

Dietary Sugar, Glycemic Load, and Pancreatic Cancer Risk in a Prospective Study

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Background: Evidence from both animal and human studies suggests that abnormal glucose metabolism plays an important role in pancreatic carcinogenesis. We investigated whether diets high in foods that increase postprandial glucose levels are associated with an increased risk of pancreatic cancer. **Methods:** In a cohort of U.S. women (n = 88 802) participating in the Nurses' Health Study, 180 case subjects with pancreatic cancer were diagnosed during 18 years of follow-up. We used frequency of intake of individual foods as reported on a food-frequency questionnaire in 1980 to calculate sucrose, fructose, and carbohydrate intakes; glycemic index (postprandial blood glucose response as compared with a reference food); and glycemic load (glycemic index multiplied by carbohydrate content). Analyses of relative risk (RR) were performed by using multivariable Cox proportional hazards models to adjust for potential confounders. All statistical tests were two-sided. **Results:** Carbohydrate and sucrose intake were not associated with overall pancreatic cancer risk in this cohort. A statistically nonsignificant 53% increase in risk of pancreatic cancer (RR = 1.53, 95% confidence interval [CI] = 0.96 to 2.45) was observed among women with a high glycemic load intake, and a similar association was observed for fructose intake (RR = 1.57, 95% CI = 0.95 to 2.57). The associations of glycemic load and fructose intakes with pancreatic cancer risk were most apparent among women with elevated body mass index (≥ 25 kg/m²) or with low physical activity. Among women who were both overweight and sedentary, a high glycemic load was associated with an RR of 2.67 (95% CI = 1.02 to 6.99; highest versus lowest quartile of intake; *P* for trend = .03), and high fructose was associated with an RR of 3.17 (95% CI = 1.13 to 8.91; *P* for trend = .04). **Conclusion:** Our data support other findings that impaired glucose metabolism may play a role in pancreatic cancer etiology. A diet high in glycemic load may increase the risk of pancreatic cancer in women who already have an underlying degree of insulin resistance. [J Natl Cancer Inst 2002; 94:1293–1300]

In 2002, an estimated 29 700 men and women will be diagnosed with pancreatic cancer in the United States (1). Since 5-year survival from pancreatic cancer is only 4% (2), prevention could have a profound impact on pancreatic cancer mortality. With the exception of cigarette smoking, few risk factors for pancreatic cancer are well established or widely accepted. Progress in understanding pancreatic cancer has been slow, for two main reasons: high fatality rates, which result in methodologic problems in retrospective studies (such as selection bias or error due to reliance on surrogate data) and relatively low incidence rates, which result in few case subjects in prospective studies.

Whether diabetes mellitus is a consequence or a cause of

pancreatic cancer has been a longstanding debate, but recent reviews favor a causal association (3,4). In a meta-analysis of epidemiologic studies, diabetes diagnosed 5 or more years prior to cancer detection was associated with a twofold increase in risk of pancreatic cancer (5), and in a recent publication (6), a 50% increase was observed for diabetes diagnosed 10 or more years prior to cancer detection. In numerous studies (7–11), overweight individuals were consistently at higher risk of pancreatic cancer compared with leaner individuals. The associations between body weight and diabetes suggest that insulin resistance may play a role in pancreatic carcinogenesis. This hypothesis was supported by a recent study (12) in which a direct link was reported between postload plasma glucose levels and pancreatic cancer risk.

Much effort has been invested in understanding how dietary factors affect postprandial glucose levels, given the direct implications for diabetics. More recently, epidemiologic studies (13–17) have examined how these glycemic measures can be applied to long-term dietary intakes. Studies (18–20) indicate that estimates of dietary glycemic load (a quantitative measure of glycemic effect) can reliably predict circulating triglycerides and high-density lipoprotein levels. Glycemic load has been related to the risk of diabetes and heart disease in several (13–15), but not all (16,17), recent prospective studies.

Given that recent studies on pancreatic cancer suggest that glucose intolerance and insulin resistance may play a role in carcinogenesis, dietary factors that increase postprandial plasma glucose levels may have a direct impact on pancreatic cancer risk. Given that high glycemic index and glycemic load have been observed to be associated with the risk of diabetes, heart disease, and lipid levels in this cohort (13,18,21), we chose to examine these variables. The glycemic index reflects the glucose response of each unit of carbohydrate-containing foods and thus provides an indication of carbohydrate quality. The glycemic load (the glycemic index multiplied by the carbohydrate content)

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reflects both the quality and quantity of dietary carbohydrates consumed. In addition, intake of simple sugars such as sucrose and fructose can also predict postprandial glucose levels (22). We examined glycemic index, glycemic load, sucrose, fructose, and carbohydrate intakes in relation to the risk of pancreatic cancer in a large prospective cohort of women with 18 years of follow-up.

SUBJECTS AND METHODS

Population

The Nurses' Health Study (NHS) was initiated in 1976 when 121 700 female registered nurses aged 30–55 years responded to a mailed questionnaire with detailed information on individual characteristics and habits. Important changes in habits (e.g., smoking, vitamin use, medication use, exercise), other factors (e.g., menopausal status, blood pressure, family history of common diseases), and disease onset were updated biennially by using mailed questionnaires. In 1980, 98 462 of the participants returned a dietary questionnaire. Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index (NDI) was searched for nonrespondents; this method has been shown to have a sensitivity of 98% (i.e., the NDI did not identify 2% of deaths) (23). This study was approved by the Human Research Committee at Brigham and Women's Hospital.

After excluding participants with 10 or more blank items on the dietary questionnaire, with an implausibly high or low caloric intake (<500 or >3500 kcal/day, respectively), or with a cancer diagnosis (other than nonmelanoma skin cancer) prior to baseline, 88 802 women were eligible for analysis.

Dietary Assessment

A 61-item food-frequency questionnaire (FFQ) was mailed to all study participants in 1980. To maximize statistical power, all eligible participants who returned the 1980 baseline questionnaire were included in the analysis. On this questionnaire, participants were asked to report their average frequency of intake over the previous year for a specified serving size of each food. Individual nutrient intakes were calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size [obtained from the U.S. Department of Agriculture (24) and supplemented with information from manufacturers] and then summing the contributions from all foods.

The glycemic index is based on the postprandial blood glucose response compared with the glucose response to a reference food. Glycemic index values for foods that appear in the food-frequency questionnaire were obtained either from published estimates (25) or from direct testing of food items at the Nutrition Center of the University of Toronto (provided by D. Jenkins). The glycemic index value is calculated by the following formula: $(\sum \text{incremental blood glucose area under the curve of test food} / \sum \text{incremental blood glucose area under the curve of reference food}) \times 100\%$. The glycemic index value for a meal containing mixed foods can be predicted as the weighted mean of the glycemic index values for each of the component foods (26,27).

Using these glycemic index values, we then calculated the average dietary glycemic load (GL) during the past year for each

participant by multiplying the carbohydrate content (grams per serving) for each food by its glycemic index value, multiplying that product by the frequency of consumption (servings of that food per day), and summing values for all food items reported:

$$\text{Individual dietary GL} = \sum [\text{glycemic index} \times (\text{carbohydrate content of food}) \times (\text{servings of food/day})]$$

Each unit of GL represents the equivalent of 1 g of carbohydrate from white bread. In addition, the overall dietary glycemic index was calculated by dividing GL by the total amount of carbohydrate; the resulting value represents the overall quality of carbohydrate intake for each participant.

In a validity study of 173 women, an FFQ was compared with four 1-week diet records. For individual food items that have high glycemic index values, correlation coefficients between the average intake assessed by two 1-week diet records completed 6 months apart and the FFQ were as follows: 0.71 for white bread, 0.77 for dark bread, 0.66 for potatoes, 0.84 for orange or grapefruit juice, and 0.56 for noncarbonated fruit drinks (includes fruit-flavored punch) (28). Correlation coefficients for total carbohydrate and sucrose were 0.45 and 0.54, respectively, when comparing two 1-week diet records and the FFQ in the same validation study of women (29).

Assessment of Nondietary Factors

Height, current weight, and smoking history (including time since quitting for past smokers) were initially reported at baseline. During follow-up, data on current weight and smoking status were obtained from the biennial mailed questionnaires. We estimated body mass index (BMI) from weight and height ($\text{kg}/\text{height in meters}^2$), as a measure of total adiposity. Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. In 1982, and biennially thereafter, participants were asked about their history of cholecystectomy. For physical activity, we derived a score on the basis of questions asked in the 1980 questionnaire ("At least once a week, do you engage in any regular activity similar to brisk walking, jogging, bicycling, etc., long enough to break a sweat?" "If yes, how many times per week?" "What activity is this?"). The physical activity variable from the 1980 questionnaire has been shown to predict the risk of non-insulin-dependent diabetes mellitus in this cohort of women (30).

Identification of Pancreatic Cancer Case Subjects

Participants were asked to report specified medical conditions, including cancers, that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next-of-kin for decedents) reported a diagnosis of pancreatic cancer, we asked for permission to obtain related medical records or pathology reports. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or phone call to the participant. If the primary cause (or secondary cause) of death as reported by a death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records or at least to confirm the diagnosis of pancreatic cancer. In the NHS, 180 confirmed incident pancreatic cancer case subjects, diagnosed between the date of return of the questionnaire in 1980 and May 31, 1998, were available for the dietary analyses.

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (May 31, 1998), whichever came first. Incidence rates of pancreatic cancer were calculated by dividing the number of incident cases by the number of person-years in each category of dietary exposure. We computed the relative risk (RR) for each of the upper categories by dividing the rates in these categories by the rate in the lowest category.

RRs adjusted for potential confounders were estimated by using Cox proportional hazards models stratified on age in years. The assumptions of proportionality were satisfied. In these models, cigarette smoking was categorized as follows [on the basis of a previous analysis of these cohorts (31)]: never smoker, quit ≥ 15 years ago, quit < 15 years ago and smoked ≤ 25 pack-years in past 15 years, quit < 15 years ago and smoked > 25 pack-years in past 15 years, current smoker with ≤ 25 pack-years in past 15 years, or current smoker with > 25 pack-years in past 15 years. In addition, we controlled for body mass index (< 23 , 23–24.9, 25–26.9, 27–29.9, ≥ 30), height (quintiles), total energy intake (quintiles), physical activity (five categories), and history of diabetes and cholecystectomy (5,32,33). History of diabetes and cholecystectomy were updated every other year with data from the follow-up questionnaires. BMI was not updated in the main analyses because pancreatic cancer is frequently associated with profound weight loss, and our previous findings showed the strongest associations between BMI in 1976 (NHS cohort baseline) and pancreatic cancer risk. Although we examined dietary associations by creating quintiles of the dietary intakes in our main analysis, we used quartiles for the stratified analyses to avoid small numbers. All *P* values are based on two-sided tests. We performed tests for trend by assigning the median value to each category and modeling this variable as a continuous variable.

We performed additional analyses by using the 1984 dietary questionnaire (which contained 126 food items) as baseline, and we performed separate analyses by using cumulative updating of the dietary exposures with follow-up data for 1984, 1986, and 1990 (34).

RESULTS

A number of baseline characteristics did not vary by glycemic load intake in this cohort of women, including height, BMI, and exercise (Table 1). Women with high glycemic load intakes were less likely to have a history of diabetes and smoked fewer pack-years of cigarettes but were more likely to have a history of cholecystectomy. Fat intake (% of total energy intake) and alcohol intake decreased across the quintiles of glycemic load intake. Carbohydrate intake and glycemic index were directly associated with glycemic load.

Among all participants, no consistent trend emerged when examining the association between carbohydrate intake and the risk of pancreatic cancer (Table 2). Similarly, sucrose intake did not increase risk substantially. After controlling for a number of risk factors, we observed a 53% increase in risk of pancreatic cancer for women in the highest quintile of glycemic load intake as compared with women in the lowest quintile. However, this increase was not statistically significant nor was it monotonic across quintiles. A similar increase (57%) that was also statis-

Table 1. Baseline characteristics (mean or percent) according to quintile of energy-adjusted glycemic load among Nurses' Health Study cohort members in 1980*

Characteristic	Quintiles of glycemic load [†]				
	1	2	3	4	5
No. of individuals	17 733	17 771	17 724	17 770	17 804
Glycemic load (median)	80	130	119	137	167
Age, y	47.2	46.9	46.8	46.6	46.2
Height, in.	64.5	64.5	64.5	64.4	64.3
Body mass index, kg/m ²	23.7	23.8	23.7	23.7	23.8
Exercise, h/wk	3.2	3.2	3.2	3.1	3.0
History of diabetes, %	2.6	2.5	2.5	1.9	2.1
Cholecystectomy, %	6.3	6.7	6.7	7.2	8.8
Current smokers, %	3.9	3.2	3.0	2.8	3.0
Cigarette smoking, pack-years [‡]	11.7	10.6	10.0	10.0	10.6
Mean daily intake					
Calories, kcal	1554	1590	1586	1559	1540
Total fat, % of kcal	45.8	41.7	38.9	36.3	31.8
Carbohydrates, % of kcal	27.0	34.7	39.1	43.3	50.4
Alcohol, g	11.8	7.2	5.4	4.2	3.0
Glycemic index [§]	68.3	71.8	73.4	75.1	78.4

*All variables (except age) are age-standardized.

[†]Quintile cutpoints are < 93 , 93–111, 112–127, 128–148, and > 148 .

[‡]Pack-years are calculated for current and past smokers.

[§]Glycemic index refers to overall daily glycemic index and is calculated as: sum of (glycemic index \times total amount of carbohydrates)/total amount of carbohydrates [see "Methods" section for details].

tically nonsignificant was observed for high intake of free fructose. No consistent association was observed for glycemic index and pancreatic cancer risk, and no association was observed for lactose intake (multivariable RR = 0.82, 95% confidence interval [CI] = 0.50 to 1.32, for highest versus lowest quintile comparison).

The effect of diet on insulin response may vary across strata of BMI or physical activity because these two factors can be strong determinants of insulin resistance, which can magnify the adverse impact of a high glycemic load (13). We would expect individuals who are overweight or sedentary to have a greater insulin response to their diet as a result of their physiologic condition compared with lean or active individuals. We examined this possibility by stratifying our analyses separately into two BMI and physical activity strata. Among women with high compared with low glycemic load or glycemic index scores, we observed a consistent, although not statistically significant, increase in pancreatic cancer risk when BMI was high (≥ 25 kg/m²). In contrast, glycemic index and glycemic load did not affect women with BMIs of less than 25 kg/m² (Table 3). Fructose intake was also associated with an elevated risk of pancreatic cancer among overweight women (RR = 1.99, 95% CI = 0.94 to 4.22; highest to lowest quartile comparison) but not among lean women. In contrast, carbohydrate intake was not related to the risk of pancreatic cancer among those women with an elevated BMI (Table 3). Small increases in risk were observed with sucrose intake for either BMI strata, but neither association was statistically significant.

Among women with low physical activity (< 3 hours of exercise per week), a high glycemic load was associated with a 75% increase in pancreatic cancer risk when compared with a low glycemic load, but this association was not statistically significant (Table 4). A statistically significant increase of 86% was observed for high versus low fructose intake among inactive

Table 2. Multivariable relative risks (MV RRs) and 95% confidence intervals (CIs) of pancreatic cancer according to quintiles of glycemic load, glycemic index, carbohydrate intake, and sugar intake in the Nurses' Health Study, 1980–1998*

	Quintile of dietary intake					<i>P</i> _{trend}
	1	2	3	4	5	
Glycemic load, g/day						
Median (range)	80 (<93)	103 (93–111)	119 (112–127)	137 (128–148)	167 (>148)	
Case subjects/PY	32/307 923	42/309 264	23/309 034	36/310 096	42/309 461	
Age-adjusted RR (95% CI)	1.0	1.33 (0.84 to 2.10)	0.90 (0.54 to 1.49)	1.16 (0.72 to 1.87)	1.41 (0.89 to 2.23)	.24
MV RR (95% CI)	1.0	1.48 (0.93 to 2.35)	1.04 (0.62 to 1.74)	1.33 (0.82 to 2.15)	1.53 (0.96 to 2.45)	.14
Glycemic index						
Median (range)	65 (<69)	70 (69–72)	74 (73–75)	77 (75–79)	81 (>79)	
Case subjects/PY	29/308 400	38/309 339	50/308 004	34/309 823	29/310 211	
Age-adjusted RR (95% CI)	1.0	1.33 (0.82 to 2.16)	1.82 (1.15 to 2.88)	1.30 (0.79 to 2.14)	1.19 (0.70 to 1.99)	.47
MV RR (95% CI)	1.0	1.46 (0.90 to 2.38)	2.00 (1.26 to 3.18)	1.39 (0.84 to 2.29)	1.16 (0.69 to 1.97)	.53
Carbohydrate, g/day						
Median (range)	110 (<126)	137 (126–146)	155 (147–164)	174 (165–185)	202 (>185)	
Case subjects/PY	33/312 397	35/312 950	38/309 417	37/305 297	37/305 715	
Age-adjusted RR (95% CI)	1.0	1.08 (0.67 to 1.73)	1.20 (0.75 to 1.91)	1.18 (0.74 to 1.88)	1.14 (0.71 to 1.82)	.53
MV RR (95% CI)	1.0	1.23 (0.76 to 1.98)	1.38 (0.86 to 2.21)	1.37 (0.85 to 2.20)	1.30 (0.81 to 2.09)	.25
Sucrose, g/day						
Median (range)	17 (<22)	26 (22–29)	33 (30–36)	41 (37–46)	55 (>46)	
Case subjects/PY	31/306 730	30/309 944	45/310 007	38/309 776	36/309 320	
Age-adjusted RR (95% CI)	1.0	0.97 (0.59 to 1.60)	1.44 (0.91 to 2.28)	1.21 (0.75 to 1.94)	1.21 (0.75 to 1.85)	.47
MV RR (95% CI)	1.0	1.05 (0.63 to 1.75)	1.70 (1.07 to 2.70)	1.44 (0.89 to 2.33)	1.34 (0.82 to 2.17)	.17
Fructose, g/day						
Median (range)	11 (<15)	18 (15–20)	24 (21–26)	31 (27–35)	45 (>35)	
Case subjects/PY	27/307 948	37/310 210	31/309 257	46/309 886	39/308 477	
Age-adjusted RR (95% CI)	1.0	1.33 (0.81 to 2.19)	1.09 (0.65 to 1.83)	1.64 (1.02 to 2.64)	1.43 (0.88 to 2.34)	.12
MV RR (95% CI)	1.0	1.49 (0.90 to 2.46)	1.28 (0.76 to 2.15)	1.90 (1.18 to 3.08)	1.57 (0.95 to 2.57)	.07

*MV RRs are from Cox proportional hazards models (see "Methods" section for details) that included height (five categories), body mass index (five categories), pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus and cholecystectomy, calorie intake, and physical activity. PY = person-years.

women (*P* for trend = .02). The five dietary variables examined did not appear to be related to the risk of pancreatic cancer among women with high physical activity levels (≥ 3 hours of exercise per week).

To examine whether the association between glycemic load and risk of pancreatic cancer is more pronounced among women who are overweight as well as sedentary, we stratified our analyses by both these factors (Table 5). Among women with high BMI (≥ 25 kg/m²) and low physical activity, the RR for pancreatic cancer was 2.67 when comparing the highest and the lowest quartiles of glycemic load (*P* for trend = .03). Substantially elevated risks were also observed for glycemic index and fructose intake among those women with high BMI and low physical activity (Table 5). Dietary intake did not appear to be related to the risk of pancreatic cancer among women who were both lean and physically active.

Our findings remained the same after excluding diabetics from the analyses. When we repeated our analyses using 1984 diet as baseline, we observed no associations for the dietary factors reported in this paper (data not shown), although the 4-year lag in follow-up (1980–1984) resulted in a loss of case subjects. Associations were slightly weaker in the analyses performed by using cumulative updating of dietary exposures (data not shown).

DISCUSSION

In this cohort of women, we observed a 53% increase in pancreatic cancer risk for those who had a high glycemic load and a 57% increase for those who had a high fructose intake; however, these associations were not statistically significant. The associations were stronger among women who were either

overweight or sedentary, two physiologic states that are associated with greater insulin resistance. In these subgroups, a statistically significant association was observed for fructose intake in the sedentary group. Dietary glycemic load, glycemic index, and fructose intakes were statistically significantly associated with the risk of pancreatic cancer among women who were overweight and sedentary but not among women who were lean and physically active.

A number of previous epidemiologic studies have examined intake of carbohydrates in relation to pancreatic cancer; however, findings have been mixed. In a large pooled case-control study (35) of 802 case subjects and 1669 control subjects from five different countries (SEARCH [Surveillance of Environmental Aspects Related to Cancer in Humans] program), pancreatic cancer risk was statistically significantly higher among those individuals consuming a high carbohydrate diet (for highest to lowest quintile comparison: RR = 2.57, 95% CI = 1.64 to 4.03, after controlling for lifetime cigarette consumption). In a separate case-control study (36), strong associations with pancreatic cancer risk were reported for carbohydrate intake and for added sugar (i.e., sugar added to coffee, cereal, fruit, and other foods) among women only (highest to lowest tertile comparison: RR = 3.5, 95% CI = 1.4 to 8.5 and RR = 3.7, 95% CI = 1.5 to 9.1, respectively). Carbohydrate intake was not associated with the risk of pancreatic cancer in two other case-control studies (37,38) that were not included in the SEARCH study.

Because of high fatality rates, case-control studies examining risk factors of pancreatic cancer have often relied on proxy information for case subjects and are, consequently, particularly prone to error and biases. To our knowledge, no prospective study has examined associations between specific macronutri-

Table 3. Multivariable relative risks (MV RRs) and 95% confidence intervals (CIs) for pancreatic cancer according to quartiles of dietary glycemic load, glycemic index, carbohydrate intake, and sugar intake, stratified by body mass index, in the Nurses' Health Study, 1980–1998*

	BMI <25 kg/m ²		BMI ≥25 kg/m ²	
	Case subjects/PY	MV RR (95% CI)	Case subjects/PY	MV RR (95% CI)
Glycemic load				
Q1 84 (<98)†	29/270 611	1.0 (referent)	14/107 647	1.0 (referent)
Q2 109 (98–119)	24/269 913	1.00 (0.58 to 1.72)	16/108 491	1.22 (0.59 to 2.51)
Q3 130 (120–142)	24/272 380	1.02 (0.59 to 1.77)	18/106 467	1.38 (0.68 to 2.79)
Q4 161 (>142)	27/267 589	1.16 (0.68 to 1.98)	24/108 732	1.77 (0.91 to 3.43)
<i>P</i> _{trend} ‡		.58		.08
Glycemic index				
Q1 66 (<70)	24/262 134	1.0 (referent)	13/116 603	1.0 (referent)
Q2 72 (70–73)	32/271 863	1.49 (0.87 to 2.54)	24/106 402	2.07 (1.05 to 4.08)
Q3 76 (74–78)	32/275 928	1.49 (0.87 to 2.55)	15/102 083	1.33 (0.63 to 2.80)
Q4 80 (>78)	16/270 569	0.73 (0.39 to 1.40)	20/106 249	1.84 (0.91 to 3.72)
<i>P</i> _{trend}		.51		.21
Carbohydrate				
Q1 114 (<132)	19/274 882	1.0 (referent)	17/109 404	1.0 (referent)
Q2 144 (132–155)	35/271 121	2.31 (1.31 to 4.09)	22/108 903	1.41 (0.74 to 2.66)
Q3 167 (156–179)	25/269 607	1.72 (0.93 to 3.16)	13/106 232	0.84 (0.41 to 1.73)
Q4 197 (>179)	25/264 883	1.68 (0.91 to 3.10)	20/106 797	1.22 (0.64 to 2.35)
<i>P</i> _{trend}		.22		.85
Sucrose				
Q1 18 (<24)	24/263 222	1.0 (referent)	20/114 057	1.0 (referent)
Q2 29 (24–32)	24/267 682	1.25 (0.70 to 2.23)	16/111 947	1.72 (0.92 to 3.23)
Q3 38 (33–43)	26/271 151	1.35 (0.77 to 2.38)	13/106 628	0.91 (0.43 to 1.90)
Q4 52 (>43)	30/278 438	1.43 (0.82 to 2.47)	23/98 704	1.26 (0.63 to 2.51)
<i>P</i> _{trend}		.22		.98
Fructose				
Q1 12 (<17)	27/275 524	1.0 (referent)	10/100 923	1.0 (referent)
Q2 20 (17–23)	21/275 111	0.89 (0.50 to 1.57)	18/104 618	1.79 (0.82 to 3.89)
Q3 28 (24–33)	32/270 470	1.41 (0.84 to 2.37)	21/108 923	2.04 (0.95 to 4.22)
Q4 42 (>33)	23/259 388	1.05 (0.60 to 1.84)	23/116 871	1.99 (0.94 to 4.22)
<i>P</i> _{trend}		.61		.12

*MV RRs are from Cox proportional hazards models (see "Methods" section for details) that included height (five categories), pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy, physical activity, and calorie intake. Women whose questionnaires were missing body mass index information were excluded from this analysis (four case subjects with pancreatic cancer). PY = person-years; Q1–Q4 = quartiles 1–4.

†Median (quartile cutpoints).

‡Test for trend.

ents and pancreatic cancer risk. To overcome some of the issues of unreliable information obtained from next-of-kin, a recent case-control study (8) relied solely on direct interviews to collect exposure data. In that study, an increase in total carbohydrate intake (as a percentage of total caloric intake) was associated with an increased risk of pancreatic cancer in women, but the association did not reach statistical significance.

Considerable evidence supports a role for insulin and insulin resistance in pancreatic cancer etiology in both animals and humans. In a recent study (39), pancreatic cancer was inhibited by the drug metformin, which reduces insulin resistance, in a hamster pancreatic adenocarcinoma model. Previous work (40) in the same hamster model demonstrated that pancreatic ductal cancers often arise from islet cells themselves or from some common progenitor cell that can give rise to both islets and duct cells. Because peripheral insulin resistance is associated with hyperactivity, and most probably the proliferation of islet cells, it may be involved in promoting pancreatic cancer.

We have previously demonstrated (18), in a subset of healthy women from the NHS, that our variable for glycemic load (estimated from the food-frequency questionnaires) can predict fasting plasma triacylglycerol and high-density lipoprotein (HDL) levels better than total carbohydrate intake. The association between triacylglycerol levels and glycemic load was even stronger among women with a BMI greater than 25 kg/m² (18)

than among women with a lower BMI, indicating that overweight women are particularly susceptible to the quality of the carbohydrates they consume, probably because of some degree of insulin resistance. In our analyses, pancreatic cancer risk increased more dramatically across quartiles of glycemic load intake among women with a BMI greater than or equal to 25 kg/m² than among those with a BMI of less than 25 kg/m².

Physical activity is another important factor that is known to modify insulin resistance (41). Therefore, like individuals with higher BMI, individuals who are inactive are likely to be more susceptible to the carbohydrate quality of foods they consume because of the strong insulin response to high glycemic foods. In our data, women who were sedentary and had high glycemic index and glycemic load intakes had elevated risks of pancreatic cancer, whereas active women did not have elevated risks.

In this cohort, carbohydrate intake was not associated with pancreatic cancer risk, and strata analyses were not always consistent with findings for glycemic load or index scores. For sucrose, which has an effect on postprandial glycemic response similar to that of white bread or potatoes (42), we observed associations that were consistent with the glycemic variables. The strongest risks for pancreatic cancer in this study were observed with fructose intake. Foods that contribute to dietary fructose (as a monosaccharide) include soda, punch, and fruit juices, which collectively account for a high percentage of di-

Table 4. Multivariable relative risks (MV RRs) and 95% confidence intervals (CIs) for pancreatic cancer according to quartiles of dietary glycemic load, glycemic index, carbohydrate intake, and sugar intake, stratified by physical activity level, in the Nurses' Health Study, 1980–1998*

	Low physical activity		High physical activity	
	Case subjects/PY	MV RR (95% CI)	Case subjects/PY	MV RR (95% CI)
Glycemic load				
Q1 84 (<98)†	18/186 199	1.0 (referent)	24/182 041	1.0 (referent)
Q2 109 (98–119)	23/181 044	1.45 (0.78 to 2.69)	15/187 837	0.70 (0.37 to 1.35)
Q3 130 (120–142)	24/183 413	1.58 (0.86 to 2.93)	19/188 078	0.87 (0.47 to 1.60)
Q4 161 (>142)	28/188 701	1.75 (0.96 to 3.18)	23/179 538	1.10 (0.61 to 1.97)
$P_{\text{trend}}^{\ddagger}$.07		.63
Glycemic index				
Q1 66 (<70)	17/165 648	1.0 (referent)	17/202 336	1.0 (referent)
Q2 72 (70–73)	31/174 316	1.92 (1.06 to 3.48)	23/193 700	1.59 (0.84 to 3.01)
Q3 76 (74–78)	21/188 292	1.26 (0.66 to 2.40)	27/181 737	2.03 (1.09 to 3.77)
Q4 80 (>78)	24/211 102	1.31 (0.70 to 2.44)	14/159 721	1.20 (0.58 to 2.47)
P_{trend}		.75		.35
Carbohydrate				
Q1 114 (<132)	20/194 559	1.0 (referent)	16/179 990	1.0 (referent)
Q2 144 (132–155)	31/186 056	1.82 (1.04 to 3.21)	24/185 281	1.71 (0.90 to 3.27)
Q3 167 (156–179)	12/181 184	0.73 (0.36 to 1.50)	25/186 207	1.78 (0.94 to 3.40)
Q4 197 (>179)	30/177 559	1.80 (1.02 to 3.19)	16/186 016	1.08 (0.53 to 2.20)
P_{trend}		.20		.82
Sucrose				
Q1 18 (<24)	20/192 062	1.0 (referent)	19/175 624	1.0 (referent)
Q2 29 (24–32)	26/182 191	1.53 (0.85 to 2.75)	22/188 477	1.30 (0.70 to 2.43)
Q3 38 (33–43)	21/179 296	1.28 (0.69 to 2.37)	19/190 697	1.10 (0.57 to 2.11)
Q4 52 (>43)	26/185 809	1.53 (0.85 to 2.77)	21/182 696	1.25 (0.66 to 2.36)
P_{trend}		.26		.64
Fructose				
Q1 12 (<17)	19/205 327	1.0 (referent)	20/161 991	1.0 (referent)
Q2 20 (17–23)	18/185 815	1.12 (0.58 to 2.13)	19/185 567	0.95 (0.50 to 1.81)
Q3 28 (24–33)	28/174 696	1.86 (1.03 to 3.35)	25/196 526	1.16 (0.63 to 2.12)
Q4 42 (>33)	28/173 520	1.86 (1.03 to 3.36)	17/193 410	0.75 (0.39 to 1.46)
P_{trend}		.02		.44

*MV RRs are from Cox proportional hazards models (see "Methods" section for details) that included height (five categories), pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus and cholecystectomy, physical activity, and calorie intake. Women whose questionnaires were missing information on physical activity were excluded from this analysis (six case subjects with pancreatic cancer). PY = person-years; Q1–Q4 = quartiles 1–4.

†Median (quartile cutpoints).

‡Test for trend.

etary glycemic load. The association observed with fructose therefore supports a role for an effect of postprandial glycemic response. However, fructose intake may be related to pancreatic cancer via other mechanisms; in a recent study (43), fructose contributed directly to oxidative stress in hamster islet tumor cells. Although fructose intake may itself play an important role in the risk of pancreatic cancer, it may also be a marker of a high-sugar diet. More studies are needed to elucidate the precise role of fructose in pancreatic carcinogenesis.

We observed a weakened association when using a cumulative updating approach for the same dietary exposures. Cumulative updating, by integrating multiple dietary assessments, is generally thought to reduce measurement error and has been shown to strengthen dietary associations with heart disease endpoints in the Nurses' Health Study cohort (44). However, because cumulative updating incorporates recent measurement of dietary intakes, cumulative updating is more likely to attenuate associations that require long latency (induction) periods. Because cancer initiation and progression is slow and occurs over many decades, an earlier dietary assessment may better represent the 'relevant' diet, especially if changes have occurred over time. It is thus possible that the relevant time period for pancreatic cancer is many years prior to the detection of this disease (which occurs at very late stages). In this situation, updating

dietary intake may lead to an attenuation of the effect of diet on pancreatic cancer risk.

The strengths of this study include a prospective design and detailed information on diet as well as potential risk factors of pancreatic cancer. The prospective design precluded recall bias and the need to use next-of-kin respondents. Moreover, because exposure data were collected before the diagnosis of any cases of pancreatic cancer, any error in recall would have attenuated rather than exaggerated a true association. Differential follow-up is unlikely to have made a material contribution to these findings, because follow-up was high (45).

Although the glycemic index is designed to reflect the postprandial glucose response of specific foods, an earlier study (46) suggested that the response may differ with the consumption of mixed meals. However, more recent work (47) has shown that the weighted average glycemic index of component foods provides an excellent estimate of the glycemic index of a meal. The dietary glycemic index has proven to be a strong predictor of several biomarkers (18) and to be independently associated with diabetes and coronary heart disease in the NHS cohort, where the FFQ was used to estimate glycemic index (13,14). Random misclassification due to eating mixed meals would underestimate a true association. Ultimately, an insulin index of foods may be a better measure of the adverse aspect of carbohydrate

Table 5. Multivariable relative risks (MV RRs) and 95% confidence intervals (CIs) for pancreatic cancer according to quartiles of glycemic index, glycemic load, and fructose intake, stratified by body mass index (BMI) and physical activity level, in the Nurses' Health Study, 1980–1998*

	BMI <25 and moderate/high physical activity		Intermediate group†		BMI ≥25 and low physical activity	
	Case subjects/PY	MV RR (95% CI)	Case subjects/PY	MV RR (95% CI)	Case subjects/PY	MV RR (95% CI)
Glycemic load						
Q1 84 (<98)‡	16/135 737	1.0 (referent)	20/173 269	1.0 (referent)	6/59 234	1.0 (referent)
Q2 109 (98–119)	8/138 924	0.64 (0.27 to 1.51)	22/172 394	1.16 (0.63 to 2.14)	8/57 563	1.53 (0.53 to 4.42)
Q3 130 (120–142)	12/137 468	0.99 (0.45 to 2.06)	20/178 841	1.03 (0.55 to 1.92)	11/55 182	2.32 (0.85 to 6.33)
Q4 161 (>142)	12/130 446	1.03 (0.48 to 2.22)	25/179 708	1.29 (0.71 to 2.33)	14/58 085	2.67 (1.02 to 6.99)
<i>P</i> _{trend} §		.79		.47		.03
Glycemic index						
Q1 66 (<70)§	11/145 948	1.0 (referent)	17/164 506	1.0 (referent)	6/57 530	1.0 (referent)
Q2 72 (70–73)	12/143 262	1.28 (0.55 to 2.97)	30/170 489	1.84 (1.01 to 3.33)	12/54 265	2.18 (0.81 to 5.81)
Q3 76 (74–78)	16/135 982	1.88 (0.85 to 4.15)	27/178 757	1.62 (0.88 to 2.98)	5/55 290	0.87 (0.26 to 2.86)
Q4 80 (>78)	9/117 382	1.24 (0.50 to 3.06)	13/190 461	0.75 (0.36 to 1.55)	16/62 979	2.77 (1.08 to 7.10)
<i>P</i> _{trend}		.40		.51		.08
Fructose						
Q1 12 (<17)§	14/122 522	1.0 (referent)	20/184 999	1.0 (referent)	5/59 796	1.0 (referent)
Q2 20 (17–23)	12/139 762	0.97 (0.44 to 2.14)	15/174 285	0.82 (0.42 to 1.60)	10/57 334	2.27 (0.77 to 6.69)
Q3 28 (24–33)	14/142 989	1.10 (0.51 to 2.38)	29/174 080	1.57 (0.88 to 2.79)	10/54 154	2.49 (0.84 to 7.36)
Q4 42 (>33)	8/137 302	0.64 (0.26 to 1.55)	23/170 849	1.25 (0.68 to 2.29)	14/58 780	3.17 (1.13 to 8.91)
<i>P</i> _{trend}		.35		.25		.04

*MV RRs are from Cox proportional hazards models that included height (five categories), pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus and cholecystectomy, and quintiles of calorie intake. Women whose questionnaires were missing information on BMI or physical activity were excluded (six case subjects with pancreatic cancer). PY = person-years; Q1–Q4 = quartiles 1–4.

†Intermediate group = either BMI ≥25 with moderate/high physical activity or BMI <25 with low physical activity.

‡Median (quartile cutpoints).

§Test for trend.

consumption, but data for this type of index are only now being developed (48).

In summary, the overall association between dietary glycemic load and pancreatic cancer risk failed to achieve statistical significance. However, the statistically significant influence of glycemic load on pancreatic cancer risk among overweight and sedentary individuals supports the hypothesis that abnormal glucose metabolism and states of relative hyperinsulinemia enhance pancreatic carcinogenesis.

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NOTES

Supported by Public Health Department research grants CA87969 and CA86102 (National Cancer Institute) and DK02767 (National Institute of Diabetes and Digestive and Kidney Diseases), National Institutes of Health, Department of Health and Human Services.

Manuscript received September 4, 2001; revised June 4, 2002; accepted July 17, 2002.