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Research Article

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Dietary Insulin Load, Dietary Insulin Index, and Colorectal Cancer

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Abstract

Background: Circulating insulin levels have been positively associated with risk of colorectal cancer; however, it remains unclear whether a diet inducing an elevated insulin response influences colorectal cancer risk. On the basis of a novel insulin index for individual foods, we estimated insulin demand for overall diets and assessed its association with colorectal cancer in the Nurses' Health Study and Health Professionals Follow-up Study.

Methods: We followed 86,740 women and 46,146 men who were free of cancer and diabetes at baseline and identified a total of 2,481 colorectal cancer cases during up to 26 years of follow-up. Dietary insulin load was calculated as a function of food insulin index and the energy content of individual foods was reported on food frequency questionnaires. Average dietary insulin index was calculated by dividing the dietary insulin load by the total energy intake.

Results: Dietary insulin load and dietary insulin index were not associated with risk of colorectal cancer. Comparing the highest with the lowest quintiles, the pooled multivariate relative risks of colorectal cancer were 0.91 (95% CI = 0.79–1.05) for dietary insulin load and 0.93 (95% CI = 0.81–1.08) for dietary insulin index. Body mass index and physical activity did not modify the association of dietary insulin load or index with colorectal cancer.

Conclusion: A diet high in foods that increase postprandial insulin levels did not increase the risk of colorectal cancer in this large prospective study.

Impact: This study is the first to investigate insulin index and load in relation to colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 19(12); 3020–6. ©2010 AACR.*

Introduction

In many observational studies, individuals with type 2 diabetes mellitus have had increased risk of colorectal cancer (1). As patients with type 2 diabetes usually have hyperinsulinemia in the early stage of their disease and insulin has growth-promoting effects, increased insulin exposure has been hypothesized as a biological mechanism whereby diabetes may be related to colorectal carcinogenesis (2, 3). Also, chronic exogenous insulin therapy significantly increases risk of colorectal cancer among patients with type 2 diabetes (4). In addition, common risk factors for type 2 diabetes and colorectal cancer, such as physical inactivity, obesity, and visceral adiposity, have been related to insulin resistance and hyperinsulinemia (2, 3).

Higher circulating insulin or C-peptide (a marker of insulin resistance and long-term insulin secretion) has been associated with increased risk of colorectal cancer in many studies (5–12). However, whether a diet inducing an elevated insulin response influences colorectal cancer risk remains unclear. Previous studies have used glycemic load and glycemic index as indicators for insulin response, most of which found no association with colorectal cancer (13). Nonetheless, glycemic load and glycemic index characterize only the influence of carbohydrate on blood glucose, which may limit their capacity for accurate estimation of insulin response because in addition to carbohydrate, protein and fat can induce insulin secretion (14).

A novel insulin index may more directly address the insulin hypothesis because it quantifies postprandial insulin response for various food items, including those with low or no carbohydrate content (14). On the basis of this new concept, the insulin response to overall diets, represented by dietary insulin load and dietary insulin index, can be further calculated. A recent study evaluated the validity of dietary insulin load in predicting the actual insulin response to a composite meal among young

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healthy subjects (mean age 24 years; $n = 10$ or 11 for each meal) who consumed 13 different meals of varying macronutrient content (15). They found that dietary insulin load was strongly correlated with observed postprandial insulin responses ($r = 0.78$, $P = 0.002$), and it provided a more accurate prediction of insulin demand than carbohydrate content or glycemic load.

In the present study, we examined the associations between these 2 insulin scores and colorectal cancer risk. To our knowledge, this study is the first to use insulin index to investigate the effect of consuming a high-insulinogenic diet on risk of colorectal cancer.

Participants and Methods

Study population

The Nurses' Health Study (NHS) enrolled 121,700 U.S. female nurses aged 30 to 55 years in 1976. The Health Professionals Follow-up Study (HPFS) enrolled 51,529 U. S. male health care professionals aged 40 to 75 years in 1986. Participants completed a baseline questionnaire and biennial follow-up questionnaires; in the NHS, diet was first assessed in 1980. The overall follow-up rate was more than 90% in the NHS and 94% in the HPFS. At baseline for the dietary analyses, we excluded participants who had cancer, left an extensive number of items blank (>9 items on the 61-item food frequency questionnaire in 1980 for the women and ≥70 items on the 131-item food frequency questionnaire in 1986 for the men), or reported implausible energy intake (<500 or >3,500 kcal per day for women and <800 or >4,200 kcal per day for men). Because diabetic patients usually change their diet, we also excluded individuals who had diabetes before baseline. This left a cohort of 132,886 participants eligible (86,740 women and 46,146 men). This study was approved by the Human Subjects Committee at Brigham and Women's Hospital and the Harvard School of Public Health.

Assessment of dietary and nondietary factors

Dietary information was collected at baseline and every 2 to 4 years thereafter. Insulin index values for individual food were obtained from published estimates (31 foods; refs. 14, 16) or provided by Dr. Jennie Brand-Miller of the University of Sydney (73 foods). U.S. food samples were shipped to the laboratory in Sydney for testing. The testing procedure has been described in detail previously (14): each person consumed a variety of test foods on separate days, with insulin measured every 15 minutes for 2 hours after consumption. The food insulin index value was calculated by dividing the area under the insulin response curve for 1,000 kJ of a test food by the area under the insulin response curve for 1,000 kJ of the reference food (glucose). The insulin index value for each test food represented the mean responses of 11 to 13 subjects. On the basis of these new analytic data and the previously published estimates, we built an insulin index database for a large number of foods listed on the food frequency questionnaires.

Using the food insulin index, we calculated the average dietary insulin load for each participant by multiplying the insulin index value of each food by its energy content and summing values for all food items reported [Σ(food insulin index × kilocalories per serving × servings per day)]. Each unit of dietary insulin load represents the equivalent insulin response generated by 1 kcal of glucose.

The dietary insulin index for the overall diet, which is the weighted mean of the insulin index values for each of the component foods, was calculated by dividing the dietary insulin load by the total energy intake [Σ(kilocalories per serving × servings per day)].

Validation studies have shown that the food frequency questionnaire is a reasonably accurate measure of a person's food intake (17, 18). For food items that have high insulin index values, the correlation coefficients between the food frequency questionnaire and 1-week diet records were as follows: 0.46 (NHS) and 0.66 (HPFS) for meat, 0.79 and 0.86 for cold breakfast cereal, 0.81 and 0.88 for skimmed milk, 0.77 and 0.37 for dark bread, and 0.71 and 0.45 for white bread.

Information on smoking, body mass index (BMI), physical activity, family history of colorectal cancer, diabetes (incident cases during follow-up), ulcerative colitis, polyps, lower endoscopy, aspirin use, and multivitamin use were updated every 2 to 4 years.

Case ascertainment

We obtained self-reported information on the occurrence of colorectal cancer on each follow-up questionnaire and asked participants for permission to access medical records to confirm diagnosis. The National Death Index was also used to identify fatalities. A total of 2,481 (1,420 in the NHS and 1,061 in the HPFS) colorectal cancer cases were identified. Among them, 1,761 (1,067 in the NHS and 694 in the HPFS) were colon cancer and 545 (323 in the NHS and 222 in the HPFS) were rectal cancer; the rest were not clearly classified for subsite.

Statistical analysis

The follow-up started from 1980 in the NHS and 1986 in the HPFS and ended with colorectal cancer diagnosis, death, or on June 30, 2006, in the NHS and January 31, 2006, in the HPFS. Dietary insulin load and dietary insulin index were energy adjusted by the residual method (19). We first analyzed dietary insulin scores derived from baseline questionnaires and then did 3 alternative analyses: using the 1984 dietary questionnaire as baseline for the NHS (because the 1984 questionnaire had more food items), updating the scores every 4 years (simple update), and updating the scores cumulatively (cumulative update). In multivariate analyses, we adjusted for BMI, physical activity, family history of colorectal cancer, lower endoscopy, diabetes (incident cases during follow-up), ulcerative colitis, history of polyps, aspirin use, multivitamin use, smoking, alcohol, and energy intake. Quintiles of main exposures and covariates were based on the

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cohort-specific intake distributions. Tests for trend were done using continuous variables of dietary insulin load and dietary insulin index. Results from the 2 cohorts were pooled to compute a summary risk estimate, using a random effects model (20).

To examine whether the associations of interest were modified by the preexisting insulin resistance, we stratified analyses by BMI (above or below 27.5 kg/m^2) and physical activity (above or below median). BMI of 27.5 kg/m^2 was used as the cutoff point because colon cancer risk mainly increased among more severe overweight or obese participants in our 2 cohorts (21, 22). Because high fiber intake may reduce insulin demand (23), we also examined the joint effect of insulin load and fiber intake by cross-classifying participants by both variables. Tests for interaction were done by the Wald test using cross-product terms.

Results

At baseline, men and women with higher insulin load were less likely to smoke and consumed less alcohol (Table 1). Although dietary insulin load and dietary insulin index were inversely associated with colorectal cancer risk in age-adjusted models, multivariate analyses showed no association in men or women or men and women combined (Table 2). The pooled multivariate relative risks (RR) of colorectal cancer for the highest versus the lowest quintile were 0.91 (95% CI = 0.79–1.05) for dietary insulin load and 0.93 (95% CI = 0.81–1.08) for dietary insulin index, and the pooled RRs did not differ greatly across quintiles. Separate analyses of colon and rectal cancer revealed no material differences in the association with dietary insulin load or dietary insulin index (Table 2). A further division of colon cancer into proximal and distal colon cancer also did not alter the findings (data not shown).

Dietary insulin load and dietary insulin index were not associated with colorectal cancer risk for individuals who were overweight, less active, or both (Table 3). None of the *P* values for the interactions were statistically significant (data not shown). Similarly, the association of insulin load with colorectal cancer risk did not vary by fiber intake: the pooled multivariate RRs for the combination of a high insulin load and a low fiber intake compared with the opposite extreme were 1.01 (95% CI = 0.83–1.22) for total fiber and 1.03 (95% CI = 0.72–1.46) for cereal fiber.

We observed no association when we used the 1984 dietary questionnaire as baseline for the NHS, or when

Table 1. Baseline characteristics of participants by quintiles of energy-adjusted dietary insulin load[a]

	NHS[b]			HPFS[b]		
	Q1	Q3	Q5	Q1	Q3	Q5
N	17,289	17,304	17,413	9,125	9,126	9,319
Dietary insulin load, energy adjusted, median	547	646	745	673	807	930
Dietary insulin index, energy adjusted, median	34	40	45	34	41	47
Dietary glycemic load, energy adjusted, median	61	84	111	96	125	148
Age, mean, y	46	46	47	55	53	53
BMI, mean, kg/m^2	23.8	24.4	24.7	25.8	25.6	25.0
Physical activity, mean, h/wk (NHS), MET-h/wk (HPFS)	3.9	3.9	3.9	19.8	21.8	22.5
Ulcerative colitis, %	0.9	1.0	1.3	0.9	1.0	1.1
Family history of colorectal cancer, %	8.0	7.4	8.0	8.2	8.5	8.3
History of lower endoscopy, %	9	10	10	28	28	29
Current smoking, %	40	27	23	17	8	5
Alcohol intake, mean, g/d	16	4	2	27	8	4
Aspirin use, %	47	47	47	31	29	29
Multivitamin use, %	35	33	35	43	41	42
Energy intake, mean, kcal	1,558	1,584	1,535	1,957	2,026	1,938
Red meat, mean, servings/d/1,000 kcal	1.0	0.9	0.7	0.6	0.6	0.4
Processed meat, mean, servings/d/1,000 kcal	0.12	0.11	0.08	0.10	0.09	0.06
Fruit and vegetable, mean, servings/d/1,000 kcal	2.4	2.7	2.9	2.7	2.8	2.9
Total fat, energy adjusted, mean, g/d	77	72	58	76	73	63
Protein, energy adjusted, mean, g/d	77	77	71	95	93	87
Carbohydrates, energy adjusted, mean, g/d	119	154	194	192	237	274

Abbreviation: MET, metabolic equivalents.

[a]All variables (except age, dietary insulin load, dietary insulin index, and dietary glycemic load) are age standardized.

[ab]Baseline: 1980 for NHS, 1986 for HPFS.

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Table 2. Dietary insulin load, dietary insulin index, and risk of colorectal cancer

	Dietary insulin load (quintiles)					P_{trend}
	1	2	3	4	5	
NHS						
Quintile median	547	608	646	683	745	
Person-years	419,379	425,767	425,292	428,077	426,756	
Colorectal						
No. of cases	297	291	298	269	265	
Age-adjusted	1.0	1.00 (0.85–1.17)	1.03 (0.88–1.21)	0.92 (0.78–1.09)	0.87 (0.73–1.02)	0.03
Multivariate[a]	1.0	1.02 (0.86–1.21)	1.07 (0.90–1.27)	0.97 (0.81–1.16)	0.92 (0.77–1.11)	0.17
Colon						
No. of cases	224	219	230	201	193	
Age-adjusted	1.0	1.00 (0.83–1.20)	1.05 (0.88–1.27)	0.92 (0.76–1.11)	0.83 (0.69–1.01)	0.03
Multivariate[a]	1.0	1.00 (0.83–1.22)	1.06 (0.87–1.29)	0.94 (0.76–1.15)	0.86 (0.70–1.07)	0.09
Rectum						
No. of cases	64	66	63	64	66	
Age-adjusted	1.0	1.05 (0.74–1.48)	1.01 (0.71–1.43)	1.01 (0.72–1.44)	1.01 (0.72–1.43)	0.66
Multivariate[a]	1.0	1.16 (0.81–1.66)	1.16 (0.80–1.69)	1.19 (0.81–1.73)	1.21 (0.82–1.77)	0.63
HPFS						
Quintile median	673	757	807	855	930	
Person-years	159,437	165,231	163,027	165,223	166,122	
Colorectal						
No. of cases	254	217	213	200	177	
Age-adjusted	1.0	0.88 (0.73–1.05)	0.89 (0.74–1.07)	0.81 (0.67–0.97)	0.72 (0.59–0.87)	<0.001
Multivariate[a]	1.0	0.96 (0.79–1.16)	1.02 (0.84–1.25)	0.97 (0.78–1.19)	0.90 (0.72–1.12)	0.29
Colon						
No. of cases	164	136	139	143	112	
Age-adjusted	1.0	0.86 (0.69–1.09)	0.90 (0.71–1.13)	0.90 (0.71–1.12)	0.70 (0.55–0.89)	0.01
Multivariate[a]	1.0	0.93 (0.73–1.18)	1.00 (0.78–1.29)	1.04 (0.81–1.35)	0.85 (0.65–1.12)	0.34
Rectum						
No. of cases	51	51	45	31	44	
Age-adjusted	1.0	1.02 (0.69–1.50)	0.98 (0.66–1.47)	0.63 (0.40–0.98)	0.92 (0.61–1.38)	0.20
Multivariate[a]	1.0	1.10 (0.73–1.66)	1.13 (0.73–1.76)	0.74 (0.45–1.21)	1.11 (0.69–1.77)	0.81
NHS and HPFS, multivariate[a,b]						
Colorectal	1.0	0.99 (0.87–1.12)	1.05 (0.92–1.19)	0.97 (0.84–1.11)	0.91 (0.79–1.05)	0.09
Colon	1.0	0.97 (0.83–1.13)	1.04 (0.89–1.21)	0.98 (0.83–1.15)	0.86 (0.72–1.01)	0.06
Rectum	1.0	1.12 (0.86–1.47)	1.14 (0.86–1.52)	0.95 (0.58–1.54)	1.15 (0.86–1.55)	0.89
	Dietary insulin index (quintiles)					P_{trend}
	1	2	3	4	5	
NHS						
Quintile median	34	38	40	42	46	
Person-years	418,534	425,664	425,518	427,728	427,828	
Colorectal						
No. of cases	304	284	282	269	281	
Age-adjusted	1.0	0.95 (0.80–1.11)	0.95 (0.81–1.12)	0.90 (0.75–1.05)	0.90 (0.76–1.06)	0.05
Multivariate[a]	1.0	0.96 (0.81–1.14)	0.98 (0.82–1.16)	0.92 (0.77–1.10)	0.95 (0.79–1.13)	0.22
Colon						
No. of cases	222	215	224	201	205	
Age-adjusted	1.0	0.98 (0.81–1.19)	1.05 (0.87–1.26)	0.91 (0.75–1.11)	0.90 (0.74–1.09)	0.06
Multivariate[a]	1.0	0.99 (0.81–1.20)	1.05 (0.86–1.28)	0.93 (0.75–1.15)	0.93 (0.75–1.15)	0.13

(Continued on the following page)

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Table 2. Dietary insulin load, dietary insulin index, and risk of colorectal cancer (Cont'd)

	Dietary insulin index (quintiles)					P_{trend}
	1	2	3	4	5	
Rectum						
No. of cases	71	66	54	59	73	
Age-adjusted	1.0	0.93 (0.67–1.31)	0.77 (0.54–1.09)	0.82 (0.58–1.16)	0.99 (0.72–1.38)	0.78
Multivariate[a]	1.0	1.01 (0.71–1.43)	0.85 (0.58–1.24)	0.92 (0.63–1.35)	1.14 (0.79–1.66)	0.50
HPFS						
Quintile median	34	38	41	43	47	
Person-years	159,133	163,853	164,305	166,404	165,344	
Colorectal						
No. of cases	252	223	213	196	177	
Age-adjusted	1.0	0.90 (0.75–1.08)	0.89 (0.74–1.07)	0.80 (0.67–0.97)	0.74 (0.61–0.90)	0.001
Multivariate[a]	1.0	0.99 (0.82–1.20)	1.03 (0.84–1.26)	0.97 (0.78–1.19)	0.92 (0.74–1.15)	0.41
Colon						
No. of cases	165	140	138	136	115	
Age-adjusted	1.0	0.87 (0.69–1.09)	0.88 (0.70–1.11)	0.85 (0.68–1.07)	0.73 (0.57–0.93)	0.01
Multivariate[a]	1.0	0.94 (0.74–1.19)	0.98 (0.77–1.26)	0.99 (0.77–1.28)	0.88 (0.67–1.16)	0.44
Rectum						
No. of cases	51	51	43	36	41	
Age-adjusted	1.0	1.04 (0.70–1.53)	0.91 (0.60–1.37)	0.74 (0.48–1.14)	0.87 (0.58–1.32)	0.26
Multivariate[a]	1.0	1.12 (0.74–1.69)	1.05 (0.67–1.64)	0.87 (0.54–1.41)	1.05 (0.65–1.69)	0.95
NHS and HPFS, multivariate[a,b]						
Colorectal	1.0	0.97 (0.86–1.10)	1.00 (0.88–1.14)	0.94 (0.82–1.07)	0.93 (0.81–1.08)	0.14
Colon	1.0	0.96 (0.83–1.12)	1.03 (0.88–1.20)	0.95 (0.81–1.12)	0.91 (0.77–1.07)	0.09
Rectum	1.0	1.05 (0.80–1.37)	0.92 (0.69–1.23)	0.89 (0.66–1.20)	1.09 (0.81–1.47)	0.66

NOTE: Dietary insulin load and dietary insulin index were measured at baseline, 1980 for NHS and 1986 for HPFS.

[a]Adjusted for age, body mass index (kg/m^2 in quintiles), physical activity (quintiles), family history of colorectal cancer (yes/no), lower endoscopy (yes/no), ulcerative colitis (yes/no), history of polyps (yes/no), aspirin use (never, 1–3, 4–7, $\geq$ 8 tablets/wk), multivitamin use (yes/no), pack-years of smoking (never smoker, 1–9, 10–24, 25–44, and $\geq$ 45 pack-years), alcohol intake (NHS: never, 0.1–4.9, 5–14.9, $\geq$ 15 g/d; HPFS: never, 0.1–9.9, 10–19.9, $\geq$ 20 g/d), and energy intake (quintiles).

[b]NHS and HPFS were pooled using random-effects models.

we used simple or cumulative updating of the dietary insulin scores, or when dietary insulin load and index were not energy adjusted by the residual method, or after excluding the first 2 years of follow-up, restricting to those without ulcerative colitis, or further adjusting for dietary glycemic load, dietary glycemic index, and intakes of red meat, fruit and vegetable, fiber, folate, calcium, and vitamin D (data not shown).

Discussion

We found little evidence that a diet with high insulin load or insulin index is related to colorectal cancer risk. Imprecise measurement of dietary insulin load and index could bias the results toward the null; however, the food insulin index, on which dietary insulin load and index were based, was developed under highly standardized conditions (14): the insulin index value for each food represented the mean insulin responses of 11 to 13 subjects who consumed the test food on separate days. In a validation study, dietary insulin load has been shown to be an accurate measure of actual postprandial insulin responses (15). Furthermore, in the NHS and the HPFS, insulin scores were correlated with plasma triglyceride levels (a marker of insulin production), confirming that the estimation of dietary insulin load and index can predict an expected biological response (Dr. K. Nimptsch, personal communication).

The lack of association in the present study is consistent with most previous studies that examined glycemic load and glycemic index in relation to colorectal cancer. A recent meta-analysis of studies up to 2008 showed that the pooled RRs of colorectal cancer were 1.06 (95% CI = 0.95–1.17; $n = 8$ cohort studies) for glycemic load and 1.04 (95% CI = 0.92–1.12; $n = 7$ cohort studies) for glycemic index (13). In contrast, high blood insulin levels have been associated with increased risk of colorectal cancer in a number of serologic studies (5–12). A recent meta-analysis that summarized epidemiologic studies up to 2007 (24) showed that the pooled RR of colorectal cancer

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Table 3. Dietary insulin load, dietary insulin index, and risk of colorectal cancer stratified by BMI and physical activity[a]

	Dietary insulin load (tertiles)			P_{trend}
	1	2	3	
BMI <27.5 kg/m^2	1.0	1.00 (0.86–1.17)	0.92 (0.81–1.04)	0.13
BMI ≥27.5 kg/m^2	1.0	1.14 (0.83–1.56)	0.90 (0.71–1.14)	0.39
High physical activity[b]	1.0	1.09 (0.95–1.25)	0.95 (0.82–1.11)	0.13
Low physical activity[b]	1.0	0.99 (0.85–1.17)	0.90 (0.76–1.07)	0.39
BMI <27.5 and high physical activity	1.0	1.05 (0.85–1.30)	0.95 (0.80–1.13)	0.14
Intermediate group	1.0	1.02 (0.86–1.20)	0.86 (0.72–1.03)	0.26
BMI ≥27.5 and low physical activity	1.0	0.94 (0.65–1.36)	0.90 (0.63–1.28)	0.44
	Dietary insulin index (tertiles)			P_{trend}
	1	2	3	
BMI <27.5 kg/m^2	1.0	0.96 (0.85–1.08)	0.91 (0.80–1.03)	0.23
BMI ≥27.5 kg/m^2	1.0	1.06 (0.80–1.40)	0.96 (0.76–1.21)	0.50
High physical activity[b]	1.0	0.95 (0.82–1.10)	0.93 (0.78–1.12)	0.31
Low physical activity[b]	1.0	1.00 (0.85–1.18)	0.89 (0.75–1.06)	0.37
BMI <27.5 and high physical activity	1.0	0.93 (0.79–1.10)	0.93 (0.78–1.10)	0.30
Intermediate group	1.0	0.98 (0.83–1.16)	0.87 (0.72–1.04)	0.23
BMI ≥27.5 and low physical activity	1.0	0.98 (0.71–1.35)	0.97 (0.68–1.38)	0.54

NOTE: NHS and HPFS were pooled using random-effects models.

Dietary insulin load and dietary insulin index were measured at baseline, 1980 for NHS and 1986 for HPFS.

[a]Adjusted for age, body mass index (kg/m^2 in quintiles), physical activity (quintiles), family history of colorectal cancer (yes/no), lower endoscopy (yes/no), ulcerative colitis (yes/no), history of polyps (yes/no), aspirin use (never, 1–3, 4–7, ≥ 8 tablets/wk), multivitamin use (yes/no), pack-years of smoking (never smoker, 1–9, 10–24, 25–44, and ≥45 pack-years), alcohol intake (NHS: never, 0.1–4.9, 5–14.9, ≥15 g/d; HPFS: never, 0.1–9.9, 10–19.9, ≥20 g/d), and energy intake (quintiles).

[b]Above or below median (NHS: 3.0 h/wk; HPFS: 11.5 MET-h/wk).

was 1.35 (95% CI = 1.13–1.61; $n = 10$ prospective studies and 1 case–control study), comparing the highest versus lowest category of insulin or C-peptide.

One explanation for the disparate findings with serum insulin and insulinogenic diets is that long-term insulin levels may not be greatly influenced by the consumption of insulinogenic foods because food intake increases postprandial insulin demand and therefore affects insulin levels only temporarily (2, 3). As insulin resistance greatly upregulates the long-term secretory tone and causes a compensatory increase in both basal insulin secretion and postload insulin responses, it is possible that insulin resistance, instead of insulinogenic food intake, is the primary contributor to the sustained hyperinsulinemia that is relevant to cancer development. In the prospective Northern Sweden Health and Disease Cohort, fasting insulin level (which mainly reflects the degree of insulin resistance) was positively associated with colorectal cancer and no association was observed for a mix of fasting and nonfasting samples (which reflects both insulin resistance and the influence of insulinogenic foods; ref. 7); in a subcohort of that study, C-peptide levels were positively associated with colorectal cancer risk among fasting women but not among nonfasting women (25). Several other studies found similar increased risk of colorectal cancer for both fasting C-peptide and a mix of fasting and nonfasting C-peptide levels (8, 12, 26); observed positive association with postprandial hyperinsulinemia may principally be due to underlying insulin resistance as well. These findings and our results suggest that high intake of insulinogenic foods alone might not be enough to induce sustained hyperinsulinemia and therefore less likely to influence colorectal cancer risk.

The insulin scores have limitations. They were developed to assess total quantity of insulinogenic food intake but were not designed to measure meal frequency and food combinations, which might also affect insulin response. Another concern is that the food insulin index values were derived from lean university students (14) whose absolute insulin response is likely to be different from that of the older and heavier subjects; however, the method is valid if the increase in insulin levels induced by a food, that is, the relative insulin response, is comparable between the 2 groups. Actually, in the biomarker validation study (Dr. Katharina Nimptsch,

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personal communication), we observed that the positive association between the insulin index and triglycerides was much stronger among overweight individuals, indicating that the general method used to develop the insulin index works among heavier subjects.

In summary, our data suggest that high intake of foods that increase postprandial insulin levels may not play a major part in colorectal cancer development. Further studies should focus on the role of insulin resistance to provide a more precise and thorough understanding of the insulin-colorectal cancer hypothesis.

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No potential conflicts of interest were disclosed.

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