Glycosylated Hemoglobin and Risk of Colorectal Cancer in Men and Women, the European Prospective Investigation into Cancer and Nutrition

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Abstract

Although large-scale prospective cohort studies have related hyperglycemia to increased risk of cancer overall, studies specifically on colorectal cancer have been generally small. We investigated the association between prediagnostic levels of glycosylated hemoglobin (HbA1c), a marker for average glucose level in blood, and colorectal cancer risk in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition cohort. One thousand and twenty-six incident colorectal cancer cases (561 men and 465 women) and 1,026 matched controls were eligible for the study. Multivariate conditional logistic regression was used to estimate odds ratios (ORS) adjusted for possible confounders. Increasing HbA1c percentages were statistically significantly associated with a mild increase in colorectal cancer risk in the whole population [OR, 1.10; 95% confidence interval (CI), 1.01,1.19 for a 10% increase in HbA1c]. In women,

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increasing HbA1c percentages were associated with a statistically significant increase in colorectal cancer risk (OR, 1.16; 95% CI, 1.01, 1.32 for a 10% increase in HbA1c) and with a borderline statistically significant increase in rectum cancer (OR, 1.22; 95% CI, 0.99,1.50 for a 10% increase in HbA1c). No significant association with cancer risk was observed in men. The results of the current study suggest a mild implication of hyperglycemia in colorectal cancer, which seems more important in women than in men, and more for cancer of the rectum than of the colon. (Cancer Epidemiol Biomarkers Prev 2008;17(11):3108–15)

Introduction

Lifestyle factors such as physical inactivity, excess body weight, and obesity have been consistently associated with increased colorectal cancer risk (1-4). These factors, particularly central obesity, have numerous metabolic consequences such as insulin resistance, hyperinsulinemia, hyperglycemia, increased serum triglycerides, and lower high-density lipoprotein cholesterol levels (5), most of which have been proposed to be potentially related to colorectal cancer development. In a number of studies, markers of hyperinsulinemia (such as C-peptide or insulin concentrations) have been associated with increased risk of colorectal cancer (6-10). Although diabetes has been repeatedly associated with an increase in colorectal cancer risk (11-13), less is known about the influence of hyperglycemia on the disease among nondiabetics. Only a few epidemiologic studies have investigated the relationship of blood glucose levels with colorectal adenoma and cancer incidence (6, 14, 15) or colorectal cancer mortality (16, 17), but all of these suggested an implication of elevated blood glucose in the etiology of the disease.

Glycosylated hemoglobin (HbA1c) is a form of hemoglobin in which a molecule of glucose is attached to the β-chain of hemoglobin after its exposure to high plasma levels of glucose. It reflects the average blood glucose levels over the past 6 to 8 weeks (18). HbA1c is currently used for monitoring metabolic control in diabetics, and it has also been proposed as a screening tool for the detection of severe glucose intolerance and diabetes (19, 20). Only few prospective epidemiologic studies have addressed the relationship of HbA1c percentages with adenoma or colorectal cancer risk (21-25) with variable results: two studies, including a case-cohort analysis undertaken within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort, indicated an increase in colorectal cancer risk with increasing HbA1c percentages (23, 25), whereas three others indicated no relationship at all (21, 22, 24). A study based on Swedish populations showed a direct association of HbA1c with colorectal cancer risk only at very high concentrations (top decile levels; ref. 15). Most of these studies had a relatively small sample size (between 67 and 380 case subjects); thus, only a few studies allowed investigation into the role of HbA1c in colon and rectal cancers separately (15, 22, 23), and when this was the case, sample size and statistical power were generally limited. The majority of these studies included only women (21, 22, 24), mainly from North American populations (21-24).

Here, we present the results of the largest prospective study thus far on HbA1c percentages and the risk of cancers of the colon and of the rectum in women and in men, including 1,026 case subjects and 1,026 matched control subjects, who were part of the EPIC study.

Materials and Methods

Study Population and Blood Sample Collection. The EPIC cohort consists of about 370,000 women and 150,000 men, mainly ages 35 to 69 y, recruited from 1992 to 1998 in 23 research centers in 10 Western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and the United Kingdom; ref. 26). Blood samples were collected from about 65% of the women and 93% of the men according to a standardized protocol (26).

Extensive questionnaire data were collected on habitual diet and lifestyle variables (27). Height, weight, and waist and hip circumferences were measured for all subjects according to standardized protocols (26), except for part of the Oxford cohort, where height, weight, and body circumferences were self-reported.

The present study includes subjects from 20 recruitment centers in 8 of the participating countries: Denmark, France, Germany, Greece, Italy, Spain, the Netherlands, and the United Kingdom. Norway was not included in the current study because blood samples were only recently collected and very few colorectal cancer cases have occurred after blood donation. Sweden was not included because an independent study of HbA1c and colorectal cancer risk has already been undertaken (15).

Follow-up for Cancer Incidence and Vital Status. Follow-up for vital status was collected through record linkage with regional/national cancer registries in all countries except Germany and Greece, where data on vital status were collected through an active follow-up. Incident cancer cases were identified through record linkage with regional cancer registries in Denmark, the Netherlands, the United Kingdom, Spain, and in most of the Italian centers (complete to December 2001). In Germany, France, Greece, and Naples, follow-up (complete to December 2002) was based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin. For each EPIC study center, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status.

Selection of Case and Control Subjects. Case subjects were selected among men and women who developed colon or rectum cancers after their recruitment into the EPIC study, and before the end of the study period (defined for each study center by the latest end-date of follow-up). For the present study, colon cancers were defined as tumors in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, and descending and sigmoid colon (C18.0-C18.7 according to the 10th Revision of the International Statistical Classification of Diseases, Injury and Causes of Death), as well as tumors that were overlapping or unspecified (C18.8 and C18.9). Cancers of the rectum were defined as tumors occurring at the recto-sigmoid junction (C19) or rectum (C20). Anal canal tumors were excluded. Colorectal cancer is defined as a combination of colon and rectal cancer cases.

Subjects who used any hormone replacement therapy or any exogenous hormones for contraception or medical purposes at blood donation (444 case women) and who had previous diagnosis of cancer (except nonmelanoma skin cancer), or who had missing information on fasting status (52 case subjects) were excluded from the study. A total of 1,026 incident cases of colorectal cancers (colon, n = 644; rectal, n = 382) were included in the present analyses as follows, divided by colon/rectum: 174/149 from Denmark, 14/1 from France, 14/13 from Greece, 75/52 from Germany, 101/41 from Italy, 62/36 from the Netherlands, 78/41 from Spain, and 126/49 from the United Kingdom.

For each case subject with colorectal cancer, one control subject was chosen at random among appropriate risk sets consisting of all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case. An incidence density sampling protocol for control selection was used, such that controls could include subjects who became a case later in time, while each control subject could also be sampled more than once. Matching characteristics for cases and controls were the study center where the subjects were enrolled in the cohort, gender, age (± 6 mo) at enrollment, time of the day at blood collection, fasting status (<3 h; 3-6 h; >6 h), and follow-up time (9). Women were also matched for menopausal status (premenopausal, postmenopausal, and perimenopause/unknown), and premenopausal women were matched for phase of menstrual cycle at blood collection (28). These latter matching criteria were considered because a study on the relationship of endogenous hormones and colorectal cancer risk is being planned on the same population (9).

Subjects were defined as diabetics according to two different criteria: the first one was based on questionnaire data (for subjects who had, at the time of recruitment, answered ''yes'' to the question ''Are you diabetic?''; n = 98), and the second one based on HbA1c percentages (subjects who answered ''no'' or had no answer at all to the previous question, but who had in the current study HbA1c levels > 6.5%; n = 113. This percentage corresponds to the top 95th percentile of HbA1c levels of subjects who answered ''no'' to the question ''Are you diabetic?'').

All participants had given their consent for future analyses of their blood samples, and the internal review board of the IARC had approved the analyses of HbA1c.

Laboratory Assays. Measurements of HbA1c were done on erythrocyte hemolysate using the high-performance liquid chromatography method with Bio-Rad variant II instrument at Karolinska University Laboratory, Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden, and are expressed in U.S. National Glycohemoglobin Standardization Program units and as percentages of hemoglobin. Intrabatch coefficients of variations were 2.5% at 5.7 HbA1c percentages, and 2.4% at 9.8 HbA1c percentages.

Data Analyses. Case-control differences were assessed using paired t tests for continuous variables and paired χ^2 tests for categorical variables. Case-control differences in HbA1c percentages were tested by conditional logistic regression analyses and results reported in consequent tables.

Conditional logistic regressions using the SAS ''PHREG'' procedure (SAS Institute) were used to assess the risk for a unit increase with anthropometric and environmental factors such as body mass index (BMI), waist circumference, waist to hip ratio (WHR), physical activity, alcohol intake, and diabetes usually reported to be associated with colorectal cancer risk. As well, odds ratios (OR) for cancer risk by quintiles of HbA1c were estimated by conditional logistic regression. Quintile cutoff points were based on the distributions of controls. ORs were also estimated on a continuous scale for a 10% increase in HbA1c percentages, which approximately represents the increase in HbA1c percentages between the lowest and the highest quintiles of the study population. Multivariate conditional logistic regression was used to estimate ORs adjusted for possible confounders other than those controlled for by matching, including smoking status (never, former, current, or missing), physical activity (inactive, moderately inactive, moderately active, active, or missing), BMI, waist circumference, WHR, height, alcohol intake, fiber intake, and education. Only covariates that resulted as being statistically different between cases and matched controls (Table 1) were retained in the final model of analyses as confounding variables (WHR and alcohol consumption).

For analyses of statistical heterogeneity between study countries, gender, or fasting status, ORs were also estimated for continuous measurements of HbA1c on the $\log_{1.1}$ scale (10% increase in HbA1c percentage). Formal tests of heterogeneity between the ORs in different EPIC subgroups were based on χ^2 statistics, calculated as the deviations of logistic β-coefficients observed in each of the subgroups, relative to the overall β-coefficient.

All statistical analyses were done using the Statistical Analysis System (SAS) software package, version 8 (SAS Institute).

Results

Baseline characteristics of the study population by anatomic site are shown in Table 1. Colon cancer case subjects had higher BMI, WHR and HbA1c percentages, and larger waist circumference compared with the control group. These differences were mirrored in case and control subjects in the rectum subgroup, but none of these differences reached statistical significance. Cases of rectal cancer had a higher current alcohol consumption compared with the control subjects, but no such difference was noted for colon cancer. The same differences between case and control subjects as in the overall population were observed when analyses were stratified by gender, except for alcohol consumption: male case subjects had a higher alcohol intake compared with control subjects, whereas no significant case-control difference was observed for women.

On a continuous scale for a unit increase, BMI, waist circumference, WHR, and alcohol intake were directly

Table 1. Description of the study population, by colon and rectal anatomic site groupings

Variable	Colon			Rectum		
	Cases	Matched controls	*P* difference* tests.	Cases	Matched controls	*P* difference*
n	644	644	—	382	382	—
Male subjects, %	53.1	53.1	—	57.3	57.3	—
Nonfasting subjects, %	72.7	72.7	—	80.1	80.1	—
Mean age, y (5th-95th percentile)						
At recruitment	59.1 (46.1-71.6)	59.1 (46.2-71.6)	0.29	58.2 (47.7-69.7)	58.2 (47.7-69.5)	0.87
At blood donation	59.2 (46.1-71.6)	59.2 (46.2-71.7)	0.32	58.3 (47.7-69.7)	58.3 (48.0-69.7)	0.96
At diagnosis	62.2 (50.0-75.0)	—	—	61.4 (50.0-73.0)	—	—
Mean y of follow-up	3.5 (0.3-7.0)	—	—	3.6 (0.6-7.3)	—	—
Mean BMI (5th-95th percentile)	27.3 (21.2-34.9)	26.9 (21.1-33.7)	0.08	27.0 (21.2-33.9)	26.6 (21.5-32.5)	0.10
Mean waist circumference	92.6 (71.0-114.0)	90.7 (71.0-110.5)	0.001	91.9 (72.0-111.0)	90.7 (69.00-110.0)	0.10
Mean WHR (5th-95th percentile)	0.89 (0.73-1.03)	0.88 (0.73-1.03)	0.02	0.90 (0.73-1.05)	0.89 (0.72-1.04)	0.15
Alcohol intake, g/d	17.6 (0-62.3)	16.4 (0-60.7)	0.51	22.1 (0.003-75.5)	17.5 (0.002-60.5)	0.004
Past use of hormone therapy, % †						
Yes	19.2	15.6	0.19	11.0	17.8	0.08
Smoking status, % ‡			0.43			0.81
Never	40.5	44.4		37.2	35.9	
Former	35.9	33.7		33.0	35.9	
Smoker	23.0	21.6		29.3	28.0	
Physical activity, %§			0.16			0.15
Inactive	16.6	13.0		16.2	13.9	
Moderately inactive	29.2	27.0		28.5	25.1	
Moderately active	43.8	48.3		43.2	44.0	
Active	9.5	11.0		11.5	14.9	
Geometric mean (5th-95th percentile)∥						
HbA1c, %	5.8 (5.2-7.1)	5.7 (5.1-6.6)		5.8 (5.1-7.5)	5.8 (5.1-6.8)	
Diabetic subjects from questionnaires, %	5.0	3.9		6.5	4.2	
Diabetic subjects HbA1c>6.5,%	9.9	6.5		11.5	8.9	
Diabetic subjects from questionnaires or HbA1c>6.5, %	11.5	7.6		13.1	10.0	

**P* values for differences in means between cases and controls determined by paired *t* tests, for smoking status and physical activity *P* values were determined by paired χ^2 tests.
† In women only.
‡ Smoking status of the remaining subjects is missing.
§ Physical activity status of the remaining subjects is missing.
∥ Mean/median and 5th-95th percentile values refer to the non-logarithmically transformed distribution.

associated with an increase in colorectal cancer risk in the overall population [OR, 1.03; 95% confidence interval (CI), 1.00, 1.05 for BMI; OR, 1.02; 95% CI, 1.01, 1.03 for waist circumference; OR, 7.02; 95% CI, 1.69, 29.14 for WHR; and OR, 1.005; 95% CI, 1.001, 1.01 for alcohol, respectively].

Increasing HbA1c percentages in the overall population were associated with an increase in the risk of colorectal cancer (OR, 1.11; 95% CI, 1.03, 1.20, for a 10% increase in HbA1c), as well as of colon cancer only, but no statistically significant association was observed for rectal cancer separately (Table 2). Adjustment for WHR slightly reduced the association between HbA1c and colon cancer risk, which lost statistical significance. An increase in cancer risk with increasing HbA1c percentage was observed for left colon (n = 304; OR, 1.07; 95% CI, 0.92, 1.25 for a 10% increase in HbA1c), as well as for right colon (n = 249; OR, 1.14; 95% CI, 0.97, 1.35) separately, although neither association reached statistical significance. The associations between HbA1c percentages and cancer risk on the overall population remained virtually the same after the exclusion of subjects from the Norfolk cohort (part of the cases in the current study were already included in a previous publication; ref. 25). As well, when subjects who developed colorectal cancer less than 6 months after blood donation were excluded from the analyses (63 case subjects), the association with risk remained practically unchanged. When subjects who developed cancer less than 1 year after blood donation (134 case subjects) were excluded, increasing HbA1c percentages were still associated with an increase in the risk of colorectal cancer, but this association lost statistical significance (OR, 1.07; 95% CI, 0.99, 1.16 for a 10% increase in HbA1c).

In men, no statistically significant association was observed at all between HbA1c percentages and colorectal cancer (Table 3) or in colon or rectal cancer separately. In women, conversely, a statistically significant increase in colorectal cancer risk (OR, 1.19; 95% CI, 1.04, 1.35 for a 10% increase in HbA1c) as well as in rectal cancer risk (OR, 1.24; 95% CI, 1.01, 1.52 for a 10% increase in HbA1c) was observed for increasing HbA1c percentages (Table 4). Adjustment for WHR and alcohol intake slightly reduced the association of HbA1c with rectal cancer risk. In the same population, an increase in the risk of colon cancer with increasing HbA1c percentages was observed, but this association did not reach statistical significance.

Among all cases and controls, a total of 211 subjects were identified as diabetics, according to baseline questionnaire data (n = 98) or according to their elevated HbA1c levels (n = 113); of these, 74 were among cases of

Table 2. Odds ratios of colorectal cancer (95% CI) by increase in HbA1c in cases and in matched controls in the study population, by cancer site

	Quintiles					OR per 10% increase in HbA1c
	1	2	3	4	5	
Colorectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	214/218	193/212	189/224	234/217	196/155	
Crude*	1.00	0.93 (0.71-1.23)	0.87 (0.66-1.16)	1.11 (0.84-1.47)	1.33 (0.98-1.80)	1.11 (1.03-1.20)
Adjusted †	1.00	0.96 (0.73-1.27)	0.88 (0.66-1.17)	1.13 (0.85-1.49)	1.30 (0.96-1.77)	1.10 (1.01-1.19)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	202/192	173/189	95/99	156/180	206/172	
Adjusted †	1.00	0.89 (0.66-1.19)	0.94 (0.66-1.33)	0.84 (0.61-1.14)	1.15 (0.85-1.57)	1.07 (0.90-1.27)
Colon	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	130/129	121/129	119/152	156/142	118/92	
Crude*	1.00	0.93 (0.65-1.33)	0.78 (0.55-1.11)	1.10 (0.77-1.55)	1.30 (0.88-1.91)	1.12 (1.01-1.24)
Adjusted †	1.00	0.97 (0.67-1.39)	0.80 (0.56-1.14)	1.10 (0.77-1.56)	1.25 (0.84-1.84)	1.09 (0.98-1.22)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	122/115	108/112	60/68	97/117	144/119	
Adjusted †	1.00	0.93 (0.64-1.37)	0.86 (0.55-1.34)	0.80 (0.54-1.17)	1.15 (0.79-1.68)	1.09 (0.88-1.34)
Rectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	84/89	72/83	70/72	78/75	78/63	
Crude*	1.00	0.93 (0.61-1.44)	1.08 (0.68-1.73)	1.15 (0.72-1.83)	1.40 (0.86-2.27)	1.10 (0.98-1.24)
Adjusted †	1.00	0.91 (0.59-1.42)	1.07 (0.66-1.73)	1.15 (0.72-1.85)	1.45 (0.88-2.38)	1.10 (0.97-1.25)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	80/77	65/77	35/31	59/63	62/53	
Adjusted †	1.00	0.81 (0.51-1.29)	1.12 (0.62-2.02)	0.91 (0.54-1.53)	1.17 (0.68-2.01)	1.04 (0.78-1.38)

*Analysis matched on EPIC recruitment center, gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women.
† Adjustment for WHR and alcohol (g/d).

colon cancer, and 50 were among cases of rectal cancer. Such diagnosis of diabetes was associated with an increase in the risk of cancers of the colorectum (OR, 1.53; 95% CI, 1.13, 2.07), colon (OR, 1.64; 95% CI, 1.10, 2.44), or rectum (OR, 1.39; 95% CI, 0.87, 2.20). A direct association of the risk of colorectal cancer, or of colon and rectal cancers separately, with diabetes was also observed in subjects who identified themselves as diabetics in the baseline questionnaire at recruitment only (n = 32 for colon and 25 for rectum subsites), although these associations did not reach statistical significance.

When subjects defined as diabetics were excluded from the statistical analyses (n = 211), an increase in colorectal cancer risk with increasing HbA1c percentages was still observed, but was no longer statistically

Table 3. Odds ratios of colorectal cancer (95% confidence intervals) by increase in HbA1c in men, by cancer site

	Quintiles					OR per 10% increase in HbA1c
	1	2	3	4	5	
Colorectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	118/127	109/103	104/110	116/120	114/101	
Crude*	1.00	1.14 (0.79-1.65)	1.03 (0.71-1.51)	1.05 (0.72-1.54)	1.25 (0.84-1.86)	1.06 (0.96-1.18)
Adjusted †	1.00	1.17 (0.80-1.69)	1.04 (0.71-1.53)	1.09 (0.74-1.60)	1.25 (0.83-1.86)	1.06 (0.95-1.17)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	112/112	94/90	56/46	7.9/93	101/101	
Adjusted †	1.00	1.05 (0.71-1.56)	1.27 (0.78-2.05)	0.87 (057-1.33)	0.99 (0.65-1.51)	0.94 (0.75-1.17)
Colon	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	68/74	70/63	63/72	74/75	67/58	
Crude*	1.00	1.23 (0.75-2.03)	0.98 (0.60-1.61)	1.10 (0.67-1.80)	1.32 (0.78-2.23)	1.10 (0.96-1.26)
Adjusted †	1.00	1.31 (0.79-2.16)	1.03 (0.62-1.70)	1.12 (0.68-1.85)	1.27 (0.75-2.17)	1.08 (0.94-1.24)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	65/65	60/52	38/30	43/57	65/67	
Adjusted †	1.00	1.19 (0.69-2.05)	1.31 (0.71-2.43)	0.82 (0.46-1.45)	0.92 (0.54-1.58)	0.92 (0.68-1.23)
Rectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	50/53	39/40	41/38	42/45	47/43	
Crude*	1.00	1.03 (0.59-1.78)	1.15 (0.64-2.10)	1.01 (0.55-1.85)	1.19 (0.65-2.19)	1.02 (0.87-1.19)
Adjusted †	1.00	0.94 (0.53-1.65)	1.18 (0.63-2.20)	1.04 (0.55-1.94)	1.35 (0.71-2.56)	1.03 (0.88-1.21)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	47/47	34/38	18/16	36/36	36/34	
Adjusted †	1.00	0.84 (0.46-1.53)	1.34 (0.60-3.02)	1.01 (0.52-1.99)	1.17 (0.58-2.35)	0.97 (0.67-1.38)

*Analysis matched on EPIC recruitment center, gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women.
† Adjustment for WHR and alcohol (g/d).

Table 4. Odds ratios of colorectal cancer (95% confidence intervals) by increase in HbA1c in women, by cancer site

	Quintiles					OR per 10% increase in HbA1c
	1	2	3	4	5	
Colorectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	96/91	84/109	85/114	118/97	82/54	
Crude*	1.00	0.72 (0.47-1.09)	0.71 (0.46-1.09)	1.14 (0.75-1.73)	1.46 (0.91-2.33)	1.19 (1.04-1.35)
Adjusted †	1.00	0.74 (0.48-1.13)	0.71 (0.46-1.10)	1.13 (0.74-1.71)	1.40 (0.87-2.24)	1.16 (1.01-1.32)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	90/80	79/99	39/53	77/87	105/71	
Adjusted †	1.00	0.72 (0.46-1.13)	0.69 (0.41-1.16)	0.78 (0.49-1.23)	1.32 (0.83-2.10)	1.28 (0.99-1.67)
Colon	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	62/55	51/66	56/80	82/67	51/34	
Crude*	1.00	0.67 (0.39-1.13)	0.62 (0.37-1.04)	1.09 (0.66-1.79)	1.34 (0.75-2.38)	1.15 (0.97-1.37)
Adjusted †	1.00	0.69 (0.40-1.18)	(0.63 0.37-1.05)	1.09 (0.66-1.82)	1.30 (0.72-2.33)	1.12 (0.93-1.34)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	57/50	48/60	22/38	54/60	79/52	
Adjusted †	1.00	0.73 (0.42-1.27)	0.55 (0.28-1.06)	0.79 (0.46-1.37)	1.38 (0.80-2.38)	1.32 (0.96-1.80)
Rectum	≤5.4	]5.4-5.6]	]5.6-5.8]	]5.8-6.1]	>6.1	
No. cases/controls	34/36	33/43	29/34	36/30	31/20	
Crude*	1.00	0.84 (0.41-1.72)	0.95 (0.44-2.06)	1.29 (0.61-2.74)	1.75 (0.78-3.92)	1.24 (1.01-1.52)
Adjusted †	1.00	0.86 (0.41-1.78)	0.95 (0.44-2.07)	1.28 (0.60-2.73)	1.67 (0.74-3.78)	1.22 (0.99-1.50)
Nondiabetics	≤5.4	]5.4-5.6]	]5.6-5.7]	]5.7-5.9]	>5.9	
No. cases/controls	33/30	31/39	17/15	23/27	26/19	
Adjusted †	1.00	0.71 (0.32-1.55)	0.99 (0.40-2.46)	0.72 (0.30-1.72)	1.15 (0.47-2.79)	1.21 (0.74-1.97)

*Analysis matched on EPIC recruitment center, gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women.
† Adjustment for WHR and alcohol.

significant, and the same was true for cancers of the colon or rectum separately (Table 2). The same trend in results was also observed when analyses were stratified by gender and by anatomic subsite, although the association between increasing HbA1c percentages and colorectal cancer risk in women was of borderline significance (Tables 3 and 4).

Tests of heterogeneity showed no differences in the association of HbA1c with cancer risk by gender, fasting status, country, or age. No statistically significant interaction has been observed between WHR (below versus above the median of the study population, stratified by gender) and HbA1c percentages ($P_{\text{interaction}} = 0.70$ for women, and $P_{\text{interaction}} = 0.90$ for men). Adjustments for height, waist, education, fiber intake, BMI, physical activity, or smoking did not alter the estimated relationships.

Discussion

In this prospective study, the largest to date on the relationship between HbA1c and colorectal cancer, we observed a mild overall increase in the risk of colorectal cancer with increasing HbA1c percentages. The increase in risk was stronger in women than in men, and, among women, stronger for rectum than for colon cancer. When statistical analyses were restricted to nondiabetic subjects, HbA1c percentages were still associated with an increase in colorectal and colon cancer risk, but this increase was no longer statistically significant.

Previous studies on HbA1c and colorectal cancer risk indicated either an increase in colorectal cancer risk with increasing HbA1c percentages (23, 25) or no relationship at all (21, 22, 24). However, all previous studies included a fairly small number of cases (between 67 and 380), and most of these included only women (21, 22, 24). The data from the current study suggest an implication of hyperglycemia in the development of colorectal cancer overall, as well as in colon and rectal cancers separately. Previous studies, including those conducted within the EPIC cohort, have consistently shown an increase in the risk of colorectal cancer, particularly of colon cancer, with excess body weight and obesity (1-3). Waist circumference and WHR, indicators of abdominal obesity and indices of hyperinsulinemia, showed the strongest and most consistent associations with risk among both men and women (4). The moderate association of colorectal cancer risk with HbA1c compared with the stronger association with abdominal obesity, observed as well in the present study, may suggest that the link between obesity and colorectal cancer is primarily mediated through mechanisms other than hyperglycemia, as hyperinsulinemia, fatty acid synthesis, lipids, or inflammation (29-33). On the other hand, the weakening of the estimates of HbA1c with cancer risk when adjusting by WHR does suggest that the relationship of WHR with colorectal cancer is partially (although modestly) mediated through hyperglycemia.

The association among HbA1c, diabetes, and colorectal cancer risk observed in the present study is less strong than the association observed in the study carried out previously within the EPIC-Norfolk cohort (25). This difference in the magnitude of associations may be due to the different criteria used for the inclusion of cancer cases (women taking exogenous hormones at the time of blood donation were excluded from the present study), or to different follow-up times.

In the current study, we used two different definitions of diabetes: the first definition was based on the information collected at blood donation; the second definition was based on HbA1c percentages. Because we did not have information about baseline glucose measurements, or oral glucose tolerance tests, we used

HbA1c as a proxy for the identification of hidden diabetes among the study subjects. We therefore defined as diabetics not only subjects with declared diabetes, but also all subjects that had HbA1c percentages >6.5%. This cutoff point is in accordance with the 2003 revised U.S. standard (American Diabetes Association[30]; ref. 34), and in the Diabetes Guidelines Europe (IDDM consensus guidelines; ref. 35),[31] in which percentages of HbA1c are considered normal when they are <6.1%. However, the use of HbA1c to identify diabetic subjects may have overestimated their percentage in our study population, because the use of HbA1c measurements by itself as a tool for the diagnosis of diabetes is still under debate (20, 36-38).

High plasma glucose concentrations have been related to a diet rich in fats and low in fibers, with low physical activity and therefore high adiposity, factors that have been shown to be related to higher colorectal cancer risk (1, 39, 40). A number of mechanisms through which hyperglycemia could increase cancer risk have been postulated, including the increase in pancreatic insulin secretion and blood levels (41, 42), the increased mitochondrial production of reactive oxygen species and oxidative stress (''glucose toxicity''; refs. 43, 44) leading to the generation of reactive oxygen species and chronic oxidative stress, and the enhanced activation of inflammatory pathways (45, 46). Another mechanism through which elevated glucose levels may enhance inflammatory responses is the increased endogenous formation of advanced glycation end products, which may activate the NFκB pathway through a specific advanced glycation end products receptor. Chronically elevated plasma glucose concentrations can also favor tumor development through increases in cellular glucose levels, increases in cellular energy (ATP) levels, and reduced activity of AMP-activated protein kinase, which has a central role in the regulation of hepatic glucose metabolism as well as a tumor suppressor role (47, 48).

In the present study, we observed a stronger relationship between hyperglycemia and colorectal cancer risk in women than in men, and more strongly so for rectal cancer than for colon cancer, although the heterogeneity in the results between tumor subsites was not statistically significant. The difference in cancer association by gender cannot be explained by a different prevalence of diabetes in women compared with men, because in our study 11.9% of men and only 8.3% of women were defined as diabetics. This difference in association may be due to the interaction of some other female hormones influencing cancer risk (4, 49, 50). The results of our study confirm the relatively strong association of diabetes with colorectal cancer risk, which seems stronger for colon than for rectum cancer.

The current study has the advantage of having a substantial number of colorectal cancer cases, which allowed separate analyses by anatomic subsite (colon and rectum) and by gender with sufficient statistical power to detect significant associations, as well as by follow-up time. Another strength of the current study is its prospective design, which may reduce the possibility that circulating levels of HbA1c could be influenced by the presence of the disease. A limitation of the current study is that only one single-blood sample has been collected per subject. HbA1c is an indicator of the average glycemia over the past 6 to 8 weeks, but how much one single HbA1c measurement could be representative of the exposure to glycemia over much longer periods is not known. Measurements of HbA1c in blood stored at −70°C have been seen to be stable over more than 10 years (51).

In conclusion, the results of the current study are supportive of a moderate role of hyperglycemia/hyperinsulinemia in colorectal cancer development. As suggested by our study results, this role could be more important in women than in men, and more for the development of rectal cancer than of colon cancer.

[30] http://www.diabetes.org
[31] http://www.idf.com

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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