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Research Article

Cancer Prevention Research

Sex-Specific Association between Family History of Diabetes and Risk of Colorectal Cancer: Two Prospective Cohort Studies

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Abstract

Type 2 diabetes (T2D) is associated with increased risk of colorectal cancer. It remains unclear whether family history of diabetes influences colorectal cancer risk and relevant biomarkers. We followed 101,323 women from the Nurses' Health Study (1982–2012) and 48,542 men from the Health Professionals Follow-up Study (1988–2012), free of cancer and inflammatory bowel disease at baseline. Participants reported whether any of their first-degree family members ever had diabetes in multiple questionnaires administered biennially. Plasma levels of colorectal cancer–related biomarkers were measured in subsets of participants from previous nested case–control studies. We documented 1,950 colorectal cancer cases in women and 1,173 colorectal cancer cases in men. After adjustment for potential confounders including obesity and diabetes, the hazard ratio (HR) for colorectal cancer among men who had family history of diabetes was 1.19 [95% confidence interval (CI), 1.04–1.36) as compared with those who did not. The corresponding HR was 1.06 among women (95% CI, 0.96–1.17). Interestingly, for individuals younger than 60 years, these associations appeared stronger among men (HR, 1.65; 95% CI, 1.15–2.38) and possibly among women (HR, 1.23; 95% CI, 0.99–1.54). Moreover, family history of diabetes was related to reduced levels of estradiol, sex hormone binding globulin (SHBG), and adiponectin in men, with a greater reduction of SHBG for those younger than 60 years (P for interaction = 0.03). In conclusion, family history of diabetes was associated with increased colorectal cancer risk in men, which may be partly mediated by altered sex hormones and adiponectin. The possible positive association in younger women needs further confirmation. *Cancer Prev Res; 11(9); 535–44. ©2018 AACR.*

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Introduction

Type 2 diabetes (T2D) and colorectal cancer are among the leading causes of morbidity and mortality in the United States (1). Emerging evidence has revealed the link between T2D and colorectal cancer, which share important risk factors (e.g., obesity, physical inactivity, and Western dietary pattern). In fact, T2D itself is significantly associated with increased incidence of colorectal cancer (2, 3). Several biological mechanisms have been suggested to play a role, including hyperinsulinemia, altered profile of adipokines and sex hormones, and chronic inflammation (4, 5).

A family history of diabetes reflects both genetic background and shared environmental risk factors (6) and is a risk factor for a range of metabolic abnormalities (7) and development of T2D (8, 9). Interestingly, an analysis in the EPIC-InterAct study showed that established lifestyle and genetic risk factors only explained a marginal proportion of the excess T2D risk associated with family history, highlighting the potential independence of family history as a risk factor (9). Because family history of diabetes can be relatively easily assessed, it may serve as a useful screening

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tool to identify individuals at increased risk of T2D and subsequent colorectal cancer. However, it remains unclear whether family history of diabetes influences the risk of colorectal cancer after accounting for established colorectal cancer risk factors including obesity and occurrence of T2D. To address this question, we conducted a prospective analysis of the association between family history of diabetes and risk of incident colorectal cancer in two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). We also evaluated the relationship between family history of diabetes and circulating levels of colorectal cancer–related biomarkers in key pathways, including insulin/insulin-like growth factor-1 (IGF-1), sex hormones, adipokine, and inflammation. Given that obesity (10) and metabolic biomarkers (11–14) have been more strongly associated with colorectal cancer risk in men than in women, we performed the analyses in women and men separately.

Materials and Methods

Study populations

The NHS is a prospective cohort study of 121,700 female registered nurses ages 30 to 55 years at enrollment in 1976. The HPFS is a prospective cohort study of 51,529 male health professionals ages 40 to 75 years at enrollment in 1986. Participants were followed with biennial questionnaires regarding demographics, medical conditions, and health-related behaviors. The follow-up rate has been greater than 90% in each cohort. These studies were approved by Institutional Review Boards of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

For the current study, the baseline was set to 1982 for the NHS and 1988 for the HPFS, when family history of diabetes was firstly assessed. At baseline, we excluded participants who reported a history of cancer (except for nonmelanoma skin cancer) or inflammatory bowel disease and those with missing reporting of age. Because family history of diabetes was assessed at multiple different time points in the cohorts (three for NHS and four for HPFS), we conducted an open cohort analysis by allowing an individual to enter the cohort the first time he or she responded to the questionnaire on family history of diabetes and additionally had provided information on major covariates including diet, physical activity, and body mass index (BMI). After exclusions, a total of 101,323 women in the NHS and 48,542 men in the HPFS were included in the analysis.

Assessment of family history of diabetes

In the NHS, women were asked to report whether any of their first-degree family members (father, mother, and/or siblings) ever had diabetes in the questionnaires mailed in 1982, 1988, and 1992. Similar data were collected in 1987, 1990, 1992, and 2008 in the HPFS. We updated family history of diabetes as a time-varying variable, and participants were defined as positive for the subsequent follow-up once they reported a family history of diabetes in any of the questionnaires. For example, if a person in the HPFS reported positive family history of diabetes in the 1992 questionnaire, but not in any of the previous questionnaires, we considered the person unexposed till 1992 and exposed thereafter.

Ascertainment of colorectal cancer

In both cohorts, cancer diagnoses were reported by participants on the biennial questionnaires. Deaths were reported by family members or the postal system, or identified through a search of the National Death Index. With consent from participants or next of kin, medical records or pathology reports were obtained and reviewed by the study physicians, who were blinded to exposure information, to confirm colorectal cancer diagnosis and extract information on anatomic location, stage, and histologic type. In this analysis, we considered both overall and anatomic subsites, including cancers in the colon, proximal colon (cecum, ascending colon, and transverse colon), distal colon (descending colon and sigmoid colon), and rectum.

Measurements of colorectal cancer–related biomarkers

Between 1989 and 1990, 32,826 women from the NHS and between 1993 and 1995, 18,159 men from the HPFS provided blood samples. The samples were sent via an overnight courier, and the majority (95%) of the samples arrived within 24 hours of phlebotomy (15, 16). Upon arrival, samples were centrifuged and aliquoted into cryotubes as plasma, buffy coat, and erythrocyte fractions, which were then stored in liquid nitrogen freezers at −130°C or colder until analysis. We used data from previous matched case–control studies nested within each of the two cohorts that have measured plasma levels of colorectal cancer–related biomarkers (12, 14, 17, 18), including C-peptide, IGF-1, IGF-binding protein (IGFBP)-1, IGFBP-3, estrone, estradiol, sex hormone binding globulin (SHBG), testosterone, adiponectin, high-molecular-weight (HMW)-adiponectin, leptin, leptin soluble receptor (leptin sR), high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor receptor (TNFR)-2. All biomarkers were measured using standard methods (Supplementary Methods).

Because biomarkers were measured in multiple batches over several years, there may be differences in mean biomarker levels by batch due to different reagents, technicians, laboratories, or participants' characteristics in each batch. We recalibrated biomarkers from all labs to have a comparable distribution to an average batch according to Rosner and colleagues' method (19). We regressed levels of biomarkers on their potential predictors including case–control status, age, menopausal status and postmenopausal hormone use (women only),

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BMI, physical activity, alcohol intake, smoking status as well as an indicator variable for each batch. Within each batch, biomarker levels were recalibrated by adding the resulting value of the coefficients for that batch minus the average of the batch coefficients. Therefore, these recalibrated levels accounted for the variability between batches that could be explained by the varying distributions of predictors.

Assessment of covariates

Using baseline and biennial questionnaires, we inquired information on smoking status, menopausal status and postmenopausal hormone use (women only), family history of colorectal cancer, multivitamin and aspirin use, lower gastrointestinal endoscopy, physical examination, and body weight. Self-reported weight was validated against technician-measured weight (20), and BMI was calculated as weight in kilograms divided by height squared in meters. Physical activity was assessed almost every 2 years using validated questionnaires (21). Hypertension and hypercholesterolemia were self-reported, with the validity of these reports confirmed on random sampling of medical records (22). A supplementary questionnaire was used to confirm self-reported cases of diabetes according to established criteria (23), and 98% of these cases were validated in comparison with medical records. Usual dietary habits were assessed by using validated semiquantitative food frequency questionnaires almost every 4 years (24).

Statistical analysis

Person-time accrued from the date when for the first time the individual responded to the information on family history of diabetes and additionally had provided information on major covariates, until the date of diagnosis of colorectal cancer, death, or the end of follow-up (June 2012 for the NHS and January 2012 for the HPFS), whichever came first. We used Cox proportional hazards models with time-varying family history of diabetes to assess its associations with overall and subsite-specific risk of colorectal cancer within each cohort. We stratified the analysis jointly by age in years at start of follow-up and calendar time of the current questionnaire cycle to control for confounding by age, calendar time, and any possible two-way interactions between these two time scales. To examine the differential associations with colorectal cancer by tumor subsites, we fitted a Cox proportional cause-specific hazards regression model using a duplication method (25, 26). $P_{\text{heterogeneity}}$ by subsite was calculated using a likelihood ratio test by comparing the mode in which the association with exposure was allowed to vary by subsite to a model in which all the associations were held constant.

In multivariable analysis, we adjusted for family history of colorectal cancer, menopausal status and postmenopausal hormone use (women only), physical activity, alcohol intake, smoking, aspirin use, multivitamin use, lower gastrointestinal endoscopy, physical examination, hypertension, hypercholesterolemia, and Alternate Healthy Eating Index (AHEI)-2010 score. We further controlled for BMI and diabetes.

We also examined whether the association between family history of diabetes and colorectal cancer differed by age ($\geq$60 years or <60 years), menopausal status (premenopausal versus postmenopausal, women only), BMI ($\geq$25 kg/m^2 or <25 kg/m^2), smoking status (ever smoker versus never smoker), alcohol intake (drinkers vs. nondrinkers), levels of physical activity (below the median versus above the median), and diabetes (yes vs. no). We constructed cross-product terms between family history of diabetes and these factors to test for their interactions by using the Wald test.

To assess the relationship between family history of diabetes and colorectal cancer–related biomarkers, we restricted the analysis to participants who had plasma measurements and excluded outliers detected by using the generalized extreme Studentized deviate many-outlier detection procedure (27). We also excluded those who had cancer or diabetes at the time of blood collection. General linear models were applied to assess the relationship between family history of diabetes and biomarker levels. We performed natural log transformation for all biomarkers to improve normality and facilitate interpretation. The percentage of difference according to family history of diabetes can be directly calculated by [exp(beta-coefficient) $-$ 1] $\times$ 100%. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc.). All P values are two-sided and a P value of < 0.05 was considered statistically significant.

Results

Characteristics of participants according to person-time of family history of diabetes are described in Table 1. The percentage of person-years reporting a family history of diabetes was 26.2% in women from the NHS and 21.2% in men from the HPFS. In both cohorts, participants with a family history of diabetes were older and more likely to have a family history of colorectal cancer and undergo physical examination as well as lower gastrointestinal endoscopy including colonoscopy and sigmoidoscopy. Moreover, participants with a family history of diabetes were more likely to use aspirin and have hypertension, hypercholesterolemia, and diabetes. Family history of diabetes was also related to a higher BMI but lower alcohol intake and physical activity. AHEI score was slightly higher comparing participants with a family history of diabetes to those without a family history of diabetes.

We documented 1,950 colorectal cancer cases during 2,598,637 person-years of follow-up in the NHS and 1,173 cases during 983,364 person-years of follow-up in the

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Table 1. Age-adjusted characteristics of participants in NHS and HPFS according to person-time of family history of diabetes

	NHS		HPFS	
	No family history of diabetes	Having family history of diabetes	No family history of diabetes	Having family history of diabetes
Person-years	976,845	346,027	400,456	107,953
Age, y[a]	61.6 (10.9)	63.1 (10.4)	64.5 (10.9)	66.2 (10.6)
White, %	97.5	96.7	95.9	94.4
BMI, kg/m^2	25.9 (5.1)	27.0 (5.5)	25.9 (3.8)	26.4 (3.8)
BMI at age 18 (NHS) or 21 (HPFS), kg/m^2	21.2 (2.8)	21.6 (3.2)	22.0 (5.4)	22.3 (5.3)
Alcohol, g/d	5.9 (10.4)	4.6 (9.1)	11.5 (15.3)	10.3 (14.1)
Physical activity, MET-h/week	17.1 (21.5)	16.4 (21.3)	29.4 (30.6)	28.9 (29.6)
Past smoker, %	41.7	41.4	45.7	47.2
Current smoker, %	14.2	12.8	5.1	5.0
Premenopausal, %	14.3	13.3	NA	NA
Multivitamin use, %	55.7	54.6	57.3	58.0
Aspirin use, %	45.4	47.6	40.1	45.5
Colonoscopy/sigmoidoscopy in the past 2 years, %	22.3	23.9	26.8	29.4
Physical examination in the past 2 years, %	65.0	67.4	53.0	59.2
Family history of colorectal cancer, %	20.2	21.9	14.8	15.9
History of hypertension, %	27.3	31.6	32.5	38.4
History of hypercholesterolemia, %	27.8	32.2	26.1	31.0
History of diabetes, %	3.6	9.9	4.1	11.4
Total energy intake, kcal/d	1,702 (543)	1,703 (541)	1,983 (633)	1,969 (636)
Protein intake, g/d	73.5 (11.2)	74.8 (11.1)	90.1 (13.8)	91.5 (13.5)
Cholesterol intake, g/d	265.5 (83.6)	267.9 (81.0)	277.7 (91.4)	279.1 (87.6)
Fiber intake, g/d	17.6 (4.7)	17.7 (4.6)	22.1 (6.5)	22.4 (6.3)
AHEI score	43.3 (9.8)	43.6 (9.5)	48.5 (10.0)	49.0 (9.8)

[a]Value was not adjusted for age.

HPFS. In age-adjusted analyses, family history of diabetes was significantly associated with increased risk of colorectal cancer in men, but not in women (Table 2). Further adjustment for health conditions, lifestyle, and diet including BMI and diabetes did not materially alter the associations, with an HR of 1.19 (95% CI, 1.04–1.36) in men and 1.06 (95% CI, 0.96–1.17) in women. In sensitivity analysis, we adjusted for indicators for early-life adiposity (BMI at 18 or 21 years) instead of updated BMI during follow-up, and the results did not appreciably change (data not shown).

When stratified by anatomic subsites of colorectal cancer, family history of diabetes was more strongly associated with distal colon and rectal cancer in men, although the heterogeneity test did not achieve statistical significance ($P = 0.20$ for colon vs. rectal cancer; $P = 0.13$ for proximal colon vs. distal colon vs. rectal cancer; Table 3). The multivariable-adjusted HRs for colorectal cancer among men who had a family history of diabetes, as compared with those who did not, were 1.31 (95% CI, 1.03–1.67) for distal colon cancer, 1.37 (95% CI, 1.04–1.82) for rectal cancer, and 0.99 (95% CI, 0.78–1.25) for proximal colon cancer. The subsite-specific association was consistently null in women.

Table 2. Family history of diabetes and risk of colorectal cancer

	NHS, having vs. no family history of diabetes	HPFS, having vs. no family history of diabetes
Cases	570/1,380	300/873
Person-years	679,947/1,918,690	208,774/774,590
Model 1[a]	1.09 (0.99–1.20)	1.20 (1.05–1.36)
Model 2[b]	1.08 (0.98–1.19)	1.22 (1.07–1.39)
Model 3[c]	1.07 (0.97–1.18)	1.20 (1.05–1.37)
Model 4[d]	1.06 (0.96–1.17)	1.19 (1.04–1.36)

[a]Model 1 was adjusted for age.
[b]Model 2 was further adjusted for family history of colorectal cancer, menopausal status and postmenopausal hormone use (women), physical activity, alcohol intake, smoking, aspirin use, multivitamin use, colonoscopy/sigmoidoscopy, physical examination, hypertension, hypercholesterolemia, and AHEI score.
[c]Model 3 was further adjusted for BMI.
[d]Model 4 was further adjusted for incidence of diabetes.

In stratified analyses by characteristics of participants (Table 4), a stronger association between family history of diabetes and colorectal cancer was observed among men who were younger than 60 years (HR, 1.65; 95% CI, 1.15–2.38), compared with those who were older (HR, 1.13; 95% CI, 0.98–1.31; P for interaction = 0.05). Similarly, family history of diabetes was more strongly associated with colorectal cancer among women younger than 60 years (HR, 1.23; 95% CI, 0.99–1.54) than those who were at least 60 years old (HR, 1.02; 95% CI, 0.91–1.14; P for interaction = 0.22). Consistent with a potential interaction with age, a trend toward a positive association was also noted for women who were premenopausal (HR, 1.27; 95% CI, 0.79–2.04), but not postmenopausal (HR, 1.05; 95% CI, 0.95–1.16; P for interaction = 0.29). No statistically significant interaction was observed by other covariates.

In men and women, family history of diabetes showed both similarities and differences in relation to plasma colorectal cancer–related biomarkers of insulin response, sex hormones, adipokine signaling, and inflammation (Table 5). In both cohorts, participants with a family

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Table 3. Family history of diabetes and risk of colorectal cancer by subsite

	NHS, having vs. no family history of diabetes	HPFS, having vs. no family history of diabetes
Colon		
Cases	447/1,086	186/578
Model 1[a]	1.08 (0.97–1.21)	1.12 (0.95–1.32)
Model 2[b]	1.07 (0.96–1.20)	1.13 (0.96–1.34)
Model 3[c]	1.06 (0.95–1.19)	1.12 (0.95–1.32)
Model 4[d]	1.05 (0.94–1.18)	1.11 (0.94–1.31)
Proximal colon		
Cases	286/654	91/312
Model 1[a]	1.13 (0.99–1.30)	1.00 (0.79–1.26)
Model 2[b]	1.12 (0.97–1.29)	1.01 (0.80–1.27)
Model 3[c]	1.11 (0.97–1.28)	1.00 (0.79–1.26)
Model 4[d]	1.10 (0.96–1.27)	0.99 (0.78–1.25)
Distal colon		
Cases	149/401	91/244
Model 1[a]	1.00 (0.83–1.21)	1.33 (1.04–1.69)
Model 2[b]	0.99 (0.82–1.19)	1.34 (1.05–1.70)
Model 3[c]	0.98 (0.81–1.18)	1.32 (1.04–1.68)
Model 4[d]	0.97 (0.80–1.17)	1.31 (1.03–1.67)
Rectum		
Cases	123/294	69/176
Model 1[a]	1.11 (0.90–1.37)	1.39 (1.05–1.83)
Model 2[b]	1.10 (0.89–1.36)	1.40 (1.06–1.85)
Model 3[c]	1.09 (0.88–1.35)	1.39 (1.05–1.83)
Model 4[d]	1.08 (0.88–1.34)	1.37 (1.04–1.82)

[a]Model 1 was adjusted for age.
[b]Model 2 was further adjusted for family history of colorectal cancer, menopausal status and postmenopausal hormone use (women), physical activity, alcohol intake, smoking, aspirin use, multivitamin use, colonoscopy/sigmoidoscopy, physical examination, hypertension, hypercholesterolemia, and AHEI score.
[c]Model 3 was further adjusted for BMI.
[d]Model 4 was further adjusted for incidence of diabetes.

history of diabetes had higher levels of fasting C-peptide (% of difference = 4.9 in men and 3.9 in women, P for both ≤ 0.04) but lower levels of SHBG (% of difference = −5.0 in men and −5.7 in women, P for both ≤ 0.02), adiponectin (% of difference = −3.9 in men and −4.3 in women, P for both ≤ 0.04), and HMW-adiponectin (% of difference = −16.2 in men and −7.1 in women, P for both ≤ 0.02). Additionally, family history of diabetes was associated with lower levels of estradiol (% of difference = −4.7, $P = 0.02$) and higher levels of leptin (% of difference = 9.0, $P = 0.006$) in men, whereas in women, family history of diabetes was associated with higher levels of IGFBP-3 (% of difference = 1.8, $P = 0.002$) and CRP (% of difference = 5.0, $P = 0.04$).

Given that a suggestive significant interaction between age and family history of diabetes was observed, we also stratified by age for the multivariable-adjusted associations between family history of diabetes and colorectal cancer–related biomarkers (Table 5). The reduction of SHBG associated with family history of diabetes was much greater among men who were younger than 60 years (% of difference = −11.6, $P = 0.003$), compared with those who were older (% of difference = −1.6, $P = 0.56$; P for interaction = 0.03).

Discussion

In two large, US prospective cohort studies, we found that family history of diabetes was associated with increased risk of colorectal cancer in men but not in women. The association was restricted to distal colon and rectal cancer in men and appeared stronger among those who were younger than 60 years for men and possibly women. Moreover, plasma levels of colorectal cancer–related biomarkers were related to family history of diabetes in a sex-specific manner.

Table 4. Family history of diabetes and colorectal cancer risk by various characteristics of participants[a]

	NHS			HPFS		
Characteristics	*N*, cases	Having vs. no family history of diabetes	*P* for interaction	*N*, cases	Having vs. no family history of diabetes	*P* for interaction
Age			0.22			0.05
<60 years	412	1.23 (0.99–1.54)		152	1.65 (1.15–2.38)	
≥60 years	1,538	1.02 (0.91–1.14)		1021	1.13 (0.98–1.31)	
Menopausal status			0.29			
Premenopausal	91	1.27 (0.79–2.04)				
Postmenopausal	1,859	1.05 (0.95–1.16)				
BMI			0.80			0.88
BMI <25 kg/m^2	865	1.08 (0.93–1.26)		438	1.20 (0.96–1.51)	
BMI ≥25 kg/m^2	1,085	1.05 (0.92–1.19)		735	1.18 (1.00–1.40)	
Smoking status			0.85			0.93
Never	777	1.10 (0.94–1.28)		362	1.14 (0.90–1.45)	
Ever	1,162	1.05 (0.92–1.19)		667	1.13 (0.94–1.35)	
Physical activity			0.25			0.36
Below median	1,098	1.02 (0.89–1.16)		647	1.28 (1.07–1.53)	
Above median	852	1.12 (0.96–1.30)		526	1.09 (0.89–1.34)	
Alcohol intake			0.73			0.38
Nondrinker	828	1.07 (0.93–1.25)		280	1.04 (0.79–1.37)	
Drinker	1,122	1.04 (0.91–1.19)		893	1.23 (1.06–1.44)	
Diabetes			0.28			0.65
No	1,803	1.08 (0.97–1.20)		1,075	1.20 (1.04–1.38)	
Yes	147	0.89 (0.64–1.23)		98	1.26 (0.84–1.90)	

[a]Model adjustment was the same as model 4, Table 2.

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Table 5. Multivariate-adjusted percentage of difference in mean levels of colorectal cancer–related biomarkers according to family history of diabetes[a]

	NHS					HPFS				
	Sample size	Mean (SD)	% of difference	*P* value	*P* for interaction by age	Sample size	Mean (SD)	% of difference	*P* value	*P* for interaction by age
Insulin										
C-peptide (ng/mL, fasting)										
Total	5,139	1.71 (0.92)	3.9	0.007	0.36	2,084	2.11 (1.13)	4.9	0.04	0.62
Age <60 years	2,352	1.65 (0.92)	5.0	0.03		820	2.05 (1.13)	1.9	0.61	
Age ≥60 years	2,787	1.76 (0.91)	2.9	0.11		1,244	2.16 (1.14)	6.6	0.03	
C-peptide (ng/mL, nonfasting)										
Total	1,385	2.63 (1.65)	0.3	0.94	0.06	1,405	3.24 (2.02)	2.4	0.56	0.50
Age <60 years	914	2.48 (1.56)	9.2	0.09		622	3.05 (1.96)	7.4	0.26	
Age ≥60 years	471	2.91 (1.77)	−12.2	0.04		783	3.39 (2.05)	−1.7	0.76	
IGF-1 (ng/mL)										
Total	7,014	156.91 (54.49)	1.1	0.20	0.62	3,219	139.73 (38.34)	2.2	0.06	0.84
Age <60 years	4,479	164.34 (54.63)	1.2	0.29		1,340	150.98 (38.27)	2.0	0.24	
Age ≥60 years	2,535	143.79 (51.70)	1.1	0.47		1,879	131.71 (36.33)	2.3	0.15	
IGFBP-1 (ng/mL)										
Total	4,212	33.59 (24.55)	−4.9	0.06	0.44	2,143	19.00 (15.22)	−7.8	0.05	0.65
Age <60 years	2,375	31.51 (24.01)	−6.0	0.09		772	17.07 (15.44)	−10.2	0.16	
Age ≥60 years	1,837	36.27 (24.98)	−3.2	0.39		1,371	20.09 (15.00)	−6.3	0.20	
IGFBP-3 (ng/mL)										
Total	7,570	4,394 (933)	1.8	0.002	0.58	3,219	3,859 (780)	0.3	0.77	0.26
Age <60 years	4,849	4,398 (904)	1.5	0.03		1,340	4,100 (743)	−1.3	0.30	
Age ≥60 years	2,721	4,389 (981)	2.0	0.05		1,879	3,687 (760)	1.4	0.25	
Sex hormones										
E1 (pg/mL)										
Total	2,906	29.61 (20.70)	−2.3	0.28	0.008	821	30.28 (9.82)	−2.4	0.40	0.20
Age <60 years	1,108	30.77 (21.08)	−10.6	0.003		281	29.22 (9.54)	2.9	0.55	
Age ≥60 years	1,798	28.90 (20.44)	1.9	0.49		540	30.83 (9.92)	−5.1	0.14	
E2 (pg/mL)										
Total	3,075	7.37 (5.14)	−0.6	0.79	0.03	1,204	24.03 (6.78)	−4.7	0.02	0.22
Age <60 years	1,166	8.11 (5.71)	−7.9	0.04		377	23.35 (6.56)	−7.8	0.04	
Age ≥60 years	1,909	6.92 (4.71)	2.7	0.31		827	24.34 (6.86)	−3.1	0.18	
SHBG (nmol/L)										
Total	4,934	81.84 (47.37)	−5.7	<0.001	0.80	1,504	31.04 (11.30)	−5.0	0.02	0.03
Age <60 years	2,522	84.00 (48.56)	−5.2	0.03		507	28.16 (10.40)	−11.6	0.003	
Age ≥60 years	2,412	79.58 (46.00)	−6.4	0.004		997	32.51 (11.45)	−1.6	0.56	
Testosterone (ng/dL)										
Total	5,081	21.27 (10.82)	−0.6	0.71	0.78	1,532	461.34 (161.55)	−3.7	0.10	0.24
Age <60 years	2,308	21.28 (10.49)	−1.3	0.58		518	467.13 (157.00)	−7.3	0.05	
Age ≥60 years	2,773	21.25 (11.09)	−0.2	0.91		1,014	458.38 (163.82)	−1.6	0.57	
Adipokines										
Adiponectin (ng/mL)										
Total	9,214	10,906 (4,505)	−4.3	<0.001	0.09	3,461	7,188 (3,764)	−3.9	0.04	0.12
Age <60 years	5,221	10,446 (4,323)	−5.7	<0.001		1,271	6,344 (2,975)	−8.7	0.002	
Age ≥60 years	3,993	11,508 (4,666)	−2.5	0.08		2,190	7,678 (4,075)	−1.1	0.66	

(Continued on the following page)

Table 5. Multivariate-adjusted percentage of difference in mean levels of colorectal cancer–related biomarkers according to family history of diabetes[a] (Cont'd)

	NHS					HPFS				
	Sample size	Mean (SD)	% of difference	*P* value	*P* for interaction by age	Sample size	Mean (SD)	% of difference	*P* value	*P* for interaction by age
HMW-adiponectin (ng/mL)										
Total	3,512	6,146 (3,748)	−7.1	0.002	0.11	284	2,319 (1,356)	−16.2	0.02	0.37
Age <60 years	1,997	5,832 (3,679)	−9.1	0.003		124	1,877 (1,186)	−23.5	0.03	
Age ≥60 years	1,515	6,559 (3,799)	−3.6	0.29		160	2,661 (1,383)	−10.8	0.25	
Leptin (pg/mL)										
Total	3,767	25.90 (16.42)	1.4	0.49	0.88	2,436	8.47 (6.15)	9.0	0.006	0.34
Age <60 years	2,430	25.80 (16.27)	1.2	0.64		963	8.31 (6.14)	9.8	0.06	
Age ≥60 years	1,337	26.08 (16.68)	2.3	0.50		1,473	8.57 (6.15)	7.8	0.06	
Leptin sR (ng/mL)										
Total	3,119	30.62 (8.97)	−1.5	0.13	0.02	1,513	27.54 (7.51)	−1.0	0.53	0.50
Age <60 years	2,001	29.87 (8.84)	0.7	0.58		594	27.43 (7.57)	0.3	0.89	
Age ≥60 years	1,118	31.96 (9.04)	−4.5	0.005		919	27.61 (7.48)	−1.7	0.39	
Inflammation										
CRP (mg/L)										
Total	9,392	3.03 (3.99)	5.0	0.04	0.38	5,085	1.69 (1.96)	0.2	0.96	0.70
Age <60 years	5,191	2.81 (3.75)	5.8	0.08		1,931	1.46 (1.84)	−0.5	0.93	
Age ≥60 years	4,201	3.30 (4.24)	3.6	0.31		3,154	1.83 (2.02)	0.9	0.82	
IL6 (pg/mL)										
Total	6,039	1.51 (1.32)	−0.9	0.61	0.18	2,824	1.34 (0.93)	1.9	0.45	0.91
Age <60 years	3,455	1.42 (1.29)	−2.2	0.35		1,179	1.10 (0.81)	0.6	0.87	
Age ≥60 years	2,584	1.63 (1.35)	0.7	0.81		1,645	1.50 (0.97)	2.3	0.48	
TNFR2 (pg/mL)										
Total	7,009	2,616 (718)	0.3	0.73	0.83	2,832	2,601 (689)	−0.6	0.56	0.52
Age <60 years	3,823	2,485 (671)	0.8	0.45		1,096	2,357 (559)	−0.2	0.89	
Age ≥60 years	3,186	2,774 (740)	−0.5	0.66		1,736	2,755 (719)	−0.7	0.60	

[a]Excluding participants with cancer or diabetes prior to or at the year of blood draw. Biomarker levels were corrected for batch-to-batch variation using the average batch method. Model was adjusted for case–control status, fasting status (except for C-peptide), age, menopausal status and postmenopausal hormone use (women only), smoking pack-years, physical activity, and BMI.

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Despite increasing evidence suggesting that T2D is associated with increased risk of colorectal cancer (2–5), no previous study has investigated whether family history of diabetes, a strong risk factor for T2D, might be related to colorectal cancer. An estimation by a statistical liability threshold model suggests that shared genetics is responsible for 68% of the association between parental history and T2D, with the remainder due to shared environmental factors (6), which is consistent with reports from empirical epidemiologic studies (28, 29). However, in the EPIC-InterAct study, adiposity, lifestyle, and a genetic risk score comprising 35 single-nucleotide polymorphisms associated with T2D only accounted for a small proportion of the risk increase related to family history of diabetes, leaving the majority of the risk unexplained, and the genetic risk score alone explained only 2% of the family history-associated T2D risk (9). Therefore, family history of diabetes may capture additional effects that are not explained by the known obesity- or diabetes-related genetic and environmental factors. The independence of family history of diabetes as a risk factor and the ease in its assessment highlight the importance for examining the influence of family history of diabetes on the subsequent risk of other metabolically related disorders, such as colorectal cancer.

In our study, family history of diabetes confers a modestly increased risk of colorectal cancer in men, even after adjusting for occurrence of T2D, suggesting that family history of diabetes or its determinants may affect the development of colorectal cancer beyond its link to T2D through sex-specific mechanisms. This is supported by the divergent findings between men and women for the associations of family history of diabetes with colorectal cancer–related biomarkers. Specifically, participants with a family history of diabetes had lower levels of sex hormones, higher C-peptide levels, and lower adiponectin levels, which have been linked to increased risk of colorectal cancer, particularly in men. For example, higher plasma levels of testosterone, SHBG, and adiponectin have been associated with reduced colorectal cancer risk in men, but not in women in prospective studies (12–14). A meta-analysis of 9 prospective studies suggested that higher circulating C-peptide was more strongly associated with increased risk of colorectal neoplasia in men (odds ratio, 2.34; 95% CI, 1.36–4.04) compared with women (odds ratio, 1.41; 95% CI, 0.89–2.25; ref. 11). There was also a divergent pattern between men and women regarding obesity and colorectal cancer risk, with generally stronger associations observed in men than in women, and sex hormones have been suggested as one of the potential pathways for such sex differences (10). Taken together, we postulate that sex hormones in particular SHBG along with adiponectin may contribute to the observed sex difference in the association between family history of diabetes and colorectal cancer.

With the etiologic heterogeneity in colorectal cancer by anatomic location being increasingly acknowledged, accumulating epidemiologic studies have identified some risk factors whose associations with colorectal cancer differ by tumor subsite. Many of the metabolically related risk factors such as obesity (30) and physical activity (31) as well as family history of colorectal cancer (32) were more strongly associated with distal colon cancer compared with proximal colon or rectal cancer. We observed that the increased risk associated with family history of diabetes was confined to distal colon and rectal cancer. Yet, it is unclear whether such subsite differences exist for sex hormones and adiponectin that potentially mediate the relationship between family history of diabetes and colorectal cancer, and future studies are warranted to determine the biological mechanisms underlying the divergent associations between family history of diabetes and subsite-specific colorectal cancer. The stronger association among younger participants (<60 years) was not surprising because young-onset colorectal cancer patients were expected to have a significant familial component and genetic predisposition (33). For the past decades, colorectal cancer incidence has been declining in the United States mainly due to screening and changes in prevalence of risk factors (34). Contrary to the overall trends, the incidence and mortality rates have been increasing among adults younger than 50 years, for whom average-risk screening is not recommended (35, 36). Young-onset colorectal cancer has been shown to be more likely to arise from distal colon and rectum, which also paralleled our finding (37).

Our study has several strengths. For the first time, we associated family history of diabetes with risk of colorectal cancer, which was further supported by the biomarker analysis. The prospective nature of the study design minimized recall and selection biases. Information on family history of diabetes was repeatedly collected, allowing for more accurate assessment of the exposure. The comprehensive assessments of demographics, lifestyle factors, and diet enabled us to finely adjust for potential confounders.

Limitations of our study also require consideration. Family history of diabetes was self-reported, but this has been shown to be accurate and no discrepancy was found by comparing reports from proband and individual family members (38). Although we adjusted for multiple important risk factors for colorectal cancer, residual confounding cannot be ruled out. Finally, our study participants were predominantly of European descent, and additional studies in other populations are warranted.

In conclusion, independent of established colorectal cancer risk factors including obesity and T2D, family history of diabetes was associated with an increased risk of colorectal cancer in men, which might be partly mediated by altered sex hormones and adiponectin. In contrast, no significant association was observed in women, although it requires further investigation. The male-specific

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association was noted for distal colon and rectum cancer, but not proximal colon cancer; and the association was stronger among men and possibly women who were younger than 60 years. These data demonstrate the role of family history of diabetes as a potential screening tool for the identification of individuals at high risk of colorectal cancer and provide additional insight into the mechanistic link between diabetes and colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: W. Ma, M. Song, E.L. Giovannucci, X. Zhang
Development of methodology: W. Ma, M. Song, X. Zhang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Song, A.S. Kværner, A.T. Chan, X. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W. Ma, A.T. Chan, X. Zhang
Writing, review, and/or revision of the manuscript: W. Ma, M. Song, A.S. Kværner, J. Prescott, A.T. Chan, E.L. Giovannucci, X. Zhang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.T. Chan, X. Zhang
Study supervision: A.T. Chan, E. Giovannucci, X. Zhang

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Cancer Prevention Research

Correction: Sex-specific Association between Family History of Diabetes and Risk of Colorectal Cancer: Two Prospective Cohort Studies

In the original version of this article (1), the names of the fifth and sixth authors, Andrew T. Chan and Edward L. Giovannucci, respectively, are incorrect. The names have been corrected in the latest online HTML and PDF versions of the article. The authors regret this error.

Reference

1. Ma W, Song M, Kværner AS, Prescott J, Chan AT, Giovannucci EL, et al. Sex-specific association between family history of diabetes and risk of colorectal cancer: two prospective cohort studies. Cancer Prev Res 2018;11:535–44.

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Sex-Specific Association between Family History of Diabetes and Risk of Colorectal Cancer: Two Prospective Cohort Studies

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