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Glycemic load, glycemic index, and pancreatic cancer risk in the Netherlands Cohort Study[1,2]

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ABSTRACT

Background: Recent studies of pancreatic cancer suggest a role for hyperinsulinemia in carcinogenesis. Because insulin is secreted in response to elevated blood glucose concentrations, dietary factors that increase these concentrations may be important in pancreatic carcinogenesis.

Objective: The objective was to examine prospectively the relation between pancreatic cancer risk and dietary glycemic load (GL), overall glycemic index (GI), and intake of total carbohydrates and mono- and disaccharides.

Design: The Netherlands Cohort Study consisted of 120 852 men and women who completed a baseline questionnaire in 1986. After 13.3 y of follow-up, 408 pancreatic cancer cases were detected, 66% of which were microscopically confirmed. A validated 150-item food-frequency questionnaire, completed at baseline, was used to calculate carbohydrate and mono- and disaccharide intakes and the GL and GI of the diet.

Results: Dietary GL, GI, or intake of carbohydrates and mono- and disaccharides were not associated with pancreatic cancer risk in this cohort. Also, the associations were not modified by sex. Our results did not change after the analysis was restricted to microscopically confirmed pancreatic cancer cases or after individuals who reported a history of diabetes at baseline were excluded from the analyses.

Conclusions: Overall, our findings do not support the hypothesis that GL, GI, or intake of carbohydrates and mono- and disaccharides are positively associated with pancreatic cancer risk. This is in agreement with previous prospective studies that investigated the relation between GL and GI and pancreatic cancer risk. *Am J Clin Nutr* 2008;87:970–7.

INTRODUCTION

Pancreatic cancer is among the most rapidly fatal cancers worldwide, with a 5-y survival rate of ≤5% (1, 2). Few consistent risk factors for pancreatic cancer have been identified, with cigarette smoking and diabetes mellitus being the most consistent (3–5).

Evidence indicates that insulin acts as a growth promoter and mitogen in the pancreas (6, 7). Furthermore, recent observational studies of pancreatic cancer suggest that high insulin concentrations, glucose intolerance, and insulin resistance may play a role in carcinogenesis, even without a diagnosis of diabetes mellitus (8–10). Type 2 diabetes seems to develop generally after prolonged periods of high insulin secretion rates, with a gradual increase in insulin resistance of the liver and peripheral tissues (10). Because insulin is secreted into the blood in response to elevated blood glucose concentrations, dietary factors increasing these concentrations may be associated with pancreatic cancer risk.

The glycemic index (GI) is a measure that can be used to quantify the postprandial glycemic effects (compared with the glucose response of a reference food, usually white bread or glucose) of individual foods items (11). Consumption of high-GI diets, ie, diets in which the carbohydrates in the foods are characterized by a high GI, have been shown to be associated with hyperglycemia and hyperinsulinemia (11), whereas low-GI meals have been shown to be associated with a lower postprandial rise in glucose and insulin, probably because of a reduced rate of glucose absorption and, therefore, a reduced postprandial rise in insulin (11). Studies that have established GI values for foods used portions that contain a fixed amount of carbohydrate (generally 50 g) rather than portions that are typically consumed (12). Hence, to estimate the total glycemic effect of the diet, the glycemic load (GL) is calculated by using both the overall GI of a diet as well as the actual amount of carbohydrates consumed in the diet (13).

Studies of the influence of dietary GI and GL on pancreatic cancer have been limited. To date, the relation between GL and GI and pancreatic cancer risk has been examined in 4 prospective studies (14–17). No associations have been found between GI and GL and pancreatic cancer risk, although Michaud et al (15) found a significantly positive association between a high GL and pancreatic cancer incidence in women who were both sedentary and overweight, factors that are associated with insulin resistance (10).

We examined the association between pancreatic cancer risk and dietary GL and GI, and total carbohydrate and mono- and disaccharide intakes, in men and women within The Netherlands Cohort Study (NLCS) on diet and cancer.

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SUBJECTS AND METHODS

Study population and follow-up of cancer

The study design of the NLCS was reported in detail elsewhere (18). Briefly, the NLCS was initiated in September 1986 and included 58 279 men and 62 573 women aged 55–69 y at the beginning of the study, which originated in 204 municipalities with computerized population registries. A self-administered questionnaire on dietary habits, lifestyle characteristics, medical history, and other potential risk factors for cancer was completed at baseline. For reasons of efficiency in questionnaire processing (which was very detailed and included open-ended question) and follow-up, the case-cohort approach (19) was used. Case subjects were enumerated from the entire cohort, whereas the person-years at risk were estimated from a random sample of 5000 subjects (2411 men and 2589 women). This subcohort was selected immediately after baseline and was followed-up for vital status information. The entire cohort is being monitored for cancer occurrence by annual record linkage to the Netherlands Cancer Registry and the Netherlands Pathology Registry (20). The follow-up was restricted to the period from baseline to December 1999, a total of 13.3 y. No subcohort members were lost to follow-up, and completeness of the follow-up was estimated to be >96% (21).

For cases and subcohort members, all prevalent cancer cases at baseline other than nonmelanoma skin cancer were excluded. Additionally, subjects with incomplete and inconsistent dietary data were also excluded from the analyses. These subjects either *1*) left >60 (of 150 items) questionnaire items blank and ate <35 items at least once per month or *2*) left one or more item blocks (grouping of items, eg, beverages) blank. Additional details are given elsewhere (22). Of the incident pancreatic cancer cases, all endocrine subtypes based on histology were excluded (islet-cell carcinomas; $n = 1$). This resulted in a final subcohort of 4438 subjects (2191 men and 2247 women) and 408 exocrine pancreatic cancer cases (217 men and 191 women). Of all pancreatic cancer cases, 66% were microscopically confirmed pancreatic cancer (MCPC; $n = 269$), whereas 34% were nonmicroscopically confirmed pancreatic cancer (NMCPC; $n = 139$). The diagnosis of the latter group was made by the treating clinician and was based on clinical symptoms, physical examinations, and imaging results and was abstracted and recorded by a trained tumor registrar (23). The NLCS was approved by the institutional review boards of the TNO Nutrition and Food Research Institute (Zeist, Netherlands) and Maastricht University (Maastricht, Netherlands).

Questionnaire

The dietary section of the questionnaire was a 150-item semiquantitative food-frequency questionnaire (FFQ), which concentrated on the habitual consumption of food and beverages during the year preceding the start of the study. Questionnaire data were key-entered and processed for all incident cases in the cohort and subcohort members in a standardized manner blinded with respect to case and subcohort status. This was done to minimize observer bias in coding and interpretation of the data. Daily mean nutrient intakes were calculated by summing the multiplied frequencies and portion sizes of all food items with their tabulated nutrient contents from the Dutch food-composition table of 1986 (24).

GI values of foods were obtained from published estimates (13). The mean of reported GI values for a food was used if these reported values varied across studies (13). Food items for which a GI had not been determined were assigned the GI of the nearest comparable food (eg, rusks, liquorice) or were calculated by using recipes (eg, Dutch spiced cake). A GI for beer could not be found and was estimated by using the type of carbohydrates (65% maltose, 35% glucose). For some food items, no GI value could be determined because of the lack of published estimates (eg, alcohol-free beer, croquettes). For >90% of the carbohydrate intake of each subject, a GI value was available. Lack of information about the GI of vegetables and legumes was resolved by calculating a mean GI for usually consumed vegetables and legumes in the NLCS. In case of multiple foods per FFQ item, a GI value was assigned to each composing food, and the GI of the item was estimated by using the weighted average of GI values based on carbohydrate content and prevalence of estimated population consumption of these foods (25). The overall dietary GI was estimated for each participant by calculating the weighted average GI of all food items eaten by using the carbohydrate intake from that item (g/d) as a weighting factor. The resulting value represents the overall quality of carbohydrate intake for each participant. In addition, the average dietary GL was calculated by multiplying the overall dietary GI by the total amount of carbohydrate, which was then divided by 100. Each unit of GL represents the equivalent of 1 g carbohydrate from glucose.

The FFQ was validated and tested for reproducibility (22, 26). Crude (and energy- and sex-adjusted) Pearson correlation coefficients between the 9-d diet record and the questionnaire for total carbohydrate and mono- and disaccharides were 0.77 (0.71) and 0.78 (0.79), respectively. For the most relevant food groups, Spearman correlation coefficients were 0.80 for bread, 0.74 for potatoes, and 0.84 for added sugar (22).

Statistical analysis

Dietary GL and GI and intake of total carbohydrates, mono- and disaccharides, and fiber were all adjusted for energy intake by the residual method (27) to enable comparison with previous studies (14–17). Pearson correlation coefficients (r) between energy-adjusted GL, GI, carbohydrates, and mono- and disaccharides and food items contributing most to energy-adjusted GL were calculated.

In the present study the overall analyses were executed on all pancreatic cancer cases. In additional analyses we restricted the analyses to MCPC cases to create a group with a higher degree of diagnostic certainty of pancreatic cancer. In a previous analysis of anthropometric measures and pancreatic cancer, a significant positive association was observed between body mass index (BMI) and pancreatic cancer risk among verified cases, which was obscured when NMCPC cases were included (28).

All analyses were conducted for both sexes combined and separately for men and women. Age-adjusted and multivariable-adjusted incidence rate ratios, or relative risks (RRs), and corresponding 95% CIs were estimated by using Cox proportional hazards models. The total person-years at risk, estimated from the subcohort, were used in the analyses (29). SEs were estimated by using the robust Hubert-White sandwich estimator to account for additional variance introduced by sampling from the cohort. This method is equivalent to the variance-covariance estimator presented by Barlow et al (30). The proportional hazards assumption was tested by using the scaled Schoenfeld residuals (31).

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RRs for energy-adjusted dietary GL and GI and intake of energy-adjusted total carbohydrates and mono- and disaccharides were estimated for quintiles (with the lowest quintile of intake regarded as the reference group) based on the sex-specific distribution in the subcohort and as continuous variables. Total energy intake (kcal/d) was included in both the age- and multivariable-adjusted models in conformity with the method described by Willett (27). The RRs for energy-adjusted total carbohydrates and mono- and disaccharides can be interpreted as the effect of an increase in these variables relative to a decrease of an equivalent amount of energy from other energy-delivering nutrients (ie, substituting these exposure nutrients for other energy-delivering nutrients). Age at baseline (y), cigarette smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking), BMI (kg/m^2), alcohol intake (g/d), fiber intake (energy-adjusted; g/d), history of diabetes mellitus (yes or no), history of hypertension (yes or no), intake of vegetables (g/d), and intake of fruit (g/d) were included in the confounder-adjusted models because they were associated with GL and affected the RR estimates. We also considered other potential confounders, including level of education, nonoccupational moderate physical activity, multivitamin use, family history of pancreatic cancer, history of cholecystectomy, history of gallstones, and history of gastric ulcer, which were not included in the final model because these variables did not change the RR estimates. To enable comparison, age-adjusted analyses were restricted to subjects included in multivariable-adjusted analyses (eg, with no missing values on confounders included in the multivariable-adjusted model). For each analysis, trends were evaluated with the Wald test by fitting ordinal exposure variables (quintiles of intake) as continuous terms.

As suggested by a previous study (15), we constructed combined categories of BMI (cutoff: 25 kg/m^2) and physical activity ($<$30 versus $\geq$30 min/d) resulting in 3 subgroups: a lean and physically active group, an overweight and physically inactive group, and an intermediate group of either lean but physically inactive individuals or overweight but physically active individuals. We stratified our analyses by these combined categories of BMI and physical activity and, in addition, performed a formal test for interaction by constructing multiplicative interaction terms for each of the exposure variables and these combined categories. Although we used quintiles of the dietary intakes in our main analysis, for the stratified analyses we used tertiles to avoid small case numbers. In additional analyses, individuals who reported a history of diabetes at baseline (n = 159) were excluded. To evaluate whether early symptoms of disease before diagnosis could have influenced the results, early cases (diagnosed within 2 y after baseline) were excluded in the additional analyses. All analyses were performed by using the STATA statistical software package (intercooled STATA, version 9; Stata Corp, College Station. TX)). All P values were based on 2-sided tests and were considered statistically significant if $<$0.05.

RESULTS

Carbohydrate intake was positively correlated with GL (r = 0.96) and GI (r = 0.26). Mono- and disaccharide intake was positively correlated with GL (r = 0.67), but not with GI (r = −0.02). For the 5 food groups contributing most to the GL, correlation coefficients with GI were 0.27 for potatoes, 0.38 for added sugar, 0.31 for bread, 0.03 for Chinese and Indonesian foods, and −0.14 for cookies, cake, and pastry. For GL, correlation coefficients were 0.27 for potatoes, 0.59 for added sugar, 0.43 for bread, 0.14 for Chinese and Indonesian foods, and 0.05 for cookies, cake, and pastry.

In **Table 1**, baseline characteristics (stratified by sex) are presented. A number of characteristics did not differ between pancreatic cancer cases and subcohort members, including age, GL and GI of the diet, and physical activity level. However, in men, there were more diabetics and smokers among pancreatic cancer cases than among subcohort members. Within the pancreatic cancer case group, most characteristics did not differ between total pancreatic cancer cases and MCPC cases, although in women a history of hypertension was higher among total pancreatic cancer cases than among MCPC cases (32.1% compared with 24.8%).

No association was found when examining the association between GL, GI, carbohydrate, mono- and disaccharide intake, and the risk of pancreatic cancer in the total population (**Table 2**). After the NMCPC cases were excluded, these findings remained. When looking at men and women separately, no significant associations were observed for GL, GI, and carbohydrate intake (data not shown). Among men, an inverse association was observed for mono- and disaccharide intake, showing a statistically significantly decreased risk of pancreatic cancer for the highest versus the lowest quintile of mono- and disaccharide intake in the multivariable-adjusted analyses (RR: 0.56; 95% CI: 0.33, 0.97; P for trend = 0.13). After the analyses were restricted to microscopically verified cases, this point estimate became nonsignificant (RR: 0.64; 95% CI: 0.34, 1.01). Among women, no association was observed for mono- and disaccharide intake. Our findings remained the same after individuals who reported a history of diabetes at baseline were excluded from the analyses (325 cases left for analyses; data not shown), although the significant decreased risk with increased mono- and disaccharide intake observed in men became nonsignificant (multivariable-adjusted RR: 0.59; 95% CI: 0.34, 1.02).

In additional analyses, we stratified by both BMI and physical activity level to test whether the risk estimates were more pronounced for overweight and inactive individuals. We observed no associations in the total pancreatic cancer case group (data not shown). When restricting the analyses to MCPC cancer cases (**Table 3**), we observed no associations for GI, but observed nonsignificantly inverse associations for GL, carbohydrate, and mono- and disaccharide intake among physically inactive and overweight people; among physically active and lean individuals, we observed nonsignificantly positive associations for these dietary measures. In addition, individuals who reported a history of diabetes at baseline were excluded from these analyses (218 cases left for analyses; data not shown). We observed a statistically significant 2-fold increased risk of pancreatic cancer for the highest versus the lowest tertile of GL (P for trend = 0.03) among lean and physically active individuals. Among overweight and inactive individuals, we observed a statistically significant decreased pancreatic cancer risk for the highest versus the lowest tertile of mono- and disaccharide intake with an RR of 0.31 (95% CI: 0.10, 0.93; P for trend = 0.03). However, the multiplicative interaction terms for these stratified analyses were not statistically significant, although the interaction between mono- and disaccharide intake and the combined categories of BMI and

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TABLE 1
Baseline characteristics of pancreatic cancer cases and subcohort members in the Netherlands Cohort Study on diet and cancer, 1986–1999[1]

	Men			Women		
Characteristic	Total pancreatic cancer cases (n = 185)	Microscopically verified cancer cases (n = 129)	Subcohort (n = 1954)	Total pancreatic cancer cases (n = 165)	Microscopically verified cancer cases (n = 105)	Subcohort (n = 2026)
Age (y)	62.1 ± 4.0	61.7 ± 3.8	61.2 ± 4.2	62.1 ± 4.2	61.1 ± 4.3	61.4 ± 4.3
Current smokers (%)	42.2	42.6	34.0	26.7	26.7	20.8
Years of smoking (y)	33.0 ± 14.7	33.5 ± 14.4	29.0 ± 15.8	14.4 ± 16.9	13.9 ± 16.5	11.4 ± 15.8
Daily intake						
Energy (kcal)	2153 ± 457	2192 ± 442	2171 ± 510	1713 ± 409	1701 ± 394	1689 ± 395
Glycemic load (g)[2]	134.9 ± 23.8	135.4 ± 22.5	136.5 ± 23.9	101.4 ± 16.9	102.2 ± 16.7	102.3 ± 17.2
Overall glycemic index[2]	60.9 ± 3.8	60.9 ± 3.3	60.6 ± 3.5	57.6 ± 3.2	58.0 ± 3.1	57.7 ± 3.3
Total carbohydrate (g)[2]	223.3 ± 37.3	223.8 ± 35.1	226.4 ± 37.4	176.9 ± 27.0	176.9 ± 25.4	178.2 ± 26.7
Mono- and disaccharides (g)[2]	99.7 ± 35.5	99.3 ± 34.0	104.6 ± 34.4	83.6 ± 26.2	82.6 ± 24.4	84.5 ± 25.1
Total fibers (g)[2]	28.6 ± 7.2	28.8 ± 7.1	28.7 ± 7.3	25.9 ± 5.3	26.1 ± 4.8	25.3 ± 5.8
Total fat (g)[2]	81.6 ± 14.1	82.3 ± 13.9	82.5 ± 14.1	84.9 ± 11.4	85.0 ± 10.5	85.3 ± 10.3
Alcohol (g)	17.4 ± 17.6	16.8 ± 17.7	14.9 ± 16.9	7.1 ± 10.9	7.0 ± 10.1	5.9 ± 9.6
Vegetables (g)	195.3 ± 94.6	199.2 ± 99.2	192.3 ± 83.7	212.9 ± 83.3	215.6 ± 81.2	196.7 ± 81.5
Fruit (g)	148.1 ± 119.5	140.6 ± 106.8	156.4 ± 115.2	197.2 ± 109.8	193.6 ± 100.4	197.0 ± 120.8
Height (cm)	176.4 ± 6.6	176.2 ± 6.6	176.5 ± 6.6	166.2 ± 6.2	165.7 ± 5.9	165.3 ± 6.1
BMI (kg/m^2)	25.3 ± 3.0	25.6 ± 2.7	24.9 ± 2.6	25.6 ± 3.6	26.1 ± 3.8	25.0 ± 3.5
Physical activity, nonoccupational (%)						
<30 min/d	14.1	16.3	17.7	24.9	25.7	22.8
30–60 min/d	35.1	31.0	30.5	30.3	31.4	31.8
60–90 min/d	24.3	23.3	19.5	24.9	21.9	23.3
>90 min/d	26.5	29.5	32.4	20.0	21.0	22.2
History of diabetes (%)	9.2	7.8	3.3	4.9	5.7	3.4
History of hypertension (%)	23.8	18.6	24.2	32.1	24.8	29.0
Level of education (%)						
Low	43.8	44.2	43.9	56.1	59.6	55.4
Medium	36.2	38.0	36.3	36.0	32.7	35.4
High	20.0	17.8	19.8	7.9	7.7	9.2

[1] The subcohort consisted of 3980 subjects, including 17 pancreatic cancer cases.
[2] Energy-adjusted intake.

physical activity, after exclusion of diabetics, was nearly significant ($P = 0.06$).

No associations were observed when we investigated whether an increased consumption of high-GI food items, such as added sugar, soft drinks, sweet sandwich spreads (eg, jam), and sweets, were associated with a higher risk of pancreatic cancer (data not shown). After the first 2 y of follow-up were excluded, the results were not substantially different (data not shown).

DISCUSSION

Our results suggest that high GL and GI and a high intake of total carbohydrates are not associated with pancreatic cancer risk. These null findings are consistent with 4 prospective studies (14–17) and with 5 (32–36) of 7 (32–38) previous case-control studies that examined GL or GI and/or carbohydrate intake in relation to pancreatic cancer risk. As regards mono- and disaccharide intake, we found inverse associations for pancreatic cancer risk in men, although these became less pronounced when the analyses were restricted to MCPC cases only.

The 1980s dietary recommendations for diabetics no longer included low simple sugar intake (39, 40), but probably not all diabetics and their practitioners were aware of these new guidelines at the time of our dietary data collection (40). Therefore, we excluded diabetics from our analyses. The observed inverse associations between increased mono- and disaccharide intake and pancreatic cancer risk in men became less pronounced, whereas all other findings remained the same. Eight studies have examined the intakes of simple (monosaccharide and disaccharide) sugars (34, 41, 42), refined sugars (35), or sucrose (14–16, 32, 42). Of these studies, just a few found an increased risk of pancreatic cancer (35, 41).

We also examined whether the association between high GL, GI, and carbohydrate and mono- and disaccharide intake and the risk of pancreatic cancer is more pronounced for subjects who are overweight as well as inactive; we found no significant association between GI and carbohydrate intake and pancreatic cancer risk. When the analyses were restricted to MCPC cases without diabetes, we observed a statistically significant decreased pancreatic cancer risk for mono- and disaccharide intake among overweight and inactive individuals. Only one previous study observed a nonsignificant inverse association between increased mono- and disaccharide intake and pancreatic cancer risk among male smokers (42), whereas 2 other studies (34, 41) did not observe such an association. This finding was unexpected and needs to be confirmed, preferably by other cohort studies. Michaud et al (15) reported a significantly positive association

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TABLE 2
Age-adjusted and multivariable-adjusted relative risks (RRs) and 95% CIs for pancreatic cancer according to quintile (Q) of glycemic load, overall glycemic index, total carbohydrates, and mono- and disaccharides for men and women in the Netherlands Cohort Study on diet and cancer, 1986–1999[1]

			Total pancreatic cancer cases (n = 350)			Microscopically verified cancer cases (n = 234)		
Nutrient	Quintile median	Person-years	Cases	RR (95% CI)[2]	RR (95% CI)[3]	Cases	RR (95% CI)[2]	RR (95% CI)[3]
Glycemic load (g/d)[4]								
Q1 (low)[5]	88	9719	83	1.00	1.00	50	1.00	1.00
Q2	98	9775	74	0.86 (0.62, 1.21)	0.93 (0.66, 1.31)	47	0.93 (0.62, 1.41)	1.01 (0.65, 1.55)
Q3	106	9667	61	0.73 (0.52, 1.03)	0.83 (0.58, 1.18)	45	0.92 (0.61, 1.39)	1.05 (0.68, 1.62)
Q4	115	9761	73	0.86 (0.61, 1.20)	0.99 (0.69, 1.41)	51	1.03 (0.69, 1.54)	1.17 (0.76, 1.81)
Q5 (high)	156	9361	59	0.72 (0.51, 1.03)	0.85 (0.58, 1.24)	41	0.85 (0.56, 1.30)	1.00 (0.63, 1.61)
P for trend				0.099	0.558		0.646	0.731
Continuous (50-g/d intake increment)				0.87 (0.67, 1.13)	1.03 (0.77, 1.39)		0.93 (0.69, 1.25)	1.08 (0.77, 1.51)
Overall glycemic index[4]								
Q1 (low)[5]	55	9772	75	1.00	1.00	43	1.00	1.00
Q2	57	9736	57	0.77 (0.54, 1.10)	0.78 (0.54, 1.12)	39	0.92 (0.59, 1.44)	0.91 (0.58, 1.44)
Q3	59	9609	76	1.05 (0.75, 1.47)	1.02 (0.72, 1.46)	48	1.15 (0.75, 1.75)	1.08 (0.69, 1.70)
Q4	61	9664	71	0.98 (0.69, 1.37)	0.94 (0.64, 1.36)	58	1.39 (0.93, 2.09)	1.30 (0.83, 2.05)
Q5 (high)	64	9502	71	1.01 (0.72, 1.42)	0.87 (0.59, 1.29)	46	1.11 (0.73, 1.71)	0.90 (0.54, 1.48)
P for trend				0.562	0.805		0.180	0.790
Continuous (5-units/d increment)				1.06 (0.89, 1.26)	0.98 (0.81, 1.19)		1.12 (0.93, 1.35)	1.00 (0.81, 1.25)
Total carbohydrate (g/d)[4]								
Q1 (low)[5]	155	9808	83	1.00	1.00	50	1.00	1.00
Q2	172	9708	70	0.84 (0.60, 1.18)	0.95 (0.66, 1.35)	46	0.93 (0.61, 1.42)	1.05 (0.68, 1.62)
Q3	184	9672	68	0.82 (0.59, 1.16)	0.98 (0.68, 1.41)	49	1.01 (0.67, 1.52)	1.21 (0.76, 1.88)
Q4	199	9700	63	0.75 (0.53, 1.06)	0.94 (0.64, 1.37)	45	0.93 (0.61, 1.40)	1.16 (0.75, 1.82)
Q5 (high)	256	9394	66	0.81 (0.58, 1.14)	1.03 (0.69, 1.52)	44	0.91 (0.60, 1.38)	1.21 (0.75, 1.95)
P for trend				0.166	0.928		0.687	0.372
Continuous (50-g/d intake increment)				0.89 (0.75, 1.06)	1.04 (0.85, 1.27)		0.91 (0.76, 1.10)	1.05 (0.84, 1.31)
Mono- and disaccharides (g/d)[4]								
Q1 (low)[5]	58	9756	89	1.00	1.00	59	1.00	1.00
Q2	77	9799	63	0.68 (0.49, 0.97)	0.77 (0.53, 1.10)	42	0.72 (0.48, 1.09)	0.84 (0.55, 1.29)
Q3	88	9637	67	0.75 (0.53, 1.05)	0.86 (0.60, 1.22)	50	0.88 (0.59, 1.30)	1.06 (0.70, 1.60)
Q4	103	9658	75	0.82 (0.59, 1.14)	0.99 (0.69, 1.41)	49	0.84 (0.57, 1.25)	1.09 (0.72, 1.66)
Q5 (high)	136	9432	56	0.62 (0.44, 0.89)	0.78 (0.52, 1.16)	34	0.59 (0.38, 0.91)	0.82 (0.50, 1.34)
P for trend				0.052	0.611		0.070	0.885
Continuous (50-g/d intake increment)				0.84 (0.68, 1.02)	0.96 (0.77, 1.20)		0.82 (0.65, 1.02)	0.99 (0.77, 1.26)

[1] RRs and 95% CIs were calculated by using Cox proportional hazards models.
[2] Adjusted for sex, age (y), and energy intake (kcal/d).
[3] Adjusted for sex, age (y), energy intake (kcal/d), smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking), alcohol (g/d), history of diabetes mellitus (yes or no), history of hypertension (yes or no), BMI (kg/m^2), and intake of vegetables (g/d), fruit (g/d), and fiber (energy-adjusted; g/d).
[4] Energy-adjusted intake.
[5] Reference category.

between pancreatic cancer risk and GL among obese and sedentary women. We were unable to reproduce this result and even found the opposite when the analyses were restricted to MCPC cases without diabetes. We observed a statistically significant increased risk of pancreatic cancer among lean and physically active individuals but no association among overweight and inactive individuals. This might have been due to a lack of power because of the small number of cases in the overweight and inactive group. This result should be interpreted with caution because this finding might have been due to chance because of the multiple comparisons that were made in the present study.

We observed no associations between increased intake of some high-GI foods (eg, added sugar, soft drinks, sweet sandwich spreads, and sweets) and pancreatic cancer risk. Very few studies have examined these relations, and they reported no associations for jam and marmalade (43) and sweets (43), but positive associations for soft drinks (43, 44) and added sugar (38, 43).

So far, findings from prospective studies investigating the relation between GL and GI and several chronic conditions, such as type 2 diabetes, coronary heart disease, and breast and colorectal cancer, have been inconsistent, showing positive (45–49) or no (50–53) associations. Another study executed in this cohort, which examined the relation between GI and GL and colorectal cancer risk, did not find an association (54).

Considerable evidence from in vitro, animal, and human observational studies supports a role for insulin in pancreatic cancer etiology; therefore, the investigation of dietary factors that influence plasma insulin concentrations seems rational. The major rationale for using GI values is based on the assumption that postprandial blood glucose responses and insulin responses are highly correlated, but some studies have shown an inconsistency

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TABLE 3
Multivariable-adjusted relative risks (RRs) and 95% CIs for microscopically verified pancreatic cancer according to tertile (T) of glycemic load, overall glycemic index, total carbohydrates, and mono- and disaccharides, stratified by BMI and physical activity level in the Netherlands Cohort Study on diet and cancer, 1986–1999[1]

		BMI < 25 kg/m^2 and moderate-to-high physical activity[2]		Intermediate group[3]		BMI ≥ 25 kg/m^2 and low physical activity[2]		
Nutrient	Tertile median	Cases/ person-years	RR (95% CI)[4]	Cases/ person-years	RR (95% CI)[4]	Cases/ person-years	RR (95% CI)[4]	*P* for interaction
Glycemic load (g/d)[5]								
T1 (low)[6]	94	21/7289	1.00	44/7244	1.00	9/1544	1.00	
T2	108	29/6772	1.86 (1.02, 3.38)	46/7403	1.14 (0.73, 1.79)	10/1895	0.76 (0.30, 1.94)	
T3 (high)	146	30/7662	1.84 (0.96, 3.52)	37/6561	0.99 (0.60, 1.63)	8/1409	0.70 (0.27, 1.81)	
P for trend			0.066		0.975		0.465	0.650
Continuous (50-g/d intake increment)			1.40 (0.84, 2.33)		0.95 (0.58, 1.54)		0.50 (0.16, 1.58)	
Overall glycemic index[5]								
T1 (low)[6]	56	30/7559	1.00	34/7028	1.00	5/1542	1.00	
T2	59	25/7340	0.91 (0.51, 1.62)	38/7223	0.98 (0.58, 1.65)	12/1265	2.93 (0.85, 10.09)	
T3 (high)	63	25/6824	0.91 (0.51, 1.63)	55/6957	1.33 (0.75, 2.37)	10/2040	1.02 (0.21, 4.88)	
P for trend			0.742		0.295		0.882	0.398
Continuous (5-units/d increment)			0.89 (0.67, 1.19)		1.10 (0.78, 1.55)		0.81 (0.45, 1.47)	
Total carbohydrate (g/d)[5]								
T1 (low)[6]	164	23/7044	1.00	51/7516	1.00	9/1615	1.00	
T2	189	30/6827	1.65 (0.91, 2.97)	44/7285	1.00 (0.66, 1.53)	10/1774	0.78 (0.32, 1.92)	
T3 (high)	243	27/7852	1.39 (0.72, 2.69)	32/6407	0.81 (0.50, 1.33)	8/1459	0.71 (0.29, 1.72)	
P for trend			0.337		0.415		0.453	0.616
Continuous (50-g/d intake increment)			1.33 (0.94, 1.88)		0.93 (0.68, 1.28)		0.61 (0.30, 1.24)	
Mono- and disaccharides (g/d)[5]								
T1 (low)[6]	66	18/7105	1.00	50/7261	1.00	14/1859	1.00	
T2	91	32/7041	2.00 (1.02, 3.91)	44/7235	1.11 (0.71, 1.74)	8/1566	0.60 (0.25, 1.45)	
T3 (high)	123	30/7578	1.92 (0.93, 3.93)	33/6711	0.96 (0.58, 1.60)	5/1423	0.39 (0.14, 1.12)	
P for trend			0.076		0.936		0.066	0.082
Continuous (50-g/d intake increment)			1.43 (0.97, 2.10)		0.82 (0.59, 1.13)		0.47 (0.21, 1.02)	

[1] RRs and 95% CIs were calculated by using Cox proportional hazards models.
[2] Moderate-to-high physical activity level = ≥30 min/d; low physical activity level = <30 min/d.
[3] Intermediate group = either BMI ≥ 25 with moderate-to-high physical activity or BMI < 25 with low physical activity.
[4] Adjusted for sex, age (y), energy intake (kcal/d), smoking (current smoking: yes or no; number of cigarettes smoked per day; number of years of smoking), alcohol (g/d), history of diabetes mellitus (yes or no), history of hypertension (yes or no), and intake of vegetables (g/d), fruit (g/d), and fiber (energy-adjusted; g/d).
[5] Energy-adjusted intake.
[6] Reference category.

in glucose and insulin responses (12, 55). Also, whereas GI values are determined on single food items, people eat meals or snacks consisting not only of carbohydrates, but also of other macronutrients. Protein stimulates insulin release, despite an unchanged or even lower blood glucose concentration, compared with carbohydrates alone (12). Dietary fat inhibits gastric emptying, which in turn slows down the absorption of carbohydrates (12), which also gives rise to a lower postprandial blood glucose response. In addition, the amount of rapidly available glucose and resistant starch, the degree of osmolality, the viscosity of the gut's contents, are other important factors influencing the degree of postprandial insulin secretion (12).

The possibility to further restrict the analyses to microscopically verified cases only, where misclassification by disease status would be less likely than among NMCPC cases (56), was one of the strengths of this study (28). Other strengths included the large sample size and detailed information on potential risk factors for pancreatic cancer. Differential follow-up is unlikely to have made a material contribution to our findings, because the completeness of follow-up was high (21). The prospective design avoided recall bias and the need to use next-of-kin respondents, but nondifferential misclassification of GL values could not be ruled out. However, because some main dietary nutrients and food items contributing to GI and GL were in general moderately to highly correlated with both the FFQ (22) and GI and GL, the questionnaire most likely adequately ranked subjects according to GL and GI values.

A limitation of our study was the use of a single measure of dietary intake that may not have been representative of the dietary habits of the study participants over the course of follow-up. However, the FFQ was tested for reproducibility by Goldbohm et al (26), who concluded that a single measurement of dietary intake in the NLCS could characterize dietary habits for a period of at least 5 y. Our estimated GI values were lower and narrower in range and variation than values reported in other large cohorts (14–16, 47), which may have yielded too little contrast between the highest and lowest quintiles to detect differences in pancreatic cancer risk. Another issue concerning the GI values should

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be mentioned. The GI values used for this FFQ were obtained from the table published by Foster-Powell et al (13), as has been used by others. However, this GI table contains mostly items from Australian or American foods and not from European foods. Recently, Henry et al (57) established GI values for a variety of foods available in the United Kingdom, which concluded that most GI values compared well with previously published values (13); however, a few values were notably different from those of Foster-Powell et al (13). It remains to be established whether values determined for American and Australian food items can be applied to European foods.

In summary, our findings do not support the hypothesis that a high GL, overall GI, and carbohydrate and mono- and disaccharide intake are associated with an increased risk of pancreatic cancer. This finding agrees with previous prospective studies that investigated the relation between GL and GI and pancreatic cancer risk.

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The authors' responsibilities were as follows—MMH: analyzed and interpreted the data, and wrote the manuscript; BAJV and LHL: participated in the design and coordination of the study and critically reviewed the manuscript; HAMB: developed the GI database and critically reviewed the manuscript; and RAG and PAvdB: conceived the study, participated in its design and coordination, and critically reviewed the manuscript. None of the authors had a financial or personal conflict of interest.

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