Null Results in Brief

Hemoglobin A_{1c} Concentrations and Risk of Colorectal Cancer in Women

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Introduction

Hyperinsulinemia and insulin resistance have been hypothesized to be involved in colorectal carcinogenesis (1, 2). Observational data evaluating the association using circulating insulin levels have been inconclusive, likely because insulin levels differ dramatically during early and late stages of insulin resistance (3-6). Measures of glucose metabolism have also been used to test the association, because high blood glucose levels tend to show high blood insulin levels. Hemoglobin A_{1c} (HbA_{1c}), a common measure of glucose metabolism, reflects average blood glucose levels over the past 6 to 8 weeks (7). HbA_{1c} is more stable than other glucose measures, such as fasting glucose, and has been suggested to be a good marker for chronic hyperinsulinemia (8, 9). Of the three studies that have assessed HbA_{1c} levels, two observed an increased risk of colorectal cancer with increasing HbA_{1c} levels (5, 10) whereas the other study reported a null association (11). Because sample sizes in these studies were relatively small or moderate, we prospectively examined HbA_{1c} levels in relation to colorectal cancer risk in a large cohort.

Materials and Methods

The Women's Health Study is a completed randomized trial evaluating low-dose aspirin and vitamin E for the primary prevention of cardiovascular disease and cancer among 39,876 women ages ≥45 years and free of cancer and cardiovascular disease at the time of enrollment beginning in 1993 (12). Upon enrollment in the study, participants completed a baseline questionnaire about their medical history and potential risk factors for colorectal cancer. Participants also filled out a 131-item food frequency questionnaire. HbA_{1c} concentrations were measured by turbidometric immunoassay in RBC using the Hitachi 911 Analyzer (Roche Diagnostics, Indianapolis, IN), and the coefficient of variation for quality control samples was 7.2%.

We first categorized women into quartiles according to the distribution of HbA_{1c} levels in all women and compared the baseline distribution of risk factors for colorectal cancer according to these quartiles. We then used Cox proportional hazards regression to estimate relative risks (RR) and 95% confidence intervals (95% CI) for colorectal cancer. We estimated the RRs with adjustment for age and randomized treatment assignment and additionally for potential risk factors for colorectal cancer assessed at baseline. Tests for trend were done by fitting the median value of each category as a continuous variable in the models. All *P*s were two sided.

Results

During an average of 10 years of follow-up between 1993 and 2004, we documented 168 incident colorectal cancer cases among 27,110 women included in the present study. The mean HbA_{1c} was 5.1 ± 0.6%, which was close to the values of the median (5.0%) and 90th percentile (5.4%). Only 3.1% of women in this cohort had HbA_{1c} levels of ≥6%. Women who had higher HbA_{1c} levels were older, heavier, physically inactive, and less likely to be current users of postmenopausal hormone therapy and multivitamins but were more likely to be current smokers and to report having had history of diabetes at baseline (Table 1). Women with higher HbA_{1c} levels also tended to consume less alcohol but had higher intakes of total energy, red meat, and total glycemic load. Family history of colorectal cancer in a first-degree relative, previous history of colon polyps, and previous colonoscopy or sigmoidoscopy examinations were not appreciably different among women across the four quartiles of HbA_{1c} levels.

Higher HbA_{1c} levels were not associated with an elevated risk of colorectal cancer in the model adjusted for age and random treatment assignment (Table 2). The risk estimates were not changed with additional adjustment for risk factors for colorectal cancer (Table 2). Compared with those in the lowest quartile of HbA1c levels, the multivariate RR for women in the highest quartile was 0.83 (95% CI, 0.52-1.33). HbA_{1c} levels were also not significantly associated with cancers of the proximal colon, distal colon, and rectum (Table 2). However, the RRs for Duke's B colorectal cancer were elevated in the higher quartiles of HbA_{1c} levels (Table 2). Potential confounding factors, including body mass index, physical activity, and intake of total glycemic load, did not modify the associations between HbA_{1c} levels and colorectal cancer risk (multivariate $P_{interaction} > 0.05$).

We also used more clinically relevant cutoff points by classifying women into four HbA_{1c} groups: <5.0, 5.0 to <5.5, 5.5 to <6.0, ≥6.0. The multivariate RRs relative to HbA_{1c} of <5.0% were 0.90 (95% CI, 0.65-1.26) for 5.0% to <5.5%, 0.71 (95% CI, 0.32-1.55) for 5.5% to 6.0%, and 1.00 (95% CI, 0.45-2.25) for

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Table 1. Age-adjusted baseline characteristics according to quartiles of HbA_{1c} levels among 27,110 women in the Women's Health Study, 1993-2004

Baseline characteristics	Quartile of HbA_{1c} (%)				
	1	2	3	4	P_{trend}
HbA_{1c}, % (median)	4.7	4.9	5.1	5.4	
Participants	6,779	6,777	6,777	6,777	
Age, mean (y)	52.3	53.5	54.5	55.8	<0.0001
Body mass index, mean (kg/m^2)	24.6	25.2	25.9	28.0	<0.0001
Aspirin users before trial (%)	11.3	11.5	11.3	12.5	0.11
Current users of postmenopausal hormones (%)	50.0	45.3	44.9	35.7	<0.0001
Current smokers (%)	9.3	12.1	12.2	12.9	<0.0001
Family history of colorectal cancer (%)	10.0	10.7	10.6	10.0	0.54
Colonoscopy or sigmoidoscopy during the past year* (%)	7.7	8.1	7.5	7.4	0.38
History of colon polyps (%)	2.6	2.5	2.4	2.6	0.80
History of diabetes at baseline (%)	0.2	0.1	0.4	8.9	<0.0001
Current users of multivitamins (%)	32.0	30.5	28.9	26.2	<0.0001
Physical activity, median (kcal/wk)	1,038	1,005	974	932	<0.0001
Total calories intake (kcal/d)	1,711	1,718	1,740	1,753	<0.0001
Alcohol intake (g/d)	5.5	4.4	3.8	2.9	<0.0001
Red meat intake (g/d)	0.7	0.7	0.7	0.8	<0.0001
Glycemic load (g/d)	116.7	117.4	119.0	118.4	0.01

NOTE: All factors except age and HbA_{1c} are age adjusted.
*From the 12-month questionnaire.

≥6.0% (P_{trend} = 0.60). The results were also not changed when we excluded 659 women (five incident colorectal cancer cases) who reported ever having had a diagnosis of diabetes at baseline (multivariate P_{trend} = 0.51).

Discussion

In this large prospective cohort of women, higher HbA_{1c} levels were not associated with an increased incidence of colorectal

Table 2. RRs and 95% CIs of colorectal cancer according to quartiles of HbA_{1c} levels in the Women's Health Study

	Quartile of HbA_{1c} (%)				
	1	2	3	4	P_{trend}
HbA_{1c}, % (range)	2.3-4.8	>4.8-5.0	>5.0-5.2	≥5.2	
Colorectal cancer					
No. cases	36	41	46	45	
RR (95% CI)*	1.00	1.00 (0.64-1.57)	1.03 (0.66-1.60)	0.89 (0.57-1.40)	0.59
RR (95% CI)†	1.00	1.02 (0.65-1.61)	0.95 (0.60-1.50)	0.83 (0.52-1.33)	0.35
Colon cancer					
No. cases	29	27	33	38	
RR (95% CI)*	1.00	0.81 (0.48-1.36)	0.89 (0.54-1.47)	0.90 (0.55-1.47)	0.84
RR (95% CI)†	1.00	0.83 (0.49-1.41)	0.81 (0.48-1.38)	0.86 (0.51-1.44)	0.65
Tumor location					
Proximal colon cancer					
No. cases	15	17	19	17	
RR (95% CI)*	1.00	0.96 (0.48-1.93)	0.95 (0.48-1.89)	0.74 (0.36-1.50)	0.37
RR (95% CI)†	1.00	0.89 (0.44-1.79)	0.73 (0.36-1.48)	0.51 (0.25-1.08)	0.06
Distal colon cancer					
No. cases	14	10	14	21	
RR (95% CI)*	1.00	0.63 (0.28-1.42)	0.81 (0.39-1.72)	1.09 (0.54-2.17)	0.51
RR (95% CI)†	1.00	0.74 (0.32-1.69)	0.91 (0.42-2.00)	1.47 (0.70-3.08)	0.17
Rectal cancer					
No. cases	7	12	12	6	
RR (95% CI)*	1.00	1.64 (0.65-4.18)	1.61 (0.63-4.12)	0.77 (0.26-2.33)	0.53
RR (95% CI)†	1.00	1.64 (0.64-4.18)	1.55 (0.60-4.01)	0.60 (0.18-1.99)	0.34
Tumor stage					
Duke's A					
No. cases	15	9	17	11	
RR (95% CI)*	1.00	0.55 (0.24-1.28)	1.14 (0.56-2.30)	0.95 (0.42-2.16)	0.72
RR (95% CI)†	1.00	0.45 (0.16-1.29)	1.53 (0.59-3.99)	1.23 (0.40-3.78)	0.48
Duke's B					
No. cases	5	13	11	11	
RR (95% CI)*	1.00	2.12 (0.74-6.05)	2.05 (0.70-6.04)	2.58 (0.86-7.78)	0.14
RR (95% CI)†	1.00	3.19 (0.83-12.26)	4.98 (1.22-20.34)	4.69 (1.14-19.30)	0.04
Duke's C					
No. cases	15	18	17	21	
RR (95% CI)*	1.00	1.09 (0.53-2.21)	1.07 (0.52-2.18)	1.54 (0.76-3.12)	0.21
RR (95% CI)†	1.00	1.35 (0.59-3.06)	0.72 (0.30-1.74)	1.27 (0.52-3.18)	0.74

*Model was adjusted for age and random treatment assignment.
†Model was adjusted for age, random treatment assignment, body mass index, family history of colorectal cancer in a first-degree relative, history of colon polyps, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, multivitamin use, menopausal status, and baseline postmenopausal hormone use.

cancer. This finding was in line with the observation of a small case-control study nested in a female cohort (11). In contrast, two other studies comprising both men and women observed a >50% increased risk of colorectal cancer among those who were in the highest category of HbA_{1c} levels (i.e., ≥5.8%; refs. 5, 10). It is notable that the positive association observed in one of the two studies came primarily from men because stratified analysis by gender revealed a nonsignificant association in women (10). Sex difference has been suggested in the studies assessing the associations of history of diabetes and obesity with incidence of colorectal cancer; the associations were much stronger in men than in women (13, 14). The null association observed in our study could also be explained by our overall low HbA_{1c} levels. The average HbA_{1c} levels among participants in the other three studies were between 5.4% and 5.8%, in contrast with a mean level of 5.1% in our cohort.

Our group had previously found that body mass index and dietary intake of glycemic load are two independent risk factors for colorectal cancer incidence in the Women's Health Study (15, 16). The null association between HbA_{1c} levels and colorectal cancer risk in the present study suggests that the link between both body mass index and glycemic load and colorectal cancer in our cohort may be mediated in larger part by complex physiologic mechanisms other than glucose levels. For instance, higher intake of glycemic load may induce alterations in lipid and lipoprotein metabolism, which stimulate the proliferation of neoplastic cells (17, 18). Higher serum triglycerides and lower high-density lipoprotein cholesterol levels have been associated with an elevated risk of colorectal cancer (19-21). Alternatively, because insulin levels differ dramatically during early and late stages of insulin resistance (22), HbA_{1c}, the time-averaged glucose measurement, may not adequately reflect insulin concentrations. In a sample of 394 women in our cohort, HbA_{1c} levels were only moderately related to circulating insulin levels (Spearman correlation = 0.22; ref. 23).

Several limitations of the present study merit considerations. First, although we controlled for other risk factors for colorectal cancer in the models, we still cannot exclude the possibility of residual confounding. Second, we only had a single baseline measurement for HbA_{1c} levels. However, HbA_{1c} levels are stable over time (24), and single baseline HbA_{1c} levels have strongly predicted the risk for cardiovascular disease and total mortality in adults, including our cohort (23, 25). Finally, because the number of cases was relatively limited, we had insufficient statistical power for subgroup analyses.

In conclusion, our data suggest that HbA_{1c} as a surrogate for chronic hyperinsulinemia does not predict risk of colorectal cancer among apparently healthy women. More examination is warranted to further explore the role of hyperinsulinemia and other metabolic abnormalities, such as dyslipidemia, in the etiology of colorectal cancer.

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