Glycemic Index, Carbohydrates, Glycemic Load, and the Risk of Pancreatic Cancer in a Prospective Cohort Study

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Abstract

Diets with high glycemic index and glycemic load have been associated with insulin resistance. Insulin resistance has been implicated in the etiology of pancreatic cancer. We prospectively investigated the associations between glycemic index, carbohydrates, glycemic load, and available carbohydrates dietary constituents (starch and simple sugar) intake and the risk of pancreatic cancer. We followed the participants in the NIH-AARP Diet and Health Study from 1995/1996 through December 2003. A baseline self-administered food frequency questionnaire was used to assess the dietary intake and exposure information. A total of 1,151 exocrine pancreatic cancer cases were identified from 482,362 participants after excluding first-year of follow-up. We used multivariate Cox proportional hazards regression models to calculate relative risks (RR) and 95% confidence intervals (95% CI) for pancreatic cancer. There were no associations between glycemic index, total or available carbohydrates, gycemic load, and pancreatic cancer risk. Participants with high free fructose and glucose intake were at a greater risk of developing pancreatic cancer (highest compared with lowest quintile, RR, 1.29; 95% CI, 1.04-1.59; *P* trend = 0.004 and RR, 1.35; 95% CI, 1.10-1.67; *P* trend = 0.005, respectively). There were no statistically significant interactions by body mass index, physical activity, or smoking status. Our results do not support an association between glycemic index, total or available carbohydrate intake, and glycemic load and pancreatic cancer risk. The higher risk associated with high free fructose intake needs further confirmation and elucidation. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1144–51)

Introduction

The nutritional contribution to the etiology of pancreatic cancer is unclear. Prediagnostic elevations in postload plasma glucose (1, 2), fasting serum and plasma glucose (3, 4), insulin (5), and plasma C-peptide levels (6) have been associated with greater risk of pancreatic cancer. Diabetes (7) and obesity (8, 9), two factors associated with insulin resistance, have been shown to increase the risk of pancreatic cancer. These observations suggest that insulin plays an important role in pancreatic carcinogenesis.

Insulin is produced by the pancreas in response to elevated blood glucose levels. In people with normal glucose metabolism, 85% to 94% of the variability of postprandial glucose and insulin responses can be explained by both the source and the amount of carbohydrates (10). Glycemic index is an indicator of carbohydrate quality because it reflects the glucose response of each unit of carbohydrate in a carbohydrate-containing food compared with the response to an equal amount of pure glucose (11). Glycemic load is an indicator of both the quality and the quantity of carbohydrates in a given food because it is the product of its glycemic index and the grams of carbohydrate from a single serving of that food (12). High–glycemic index diets have been associated with hyperinsulinemia and may induce insulin resistance (13). High–glycemic load diets have been associated with increased risk of type 2 diabetes in women (14) and men (15), and of cardiovascular disease in women (12).

If high–glycemic index or high–glycemic load diets increase the risk of insulin resistance and if hyperinsulinemia and peripheral insulin resistance are possible risk factors for pancreatic cancer, we would hypothesize that such diets also increase the risk of developing pancreatic cancer. Therefore, we prospectively examined the relationship between dietary glycemic index, carbohydrates, glycemic load, starch, and simple sugar and the risk of pancreatic cancer in a large cohort study.

Materials and Methods

Study Population. The NIH-AARP Diet and Health Study was established in 1995-1996. Details of the study design and questionnaire have been described elsewhere (16). Briefly, a self-administered baseline food frequency questionnaire (FFQ) was mailed to 3.5 million AARP members ages 50 to 71 y who resided in six U.S. states (California, Florida, Louisiana, New Jersey, North

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Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI). The questionnaire was returned by 617,119 members, and 567,169 participants completed the questionnaire satisfactorily (16). The study was approved by the National Cancer Institute Special Studies Institutional Review Board. Informed consent was obtained from all participants by virtue of completing the questionnaire.

We excluded participants with duplicate responses (n = 179) and participants who moved out of the study areas before returning the FFQ (n = 321), died before study entry (n = 261), or withdrew (n = 6). From the remaining 566,402 participants, we further excluded participants who had the questionnaire completed by proxy respondents (n = 15,760), had prevalent cancer cases as identified through cancer registries at baseline (n = 8,583), had extreme energy intake (i.e., more than two interquartile ranges above the 75th or below the 25th percentile of log-transformed energy intake, corresponding to <416 kcal/d and >6,138 kcal/d for men and <322 kcal/d and >4,818 kcal/d for women; n = 4,792), and had <1 y of follow-up (n = 6,726). Because diabetics tended to consume carbohydrate-modified diets, we excluded them from the main analysis and did a separate analysis among people who had self-reported diabetes (n = 48,179). Our final analytic cohort consisted of 482,362 members, including 280,542 men and 201,820 women.

Cohort Follow-up and Case Ascertainment. Person-time was calculated from 1 y after the response to the questionnaire to the date of pancreatic cancer diagnosis, moving out of the study areas, death from any cause, or December 31, 2003, whichever came first. In addition to the participants who resided in the eight initial study areas, the participants who moved to Texas, Nevada, and Arizona were followed up. Vital status was ascertained by annual linkage to the Social Security Administration Death Master File. Our outcome of interest was incident adenocarcinoma of the exocrine pancreas (ICD-O-3 code C25.0-C25.9, excluding C25.4). Our case definition excluded histology types 8150-8155, 8240, 8246, and 8502 because the etiology of these cancers is thought to be different. We identified 1,006 incident cases by linking cohort members to 11 State Cancer Registries and 145 cases from the National Death Index. According to the cancer registry, of 1,006 cases, 71.4% (n = 719) were microscopically confirmed, 16.6% (n = 167) were diagnosed by cytology, 6.6% (n = 66) were diagnosed by radiology/imaging technique, 2.5% (n = 25) were diagnosed by other clinical approach, and 2.9% (n = 29) had unknown diagnosis method.

Dietary Assessment. The FFQ assessed diet intakes by querying the usual frequency of consumption and portion size of 124 food items and asking 21 questions about low-fat, sugar-free, or high-fiber versions of foods consumed over the last 12 mo before baseline (16). We calculated daily nutrient intake by multiplying the daily frequency of each consumed food item by the nutrient value of sex-specific portion size using national dietary data and the nutrient database from US Department of Agriculture and Continuing Survey of Food Intakes by Individuals (CSFII) 1994-1996 as described previously (16). Total sugar intake was the sum of the simple sugar intake. The glycemic index and glycemic load values in the NIH-AARP nutrient database were determined using methods describe in detail elsewhere (17). Briefly, the list of foods was condensed into 225 nutritionally similar groupings of individual foods. Using an international table of measured glycemic index values for specific foods compiled by Foster-Powell et al. (18), we assigned glycemic index values to each of the individual CSFII foods in these 225 food groups. The method of linkage was by manual review of the glycemic index table to identify those foods that, in the judgment of the investigators, were the best matches for each of the CSFII foods. When the CSFII foods did not match any of the foods in the international table of published values, a series of decision criteria were used to assign the glycemic index value. We then computed sex- and serving size–specific glycemic load for each of the 225 food groups using the weighted mean methods as described by Subar et al. (19). Because glycemic load is designed to be an indicator of the glycemic effect of a food that is inherently a function of the carbohydrate available for digestion and absorption, when calculating glycemic load, we defined available carbohydrate to be the CSFII-based value of grams of carbohydrate per serving minus the CSFII value for grams of dietary fiber per serving (17). The average glycemic load per day for each participant was the sum of the glycemic loads for the total servings of all carbohydrate-containing foods consumed. Therefore, glycemic load represents both the quality and the quantity of carbohydrate intake. The total glycemic index value for each participant was calculated by dividing the glycemic load by available carbohydrate intake, which represents the overall quality of carbohydrate intake.

Other Exposure Assessment. Information on demographic and nondietary exposures, including age, sex, race, educational level, history of diabetes, smoking habits, and physical activity at work and at home, was also queried from the baseline self-administered FFQ (16). Body mass index (BMI) was computed based on self-reported weight and height information (kg/m^2). Participants reported whether they smoked ≥100 cigarettes cumulatively during their entire life to define ever smokers and never smokers. Ever smokers were asked to report how long they had stopped smoking and how many cigarettes they consumed per day on average. Participants reported how often (never, rarely, 1 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, ≥5 times per week) they had engaged in physical activity that lasted at least 20 min and caused increased breathing or heart rate, or worked up a sweat at work or home. One percent of participants with missing physical activity information were assigned to the most common category, 3 to 4 times per week.

Statistical Analyses. Dietary and nutrient intakes were energy-adjusted using the density method. Glycemic index was not energy-adjusted because the quality of carbohydrate consumed should not be inherently related to total energy intake. Pearson correlation coefficients (r) among glycemic index, carbohydrates, glycemic load, and total sugar intake were calculated. Cox proportional hazards regression models, with age as the underlying time metric, were used to estimate the relative risks (RR) and 95% confidence intervals (CI) of developing pancreatic cancer according to quintiles of glycemic index,

glycemic load, total and available carbohydrate intake, starch, disaccharides (sucrose, lactose, and maltose), monosaccharide (free fructose, free glucose, and galactose), and total simple sugar. The Wald test was used to test the linear trend across each exposure variable by taking the ordinal variable (quintile of the intake) as a continuous term in the models. In a separate analysis among 48,179 diabetics, we estimated the RRs and 95% confidence intervals of pancreatic cancer according to the quartile of each dietary nutrient so as to have an adequate number in each category. We presented sex-combined results because the associations between nutrient intakes and cancer risk were not statistically significantly modified by sex.

Age, sex, and total energy intake (kcal/d, log-transformed) were included in the minimally adjusted models. Energy-adjusted intakes of saturated fat (g/1,000 kcal/d) and red meat intake (g/1,000 kcal/d), alcohol use (five-category drink level), BMI (categorized as <20, 20-<25, 25-<30, ≥ 30 kg/m^2, and missing), and smoking variable were adjusted in the multivariate models. These putative risk factors were associated with both the exposures and pancreatic cancer risk, and their addition in the stepwise selection model changed the risk estimate by >10% except for BMI. A smoking variable with finer categories was generated in order to account for its confounding effect: never smokers, quit ≥10 y and smoked <20 cigarette/d, quit ≥10 y and smoked ≥20 cigarette/d, quit 5 to 9 y and smoked <20 cigarette/d, quit 5 to 9 y and smoked ≥20 cigarette/d, quit 1 to 4 y and smoked <20 cigarette/d, quit 1 to 4 y and smoked ≥20 cigarette/d, current smokers with <20 cigarette/d, current smokers with ≥20 cigarette/d, and a missing category. Total fiber intake was not included in the model because the addition of this term in the model did not change the risk estimates by >5%.

Because dietary intake can influence insulin level particularly among individuals who had a previous impaired insulin sensitivity condition due to such factors as obesity, physical inactivity, and smoking, we explored whether the associations between nutrient intakes and risk varied significantly by these factors. The cross-product term was generated using quintiles of glycemic index, glycemic load, free fructose and glucose intake and BMI (cutpoint 30 kg/m^2), physical activity (<3-4 times per week or >3-4 times per week), and smoking status (never versus ever). We examined the interaction on the multiplicative scale and we tested the significance of the interaction terms in the Cox regression models using the likelihood ratio test. Trends in the RRs were examined using the Wald test by treating the interaction term as the continuous variable. The participants with missing value of BMI or smoking status were excluded from the respective stratified analyses. To examine reverse causality, a lag analysis was done by excluding participants with <2 y of follow-up. We also did the sensitivity analyses among 719 microscopically confirmed cases. All analyses were done using STATA 9.0 (Stata Corporation) or SAS 9.0 (SAS Institute). All P values were based on two-sided tests and considered statistically significant at an α level of < 0.05.

Table 1. Selected characteristics of participants according to quintiles (Q) of glycemic index and energy-adjusted glycemic load

Characteristics (mean or proportion)	Glycemic index					Glycemic load				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Glycemic index	48.7	52.0	53.9	55.8	58.9	52.3	53.4	53.8	54.2	55.6
Total carbohydrate, g/1,000kcal/d	136	133	130	129	130	99	121	133	144	162
Glycemic load, g/1,000kcal/d	60.1	63.2	64.4	66.4	71.7	47.4	58.6	65.0	71.5	83.3
Age at entry of cohort (y)	63	63	63	63	63	63	63	63	63	63
Race, %African American	2.8	2.8	3.1	3.6	5.1	2.0	2.4	3.1	3.8	6.2
Education, % college or post college	42.5	43.8	42.3	38.5	29.8	41.5	40.8	39.8	38.4	35.8
BMI, kg/m^2	26.5	26.7	26.9	27.0	27.0	27.3	27.2	26.9	26.6	26.1
Physical activity, % active*	53.9	51.8	48.5	44.6	39.2	42.8	46.4	48.1	50.2	50.5
Smoking history										
Never smokers, %	36.6	37.2	36.8	35.0	31.6	24.4	33.2	37.3	40.6	41.7
Former smokers, %	48.5	49.5	49.2	49.1	47.7	53.0	50.4	48.7	47.0	45.0
Current smokers, %	10.6	9.6	10.4	12.4	17.1	18.6	12.6	10.4	8.9	9.5
Missing	4.3	3.6	3.6	3.5	3.6	4.0	3.9	3.6	3.5	3.7
Dietary and nutrient intake per day †										
Total energy intake, kcal	1,808	1,790	1,810	1,850	1,896	2,044	1,864	1,798	1,737	1,713
Total fat, g/1,000kcal	29.4	32.2	33.8	35.2	36.1	38.2	37.2	34.2	31.1	26.0
Saturated fat, g/1,000 kcal	9.4	10.0	10.5	10.9	11.1	12.1	11.7	10.7	9.6	7.9
Red meat, g/1,000 kcal	26.1	31.2	34.6	37.6	39.7	46.5	39.7	33.6	28.0	21.3
Alcohol, g	20.8	12.9	11.7	10.4	7.8	38.9	10.8	6.7	4.5	2.8
Folate intake, μg/1,000 kcal	374	347	323	296	258	272	305	326	344	352
Fiber intake, g/1,000 kcal	12.2	11.7	11.0	10.1	8.9	8.5	10.3	11.2	11.9	12.0
Available carbohydrate constituents (g/1,000 kcal/d) †										
Starch	42.6	48.2	50.3	51.6	53.7	40.8	47.7	50.7	53.1	54.1
Sucrose	22.4	22.4	22.6	23.7	26.4	15.3	20.3	23.4	26.4	32.0
Fructose	15.9	14.3	13.1	12.6	12.7	8.1	10.8	12.9	15.3	21.4
Glucose	14.4	13.4	12.6	12.2	13.7	8.4	10.7	12.4	14.5	19.7
Total sugar	68.0	61.3	58.0	57.1	58.6	41.0	52.4	59.6	67.1	82.8

*Active physical activity is defined as at least 20 min that caused increases in breathing or heart rate, or worked up a sweat for at least 3 times per week.
†Dietary and nutrient variables adjusted for total energy intake using density methods.

Table 2. Relative risks of pancreatic cancer in relation to daily intake of glycemic index, carbohydrates, and glycemic load

	Quintiles					*P* trend*
	1	2	3	4	5	
Glycemic index						
Range	24.5-46.2	46.2-48.4	48.4-50.3	50.3-52.6	≥52.6	
Case/Person-year	206/597,452	235/603,984	216/606,201	222/608,882	271/620,128	
RR† (95% CI)	1.00	1.11 (0.92-1.34)	1.00 (0.83-1.21)	1.03 (0.85-1.24)	1.26 (1.05-1.51)	0.05
RR‡ (95% CI)	1.00	1.05 (0.87-1.27)	0.96 (0.80-1.17)	0.92 (0.76-1.12)	1.09 (0.90-1.32)	0.78
Total carbohydrate (g/1,000 kcal/d)						
Range	9.0-111.2	111.2-125.1	125.1-137.1	137.1-151.5	≥ 151.5	
Case/Person-year	278/583,260	230/597,078	215/607,582	225/618,117	203/630,611	
RR† (95% CI)	1.00	0.81 (0.68-0.96)	0.74 (0.62-0.89)	0.77 (0.64-0.92)	0.69 (0.57-0.83)	0.001
RR‡ (95% CI)	1.00	0.92 (0.76-1.11)	0.96 (0.78-1.20)	1.10 (0.86-1.41)	1.12 (0.84-1.50)	0.26
Available carbohydrate (g/1,000 kcal/d)						
Range	8.7-101.9	101.9-114.7	114.7-125.7	125.7-138.9	≥138.9	
Case/Person-year	276/580,193	232/595,488	211/607,520	229/619,984	203/633,463	
RR† (95% CI)	1.00	0.82 (0.69-0.98)	0.73 (0.61-0.88)	0.78 (0.66-0.94)	0.70 (0.58-0.84)	<0.001
RR‡ (95% CI)	1.00	0.94 (0.77-1.14)	0.96 (0.77-1.18)	1.11 (0.88-1.40)	1.11 (0.84-1.46)	0.25
Glycemic load (g/1,000 kcal/d)						
Range	4.0-54.5	54.5-61.6	61.6-67.7	67.7-74.9	≥74.9	
Case/Person-year	277/581,799	210/592,017	226/608,058	236/620,894	202/633,879	
RR† (95% CI)	1.00	0.75 (0.62-0.90)	0.78 (0.66-0.94)	0.80 (0.67-0.95)	0.68 (0.57-0.82)	<0.001
RR‡ (95% CI)	1.00	0.86 (0.71-1.05)	1.03 (0.84-1.26)	1.01 (0.81-1.26)	0.95 (0.74-1.22)	0.83

NOTE: All Cox proportional hazard regression models were run using age as the underlying time metric.
*Linear trend was tested using the Wald test by treating the ordinal variables as the continuous variable.
†Adjusted for age, sex, and total energy intake (log-transformed).
‡Adjusted for age, sex, total energy intake (log-transformed), smoking variables, alcohol use (5-category drink level), energy-adjusted saturated fat and red meat intake, and BMI (categorical). A smoking variable with finer categories was generated in order to account for its confounding effect: never smokers, quit ≥10 y and smoked <20 cigarette/d, quit ≥10 y and smoked ≥20 cigarette/d, quit 5-9 y and smoked <20 cigarette/d, quit 5-9 y and smoked ≥20 cigarette/d, quit 1-4 y and smoked <20 cigarette/d, quit 1-4 y and smoked ≥20 cigarette/d, current smokers with <20 cigarette/d, current smokers with ≥20 cigarette/d, and a missing category.

Results

The average duration of follow-up was 7.2 years for the whole cohort. A total of 1,151 pancreatic cancer cases (733 men and 418 women) were included in the current analysis. The means (± SD) for glycemic index were 54.1 (± 3.8) in men and 53.5 (± 3.8) in women. The means (± SD) for energy-adjusted total carbohydrate intake were 128.4 (± 24.6) in men and 136.4 (± 23.9) in women. The means (± SD) for energy-adjusted glycemic load were 64.0 (± 13.2) for men and 66.7 (± 12.5) for women. The major foods contributing to glycemic load in this study population were white bread/rolls (5.76% of total glycemic load), orange/grape fruit juice (5.45%), whole grain bread/rolls (5.19%), white potatoes (4.04%), rice/grains (3.81%), bananas (3.63%), sugar-sweetened soft drinks (3.55%), and pasta (2.94%). Glycemic index had no correlation with total carbohydrate intake ($r = -0.05$) and total sugar intake ($r = -0.14$). Glycemic load had moderate positive correlation with glycemic index ($r = 0.33$), and strong positive correlation with total carbohydrate intake ($r = 0.91$) and total sugar intake ($r = 0.71$).

Table 1 summarizes the characteristics of the study population across the quintiles of glycemic index and energy-adjusted glycemic load. Compared with those in the lower quintile of glycemic index, those in the highest quintile were more likely to be current smokers, to be less physically active, to have lower folate and fiber intake, and to have a higher BMI. They consumed more total energy, saturated fat, and red meat. The characteristics of the participants across increasing quintiles of glycemic load were not in agreement with those of glycemic index in that the participants with higher glycemic load values were more likely to have a healthy lifestyle profile.

The assumption of proportionality was not violated for exposure variables and confounding factors using Grambsch and Therneau's test. The RRs all referred to the highest quintile compared with the lowest. Table 2 shows that there was no association between glycemic index value, total and available carbohydrate intake, or glycemic load and incident pancreatic cancer. In the minimally adjusted Cox regression models, carbohydrate intake and glycemic load had strong inverse associations with pancreatic cancer. However, these associations were not seen in the multivariate models.

Table 3 shows that high free fructose and free glucose intake were associated with slightly increased risk of pancreatic cancer. The adjusted RR for the highest (≥18.4 g/1,000 kcal/day) compared with the lowest quintile of fructose (≤7.29 g/1,000 kcal/day) was 1.29 (95% confidence interval, 1.04-1.59; *P* trend = 0.004). The adjusted RR for the highest (≥17.4 g/1,000 kcal/day) compared with the lowest quintile of glucose intake (0.45 ~ 8.09 g/1,000 kcal/day) was 1.35 (95% confidence interval, 1.10-1.67, *P* trend = 0.005). We did not find an association of sucrose intake with pancreatic cancer risk.

There were no statistically significant interactions between risk of pancreatic cancer and nutrient intakes by BMI, physical activity, and smoking status. Table 4 shows that the associations between free fructose and free glucose intake and risk were more evident in participants who were ever smokers.

The participants with self-reported diabetes had significantly lower intakes of all nutrients we examined than did nondiabetics except for starch. A total of 200

self-reported diabetic participants developed pancreatic cancer during the follow-up. None of the nutrients had a statistically significant association with the risk of pancreatic cancer in this subgroup as estimated by the multivariate models (data not shown).

After we further excluded participants who died or were censored in the second year of follow-up, the results were essentially the same. Similarly, the relative risks did not change meaningfully after we limited our analysis to the 719 cases that were microscopically confirmed. The inclusion or exclusion of the outliers of intake of glycemic load did not change our results. We observed the same pattern of associations when quartiles of intakes were used in the models.

Discussion

In older Americans in the NIH-AARP Diet and Health Study, we did not detect associations between glycemic index, carbohydrate intake, and glycemic load and the risk of pancreatic cancer. High free fructose and, less strongly, high free glucose intake were associated with increased risk of pancreatic cancer.

Epidemiologic studies on the relationship of total carbohydrate intake with the risk of pancreatic cancer have been fairly inconsistent. Six case-control studies have reported a positive association (20); one case control study (21) and one cohort study of Finnish male smokers (22) have reported an inverse association. The remaining studies, including five large prospective cohort studies (23-27), showed no association. The heterogeneity of study findings can be attributable to the small number of cases; the variations in study design, study instruments, and study populations (20); and the incomplete control of confounding factors (28). Our study, without many of these limitations, showed no association between total and available carbohydrate intake and the risk of pancreatic cancer. Six prospective cohort studies have investigated the association between glycemic index and glycemic load in relation to the risk of pancreatic cancer and consistently found no associations (23-27, 29). Our study, with by far the largest sample size, was consistent with these studies. The associations diminished after confounding factors were adjusted in the models. Glycemic load turned to reflect more dimensions of dietary intake, such as less red meat and fat intake, than just carbohydrate quality and quantity (30).

Table 3. Relative risks of pancreatic cancer in relation to daily intake of available carbohydrate constituents

Nutrient intake (g/1,000 Kcal/d)	Quintiles					*P-trend**
	1	2	3	4	5	
Starch						
Range	0.55-39.2	39.2-46.0	46.0-51.8	51.8-59.0	≥59.0	
Cases	260	257	215	214	205	
RR† (95% CI)	1.00	1.04 (0.87-1.24)	0.88 (0.73-1.07)	0.93 (0.76-1.12)	0.95 (0.78-1.16)	0.32
Sucrose						
Range	0.45-14.9	14.9-19.2	19.2-23.7	23.7-30.0	≥30.0	
Cases	231	212	217	261	230	
RR† (95% CI)	1.00	0.92 (0.76-1.12)	0.93 (0.76-1.13)	1.11 (0.93-1.34)	0.95 (0.78-1.16)	0.68
Lactose						
Range	0-3.06	3.06-5.24	5.24-7.85	7.85-12.2	≥12.2	
Cases	226	250	226	237	212	
RR† (95% CI)	1.00	1.07 (0.89-1.28)	0.97 (0.90-1.18)	1.02 (0.84-1.23)	0.89 (0.73-1.09)	0.22
Maltose						
Range	0-1.09	1.09-1.44	1.44-1.80	1.80-2.34	≥2.34	
Cases	254	224	212	226	235	
RR† (95% CI)	1.00	0.97 (0.81-1.17)	0.93 (0.77-1.12)	1.02 (0.85-1.23)	1.07 (0.88-1.29)	0.45
Free fructose						
Range	0.10-7.29	7.29-10.2	10.2-13.4	13.4-18.4	≥18.4	
Cases	245	221	229	233	223	
RR† (95% CI)	1.00	1.01 (0.83-1.22)	1.13 (0.94-1.37)	1.22 (1.00-1.49)	1.29 (1.04-1.59)	0.004
Free glucose						
Range	0.45-8.09	8.09-10.5	10.5-13.2	13.2-17.4	≥17.4	
Cases	245	225	257	205	219	
RR† (95% CI)	1.00	1.04 (0.86-1.25)	1.32 (1.09-1.58)	1.12 (0.91-1.37)	1.35 (1.10-1.67)	0.005
Galactose						
Range	0-0.04	0.04-0.07	0.07-0.10	0.10-0.18	≥0.18	
Cases	274	244	230	208	195	
RR† (95% CI)	1.00	0.99 (0.83-1.18)	0.96 (0.80-1.1)	0.88 (0.75-1.07)	0.91 (0.75-1.11)	0.19
Total sugar						
Range	2.16-42.0	42.0-52.4	52.4-62.5	62.5-75.8	≥75.8	
Cases	223	246	228	250	204	
RR† (95% CI)	1.00	1.14 (0.94-1.38)	1.10 (0.90-1.34)	1.23 (1.01-1.51)	1.10 (0.88-1.38)	0.28

NOTE: All Cox proportional hazard regression models were run using age as the underlying time metric.

*Linear trend was tested using the Wald test by treating the ordinal variables as the continuous variable.

†Adjusted for age, total energy intake (log-transformed), energy-adjusted saturated fat and red meat intake, alcohol use (5-category drink level), smoking variables, and BMI (categorical). A smoking variable with finer categories was generated in order to account for its confounding effect: never smokers, quit ≥10 y and smoked <20 cigarette/d, quit ≥10 y and smoked ≥20 cigarette/d, quit 5-9 y and smoked <20 cigarette/d, quit 5-9 y and smoked ≥20 cigarette/d, quit 1-4 y and smoked <20 cigarette/d, quit 1-4 y and smoked ≥20 cigarette/d, current smokers with <20 cigarette/d, current smokers with ≥20 cigarette/d, and a missing category.

Table 4. Interaction of daily intake of glycemic index, glycemic load, fructose, and glucose (quintile, Q) with body mass index, physical activity, and smoking in modifying risks of pancreatic cancer

	Cases	RR (95%CI)*					$P^{\dagger}$, $P^{\ddagger}$
		Q1	Q2	Q3	Q4	Q5	
Glycemic index							
BMI <30 kg/m^2	910	1.00	1.06 (0.86-1.32)	0.92 (0.74-1.14)	0.99 (0.80-1.23)	1.14 (0.93-1.41)	
BMI ≥ 30 kg/m^2	214	1.07 (0.75-1.52)	1.19 (0.86-1.65)	1.06 (0.76-1.48)	0.85 (0.60-1.22)	0.93 (0.66-1.30)	0.99, 0.44
Less physical activity§	621	1.00	1.43 (0.99-2.07)	1.08 (0.74-1.58)	1.23 (0.85-1.76)	1.24 (0.88-1.76)	
More physical activity§	530	1.18 (0.85-1.65)	1.19 (0.85-1.65)	1.11 (0.79-1.54)	1.02 (0.72-1.42)	1.24 (0.89-1.73)	0.57, 0.22
Never smokers	313	1.00	1.23 (0.87-1.72)	0.92 (0.64-1.32)	0.87 (0.60-1.27)	1.17 (0.82-1.67)	
Ever smokers	783	1.46 (0.89-2.40)	1.51 (0.92-2.47)	1.47 (0.90-2.41)	1.44 (0.88-2.35)	1.58 (0.97-2.56)	0.75, 0.65
Glycemic load							
BMI <30 kg/m^2	910	1.00	0.83 (0.66-1.03)	1.03 (0.82-1.29)	1.05 (0.83-1.34)	0.94 (0.72-1.23)	
BMI ≥ 30 kg/m^2	214	1.05 (0.79-1.40)	0.96 (0.69-1.33)	0.80 (0.55-1.16)	1.02 (0.71-1.47)	0.92 (0.60-1.40)	0.96, 0.57
Less physical activity§	621	1.00	0.97 (0.71-1.33)	1.12 (0.82-1.54)	1.16 (0.83-1.61)	0.90 (0.62-1.30)	
More physical activity§	530	1.07 (0.83-1.37)	0.86 (0.65-1.13)	0.94 (0.71-1.25)	1.04 (0.78-1.39)	0.99 (0.72-1.36)	0.54, 0.56
Never smokers	313	1.00	0.99 (0.65-1.51)	1.33 (0.90-1.98)	1.21 (0.80-1.82)	1.18 (0.77-1.80)	
Ever smokers	783	1.85 (1.10-3.09)	1.53 (0.90-2.58)	1.62 (0.95-2.76)	1.79 (1.04-3.05)	1.55 (0.90-2.69)	0.99, 0.39
Fructose (g/1,000 kcal)							
BMI <30 kg/m^2	910	1.00	1.05 (0.85-1.30)	1.16 (0.94-1.44)	1.32 (1.07-1.64)	1.28 (1.02-1.62)	
BMI ≥ 30 kg/m^2	214	1.12 (0.83-1.51)	0.97 (0.68-1.37)	1.17 (0.83-1.64)	0.94 (0.63-1.39)	1.49 (1.06-2.10)	0.18, 0.26
Less physical activity§	621	1.00	0.94 (0.69-1.28)	1.05 (0.77-1.44)	1.40 (1.03-1.89)	1.15 (0.83-1.60)	
More physical activity§	530	0.90 (0.70-1.17)	0.98 (0.76-1.27)	1.08 (0.84-1.40)	1.06 (0.82-1.38)	1.22 (0.93-1.60)	0.53, 0.98
Never smokers	313	1.00	1.06 (0.72-1.54)	0.88 (0.60-1.30)	0.97 (0.67-1.42)	1.06 (0.73-1.56)	
Ever smokers	783	1.28 (0.77-2.10)	1.24 (0.74-2.05)	1.55 (0.94-1.58)	1.66 (1.00-2.77)	1.63 (0.97-2.73)	0.02, 0.40
Glucose (g/1,000 kcal)							
BMI <30 kg/m^2	910	1.00	1.12 (0.90-1.37)	1.32 (1.07-1.63)	1.22 (0.97-1.52)	1.35 (1.07-1.71)	
BMI ≥ 30 kg/m^2	214	1.12 (0.83-1.52)	0.87 (0.61-1.26)	1.48 (1.08-2.03)	0.85 (0.56-1.29)	1.55 (1.10-2.18)	0.19, 0.15
Less physical activity§	621	1.00	1.16 (0.86-1.58)	1.19 (0.87-1.64)	1.38 (1.00-1.89)	1.28 (0.92-1.78)	
More physical activity§	530	1.00 (0.77-1.29)	1.01 (0.77-1.31)	1.35 (1.04-1.75)	1.02 (0.77-1.34)	1.32 (1.00-1.74)	0.59, 0.88
Never smokers	313	1.00	1.00 (0.67-1.47)	1.09 (0.76-1.58)	1.09 (0.75-1.58)	1.04 (0.71-1.53)	
Ever smokers	783	1.32 (0.81-2.71)	1.35 (0.82-2.24)	1.78 (1.08-2.94)	1.43 (0.86-2.39)	1.83 (1.10-3.05)	0.03, 0.56

NOTE: All Cox proportional hazard models were run using age as underlying time metric.

*Adjusted for age, total energy intake (log-transformed), alcohol use (5-category drink level), energy-adjusted saturated fat and red meat intake, smoking variables, and BMI (categorical). A smoking variable with finer categories was generated in order to account for its confounding effect: never smokers, quit ≥10 y and smoked <20 cigarette/d, quit ≥10 y and smoked ≥20 cigarette/d, quit 5-9 y and smoked <20 cigarette/d, quit 5-9 y and smoked ≥20 cigarette/d, quit 1-4 y and smoked <20 cigarette/d, quit 1-4 y and smoked ≥20 cigarette/d, current smokers with <20 cigarette/d, current smokers with ≥20 cigarette/d, and a missing category.

†Linear trend was tested using the Wald test by treating the ordinal variables as the continuous variable.

‡*P* values for likelihood ratio test for interaction term.

§Less physical activity is defined as physical activity at least 20 minutes that caused increases in breathing or heart rate for less than 3-4 times per week. More physical activity is physical activity at least 20 minutes that caused increases in breathing or heart rate for 3-4 times or more per week.

Evidence supporting a role of insulin in pancreatic cancer development comes from a variety of studies. Insulin acted as a growth factor for mucosal cells *in vitro* (31). Increased serum insulin can act indirectly as a growth factor by up-regulating systemic insulin-like growth factor (IGF)-I activity (32). Although two previous studies found no association between the risk of pancreatic cancer and prediagnostic plasma levels of IGF-I, IGF-II, or IGF binding protein (BP)-3 (33, 34), one study found that low plasma IGFBP-1 levels significantly predicted an increased risk of pancreatic cancer (35) and one found that high serum levels of IGF-I and IGFBP-3 may be associated with an increased risk of death from pancreatic cancer (36). Frequent consumption of high–glycemic load foods may increase the risk of pancreatic cancer by inducing hyperglycemia, increasing insulin demand, and leading to insulin resistance.

To date, however, no epidemiologic study has provided evidence to support the hypothesis that high glycemic index or glycemic load *per se* increases the risk of pancreatic cancer. Our failure to detect a positive association, if one were to exist, could partially be due to the limitations of the current study. Firstly, because the total carbohydrate and glycemic index values of our study might be lower than those reported in other populations (27, 37), and glycemic index values have a narrower range (38, 39), the contrast between ''high'' and ''low'' levels could be insufficient to observe an association if one exists. However, those studies that had higher and wider ranges of glycemic index or glycemic load did not find an association either. Secondly, the random measurement error in evaluating dietary intake using the FFQ could attenuate our risk estimates towards the null. Nevertheless, the energy-adjusted Pearson correlation coefficient for total carbohydrate intake between the FFQ and two nonconsecutive 24-hour recalls were 0.71 for men and 0.64 for women in a validation study (40).

The lack of association we found between glycemic index/glycemic load and the risk of pancreatic cancer could be true. At a biological level, glycemic index is originally conceived as an inherent property of the food, but not as a metabolic response of an individual to the food (41). Thus if glycemic index and glycemic load do not in fact affect metabolic response, they will not be relevant to health outcomes. Furthermore, it is still a

matter of considerable debate whether the glycemic index of individual foods is maintained in mixed meals. Along the same line, because the glycemic index of a food describes an acute physiologic event (2-hour postprandial glucose response) elicited under controlled experiment conditions, the impact of dietary glycemic index as a long-term exposure remains a question (30). A recent Danish study did not find associations of glycemic index, total carbohydrate intake, and glycemic load with insulin resistance in nondiabetic women and men (37). Alternatively, other than glycemic index, it may be more constructive to use an insulin index (42) or a fructose index (43) as a measure of the relevant exposure to carbohydrate-containing food.

Two case-control studies have found that high starch (22, 44) and simple sugar (45) intake increased pancreatic cancer risk in men. However, our findings were in line with previous findings that showed overall null associations of starch, sucrose (20, 23, 24, 26), simple sugars (27, 44), and total sugar (24, 26) with risk. Our finding that high free fructose intake increased risk offered a support to what was observed in the Nurses' Health Study (23) and in the Multiethnic Cohort Study (26). Although we could not exclude the possibility that this was a chance finding given the many hypotheses we tested, the stronger associations seen among ever smokers offered a certain consistency to this observation. Dietary fructose *per se* does not produce a glycemic response, but fructose is the only sugar that raises uric acid concentration in humans (46, 47). Uric acid can block the ability of insulin to regulate how body cells use and store sugar and other nutrients for energy. High uric acid concentration can lead to obesity (48), metabolic syndrome (49), and type 2 diabetes (50). Serum uric acid concentration has been shown to have a strong positive association with the risk of pancreatic cancer mortality in men (1). Our subsequent analysis showed that the increased risk was attributable to free fructose from fruit and fruit juice, but not free fructose from soft drinks or other nonnatural resources. In line with this, we did not find an association between added sugar and sugar-sweetened food and the risk of pancreatic cancer (51). In our study population, the amount of free fructose from fruit and fruit juice was much higher than that from other sources (e.g., soda and soft drinks). The further analysis showed that fruit, but not fruit juice, was associated with a greater risk of pancreatic cancer. This finding was consistent with that of the Multiethnic Cohort Study (26). However, the metabolic function of the transient increase in uric acid after fruit consumption is unknown. The positive association between the risk of pancreatic cancer and high glucose intake has not been reported before, which was likely due to the fact that glucose and fructose are equally present and track together in foods.

In the Nurses' Health Study, glycemic load has been positively associated with the risk among sedentary and obese women but not among normal weight and active women (23). However, we did not provide evidence to support the hypothesis that glycemic index, glycemic load, or carbohydrates modify pancreatic cancer risk differentially in people with different states of energy homeostasis. We found that higher free fructose intake conferred a greater risk among ever smokers. This observation could also be a chance finding given the multiple analyses done. Nevertheless, it has been indicated that compared with nonsmokers, chronic cigarette smokers are at a greater risk of developing insulin resistance (52, 53).

In summary, our study did not support the hypothesis that high glycemic index or glycemic load diets increase pancreatic cancer risk. The possibility that carbohydrates contribute to the pancreatic cancer risk among individuals who had different states of energy homeostasis needs further investigation. The findings of the higher risk associated with high free fructose and glucose intake need confirmation and elucidation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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