Preliminary Communication: Glycated Hemoglobin, Diabetes, and Incident Colorectal Cancer in Men and Women: A Prospective Analysis from the European Prospective Investigation into Cancer–Norfolk Study

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Abstract

Background: Increasing evidence suggests that abnormal glucose metabolism may be associated with increased risk of colorectal cancer. Methods: We examined the relationship between known diabetes and glycated hemoglobin (HbA1c) concentrations measured in 1995 to 1997 and subsequent incident colorectal cancer after 6 years follow-up in 9,605 men and women ages 45 to 79 years in the European Prospective Investigation into Cancer–Norfolk Study. Results: Among individuals not known to have cancer at the baseline survey, there were 67 incident colorectal cancers. HbA1c concentration appeared continuously related to incident colorectal cancer risk, with lowest rates observed in those with HbA1c below 5%. Known diabetes was also associated with incident colorectal cancer, with relative risk (RR) 3.18 and 95% confidence interval (CI) 1.36-7.40 ($P < 0.01$) adjusting for age and sex and RR 2.78 and 95% CI 1.10-7.00 ($P = 0.03$) adjusting for age, sex, body mass index, and smoking compared with those without known diabetes. The RR (95% CI) of incident colorectal cancer per 1% absolute increase in HbA1c was 1.34 (1.12-1.59; $P < 0.001$). HbA1c concentrations appeared to explain the increased colorectal cancer risk associated with diabetes in multivariate models. Conclusions: Known diabetes was associated with ~3-fold risk of colorectal cancer in this analysis; this increased risk was largely explained by HbA1c concentrations, which appears continuously related to colorectal cancer risk across the population distribution. (Cancer Epidemiol Biomarkers Prev 2004;13(6):915–9)

Introduction

There is increasing evidence that abnormal glucose metabolism is associated with increased risk of colorectal cancer. The similarity of risk factors for colorectal cancer and diabetes has led to the hypothesis that both may share common etiologic factors such as physical activity, diet, or obesity (1, 2). One of the most plausible mechanisms is through insulin and insulin-like growth factors, which are involved in regulation of cell growth (1, 3). Insulin, in particular, is an important growth factor for colonic epithelial cells. High blood glucose levels may lead to hyperinsulinemia. However, an association between diabetes and colon cancer risk has not been consistently observed (4-17). One possible explanation was that, in later stages of diabetes, insulin levels might decline, which may result in variable associations between diabetes per se and cancer risk. Thus, intermediate markers such as measures of glucose metabolism may be better indicators of the pathophysiologic processes involved in colon cancer than established disease status. Common measures of glucose metabolism are fasting glucose levels, the oral glucose tolerance test, and glycated hemoglobin (HbA1c). It is often not feasible to obtain oral glucose tolerance tests or even fasting samples in large population studies. Glycated HbA1c is an integrated indicator of average blood glucose concentrations over the preceding 3 months and is particularly useful for characterizing dysglycemia in population-based studies because it is simpler than the oral glucose tolerance test and does not require the participant to fast (18).

We examined the relation between known diabetes and glycated HbA1c concentrations and incident colorectal cancer in a prospective population study of men and women after an average of 6 years follow-up.

Methods

The European Prospective Investigation into Cancer–Norfolk Study is a prospective population study of 25,623 men and women ages 45 to 79 years resident in

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Norfolk, United Kingdom, recruited from general practice registers [detailed elsewhere (18)]. The study was approved by the Norwich Ethics Committee, and participants gave signed informed consent. Between 1993 and 1997, participants completed a health and lifestyle questionnaire by post. Medical history was ascertained with the question ''Has a doctor ever told you that you have any of the following?'' followed by a list of conditions that included diabetes and cancer. People with known diabetes were defined as those who responded ''yes'' to the diabetes option of this question. Smoking history was derived from yes/no responses to the questions ''Have you ever smoked as much as one cigarette a day for as long as a year?'' and ''Do you smoke cigarettes now?''

Participants then attended a clinic a few weeks later for a health examination carried out by trained nurses. Body mass index (BMI) was estimated as weight (kilograms)/height (meters)^2. Nonfasting blood samples were taken; samples for assay were stored in a refrigerator at 4°C until transported within a week of sampling for assay at the Department of Clinical Biochemistry, University of Cambridge. Starting from 1995, when funding became available, glycated HbA1c was measured on fresh EDTA blood samples using HPLC on a Bio-Rad Diomat (Hemel Hempstead, UK) (19).

All participants are flagged for death certification and cancer incidence at the Office of National Statistics, United Kingdom, with vital status ascertained on the whole cohort. Death certificates were coded by nosologists according to the *International Classification of Diseases Ninth Revision*. Colorectal cancer death was defined as *International Classification of Diseases* 153 to 154.1 and underlying cause of death as *International Classification of Diseases* 159. All participants are additionally flagged for cancer incidence at the East Anglia Cancer Registry, which ascertains accurately over 95% of cancer cases occurring in East Anglia. Participants were identified as having incident colorectal cancer during follow-up if they died with colorectal cancer as underlying cause on the death certificate or were identified as having colorectal cancer through the Cancer Registry database.

We report results for follow-up to January 2003, an average of about 6 years. Of the 67 incident colorectal cancers identified, 22 (33%) were fatal events, 47 were in the colon, 13 were in the rectum, and 7 were combined colorectal cancers.

This analysis included all men and women ages 45 to 79 years who completed the health and lifestyle questionnaire and had available HbA1c measurement between 1995 and 1997. Of the 10,232 people with available HbA1c measures, 627 reported prevalent cancer at baseline survey and were excluded, leaving 9,605 men and women. We divided the cohort into five categories based on baseline data: those with known diabetes, those likely to have previously undiagnosed diabetes (without a personal history of diabetes but with a HbA1c concentration of ≥7%) and then the remainder by 1% intervals for HbA1c (<5%, 5% to 5.9%, and 6.0% to 6.9%). We compared the mean glycated HbA1c levels, prevalence of known diabetes, and other characteristics at the baseline survey in those who subsequently developed colorectal cancer with those who did not. We then examined the incident colorectal cancer rates by HbA1c and diabetes category. Relative risks (RR) after adjusting for age and sex and then adjusting for age, sex, BMI, and cigarette smoking habit were calculated using the Cox proportional hazards model. The Cox model was also used to determine the independent contributions of HbA1c, modeled as a continuous variable, and known diabetes to incident colorectal cancer, after adjusting for age, sex, BMI, and cigarette smoking habit, in the whole cohort and in predefined subgroups. Age and BMI were adjusted for as continuous variables. Follow-up time was calculated from the survey visit to the date of first cancer diagnosis from cancer registry or death.

Results

Table 1 shows characteristics of the 67 men and women who subsequently developed colorectal cancer during follow-up compared with the rest of the cohort who did not. The prevalence of known diabetes was significantly higher in those with incident colorectal cancer as was the mean glycated HbA1c concentration. As expected, those who developed colorectal cancer were significantly older. However, they were not significantly different with respect to BMI, cigarette smoking habit, or sex distribution. After adjusting for age, sex, and BMI using analysis of covariance, mean glycated HbA1c concentrations still differed significantly between those with incident colorectal cancer and the rest of the cohort.

Table 2 shows incident colorectal cancer rates and age and risk factor adjusted RRs by category of HbA1c concentration and known diabetes. Individuals with known diabetes or undiagnosed diabetes (i.e., HbA1c ≥7% but no reported diabetes) had a mean HbA1c concentration of 8.2% compared with a mean HbA1c concentration of 5.2% ($P < 0.0001$). Individuals with known or undiagnosed diabetes had about 4-fold risk of incident colorectal cancer compared with individuals with glycated HbA1c below 5%; this was only slightly attenuated to a RR of 3.5 after adjusting for smoking and BMI. Even in those individuals who did not have known diabetes, there was a continuous relationship of increasing colorectal cancer risk with increasing glycated HbA1c concentration throughout the whole population distribution, with lowest rates in those with glycated HbA1c below 5%. This trend was consistent in men and women but appeared stronger in men.

Table 3 shows the independent multivariate relationship of HbA1c and diabetes status with incident colorectal cancer after adjusting for age and sex alone and then adjusting for age, sex, BMI, and cigarette smoking habit. Additional adjustment for hormone replacement therapy use in women and alcohol intake did not materially change the estimates (data not shown). Known diabetes status was associated with RR 3.2, attenuated to 2.8 after adjusting for smoking and BMI. An absolute increase of 1% in glycated HbA1c concentration was associated with a 33% increase in risk of colorectal cancer. When both glycated HbA1c and known diabetes were both included in the same multivariate model, glycated HbA1c remained a significant risk predictor, but diabetes status was no longer significant. The significant increased risk of diabetes with colorectal cancer appeared largely mediated through glycated

Table 1. Comparison of variables in 9,605 men and women ages 45 to 79 years without history of cancer at baseline survey according to subsequent incident colorectal cancer, 1993 to 2002

		No incident cancer	Incident colorectal cancer	*P*
Men and women	*n*	9,538	67	
Age (y)	Mean (SD)	58.9 (8.8)	65.8 (7.2)	<0.001
BMI (kg/m^2)	Mean (SD)	26.4 (3.9)	27.2 (3.9)	0.10
Glycated HbA1c (%)	Mean (SD)	5.35 (0.85)	5.86 (1.25)	<0.001
Age, BMI, and sex adjusted	Mean (SE)	5.35 (0.008)	5.70 (0.10)	0.001
Men	% (*n*)	46.2 (4,409)	53.7 (36)	0.22
Smokers, current	% (*n*)	11.8 (1,117)	9.0 (6)	0.80
History of diabetes, yes	% (*n*)	2.3 (215)	9.0 (6)	0.004
Men	*n*	4,409	36	
Age (y)	Mean (SD)	59.2 (8.8)	65.2 (7.7)	<0.001
BMI (kg/m^2)	Mean (SD)	26.6 (3.3)	27.0 (3.2)	0.146
Glycated HbA1c (%)	Mean (SD)	5.40 (0.91)	5.99 (1.26)	<0.001
Age and BMI adjusted	Mean (SE)	5.40 (0.014)	5.87 (0.15)	0.002
Smokers, current	% (*n*)	12.3 (540)	8.3 (3)	0.73
History of diabetes, yes	% (*n*)	3.3 (144)	13.9 (5)	0.006
Women	*n*	5,129	31	
Age (y)	Mean (SD)	58.5 (8.8)	66.4 (6.5)	<0.001
BMI (kg/m^2)	Mean (SD)	26.2 (4.4)	27.5 (4.7)	0.13
Glycated HbA1c (%)	Mean (SD)	5.31 (0.80)	5.71 (1.23)	0.005
Age and BMI adjusted	Mean (SE)	5.31 (0.01)	5.51 (0.14)	0.14
Smokers, current	% (*n*)	11.3 (577)	9.7 (3)	0.93
History of diabetes, yes	% (*n*)	1.4 (71)	3.2 (1)	0.35

HbA1c level. The relationships were consistent in separate analyses of subgroups including men and women, fatal and nonfatal cases, and after excluding persons with follow-up time of <2 years. This study did not have adequate statistical power to assess possible sex differences in the relationship between glycated HbA1c and cancer risk. Tests of interaction for sex and glycated HbA1c in predicting colorectal cancer risk, whether HbA1c was used as a continuous or as a categorical variable, were not significant (P = 0.90 and 0.76, respectively). When glycated HbA1c was analyzed as a continuous rather than a categorical variable as in Table 3, the RR estimates did not significantly differ between men and women.

Discussion

Established diabetes appeared to be a strong risk factor for incident colorectal cancer, with a 3-fold RR. The increased risks of diabetes appeared to be mediated largely through HbA1c concentration, as the effect of diabetes was not significant when HbA1c was included in the regression model. HbA1c significantly predicted incident colorectal cancer independent of diabetes, obesity, and smoking habit and was below the threshold commonly accepted for diagnosis of diabetes with an apparent gradient through the whole population range from <5% to 6.9.%. An increase in HbA1c of 1% was associated with 33% increase in colorectal cancer risk.

Table 2. Incident colorectal cancer rates and RRs* adjusted for age and age, sex, smoking, and BMI by category of glycated HbA1c level and known diabetes status in 9,605 men and women ages 45 to 79 years without known cancer at baseline, 1995 to 2003

	Level of glycated HbA1c (%)				Known diabetes	*P* (Trend)
	<5%	5.0-5.9%	6.0-6.9%	≥7%		
Men and women (*n*)	2,627	5,721	899	137	221	
Rate/100 (*n* of events)	0.4 (10)	0.6 (35)	1.4 (13)	2.2 (3)	2.7 (6)	<0.001
RR (95% CI), age and sex adjusted	1 (reference)	1.13 (0.56-2.30)	1.93 (0.83-4.47)	2.94 (0.80-10.85)	4.02 (1.44-11.22)	
RR (95% CI), age and risk factor† adjusted	1 (reference)	1.07 (0.53-2.20)	1.95 (0.84-4.56)	2.85 (0.76-10.7)	3.35 (1.12-10.00)	
Men (*n*)	1,152	2,634	434	76	149	
Rate/100 (*n* of events)	0.3 (4)	0.7 (18)	1.6 (7)	2.6 (2)	3.4 (5)	<0.001
RR (95% CI), age adjusted	1 (reference)	1.64 (0.55-4.85)	3.10 (0.90-10.73)	4.94 (0.89-27.35)	6.96 (1.84-26.34)	
RR (95% CI), age and risk factor† adjusted	1 (reference)	1.61 (0.54-4.82)	3.40 (0.97-11.92)	5.19 (0.92-29.38)	6.02 (1.47-24.65)	
Women (*n*)	1,475	3,087	465	61	72	
Rate/100 (*n* of events)	0.4 (6)	0.6 (17)	1.3 (6)	1.6 (1)	1.4 (1)	0.03
RR (95% CI), age adjusted	1 (reference)	0.77 (0.30-1.98)	1.14 (0.36-3.68)	1.58 (0.19-13.46)	1.57 (0.19-13.14)	
RR (95% CI), age and risk factor† adjusted	1 (reference)	0.70 (0.27-1.82)	1.08 (0.33-3.50)	1.36 (0.15-12.04)	1.38 (0.16-11.76)	

*Based on Cox proportional hazards model.
†Risk factors are BMI and cigarette smoking habit and sex for the sex combined analyses.

Table 3. Independent RRs* for incident colorectal cancer of glycated HbA1c and diabetes in 9,605 men and women ages 45 to 79 years, 1995 to 2002

		Age and sex adjusted, RR (95% CI)	*P*	Age, sex, and risk factor† Adjusted, RR (95% CI)	*P*
All incident colorectal cancer (n = 67/9,605)					
Model 1	HbA1c (per 1% increase)	1.33 (1.11-1.56)	0.001	1.34 (1.12-1.59)	0.001
Model 2	Diabetes history (yes vs. no)	3.18 (1.36-7.40)	0.007	2.78 (1.10-7.00)	0.03
Model 3	HbA1c (per 1% increase)	1.24 (0.99-1.55)	0.05	1.30 (1.04-1.61)	0.02
	Diabetes history (yes vs. no)	1.76 (0.60-5.18)	0.30	1.35 (0.43-4.24)	0.61
Colorectal cancer mortality only (n = 22/9,605)					
Model 1	HbA1c (per 1% increase)	1.30 (0.95-1.78)	0.10	1.32 (0.96-1.81)	0.04
Model 2	Diabetes history (yes vs. no)	4.78 (1.39-16.44)	0.01	3.60 (0.81-15.89)	0.09
Model 3	HbA1c (per 1% increase)	1.07 (0.70-1.64)	0.76	1.28 (0.85-1.92)	0.25
	Diabetes history (yes vs. no)	4.04 (0.77-21.15)	0.09	1.83 (0.26-12.81)	0.52
Colorectal cancer nonfatal cases (n = 45/9,605)					
Model 1	HbA1c (per 1% increase)	1.35 (1.10-1.66)	0.004	1.33 (1.08-1.64)	0.007
Model 2	Diabetes history (yes vs. no)	2.33 (0.72-7.60)	0.16	2.42 (0.72-7.74)	0.15
Model 3	HbA1c (per 1% increase)	1.35 (1.06-1.73)	0.02	1.33 (1.03-1.70)	0.03
	Diabetes history (yes vs. no)	1.00 (0.24-4.12)	0.99	1.07 (0.26-4.47)	0.92
Excluding cases occurring within 2 years follow-up (n = 58/9,517)					
Model 1	HbA1c (per 1% increase)	1.31 (1.08-1.58)	0.005	1.31 (1.08-1.59)	0.006
Model 2	Diabetes history (yes vs. no)	3.77 (1.61-8.86)	0.002	3.32 (1.31-8.42)	0.01
Model 3	HbA1c (per 1% increase)	1.17 (0.91-1.51)	0.22	1.21 (0.95-1.56)	0.13
	Diabetes history (yes vs. no)	2.48 (0.82-7.56)	0.11	1.96 (0.60-6.45)	0.27
Men only, all incident colorectal cancers (n = 36/4,445)					
Model 1	HbA1c (per 1% increase)	1.38 (1.12-1.69)	0.002	1.41 (1.15-1.73)	0.001
Model 2	Diabetes history (yes vs. no)	3.89 (1.50-10.10)	0.005	3.37 (1.17-9.72)	0.02
Model 3	HbA1c (per 1% increase)	1.25 (0.95-1.66)	0.11	1.35 (1.04-1.76)	0.02
	Diabetes history (yes vs. no)	2.14 (0.61-7.51)	0.23	1.45 (0.38-5.59)	0.59
Women only, all incident colorectal cancers (n = 31/5,160)					
Model 1	HbA1c (per 1% increase)	1.23 (0.89-1.69)	0.22	1.20 (0.86-1.68)	0.28
Model 2	Diabetes history (yes vs. no)	1.77 (0.24-13.01)	0.57	1.71 (0.23-12.64)	0.60
Model 3	HbA1c (per 1% increase)	1.23 (0.84-1.79)	0.29	1.20 (0.81-1.78)	0.26
	Diabetes history (yes vs. no)	0.97 (0.09-10.06)	0.98	1.02 (0.10-10.60)	0.98

*Based on Cox proportional hazards model.
†Risk factors are BMI and cigarette smoking habit and sex for the sex combined analyses.

The associations between diabetes and HbA1c and colorectal cancer did not appear to be explained by confounding with other possible cancer risk factors, particularly BMI and smoking, which in any case in this cohort, were not strong risk factors for colorectal cancer.

This study has limitations. Incident colorectal cancer cases were identified using record linkage with cancer registry and mortality databases. While we could ascertain all deaths in the cohort, relying on cancer registry data may underestimate nonfatal colorectal cancer cases. However, underestimation or random misclassification of colorectal cancer cases in the population is likely to attenuate the any relationships observed with HbA1c and diabetes.

Apparently, persons with known diabetes may be more likely to be admitted to hospital and to have colorectal cancer diagnosed through screening, for example. Although increased and biased ascertainment of cancer may be associated with known diabetes, these would not explain the relationship with HbA1c in people without known diabetes.

We previously reported a strong relationship between glycated HbA1c, diabetes, and cardiovascular disease and total mortality in men in a 3-year follow-up (19). Competing causes of mortality are again more likely to reduce any associations with colorectal cancer.

Investigators have proposed many possible mechanisms for an association between abnormal glucose tolerance and cancer risk. One of the most likely is that both reflect some common exposure such as diets high in fats and energy and low in dietary fiber, which may be more carcinogenic, or low levels of physical activity, leading to adiposity-related hormonal effects. Increasing attention has focused on the role of insulin and insulin-like growth factors, which are involved in regulation of cell growth including differentiation and apoptosis and are plausibly implicated in colon carcinogenesis as they have been shown to have particular effects in colonic epithelial cells. Giovannucci has reviewed this extensively elsewhere (1, 3). Chronic hyperglycemia may result in hyperinsulinemia. We did not have measures of insulin. Nevertheless, glycated HbA1c, a marker of blood glucose levels over the past few months, may be a good indicator of metabolic processes influencing levels of insulin or insulin-like growth factors.

Some early case-control studies and some recent prospective studies have suggested an association between diabetes and colorectal cancer risk, but findings have not been entirely consistent. Giovannucci has suggested that this may be due to the changing course of diabetes; hyperinsulinemia is apparent in the early

stages of insulin resistance, but with worsening disease, β cell failure may lead to hypoinsulinemia. Thus, differences in duration and severity of diabetes may explain the variable associations observed between diabetes and cancer. Indeed, several studies have reported stronger associations between impaired glucose tolerance and cancer than diabetes per se and cancer. Saydah et al. (13) reported in the National Health and Nutrition Examination Survey II cohort that impaired glucose tolerance was associated with significantly increased risk of cancer mortality [RR 1.87, 95% confidence interval (CI) 1.06-3.31], but diabetes was not (RR 1.31, 95% CI 0.48-3.56 for undiagnosed diabetes; RR 1.13, 95% CI 0.49-2.62 for established diabetes). Schoen et al. (15) reported that there was a nonsignificantly increased risk of incident colon cancer for impaired glucose tolerance and diabetes combined, but after excluding those with diabetes, there was a RR (95% CI) 2.4 (1.2-4.7) of colorectal cancer for those in the top compared with bottom quartile for 2-hour postload oral glucose challenge. Colangelo et al. (4) reported that, after excluding participants with diabetes, there was a trend of increased colorectal cancer mortality risk for postload plasma glucose with RR (95% CI) 1.64 (1.13-2.37) for those with postload plasma glucose above 200 mg/dL. There are fewer reports on glycated HbA1c: Platz et al. (12) found no significant relationships between glycated HbA1c and colorectal cancer and adenoma in a nested case-control analysis in the Nurses Health Study but stated that they could not exclude a modestly elevated risk. In a community-based U.S. cohort, those in the highest quartile of glycated HbA1c had a slightly increased risk of colorectal cancer (odds ratio 1.57, 95% CI 0.94-2.60; ref. 14).

Sex differences have been suggested. While several studies do not show sex specific data, in several studies, the relationships have generally been stronger in men compared with women. One prospective study (17) reported a RR (95% CI) of diabetes for colorectal cancer of 1.30 (1.03-1.65) in men compared with 1.16 (0.87-1.53) in women. However, Hu et al. (20) reported that diabetes was associated with a significantly elevated RR 1.43 for total colorectal cancer and RR 2.39 for fatal colorectal cancer in women in the prospective Nurses Health Study. Apparently, other factors in women such as estrogen may modify colorectal cancer risk. The Women's Health Initiative found lower colorectal cancer in women randomized to estrogen plus progestin (21). In the current study, the relationship between diabetes and colorectal cancer appeared to be stronger in men than in women, but there was limited power to address possible sex differences.

An association between diabetes and colorectal cancer has been postulated in previous studies. Our findings suggest that elevated glycated HbA1c concentrations even at levels below those used for diagnosis of diabetes may be associated with increased colorectal cancer risk. If confirmed, this association may help our understanding of the pathophysiology of colorectal cancer and inform preventive strategies.

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