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); multivitamin supplement use (yes or no); alcohol consumption (0, >0–4, 5–14, and ⩾15 g/day); average hours per week of moderate or vigorous activity (<1, 1–1.9, 2–3.9, 4–6.9, and ⩾7); aspirin use (yes or no); parental history of colorectal cancer (yes or no); and red meat quintile categories (0–0.57, 0.58–0.85, 0.86–1.13, 1.14–1.50, and >1.50 servings/day).

‡The sum of proximal, distal, and rectal cancers (total of 783 cases) does not add to the total number of colorectal cancers (total of 892 cases) because of missing data on the subsite.

intake, the RR was 1.43 (95% CI = 1.10–1.87; $P = .009$). The positive association was stronger for colon cancer (RR = 1.49; 95% CI = 1.09–2.06; $P = .01$) than for rectal cancer (RR = 1.11; 95% CI = 0.56–2.21; $P = .76$). History of diabetes was associated with increased risk of both proximal and distal colon cancers. The multivariate RRs were 1.56 (95% CI = 1.07–2.28; $P = .02$) for advanced colorectal cancer and 2.39 (95% CI = 1.46–3.92; $P = .0005$) for fatal colorectal cancer. In stratified analyses by menopausal status, regular exercise at least once per week (no or yes), and body mass index (⩽27 kg/m^2 versus >27 kg/m^2), we found positive associations across different strata of these variables and observed no statistically significant interactions between these variables and diabetes.

We conducted secondary analyses using diabetes classified by the supplementary questionnaire as the exposure variable (5434 women were classified as type 2 diabetes by the supplementary questionnaire). The age-adjusted RR of colorectal cancer was 1.49 (95% CI = 1.11–1.99), and the multivariate RR was 1.36 (95% CI = 1.01–1.84). The wide CIs were due to smaller number of colorectal cancer case patients (n = 48) in the diabetic group.

The positive associations were strongest among women whose diabetes had been diagnosed for 11–15 years (Table 3). Compared with nondiabetics, the multivariate RRs for this group were 2.30 (95% CI = 1.43–3.71; $P = .0006$) for colorectal cancer, 2.83 (95% CI = 1.67–4.78; $P = .0001$) for colon cancer, 2.25 (95% CI = 1.11–4.58; $P = .02$) for advanced colorectal cancer, and 3.96 (95% CI = 1.72–9.12; $P = .001$) for fatal colorectal cancer. (We did not analyze rectal cancer because of the small number of cases.) These RRs diminished among women whose diabetes had been diagnosed for more than 15 years, although positive associations remained.

Discussion

In this large prospective study of women, we observed a significant positive association between history of diabetes and risk of colorectal cancer. After we accounted for age, body mass index, and other potential confounders, diabetic women had a 43% increased risk of colorectal cancer and a 49% increase in colon cancer compared with nondiabetic women.

Physician-diagnosed diabetes was reported by the participants, but with high accuracy according to additional information obtained from supplemental questionnaires asking about symptoms and treatment and a validation study using medical record review *(14)*. Some diabetics may have been undiagnosed, but this percentage would be relatively small compared with that in the general population because of the nurses' relative greater access to medical care. Moreover, misclassification in the diagnosis of diabetes would tend to attenuate any true association between diabetes and colon cancer. In additional analyses, we found a similar positive association when confirmed diabetes (based on women who returned the supplementary questionnaires) was used as an exposure variable.

Detection bias is the most plausible alternative explanation for the observed positive association because, among diabetics, early colorectal cancer may be more likely to be diagnosed as a result of a heightened screening and detection. Several lines of evidence, however, argue against this explanation. First, we found that the positive association was stronger for advanced and fatal colorectal cancers, which would be less prone to detection and diagnostic biases. Second, the increased risk was stronger among women

Table 3. Years since diagnosis of diabetes and relative risks (RRs) and 95% confidence intervals (CIs) of colorectal cancer*

	No diabetes	Years since diagnosis of diabetes		
		≤10 y	11–15 y	>15 y
Colorectal cancer				
No. of case patients	830	32	18	11
Person-years	1 938 221	28 040	12 433	21 051
Age-adjusted RR (95% CI)	1.0 (referent)	1.41 (0.99–2.02)	2.46 (1.53–3.94)	1.11 (0.61–2.01)
Multivariate RR† (95% CI)	1.0 (referent)	1.29 (0.89–1.85)	2.30 (1.43–3.71)	1.08 (0.59–1.96)
Colon cancer				
No. of cases	564	19	15	8
Age-adjusted RR (95% CI)	1.0 (referent)	1.30 (0.82–2.07)	2.97 (1.77–4.99)	1.15 (0.57–2.31)
Multivariate RR† (95% CI)	1.0 (referent)	1.18 (0.74–1.89)	2.83 (1.67–4.78)	1.13 (0.56–2.28)
Advanced colorectal cancer				
No. of cases	383	15	8	7
Age-adjusted RR (95% CI)	1.0 (referent)	1.42 (0.84–2.40)	2.46 (1.22–5.00)	1.53 (0.72–3.24)
Multivariate RR† (95% CI)	1.0 (referent)	1.33 (0.78–2.26)	2.25 (1.11–4.58)	1.46 (0.69–3.10)
Fatal colorectal cancer				
No. of cases	158	8	6	5
Age-adjusted RR (95% CI)	1.0 (referent)	2.02 (0.98–4.20)	4.55 (1.99–10.4)	2.46 (1.01–6.03)
Multivariate RR† (95% CI)	1.0 (referent)	2.01 (0.96–4.23)	3.96 (1.72–9.12)	2.13 (0.86–5.22)

*The total number of cancers among diabetics for all categories except fatal colorectal cancer are smaller than those in Table 2 because of missing information on the time of diagnosis.

†Models included age (age groups: <49, 50–54, 55–59, 60–64, and ≥65 years); time periods (June 1976–June 1978 and similar time periods in the following years: 1978–1980, 1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, and 1992–1994); body mass index (weight in kg/height in m^2) (<20.0, 20.0–20.9, 21.0–21.9, 22.0–22.9, 23.0–23.9, 24.0–24.9, 25.0–25.9, 26.0–27.9, 28.0–30.9, and ≥31.0); pack-years of cigarette smoking before age 30 (pack-years = number of packs per day × years of smoking; continuous variable); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); multivitamin supplement use (yes or no); alcohol consumption (0, >0–4, 5–14, and ≥15 g/day); average hours per week of moderate or vigorous activity (<1, 1–1.9, 2–3.9, 4–6.9, and ≥7); aspirin use (yes or no); parental history of colorectal cancer (yes or no); and red meat quintile categories (0–0.57, 0.58–0.85, 0.86–1.13, 1.14–1.50, and >1.50 servings/day).

who had diabetes for a considerable amount of time (i.e., 11–15 years). Enhanced surveillance and detection are probably more likely to occur in the first several years following diagnosis. Finally, utilization of colonoscopy or sigmiodoscopy was comparable among diabetic and nondiabetic women (28% and 26%, respectively, by 1992).

Confounding is another concern but was unlikely to explain our findings. As shown in Table 1, colon cancer risk profiles were generally similar between diabetics and nondiabetics. Body mass index and lack of physical activity are potentially the most important known confounders for the positive association between diabetes and colon cancer. However, a statistically significant association persists even after adjustment for these variables, both of which were assessed multiple times during follow-up and the repeated assessments were used in the analyses. Some of the covariates, such as alcohol consumption, red meat intake, and multivitamin use, were first measured in 1980 rather than in 1976. However, when we controlled for these variables, the multivariate RRs were similar to the age-adjusted ones; thus, any uncontrolled confounding due to incomplete data for these variables was unlikely to account for the observed association between diabetes and colorectal cancer. Also, analyses using 1980 as baseline yielded similar results.

Previous epidemiologic studies of diabetes and colorectal cancer have suggested a positive association, but the data are not entirely consistent. Two studies of diabetic patients using external population comparisons *(3,5)* have found a small and nonsignificant excess in rate of colorectal cancer in men but not in women. In a case–control study conducted in Italy, history of diabetes was significantly associated with risk of both colon cancer (odds ratio [OR] = 1.7) and rectal cancer (OR = 1.5) *(8).* In a subsequent larger case–control study conducted by the same group *(9),* the OR was 1.2 for colon cancer and 1.5 for rectal cancer. The former study found the strongest association among subjects whose diabetes had been diagnosed for 5–9 years, and the latter found a stronger association among subjects who had diabetes for 10 years or more. Neither study examined the association among women who had diabetes for a longer duration. In our study, we observed a weaker positive association for rectal cancer, but the number of rectal cancer cases among diabetics was small (nine cases). In parallel, associations between obesity and a sedentary lifestyle have usually been observed with colon cancer but not with rectal cancer *(1).* In addition, we found that the positive association for colorectal cancer was greatest within 11–15 years after diagnosis of diabetes and diminished after 15 years of diagnosis (*see* the explanations *below*). In the only previous prospective cohort study *(11),* the RRs of colorectal cancer were 1.30 for men and 1.16 for women. However, in this study, status of diabetes was not updated during follow-up. The observed weaker associations were probably a result of prolonged follow-up.

Hyperinsulinemia has been proposed to be the underlying link between diabetes and colon cancer *(1).* This insulin–colon cancer hypothesis is based on strong epidemiologic evidence that major environmental risk factors for type 2 diabetes (such as high body mass index, increased central obesity, sedentary lifestyle, and possibly higher intake of refined carbohydrates) are remarkably similar to those for colon cancer. There is strong evidence that these factors are important determinants of insulin resistance and hyperinsulinemia *(21,22).* Since insulin is an important growth factor for colonic mucosal cells and colonic cancer cells and a mitogen of tumor cell growth *in vitro (23,24)*

and a colon tumor promoter *in vivo (25)*, high plasma insulin levels may mediate the effect of these factors on the risk of colon cancer. Based on the insulin hypothesis, the expected relationship between type 2 diabetes and colon cancer is complex because, at the early stage of type 2 diabetes, hyperinsulinemia exists but, in later stages, pancreatic beta cell malfunction leads to a hypoinsulinemic response. As expected *a priori*, we found that the increased risk of colorectal cancer diminished among women who had had diabetes for a long duration (i.e., after 15 years from diagnosis). However, the insulin hypothesis cannot be directly confirmed by these data because we did not measure plasma insulin levels and, also, the induction period for an effect of insulin on colon cancer risk is unknown.

Another line of evidence for the proposed insulin–colon cancer relationship is the observation that a high glycemic index diet, which has been associated with risk of type 2 diabetes *(26,27)* and coronary heart disease *(28)*, is also associated with risk of colon cancer *(29)*. A dietary glycemic index is used to quantify the response of blood glucose and insulin to a diet *(30,31)*. The higher the glycemic index, the greater the glycemic and insulinemic responses. In a case–control study, Slattery et al. *(29)* found a positive association between dietary glycemic index and colon cancer. Higher intake of refined sugars, which produces a sharp glycemic response due to readily absorbable glucose, has been associated with increased risk of colon cancer in one prospective cohort study *(32)* and a number of case–control studies *(33–37)*. In addition, higher intake of rapidly digestible starches, such as breads, potatoes, cakes, and dessert, may also increase risk of colon cancer *(38)*. These findings suggest that glycemic and insulinemic responses may contribute to the effect of diet on the risk of colon cancer.

Besides insulin, several other mechanisms for the positive association have been proposed, including elevated levels of fecal bile acid associated with increased blood glucose and triglyceride levels *(2)* and slower bowel transit *(11)*, which contributes to increased exposure to toxic substances and increased production of carcinogenic bile acids among diabetics.

In conclusion, our data provide support for the hypothesis that type 2 diabetes is associated with increased risk of colon cancer in women. These findings provide further epidemiologic evidence for the hypothesis that hyperinsulinemia, a compensatory response to insulin resistance, may be an underlying pathway for the development of colon cancer.

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NOTES

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