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Glycemic index, glycemic load, and the risk of pancreatic cancer among postmenopausal women in the women's health initiative observational study and clinical trial

M. S. Simon,
Karmanos Cancer Institute, Department of Oncology, Wayne State University, 4100 John R, 4221, HWCRC, Detroit, MI, USA

Population Studies and Prevention Program, Karmanos Cancer Institute at Wayne State University, Detroit, MI, USA

J. M. Shikany,
Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

M. L. Neuhouser,
Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

T. Rohan,
Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

K. Nirmal,
Lone Star Cancer Associated, PA, San Antonio, TX, USA

Y. Cui, and
Office of Health Assessment and Epidemiology, Los Angeles County Public Health Department, Los Angeles, CA, USA

J. Abrams
Karmanos Cancer Institute, Department of Oncology, Wayne State University, 4100 John R, 4221, HWCRC, Detroit, MI, USA

M. S. Simon: Simonm@karmanos.org

Abstract

Background—Several reports have suggested that conditions associated with hyperinsulinemia and insulin resistance, such as diets high in carbohydrates, may influence the risk of pancreatic cancer, although results from prior studies have been mixed.

Methods—We utilized data from the population-based women's health initiative (WHI) cohort to determine whether dietary factors that are associated with increased postprandial blood glucose levels are also associated with an increased risk of pancreatic cancer. The WHI included 161,809 postmenopausal women of ages 50–79, in which 332 cases of pancreatic cancer were identified over a median of 8 years of follow-up; 287 of these cases met the criteria for analysis. A validated 122-item food frequency questionnaire was used to estimate dietary glycemic load (GL), glycemic index (GI), total and available carbohydrates, fructose and sucrose. Baseline questionnaires and physical exams provided information on demographic, medical, lifestyle, and anthropometric characteristics. Cox proportional hazards models were used to estimate hazard ratios (HR) and

Correspondence to: M. S. Simon, Simonm@karmanos.org.

95% confidence intervals (CI) for the association between the exposures of interest and pancreatic cancer risk, with adjustment for potential confounders.

Results—Dietary GL, GI, carbohydrates, fructose, and sucrose were not associated with increased risk of pancreatic cancer. The multivariable adjusted HR for the highest vs. the lowest quartile of GL was 0.80 (95% CI = 0.55–1.15, trend $p = 0.31$) and 1.13 (95% CI = 0.78–1.63, trend $p = 0.94$) for GI. The results remained negative when individuals with a history of diabetes were excluded.

Conclusions—Our results do not support the hypothesis that dietary intake of carbohydrates is associated with increased risk of pancreatic cancer.

Keywords

Glycemic index; Glycemic load; Pancreatic neoplasms; Prospective cohort

Introduction

The American Cancer Society has estimated that in 2009 there were approximately 42,470 new cases of pancreatic cancer in the United States and 35,240 deaths as a result of this disease (http://www.cancer.org/docroot/STT/stt_0.asp). The etiology of pancreatic cancer is not well understood. Smoking is the strongest risk factor for pancreatic cancer, with an estimated attributable fraction of 20% [1]. In addition, both diabetes mellitus [2] and obesity [3] are well-established risk factors for pancreatic cancer. In this regard, there is much evidence that hyperglycemia, insulin resistance, and hyperinsulinemia play a role in pancreatic carcinogenesis [2–9]. Consequently, due to the direct relationship between blood glucose concentrations and insulin secretion, dietary factors that increase glucose concentration may be linked to pancreatic cancer risk.

Dietary glycemic index (GI) is an estimate of the quality of carbohydrates ingested in the diet [10], while dietary glycemic load (GL) reflects both the quality and quantity of carbohydrates ingested. Diets high in GI and GL have been associated with obesity [11, 12], diabetes mellitus [13], hyperlipidemia [14], heart disease [15], and stroke [16]. Prior evaluations of the association between carbohydrate intake and pancreatic cancer risk have revealed mixed results [17–25]. One large cohort study demonstrated an increased risk of pancreatic cancer with increased consumption of foods high in sugar and added sugars [17], while in another cohort study no association was seen [18]. Seven cohort studies [19–25] and two meta-analyses [26, 27] have assessed the relationship between dietary GI, GL, and other measures of dietary carbohydrate intake and pancreatic cancer. None of these studies have demonstrated a significant overall relationship between GL, GI, or other measures of carbohydrate intake and pancreatic cancer risk, although in one study, a significant positive association was observed among a subgroup of sedentary and overweight women in the highest quartile of both GL and fructose [24].

In view of the inconclusive nature of the epidemiologic data to date, we used data from the multicenter women's health initiative (WHI) study to assess the relationship between measures of carbohydrate intake and pancreatic cancer risk. In order to maximize the number of pancreatic cancer cases available for analysis, the cohort included participants in both the WHI observational study (OS) and clinical trials (CT).

Materials and methods

The women's health initiative

The WHI is a large population-based study designed to evaluate factors associated with chronic diseases, including cancer, heart disease, and osteoporosis, among a cohort of postmenopausal women in the United States [28]. The WHI design and recruitment methodologies have been previously described [28–30]. In brief, women between the ages of 50 and 79 years were recruited between 1993 and 1998 from among four major racial and ethnic groups at 40 clinical centers throughout the United States. The WHI was comprised of a CT component (n = 68,132), which included three overlapping randomized controlled trials and an OS component (n = 93,676), which included women recruited specifically to the OS as well as women who were ineligible to participate in the CT.

Dietary assessment and other study variables

Dietary intake in the 3 months prior to enrollment was assessed by a self-administered 122-item food frequency questionnaire (FFQ), which was completed by all WHI participants at study entry and described in detail previously [31]. The FFQ consisted of three main sections including adjustment questions, foods and food groups, and summary questions. Adjustment questions pertained to food purchasing and preparation and were used in the analysis software to adjust calculations of the nutrient content of specific foods. The food and food groups section consisted of 122 line items detailing usual frequency of food intake and portion size. The summary section consisted of questions regarding usual intake of fruits and vegetables and of added fats. The WHI FFQ resulted in estimates of nutrient intake similar to those obtained from short-term and more precise measures of dietary recall. This was demonstrated in 113 women among whom the mean intake of most nutrients estimated by the FFQ were within 10% of the intake measured by food records and dietary recalls [31]. Data from the FFQ were processed using the Nutrition Data Systems for Research (NDSR, version 2005) (Nutrition Coordinating Center, University of Minnesota).

The derivation and use of GI and GL values for the WHI have been previously described [32]. GI is an estimate of the quality of carbohydrates ingested in the diet, and values for GI are derived from the glucose area under the plasma glucose concentration versus time curve (AUC) in response to a given amount of carbohydrate (usually 50 g) compared to the AUC of 50 g of a carbohydrate standard (white bread or glucose) [10, 33, 34]. GL is calculated as the sum of the GI of each food item multiplied by the dietary carbohydrate content in the reported serving size of that food and reflects both the quality and quantity of carbohydrates ingested. Since GI and GL values were not a part of the original WHI FFQ nutrient database, a set of GI and GL values was developed for all line items on the FFQ and tested on a random sample of completed WHI FFQs [32]. Individual GI values for each food containing at least five grams of total carbohydrate per medium portion were obtained primarily from published tables [34]. For foods not listed, GI values were imputed from foods with similar carbohydrate and fiber content.

The primary dietary exposures evaluated in this study included dietary GL, GI, total carbohydrates, sucrose, and fructose. Since estimates of total carbohydrates are inclusive of the dietary intake of fiber [35] and diets high in soluble fiber are associated with low GI values [36], GL was analyzed based on both total and available carbohydrates (total carbohydrate—fiber).

Baseline demographic, medical, and lifestyle information was also collected from CT and OS participants on enrollment. Weight and height were measured during the baseline examination using calibrated balance beam scales and stadiometers, respectively. Physical

activity was estimated from the questionnaire data and analyzed as the amount of reported moderate to strenuous physical activity of more than 20 min duration.

Case ascertainment

Cancer diagnoses were elicited annually in the OS and semi-annually in the CT by mailed or telephone questionnaires. Participant self-reports or next-of-kin reports of pancreatic (and other) cancer were verified by centrally trained physician adjudicators at the WHI Clinical Centers after review of medical records and pathology reports [37]. All pancreatic cancer cases included in this analysis were exocrine cancers of the head, body or tail of the pancreas.

Exclusions

We excluded 736 members of the original cohort of 161,809 who had an unknown history of pancreatic cancer; and 1,395 for whom it was not known whether they had a previous history of cancer, 14,783 who had a history of a previously diagnosed cancer, 4,387 who had unreliable FFQ results (defined as a total energy intake of <600 or >5,000 kcal per day), and 752 women with extreme values of body mass index (BMI) (defined as<15 or>50 kg/m^2). Our remaining analytic cohort consisted of 139,503 non-cases and 287 cases of pancreatic cancer.

Statistical analysis

Chi-square tests were used to evaluate differences in nominal variables between cases and non-cases, and Cuzick's trend test was used for ordinal variables and *t*-tests for continuous variables.

Using only the control group and excluding individuals with diabetes, energy-adjusted quartiles of the dietary factors of interest were computed using the residuals from the regression of each dietary variable on energy and adjusting the result to an energy intake of 2,000 kcal [38].

Crude hazard ratios (HR) and 95% confidence intervals (CI) were computed by using quartiles of the energy- adjusted dietary factor in a model parameterized with indicator variables. Multivariable models were used to adjust for age (≤60 vs. >60 years), race (white vs. other), income (<$35,000 vs. ≥$35,000) BMI (<25 vs. 25–29.9 or ≥30), frequency of moderate to strenuous physical activity lasting more than 20 min (some acts of limited duration, 2–3 times per week vs. 4 or more times per week), history of diabetes (yes vs. no), alcohol use (never or light, past, 1 –<7 drinks per week or ≥7 or more drinks per week), and smoking status (never, past, current; as well as amount in terms of cigarettes per day and years of exposure). We assessed whether the effect of dietary factors on the risk of pancreatic cancer depends on the level of BMI and activity evaluating this using both tertiles and quartiles for each dietary factor of interest. All statistical tests were two sided. History of pancreatitis was not evaluated because this information was collected only for OS participants of whom less than 0.05% reported a history of pancreatitis. Because of the large sample size, we considered results with $p \leq 0.01$ to be statistically significant and results with $0.01 < p \leq 0.05$ to be of marginal statistical significance. Statistical analyses were conducted using Stata 11.0 (StataCorp, College Station, TX).

Results

Women in the highest quartiles of GL were more likely to be younger and to be obese based on BMI and WHR. Women in the highest quartiles of GL also appeared to have a healthier lifestyle with a lower incidence of diabetes and were less likely to be frequent drinkers or

smokers (Table 1). Race, income, and participation in moderate physical activity did not vary much by quartile of GL.

Table 2 shows the crude and multivariable adjusted HR's of pancreatic cancer risk across quartiles of energy-adjusted dietary variables. After multivariable adjustment, there was no evidence of a significant association for any of the dietary factors studied. The multivariable adjusted HR for the highest vs. the lowest quartile of GL was 0.80 (95% CI = 0.55–1.15, trend $p = 0.31$) and 1.13 (95% CI = 0.78–1.63, trend $p = 0.94$) for GI (both based on total carbohydrates). These results did not change after exclusion of women with a history of diabetes mellitus (data not shown).

When the analyses were repeated for each stratum of BMI (<18.5, 18.5–24.9, ≥30 kg/m^2) and for the two strata of physical activity (1 or more episodes per week of moderate to strenuous physical activity vs. less episodes) using both tertiles and quartiles for each dietary factor of interest, there was no evidence of an association between any of the dietary factors with an increased risk of pancreatic cancer (data not shown).

Discussion

We hypothesized that a diet high in carbohydrates is associated with an increased risk of pancreatic cancer through the effects of hyperinsulinemia and insulin resistance. However, the results reported here for the WHI cohort do not support a relationship between pancreatic cancer and GL, GI or other measures of carbohydrate intake that have been previously suggested by in vitro [8] and animal studies [2, 3, 39, 40], as well as other population-based studies [5, 6, 41, 42].

GL and GI are dietary constructs that are useful for estimating the effect of dietary carbohydrates on the endogenous insulin response on a population basis [10]. There have been seven prior cohort studies [19–25] and two meta-analyses [26, 27] that assessed the relationship between pancreatic cancer risk, GL, GI, and other measures of carbohydrate intake. None of these studies, including the two meta-analyses, have provided evidence of positive associations between GL and GI and pancreatic cancer.

It has been suggested that the effect of high GL and GI diets may be most evident among obese or sedentary individuals who are more prone to insulin resistance and hyperinsulinemia. Subset analysis in the Nurses Health Study Cohort [24] showed a significant increase in pancreatic cancer risk among women in the highest quartile of GL, GI, and fructose intake among women who were both overweight (≥25 kg/m^2) and sedentary (<3 h of exercise per week), although the hazards ratios reported had wide confidence intervals and were based on results of a small number of affected participants [24]. Our data did not substantiate these findings when we looked for interaction using both tertiles and quartiles of the dietary factors of interest.

Other studies evaluating the interaction of GI and GL with weight and/or physical activity have shown inconsistent results. There was no significant interaction by BMI or physical activity in the Canadian National Breast Cancer Screening Study [20]. In the Multiethnic Cohort study, there was no overall association, but a significantly increased risk of pancreatic cancer across quartiles of sucrose intake only among overweight participants, and a non-significant increased risk for overweight individuals with a high level of physical activity [21]. In the Netherlands Cohort, there was a non-significant inverse association for GL and carbohydrates among the physically inactive and overweight individuals, and a non-significant increased risk among physically active and lean individuals [19]. In the ACS Prevention Study II, there was a marginally significant increase in pancreatic cancer risk associated with carbohydrate intake among overweight (>25 kg/m^2) and sedentary women

(6+ h spent sitting per day) but no associations were observed for GL and GI [23]. In another cohort study, a positive association between GI and overall cancer risk was seen among overweight individuals, although no association was seen specifically for GI and pancreatic cancer [23]. In summary, while biologically plausible, a relationship between measures of carbohydrate intake and pancreatic cancer that was observed in the Nurses Health Study [24] has not been replicated by others and therefore, may just be due to chance.

The strengths of our study include a large well-established cohort with a relatively long median follow-up period of 8 years (follow-up in other cohort studies ranged from 8 to 18 years) computation of GL and GI from a validated dietary assessment instrument and confirmation of cancer outcomes. GI and GL values were derived from an FFQ designed specifically for the WHI [31], and the addition of GI and GL values to the FFQ nutrient database was done in a systematic and well-documented manner [32].

A major limitation of this and other studies though was the inability of the dietary instruments used to capture the true range of GI and GL [26]. As shown in Table 2, we had a fairly wide range of exposure to carbohydrates and GL, although the range for GI was relatively narrow. A global weakness of this type of study design is that the semiquantitative FFQ was not designed to assess dietary GI and GL, and the assessment of GI and GL by FFQ has not been validated using other dietary methods or against an objective standard [43]. In addition the limited variety of food items on most FFQs can limit the measureable range of GI and GL. Whereas uniform definitions of GL and GI are used across the cohort study designs, quartile or quintile definitions of exposure are unique for each study population and therefore, cannot necessarily be generalized to other groups. Lastly, it should be noted that while the overall size of the WHI cohort is large, the number of cases of pancreatic cancer available for analysis after exclusions was relatively small (287), although comparable to the number of cases available in the other cohort analyses (the number of cases in other cohorts ranged from 112 to 434), and the WHI was not explicitly powered for pancreatic cancer.

In summary, the results of this study provide no evidence that increased GI, GL, and other measures of carbohydrate intake are associated with increased risk of pancreatic cancer in WHI participants. These results are in accord with those of two large meta-analyses, both of which included the previously cited cohort studies [26, 27].

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Table 1

Demographic, physical, medical, and lifestyle characteristics by quartiles of glycemic load

	Quartile 1 *n* = 35,353 (%)	Quartile 2 *n* = 34,909 (%)	Quartile 3 *n* = 34,712 (%)	Quartile 4 *n* = 34,815 (%)
Age 60 or older				
No	36	37	39	43
Yes	64	63	61	57
Race				
White	80	85	86	83
Black	11	8	7	9
Other	10	8	7	8
Education				
HS or less	25	22	20	21
College	50	49	49	47
Postgraduate	25	29	31	31
Income $35,000 or more				
No	42	39	39	42
Yes	58	61	61	58
BMI				
Normal (<25)	37	38	36	30
Overweight (25–29.9)	36	35	35	34
Obese (≥30)	27	27	29	36
Waist-to-hip ratio				
<0.81	50	52	52	48
0.81–0.85	25	23	23	25
>0.85	26	24	24	28
Moderate to strenuous activity>20 min day				
No activity	17	15	14	16
Some activity of limited duration	42	40	40	41
2–3 episodes per week	17	19	19	17
4 episodes per week	24	27	28	26
Diabetes ever				
No	93	94	95	95
Yes	7	6	5	5
Alcohol use				
Never or light drinker	43	43	44	46
Past drinker	18	17	18	20
1–7 or more drinks per week	26	27	27	25
7 or more drinks per week	14	13	11	9
Smoking status				
Never smoked	49	51	52	53
Past smoker	42	43	42	41
Current smoker	9	7	6	6

	Quartile 1 ***n*** **= 35,353 (%)**	**Quartile 2** ***n*** **= 34,909 (%)**	**Quartile 3** ***n*** **= 34,712 (%)**	**Quartile 4** ***n*** **= 34,815 (%)**
Years a regular smoker				
Less than 5 years	13	14	15	15
5–9 years	9	10	11	11
10–19 years	20	22	23	22
20–29 years	22	22	22	22
30–39 years	20	19	17	18
40–49 years	12	11	10	10
50 or more years	4	3	2	2
Smoke Or smoked, cigarettes/day				
Less than 5	5	5	5	5
5–14	19	19	19	19
15–24	33	33	33	32
25–34	29	29	29	28
35–44	9	9	9	10
45 or more	5	5	6	6

Quartiles of glycemic load based on available carbohydrates (total carbohydrate—fiber) and adjusted for energy standardized to 2,000 kcal

BMI body mass index (kg/m^2)

Table 2

Risk of pancreatic cancer associated with quartiles of energy-adjusted dietary variables

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value[a]
Dietary glycemic load based on available carbohydrates[b]					
Median (Range)	98 (<107)	113 (107–118)	123 (118–130)	139 (>130)	
Cases/PYRS	89/279,372	68/275,810	72/274,037	58/271,243	
Crude RR (95% CI)	1.00	0.77 (0.56, 1.06)	0.83 (0.61, 1.13)	0.67 (0.48, 0.94)	0.03
MV adjusted HR (95% CI)[c]	1.00	0.78 (0.54, 1.10)	0.85 (0.60, 1.21)	0.78 (0.54, 1.13)	0.25
Dietary glycemic load based on total carbohydrates[d]					
Median (Range)	105 (<115)	121 (115–127)	133 (127–140)	150 (>140)	
Cases/PYRS	88/278,658	66/275,648	74/274,518	59/271,638	
Crude RR (95% CI)	1.00	0.76 (0.55, 1.04)	0.85 (0.63, 1.16)	0.69 (0.50, 0.96)	0.05
MV adjusted HR (95% CI)	1.00	0.77 (0.54, 1.10)	0.87 (0.61, 1.24)	0.80 (0.55, 1.15)	0.31
Dietary glycemic index (using total carbohydrates)					
Median (Range)	48 (<50)	51 (50–52)	54 (52–55)	56 (>55)	
Cases/PYRS	67/274,720	80/274,658	64/275,629	76/275,455	
Crude RR (95% CI)	1.00	1.19 (0.86, 1.65)	0.95 (0.68, 1.34)	1.13 (0.81, 1.57)	0.83
MV adjusted HR (95% CI)	1.00	1.26 (0.89, 1.77)	0.94 (0.65, 1.37)	1.13 (0.78, 1.63)	0.94
Dietary total carbohydrates (G)					
Median (Range)	203 (<219)	230 (219–241)	252 (241–265)	285 (>265)	
Cases/PYRS	93/279,013	63/275,786	69/274,142	62/271,531	
Crude RR (95% CI)	1.00	0.69 (0.50, 0.94)	0.76 (0.55, 1.03)	0.69 (0.50, 0.95)	0.03
MV adjusted HR (95% CI)	1.00	0.70 (0.49, 1.00)	0.78 (0.54, 1.10)	0.80 (0.56, 1.15)	0.31
Dietary sucrose (G)					
Median (Range)	32 (<37)	41 (37–45)	48 (45–53)	60 (>53)	
Cases/PYRS	68/286,156	81/276,040	70/271,381	68/266,895	
Crude RR (95% CI)	1.00	1.24 (0.90, 1.71)	1.09 (0.78, 1.52)	1.07 (0.77, 1.50)	0.89
MV adjusted HR (95% CI)	1.00	1.29 (0.90, 1.85)	1.20 (0.82, 1.74)	1.30 (0.89, 1.89)	0.25
Dietary fructose (G)					
Median (Range)	13 (<16)	19 (16–21)	24 (21–27)	33 (>27)	
Cases/PYRS	76/281,384	88/275,160	72/273,081	51/270,847	

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value[a]
Crude RR (95% CI)	1.00	1.19 (0.87, 1.61)	0.98 (0.71, 1.35)	0.70 (0.49, 1.00)	0.02
MV adjusted HR (95% CI)	1.00	1.13 (0.80, 1.60)	1.09 (0.77, 1.55)	0.79 (0.54, 1.17)	0.20

[a]The *p*-value is a test of linear trend across quartiles

[b]Available carbohydrates are equal to total carbohydrates minus dietary fiber content

[c]MV Adjusted HR—Multivariable adjusted Hazard Ratio adjusted for age, race, income, BMI, physical activity, history of diabetes, alcohol use, and smoking status

[d]Estimates of total carbohydrate are inclusive of dietary intake of fiber