Diabetes Mellitus and Subsite-Specific Colorectal Cancer Risks in the Iowa Women's Health Study

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Abstract

Objective: **Controversy remains regarding the association between type 2 diabetes mellitus (DM) and colorectal cancer (CRC) risk. To clarify and extend the existing data, we prospectively evaluated the association between self-reported type 2 DM (onset at >30 years of age) and incident CRC, overall and by anatomic subsite, among postmenopausal women in the Iowa Women's Health Study (n = 35,230).**

Methods: **After 14 years of follow-up, a total of 870 incident CRC cases were identified through annual linkage to the Iowa Cancer Registry. DM was analyzed as reported at baseline and as a time-dependent variable using information obtained during follow-up. CRC risks were estimated using Cox proportional hazards regression models.**

Results: **After adjusting for age, body mass index and other potential confounding variables, the relative risk (RR) for women with DM versus women without DM was modestly increased at 1.4 [95% confidence interval (95% CI), 1.1-1.8]. By anatomic subsite, the RR for proximal colon cancer was statistically significantly increased (RR, 1.9; 95% CI, 1.3-2.6), whereas the RRs for distal colon (RR, 1.1; 95% CI, 0.6-1.8) and rectal cancer (RR, 0.8; 95% CI, 0.4-1.6) were not statistically different from unity. Analyses that included DM ascertained at baseline and follow-up yielded similar results.**

Conclusion: **In this large, prospective study of postmenopausal women, the association between DM and incident CRC was found to be subsite specific. If confirmed by others, this finding implies that CRC prevention strategies among type 2 DM patients should include examination of the proximal colon.** (Cancer Epidemiol Biomarkers Prev 2005; 14(1):133–7)

Introduction

Nearly 150,000 incident colorectal cancer (CRC) cases are diagnosed each year in the United States (1). Further characterization of potentially modifiable CRC risk factors could facilitate improved prevention strategies. Excess total energy intake, high glycemic index, obesity, and physical inactivity have all been linked to increased CRC risk. As noted by others (2, 3), these risk factors are also associated with elevated circulating insulin concentration. Insulin exhibits procarcinogenic effects in a variety of cell culture and animal model systems (4-7). In human observational studies, direct and indirect (i.e., C-peptide) measures of serum or plasma insulin concentration have been positively associated with CRC risk as well (8-11). Thus, hyperinsulinemia represents a unifying mechanism through which multiple exposures might influence colorectal carcinogenesis.

Patients with type 2 (adult-onset) diabetes mellitus (DM) experience hyperinsulinemia during the early stages of their disease (12-14). To date, observational studies have provided inconclusive results regarding the association between type 2 DM and CRC risk, as recently reviewed (12, 15). Limited attention to tumor subsite may have contributed to the discrepant results. Wei et al. found that risk factor profiles differed for colon and rectal cancer in two large prospective cohorts (16), but DM was not included in their analyses. In fact, relatively few reports (17-20) have included subsite-specific CRC risks associated with DM. Because tumors in the proximal and distal colon and rectum differ with respect to their population distribution (21, 22), clinicopathologic features (23), and proposed genetic pathways (24, 25), further investigation of DM and other CRC risk factors by anatomic subsite seems prudent and has been advocated by others (16, 21, 22).

In the present study, we examined associations between type 2 DM and incident CRC, overall and by anatomic subsite, among postmenopausal women in the Iowa Women's Health Study (IWHS). The large sample size, baseline and follow-up questionnaire data, and comprehensive case ascertainment from this cohort allowed us to thoroughly assess DM-associated CRC risks, including adjustment for potential confounding variables.

Materials and Methods

Approval for the present study was obtained from the Institutional Review Boards for Human Research at Mayo Clinic Rochester and the University of Minnesota, Twin Cities Campus. Details regarding the methods used for recruitment and enrollment of IWHS subjects have been reported elsewhere (26). In brief, a 16-page questionnaire was mailed out to 99,826 randomly selected women, ages 55 to 69 years, who resided in Iowa and held a valid driver's license at baseline (January 1986). Baseline questionnaires were returned by 41,836 women (42%) who constitute the IWHS cohort. Demographic characteristics and CRC incidence rates have been shown to be similar among initial responders and nonresponders (27). Information regarding potential CRC risk

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factors, place of residency, and vital status were updated periodically by follow-up surveys, which had high response rates (1987, 91%; 1989, 89%; 1992, 83%; 1997, 79%).

Prevalent DM status was determined from the baseline questionnaire by asking ''Have you ever been told by a doctor that you have sugar diabetes (diabetes mellitus)?'' Age at DM diagnosis was also requested. Women were also asked if they had ever taken insulin or ''pills for sugar diabetes (or to lower blood sugar).'' Incident DM (i.e., diagnosed after baseline) was ascertained at each of the follow-up surveys.

Weight and height were recorded at baseline and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. A paper tape measure was included with the baseline questionnaire and subjects were asked to document waist (measured 1 in. above the umbilicus) and hip (maximal protrusion) circumferences, which were used to compute the waist-to-hip ratio. Measurements obtained by this method have been shown to be reliable and accurate (28). Physical activity was assessed from several questions that asked about the frequency of moderate and vigorous leisure time activities. These responses were used to generate a three-level activity index, which has been inversely associated with coronary heart disease mortality rate among IWHS participants (29). Dietary habits were assessed at baseline using a 127-item food frequency questionnaire similar to that used in the Nurses' Health Study (30).

Women who reported a past history of cancer (other than skin cancer) at baseline were excluded (n = 3,830). Subjects who had implausible energy intakes (<500 or >5,000 kcal/d) or had ≥30 missing values on the food frequency questionnaire were also excluded (n = 3,102). Because our primary objective was to address type 2 DM as a risk factor for CRC, subjects with probable type 1 DM (onset of DM at ≤30 years of age) and subjects with DM of indeterminate type (age at onset not specified) were excluded as well (n = 112 and n = 200, respectively).

For IWHS subjects continuing to reside in Iowa, verification of incident CRC was done through annual linkage with the Iowa Cancer Registry, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Deaths that occurred outside of Iowa or among nonresponders to the follow-up surveys were identified through linkage with the National Death Index of the National Center for Health Statistics. Colon cancer cases comprised codes 18.0 to 18.9 and rectal cancers cases comprised codes 19.9 and 20.9 by the WHO's *International Classification of Oncology, Second Edition*. For analyses of proximal and distal colon cancers, *International Classification of Oncology, Second Edition* codes18.0 to 18.5 and 18.6 to 18.7 were employed, respectively. Women with incident CRC were considered to contribute time at risk from baseline until the date of first CRC diagnosis. For women without incident CRC, follow-up time was accrued until the date of death, migration out of Iowa, loss to follow-up, or administrative censoring on December 31, 1999.

Baseline variables were compared between diabetics versus nondiabetics and cases versus noncases using Student's t tests and χ^2 tests, as appropriate. Associations between type 2 DM and incident CRC were estimated by relative risk (RR) and 95% confidence interval (95% CI), based on age-adjusted and multivariate-adjusted Cox proportional hazards regression models. BMI, dietary calcium, vitamin E, and total calories were chosen a priori as covariates in the regression models. We also tested the effects of some additional selected variables (i.e., smoking status, physical activity, waist-to-hip ratio, hormone replacement therapy, multivitamin use, and dietary intakes of red meat, carbohydrates, sucrose, folate, and methionine). We conducted a sensitivity analysis examining the relationship of these variables with the independent and dependent variables and examined the effect of adding these variables, in combination, on the variable estimate. The change in variable estimate for DM was <10% and it reduced the number of cases due to missing data on these covariates. Thus, we present data from the a priori adjusted model.

For women with prevalent DM, duration of DM was analyzed in categories chosen to facilitate comparison with a previous study (19) and type of DM therapy was analyzed as a categorical variable [diet alone, oral agent(s), and insulin treatment]. Incident DM diagnoses were accounted for by modeling DM as a time-dependent variable. Follow-up nonresponders with no prior self-reports of prevalent or incident DM were considered to be nondiabetic. Potential interactions between DM and other relevant predictor variables were formally evaluated by comparing the −2 log-likelihoods of proportional hazards regression models with and without the cross-product (interaction) term. All statistical analyses were done using SAS computer software (SAS Institute, Carey, NC).

Results

Following exclusions, the analysis cohort consisted of 34,972 women. Prevalent type 2 DM was reported by 1,900 subjects (Table 1). Compared with nondiabetics, women who reported DM at baseline were slightly older and heavier. Conversely, total energy intake and vitamin E intake were lower among women with prevalent DM. During the follow-up period, 870 incident CRC cases were identified (Table 2). Baseline age, BMI, and prevalent type 2 DM were higher among women who developed CRC, whereas total energy intake, calcium intake, and vitamin E intake were higher among noncases. These findings are in keeping with recent reports from this cohort (31).

In age-adjusted models, prevalent type 2 DM was associated with a RR of 1.5 (95% CI, 1.2-2.0) for any CRC. Further adjustment for potential confounding factors resulted in a slightly attenuated multivariate RR of 1.4 (95% CI, 1.1-1.8; Table 3). Multivariate models were also fit to assess DM duration and type of DM therapy. DM duration was analyzed across categories of 0-4, 5-12, and ≥13years. Subjects in the 5-12-year duration category had a higher RR for any CRC (RR, 1.6; 95% CI, 1.1-2.4) than subjects in either the 0-4-year category (RR, 1.4; 95% CI, 1.0-2.1) or the 13-40-year category (RR, 1.1; 95% CI, 0.6-1.8). Thus, there was no apparent trend across duration categories (P for trend > 0.05). Type of DM therapy seemed to have minimal influence on CRC risk, with RRs of 1.5 (95% CI, 1.0-2.1) for diet alone, 1.5 (95% CI, 1.0-2.2) for oral agents, and 1.1 (95% CI, 0.6-1.9) for insulin treatment. CRC risk was further estimated after incorporating additional incident DM diagnoses reported during the follow-up period (n = 1,782). Modeling type 2 DM as a time dependent variable (i.e., prevalent and incident cases combined), the multivariate-adjusted RR for CRC was 1.2 (95% CI, 1.0-1.5), which was similar to that based on prevalent type 2 DM alone.

When analyzed by anatomic subsite (Table 3), prevalent type 2 DM was associated with a statistically significant increase in proximal colon cancer risk (RR, 2.0; 95% CI, 1.4-2.7). However, distal colon cancer (RR 1.1; 95% CI, 0.6-1.8) and rectal cancer (RR, 0.8; 95% CI, 0.4-1.6) were not associated with type 2 DM. Two other factors that may have modified our observed CRC risk associations, BMI and hormone replacement therapy use, did not seem to have different effects by anatomic subsite. In models adjusted for DM, BMI was associated with similar increased risk at all three anatomic subsites examined (data not shown). Ever versus never hormone replacement therapy use was negatively associated with cancers of the proximal colon (RR, 0.8; 95% CI, 0.6-1.0), distal colon (RR 0.7; 95% CI, 0.5-0.9), and rectum (RR, 0.9; 95% CI, 0.5-1.4). In addition, DM and hormone replacement therapy use seemed to be independent in their effects as none of the χ^2 tests for interaction between DM and

Table 1. Age-adjusted baseline characteristics of subjects by type 2 DM status: IWHS, 1986

Variable	Type 2 DM status*		
	Yes (n = 1,900)	No (n = 33,072)	P
Age, mean ± SE (y)	62.3 ± 0.1	61.5 ± 0.02	0.0001
Body mass index, mean ± SE (kg/m^2)	30.6 ± 0.1	26.8 ± 0.03	0.0001
Total energy intake, mean ± SE (kcal/d)	1,751 ± 14	1,801 ± 3	0.0007
Calcium, mean ± SE (mg/d)†	1,076 ± 12.7	1,097 ± 3.1	0.12
Vitamin E, mean ± SE (mg/d)	58.8 ± 3.4	67.2 ± 0.8	0.02

*Type 2 (age of onset >30 years) DM status determined by self-report at baseline.
†Including supplements.

hormone replacement therapy use at these subsites warranted rejection of the null hypotheses.

Discussion

In this large, population-based cohort study of postmenopausal women, we found that type 2 DM was associated with a 40% increase in the risk for incident CRC. By anatomic subsite, type 2 DM was significantly associated with proximal colon cancer risk but not distal colon or rectal cancer risk. BMI and physical activity index were adjusted in multivariate regression models and did not seem to explain our findings. These data support the hypothesis that hyperinsulinemia, alone or in combination with other factors related to type 2 DM, is positively associated with CRC risk and raise the possibility that its procarcinogenic effects may differ by anatomic subsite within the colorectum.

Interpretation of data from previous observational studies of type 2 DM and CRC risk is partially compromised by design limitations such as comparison to external or hospital-based controls, lack of adjustment for potentially relevant covariates, and small sample size (15). In the prospective studies reported to date, null associations were observed in early, relatively small cohort studies (i.e., fewer than 200 CRC cases in each; refs. 32-38), whereas statistically significantly positive risk associations have been observed in more recent, larger cohort studies (i.e., >700 CRC cases in each; refs. 18, 19, 39, 40). Among the latter reports, Wiederpass et al. (18) found that incident colon cancers (standardized incidence ratio, 1.42; 95% CI, 1.30-1.55 for women and standardized incidence ratio, 1.37; 95% CI, 1.24-1.50 for men) and incident rectal cancers (standardized incidence ratio, 1.10; 95% CI, 0.95-1.26 for women and standardized incidence ratio, 1.36; 95% CI, 1.21-1.52 for men) were more common among Swedish patients with a hospital discharge diagnosis of DM (n = 153,852), based on univariate risk models. Fatal colon and rectal cancer cases were also associated with DM, arguing against the possibility of a major contribution from surveillance bias. Among subjects enrolled in the first Cancer Prevention Study of the American Cancer Society (n = 866,433), Will et al. (39) found that CRC incidence was 30% higher among men with DM (RR, 1.30; 95% CI, 1.03-1.65) and 16% higher among women with DM (RR, 1.16; 95% CI, 0.87-1.53) after adjusting for multiple potential confounding variables. DM was not significantly associated with CRC mortality in either gender group. However, because DM status was only ascertained at baseline, these risk estimates may have been attenuated by misclassification of subjects who developed glucose intolerance during the 13-year follow-up period.

In the Nurses' Health Study (n = 118,403; ref. 19), history of adult-onset DM was recorded at baseline and during follow-up by use of biennial questionnaires. After 18 years of follow-up, women with DM were significantly more likely to develop incident (RR, 1.43; 95% CI, 1.10-1.87) and fatal (RR, 2.39; 95% CI, 1.46-3.92) CRC compared with women without DM, based on risk models that adjusted for age, BMI, menopausal status, physical activity level, and other potentially relevant covariates. In a population-based study from Norway (n = 75,219), Nilsen et al. (40) observed a positive association between baseline DM status and incident CRC among women (RR, 1.55; 95% CI, 1.04-2.31) but not men (RR, 0.66; 95% CI, 0.35-1.24) after 12 years of follow-up. Blood glucose level of ≥8.0 mmol L^{-1} (nonfasting) was also a risk factor among women (RR, 1.98; 95% CI, 1.31-2.98), but neither BMI nor leisure time physical activity level was associated with CRC risk in this gender group.

Subsite-specific CRC risks among patients with DM have been described in three previous observational studies (17-19). In a multiethnic, case-control study from Hawaii, Le Marchand et al. (17) reported increased distal colon cancer (not including rectal cancer) risks for DM among both women [odds ratio (OR), 3.0; 95% CI, 1.2-7.1] and men (OR, 1.9; 95% CI, 1.1-3.5). Proximal colon cancer risk was also increased for DM among women, but the point estimate was not statistically significant (OR, 1.7; 95% CI, 0.7-4.4). As evidenced by the relatively wide confidence intervals, these ORs were based on small subject numbers. In the Swedish cohort study reported by Wiederpass et al. (18), proximal colon cancer risk for DM was slightly

Table 2. Age-adjusted baseline characteristics of subjects by incident CRC diagnosis: IWHS, 1986

Variable	Incident CRC		
	Yes (n = 870)	No (n = 34,102)	P
Age, mean ± SE (y)	62.4 ± 0.1	61.5 ± 0.02	0.0001
Body mass index, mean ± SE (kg/m^2)	27.7 ± 0.1	27.0 ± 0.02	0.0001
Prevalent type 2 DM, % ± SE	7.6 ± 0.8	5.4 ± 0.1	0.01
Total energy intake, mean ± SE (kcal/d)	1,759 ± 21	1,799 ± 3	0.06
Calcium, mean ± SE (mg/d)*	1,017 ± 19	1,098 ± 3	0.0001
Vitamin E, mean ± SE (mg/d)*	55.3 ± 5.1	67.0 ± 0.8	0.02

*Including supplements.

Table 3. Associations between prevalent type 2 DM and incident CRC, overall and by anatomic subsite: IWHS, 1986 to 1999

Type 2 DM*	CRC RISK							
	Overall		Proximal colon		Distal colon		Rectum	
	Cases (person-years)	RR (95% CI)†	Cases (person-years)	RR (95% CI)†	Cases (person-years)	RR (95% CI)†	Cases (person-years)	RR (95% CI)†
No DM (n = 33,072)	804 (419,681)	1.0 (—)	362 (419,565)	1.0 (—)	243 (419,863)	1.0 (—)	187 (422,505)	1.0 (—)
Prevalent DM (n = 1,900)	66 (21,686)	1.4 (1.1-1.8)	40 (21,682)	1.9 (1.3-2.6)	16 (21,750)	1.1 (0.6-1.8)	9 (21,885)	0.8 (0.4-1.6)

*Prevalent type 2 (age of onset >30 years) DM status determined by self-report at baseline.
† Multivariate risk estimates (95% CIs) accounting for age, BMI, total energy intake, calcium intake and vitamin E intake using continuous and categorical variables as defined in Table 1.

higher than distal colon or rectal cancer risk, but statistically significant associations of similar magnitude were observed throughout the colorectum. In the Nurses' Health Study (19), incident proximal colon cancer risk (RR, 1.64; 1.04-2.60) for DM was markedly higher than either distal colon (RR, 1.38; 95% CI, 0.88-2.15) or rectal (RR, 1.11; 95% CI, 0.56-2.21) cancer risk. These latter findings are similar to our observations, although the difference in risk across subsites was more pronounced among IWHS subjects.

Hyperinsulinemia resulting from impaired glucose tolerance represents the leading hypothesis for an association between DM and CRC risk (12, 15). Insulin levels are elevated during the early stages of type 2 DM, but progressively decline as pancreatic β cells become increasingly dysfunctional (12-14). Insulin has been shown to stimulate proliferation *in vitro*, induce mitogenesis in animal models, and increase the bioavailability of insulin-like growth factor I, which may independently or co-dependently promote tumorigenesis (4-6). Insulin also seems to affect farnesyl transferase activity, which may promote carcinogenesis through a *ras*-mediated pathway (15). Furthermore, insulin up-regulates leptin expression (41, 42). In rodent models, leptin has been shown to increase cellular proliferation in the proximal colon, but not in the distal colon or rectum (43). Despite the compelling hyperinsulinemia hypothesis, few studies have directly examined serum or plasma insulin levels and CRC risk (8, 10, 11). Some, but not all, prior studies have described positive risk associations between insulin-related biomarkers (including C-reactive protein, insulin-like growth factors I and II) and colorectal neoplasia (9, 11, 44, 45). However, because venipuncture samples were not collected from IWHS participants at baseline, we were unable to directly assess the utility of measuring insulin and insulin-related biomarker levels to predict incident CRC in our study.

If hyperinsulinemia is etiologically involved in colorectal carcinogenesis, it might be expected that duration of DM would affect the observed risk association. Indeed, we found that overall CRC risk was higher among women with DM diagnosed 5-12 years earlier, compared with women with DM of either shorter or longer duration. These data seem to be consistent with the hyperinsulinemia hypothesis, assuming a moderate latency period from the time of initial exposure. Although slightly different categories were used, women with DM of intermediate duration (11-15 years) were at highest risk for incident CRC in the Nurses' Health study as well. Clinical severity of DM may also modify the CRC risk association. We analyzed type of DM therapy as an indirect marker for this variable but found no apparent association with incident CRC. Because medical records were not readily available for the entire IWHS cohort, we were unable to confirm the self-reported DM therapy data.

Dietary glycemic load (i.e., glycemic index × carbohydrate content) is positively associated with postprandial glucose concentration, serum insulin level, and risk of developing type 2 DM (46, 47). Emerging data suggest that glycemic load may be an independent risk factor for CRC (47–49), although not all studies support this hypothesis (50). Interestingly, Slattery et al. found that high glycemic index from dietary sugars was more strongly associated with proximal colon cancer risk (OR, 1.7; 95% CI, 1.1-2.7 for women; OR, 1.6; 95% CI, 1.1-2.3 for men) than distal colon cancer risk (OR, 1.4; 95% CI, 0.9-2.2 for women; OR, 1.5; 95% CI, 1.0-2.2 for men) in a population-based case-control study (48). Further analysis of glycemic load as a predictor of incident CRC, overall and by subsite, in the IWHS is planned.

Our prospective, population-based cohort study has several strengths relative to previous investigations of type 2 DM and CRC risk. Comprehensive baseline questionnaire data allowed us to model type 2 DM as an independent risk factor for CRC after adjusting for multiple potential confounding factors. Follow-up information regarding incident DM diagnoses further permitted time-dependent analyses of this exposure variable. The large, well-classified case sample also afforded evaluation of subsite-specific risk associations with adequate statistical power. One limitation of our study was the reliance on self-reported DM status. However, previous studies have shown that self-reported DM has reasonable validity when compared with physician diagnoses (51, 52). Of potentially greater concern, up to 50% of DM patients may be unrecognized in the general population (53). Yet, misclassification of DM due to underreporting would generally lead to an attenuated RR estimate. Greater utilization of health care services by type 2 DM patients could result in surveillance bias. We were not able to examine this variable in our study cohort. Based on data from the Behavioral Risk Factor Surveillance System, DM patients seem to be less compliant with preventive health recommendations in general (54) and subgroups of DM patients (ethnic minorities, persons of low socioeconomic status) may be less likely to undergo CRC screening (55), which again could have resulted in underestimated CRC risk in our study population.

Observations from our study suggest that, in addition to dietary modification and glycemic control, CRC screening should be emphasized as an important preventive health measure among postmenopausal women with type 2 DM (assuming overall health status is appropriate for screening). If these data are confirmed by other studies, health care providers should further consider screening methods that allow evaluation of the proximal colon for patients with type 2 DM. Characterization of the molecular mechanisms underlying the positive association between type 2 DM and CRC may inform novel, targeted chemoprevention strategies as well. For now, adherence to general guidelines developed to increase quality of life (56) is sensible and might yield reductions in the incidence rates for both of these chronic diseases.

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