

Dietary insulin load, dietary insulin index, and risk of pancreatic cancer^{1–3}

Ying Bao, Katharina Nimptsch, Brian M Wolpin, Dominique S Michaud, Jennie C Brand-Miller, Walter C Willett, Edward Giovannucci, and Charles S Fuchs

ABSTRACT

Background: Although hyperinsulinemia and insulin resistance have been hypothesized to be involved in pancreatic carcinogenesis, studies that have examined glycemic load or individual dietary components that influence glucose concentrations have yielded inconclusive results.

Objective: Our objective was to investigate whether dietary insulin load and dietary insulin index are associated with the risk of pancreatic cancer.

Design: We prospectively followed 86,740 women and 46,147 men who were free of cancer and diabetes at baseline in the Nurses' Health Study and the Health Professionals Follow-Up Study. During ≤ 26 y of follow-up, 691 pancreatic cancer cases were documented. Dietary insulin load was calculated as a function of the food insulin index, and the energy content of individual foods was reported on food-frequency questionnaires. The dietary insulin index was calculated by dividing the dietary insulin load by the total energy intake.

Results: Dietary insulin load and dietary insulin index were not associated with the overall risk of pancreatic cancer. In a comparison of the highest with the lowest quintiles, the pooled multivariate RRs of pancreatic cancer were 1.05 (95% CI: 0.82, 1.34) for dietary insulin load and 0.96 (95% CI: 0.75, 1.23) for dietary insulin index. In individuals with an elevated BMI (in kg/m^2 ; ≥ 27.5) or with low physical activity, a high insulin load was associated with small, nonsignificant increases in the risk of pancreatic cancer; in a comparison of the highest with the lowest tertile of intake, the positive association became more apparent in those who were both overweight and inactive (RR: 2.03; 95% CI: 1.05, 3.93; P -trend = 0.04).

Conclusions: A diet that induces an elevated postprandial insulin response does not influence the overall risk of pancreatic cancer. However, a diet with a high insulin load may increase the risk in individuals with a preexisting state of insulin resistance. *Am J Clin Nutr* doi: 10.3945/ajcn.110.011205.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in the United States (1); however, the etiology of this cancer has not been precisely understood. Hyperinsulinemia and insulin resistance have been hypothesized to play important roles in the development of pancreatic cancer because higher circulating insulin, glucose, or C-peptide (a marker of insulin resistance and long-term insulin secretion) has been associated with an increased risk of

pancreatic cancer (2, 3). In addition, many of the proposed risk factors for pancreatic cancer, including obesity, sedentary lifestyle, and type 2 diabetes mellitus, have been related to hyperinsulinemia and insulin resistance (4). A plausible underlying biological mechanism involves the growth-promoting effect of excess insulin or insulin-like growth factors (4).

The association between hyperinsulinemia and pancreatic cancer suggests that a diet inducing an elevated insulin response may contribute to tumor growth. The glycemic load and glycemic index, which characterize the influence of carbohydrate intake on blood glucose, have been used as an indicator of insulin response. Previous studies showed that glycemic load and glycemic index were not appreciably associated with the overall risk of pancreatic cancer in most studies, although positive associations were observed in some studies (5). Similarly, studies examining individual dietary components that affect glucose concentrations, such as carbohydrate and sugar, also yielded inconsistent results for pancreatic cancer (6–14). However, carbohydrate is not the only stimulus for insulin secretion: protein intake also leads to an insulin response, and the addition of fat to a carbohydrate source can increase the insulin response without increasing glycemia (15). Because etiologic hypotheses addressing the risk of cancer are primarily related to hyperinsulinemia rather than to hyperglycemia per se, the use of glycemic load, glycemic index, or individual dietary components that influence glucose concentrations is indirect and conceptually suboptimal.

Therefore, an insulin index was developed to quantify postprandial insulin response for individual foods, including those with low or no carbohydrate content (15). A recent study showed that this new concept allows a more accurate prediction of insulin

¹ From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (YB, EG, and CSF); the Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, MA (BMW and CSF); the Departments of Epidemiology (DSM, EG, and WCW) and Nutrition (KN, EG, WCW), Harvard School of Public Health, Boston, MA; the Department of Epidemiology and Public Health, Imperial College London, United Kingdom (DSM); the Institute of Obesity, Nutrition, and Exercise, University of Sydney, Sydney, Australia (JCBM).

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³ Address correspondence to Y Bao, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115. E-mail: ying.bao@channing.harvard.edu.

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demand than do carbohydrate content or glycemic load (16). On the basis of this new classification, we built an insulin index database for a large number of foods listed on the food-frequency questionnaires in 2 prospective cohort studies. We further calculated the insulin response to a total diet, represented by dietary insulin load and dietary insulin index. We used these 2 insulin scores to investigate whether diets high in foods that increase postprandial insulin concentrations are associated with the risk of pancreatic cancer. In addition, because individuals who already have underlying insulin resistance may have a greater insulin response to their diet than do those who have normal insulin sensitivity (10), we further examined the associations of interest in obese and/or inactive participants.

SUBJECTS AND METHODS

Study population

The NHS⁴ was established in 1976 when 121,700 US female nurses aged 30–55 y responded to a mailed questionnaire. The HPFS was initiated in 1986 when 51,529 US male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) aged 40–75 y completed a baseline questionnaire. Follow-up questionnaires were sent to participants every 2 y to update information on new disease diagnoses and potential risk factors for chronic diseases. The overall follow-up rate was >90% in both cohorts.

For the current analysis, follow-up started in 1980 in the NHS and in 1986 in the HPFS, when dietary information was first assessed. At baseline, we excluded individuals who had been previously diagnosed with cancer or diabetes (because diabetic patients usually limit their intake of insulinogenic foods), left an extensive number of items blank on the food-frequency questionnaire, or reported an implausible energy intake (<500 or >3500 kcal/d for women and <800 or >4200 kcal/d for men), which left a cohort of 132,887 participants eligible (86,740 women and 46,147 men). This study was approved by the Human Subjects Committee at Brigham and Women's Hospital and the Harvard School of Public Health.

Dietary assessment

Dietary intake was obtained from the NHS participants via validated semiquantitative food-frequency questionnaires in 1980, 1984, and 1986 and every 4 y thereafter and from the HPFS participants every 4 y since 1986. Participants were asked to report their average frequency of intake over the preceding 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 and then summing the contributions from all foods.

The insulin index for each food compares its postprandial plasma insulin response relative to a reference food. Insulin index values for foods that appeared in the food-frequency questionnaire were obtained either from published estimates (31 foods) (15, 17) or from direct testing of food items at the University of

Sydney, Australia (73 foods; provided by Jennie Brand-Miller). US food samples were shipped to the laboratory in Sydney for testing. The testing procedure was described in detail previously (15): each person consumed a variety of test foods on separate days, with insulin measured every 15 min for 2 h after consumption. The insulin index value was calculated by dividing the area under the insulin response curve for 1000 kJ (239 kcal) of a test food by the area under the insulin response curve for 1000 kJ (239 kJ) of the reference food (glucose). The insulin index value for each food represented the mean responses of 11 to 13 subjects.

Using these insulin index values, we then calculated the dietary insulin load during the past year for each participant by multiplying the insulin index value of each food by the total energy intake contributed by that food and summing values for all food items reported:

$$\begin{aligned} \text{Dietary insulin load} = & \Sigma[\text{insulin index of food} \\ & \times \text{energy content of food (kcal/serving)} \\ & \times \text{frequency of consumption (servings of food/d)}] \end{aligned} \quad (1)$$

Each unit of dietary insulin load represents the equivalent insulin response generated by 1 kcal glucose. In the NHS, the top 10 food sources for dietary insulin load were mashed potatoes, beef, skim milk, cold breakfast cereal, dark bread, white bread, yogurt, orange juice, pizza, and English muffin; in the HPFS, the top 10 food sources were mashed potatoes, cold breakfast cereal, beef, dark bread, skim milk, white bread, pancake, orange juice, pizza, and banana.

The dietary insulin index for the overall diet, which is the weighted mean of the insulin index value for each of the component foods, was calculated by dividing the dietary insulin load by the total energy intake:

$$\begin{aligned} \text{Dietary insulin index} = & \text{dietary insulin load} / \{ \Sigma[\text{energy content of food} \\ & \text{(kcal/serving)} \times \text{frequency of consumption} \\ & \text{(servings of food/d)}] \} \end{aligned} \quad (2)$$

The validity of the food-frequency questionnaires was assessed by comparison with 1-wk diet records (18, 19). The food-frequency questionnaire was found to be a reasonably accurate measure of the individual foods from which the dietary insulin load and dietary insulin index were derived; for example, the correlation coefficients between the food-frequency questionnaire and diet records were as follows: 0.46 (NHS) and 0.66 (HPFS) for meat, 0.79 and 0.86 for cold breakfast cereal, 0.81 and 0.88 for skim milk, 0.77 and 0.37 for dark bread, and 0.71 and 0.45 for white bread.

Brand-Miller et al (16) recently assessed the validity of dietary insulin load in predicting the actual insulin response. Healthy participants ($n = 10$ or 11 for each meal) consumed 13 different isoenergetic (2000 kJ) mixed meals of varying macronutrient content. Despite the limited statistical power, they found that dietary insulin load was strongly correlated with observed postprandial insulin responses ($r = 0.78$, $P = 0.002$), which suggests that dietary insulin load may be a valid measure of actual insulin response to composite meals.

⁴ Abbreviations used: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; MET-h, metabolic equivalent hours.

Identification of pancreatic cancer cases

In both cohorts, when a participant (or next of kin for decedents) reported a diagnosis of pancreatic cancer on a biennial follow-up questionnaire, we asked permission to obtain the participant's medical records. We also searched the National Death Index to identify deaths among nonrespondents. If the primary cause of death on the death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records. Study physicians who were blinded to the participants' risk factor status reviewed medical records and assigned cancer diagnoses and causes of death. A total of 691 (403 in the NHS and 288 in the HPFS) pancreatic cancer cases were identified during the follow-up period.

Assessment of nondietary factors

Information on smoking and diabetes were assessed at baseline and updated biennially in both cohorts. BMI was calculated from height and weight reported at baseline because pancreatic cancer is frequently associated with profound weight loss, and our previous findings showed the strongest associations between BMI at baseline and pancreatic cancer risk (10). Information on physical activity was also obtained from the baseline questionnaires: in the NHS, data on hours per week of physical activities were collected; in the HPFS, leisure-time physical activity was measured on 10 common activities and the information was summed and calculated as MET-h.

Statistical analysis

We computed person-time 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 (30 June 2006 in the NHS and 31 January 2006 in the HPFS), whichever came first. RRs and 95% CIs were estimated by Cox proportional hazards models, with age and calendar time as the primary time scales. Dietary insulin load and dietary insulin index were energy-adjusted by the residual method (20) and then analyzed in quintiles based on the distributions observed in each cohort, with the lowest quintile as the reference group.

We first analyzed dietary insulin scores derived from baseline questionnaires and then conducted 3 alternative analyses: using the 1984 dietary questionnaire as baseline for the NHS (because the 1984 questionnaire had more food items), updating the scores every 4 y (simple update), and updating the scores cumulatively (cumulative update). In multivariate analyses, we adjusted for height (quintiles), BMI (kg/m^2 in quintiles), diabetes (yes or no, incident cases of type 2 diabetes during the follow-up period), physical activity (quintiles), pack-years of smoking [never smoker or current smoker (1–9, 10–24, 25–44, or ≥ 45 pack-years)], and energy intake (quintiles). We further adjusted for intakes of alcohol, red meat, fruit and vegetables, fiber, folate, calcium, and vitamin D. Linear trends were tested by the Wald test of a score variable that contained median values of intake categories.

In a sensitivity analysis, we performed a series of lag analyses, excluding the first 2, 4, 6, 8, or 10 y of follow-up for all participants to rule out an effect of subclinical pancreatic cancer on dietary intake. We also repeated analyses in which dietary insulin

load and dietary insulin index were not energy-adjusted by the residual method.

Because individuals who are obese and individuals who are less active tend to have a greater insulin response to their diet than do lean or active individuals (10), we further stratified analyses by BMI (<27.5 compared with ≥ 27.5) and physical activity (high compared with low, use median as the cutoff). We chose 27.5 as the cutoff for BMI because the increase in risk of pancreatic cancer was mainly in obese men and women in our cohorts (21), and a BMI of ≥ 27.5 (ie, we divided the overweight group in half and considered the high overweight group and the obese group) could indicate obesity and still provide enough cases to allow reliable analysis. To further examine whether the associations of our interest are more pronounced in those with presumed greater insulin resistance, we analyzed the associations in subgroups defined by the combination of BMI and physical activity. We also examined whether cigarette smoking (never, past, or current) modified the associations of interest. Tests for interaction were performed with the Wald test by using the cross-product term of the median trend variable with the stratification variable.

For all analyses, the data were analyzed separately for each cohort, and cohort-specific RRs were then pooled to compute a summary RR by using a random-effects model that allows for between-study heterogeneity (22). Tests of heterogeneity were calculated by using the Q statistic (22).

RESULTS

At baseline, the median dietary insulin load was 646 in women and 808 in men, and the median dietary insulin index was 40 in women and 41 in men. In both cohorts, participants in the upper quintiles of dietary insulin load were less likely to smoke and consumed more carbohydrates and less fat and alcohol (**Table 1**). Women with a high insulin load had a higher BMI, whereas men with a high insulin load had a lower BMI. Age, height, and multivitamin use did not vary remarkably across quintiles of dietary insulin load.

Dietary insulin load and dietary insulin index were not related to the overall risk of pancreatic cancer in age-adjusted or multivariate analyses (**Table 2**). No statistically significant heterogeneity was found between the NHS (women) and HPFS (men) (P -heterogeneity for the highest compared with the lowest quintile = 0.73 for dietary insulin load and 0.74 for dietary insulin index). The pooled multivariate RRs of pancreatic cancer for the highest compared with the lowest quintiles were 1.05 (95% CI: 0.82, 1.34) for the dietary insulin load and 0.96 (95% CI: 0.75, 1.23) for the dietary insulin index, and the pooled RRs did not differ greatly across quintiles.

Similar associations between dietary insulin scores and overall risk of pancreatic cancer were observed when we used the 1984 dietary questionnaire as baseline for the NHS or when we used simple or cumulative updating of the dietary insulin scores (data not shown).

A small, nonsignificant increase in risk of pancreatic cancer was observed for a high insulin load in individuals with elevated BMI (**Table 3**: pooled multivariate RR: 1.32; 95% CI: 0.86, 2.00, highest compared with lowest tertiles of intake; P -heterogeneity between NHS and HPFS = 0.73) or with low physical activity (pooled multivariate RR: 1.30; 95% CI: 0.97, 1.74, highest compared with lowest tertiles of intake; P -heterogeneity

TABLE 1Baseline characteristics of participants by quintile (Q) of energy-adjusted dietary insulin load¹

	NHS ²			HPFS ²		
	Q1	Q3	Q5	Q1	Q3	Q5
<i>n</i>	17,289	17,304	17,413	9125	9127	9319
Median dietary insulin load, energy-adjusted	547	646	745	673	807	930
Median dietary insulin index, energy-adjusted	34	40	45	34	41	47
Median dietary glycemic load, energy adjusted	61	84	111	96	125	148
Age (y)	46.5 ± 6.9 ³	46.0 ± 7.2	46.4 ± 7.4	54.6 ± 9.3	53.3 ± 9.7	53.6 ± 10.0
Height (inches) ⁴	64.6 ± 2.4	64.5 ± 2.4	64.4 ± 2.4	70.1 ± 3.0	70.1 ± 2.8	70.0 ± 2.7
BMI (kg/m ²)	23.8 ± 4.0	24.4 ± 4.5	24.7 ± 4.7	25.8 ± 3.3	25.6 ± 3.3	25.0 ± 3.1
Physical activity (h/wk for NHS; MET-h/wk for HPFS)	3.9 ± 2.9	3.9 ± 2.9	3.9 ± 2.9	19.7 ± 26.8	21.8 ± 35.2	22.5 ± 30.2
Current smoking (%)	40	27	23	17	8	5
Alcohol intake (g/d)	16.3 ± 16.5	4.2 ± 6.3	2.1 ± 4.1	26.9 ± 22.4	8.2 ± 9.4	3.8 ± 5.8
Multivitamin use (%)	35	33	35	43	41	42
Energy intake (kcal)	1558 ± 529	1584 ± 486	1535 ± 504	1957 ± 634	2026 ± 619	1938 ± 604
Total fat intake, energy-adjusted (g/d)	77 ± 15	72 ± 11	58 ± 11	76 ± 16	73 ± 12	63 ± 13
Protein intake, energy-adjusted (g/d)	77 ± 15	77 ± 14	71 ± 16	95 ± 20	93 ± 15	87 ± 14
Carbohydrate intake, energy-adjusted (g/d)	120 ± 30	154 ± 25	194 ± 29	192 ± 35	237 ± 30	274 ± 36

¹ All variables (except for age, dietary insulin load, dietary insulin index, and dietary glycemic load) were age standardized. MET-h, metabolic equivalent hours; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

² Baseline: 1980 for NHS, 1986 for HPFS.

³ Mean ± SD (all such values).

⁴ 1 inch = 2.54 cm.

between NHS and HPFS = 0.76). The positive association became more apparent in those who were both overweight and sedentary (RR: 2.03; 95% CI: 1.05, 3.93, highest compared with lowest tertiles of intake; *P*-trend = 0.04; *P*-heterogeneity between NHS and HPFS = 0.58). The test for interaction showed a borderline significant difference between the trend in the obese and inactive groups and that in the lean and active groups (*P*-interaction = 0.05). Smoking did not modify the associations of pancreatic cancer with insulin index or insulin load (data not shown).

Our findings remained essentially unchanged after the exclusion of the first 2, 4, 6, 8, or 10 y of follow-up or further adjustment for intakes of alcohol, red meat, fruit and vegetables, fiber, folate, calcium, and vitamin D (data not shown). Similar results were obtained when dietary insulin load and dietary insulin index were not energy-adjusted by using the residual method (data not shown).

DISCUSSION

In this large cohort of US men and women, a diet inducing postprandial hyperinsulinemia was not related to the overall risk of pancreatic cancer. However, a diet with a high insulin load may increase the risk in individuals who were both overweight and sedentary. To our knowledge, this study was the first to use insulin scores to assess the effect of consumption of a high insulinogenic diet on pancreatic cancer.

The observed lack of an overall association is consistent with most studies that examined the association of risk with glycemic load and glycemic index, which reflects the postprandial glucose response of carbohydrate-containing foods and has been used as an indicator of insulin response to different diets. In most studies, the glycemic load and glycemic index were not associated with pancreatic cancer risk (7–10, 12, 14, 23), although an increased risk with glycemic load was observed in the NHS (10). A recent meta-analysis of studies up to 2008 showed that the pooled RRs

of pancreatic cancer were 1.01 (95% CI: 0.86, 1.19; *n* = 6 cohort studies) for glycemic load and 0.99 (95% CI: 0.83, 1.19; *n* = 5 cohort studies) for the glycemic index (5).

The null findings from these previous studies and the current study indicate that an insulinogenic diet alone might not be important in pancreatic carcinogenesis. In contrast, serologic studies showed that high blood insulin or C-peptide concentrations were associated with an increased risk of pancreatic cancer (2, 3). In a cohort of male smokers, fasting serum insulin in the highest compared with the lowest quartile showed a significant 2-fold increased risk (RR: 2.01; 95% CI: 1.03, 3.93) (2); in a previous analysis of our cohorts of US men and women, nonfasting C-peptide in the highest compared with the lowest quartiles was associated with a significant 4-fold increased risk (RR: 4.24; 95% CI: 1.30, 13.80) (3).

The discrepancy between studies assessing an insulinogenic diet and those examining circulating or C-peptide likely reflect a variety of factors. As shown in **Figure 1**, factors that increase insulin resistance (decreased peripheral response to insulin), including overconsumption, obesity, and physical inactivity, will produce a compensatory fasting and postprandial hyperinsulinemia when pancreatic β cell function is adequate; whereas insulinogenic diets increase the insulin demand after meals, thereby transiently influencing postprandial insulin concentrations (4, 24). Because insulin resistance greatly upregulates long-term basal insulin secretion, it is possible that sustained hyperinsulinemia is largely determined by the degree of insulin resistance rather than by the insulinogenic content in a diet. This may explain the overall null association in our analysis between insulinogenic diets and pancreatic cancer that is related to circulating insulin and C-peptide concentrations in previous prospective studies.

Evidence supports the notion that insulin resistance plays a key role in pancreatic carcinogenesis. Fasting insulin, a reasonably reliable measure of insulin resistance, was positively associated

TABLE 2
Dietary insulin load, dietary insulin index, and risk of pancreatic cancer by quintile (Q)¹

	Q1	Q2	Q3	Q4	Q5	P-trend
Dietary insulin load						
NHS						
Quintile median	547	608	646	683	745	
No. of cases	81	80	77	82	83	
Person-years	421,316	427,854	427,166	430,003	428,478	
Age-adjusted	1.0	1.01 (0.74, 1.37) ²	0.96 (0.70, 1.31)	1.02 (0.75, 1.38)	1.01 (0.74, 1.37)	0.95
Multivariate-adjusted ³	1.0	1.07 (0.78, 1.46)	1.03 (0.75, 1.41)	1.09 (0.80, 1.49)	1.09 (0.79, 1.48)	0.61
HPFS						
Quintile median	673	757	807	855	930	
No. of cases	59	69	49	59	52	
Person-years	160,898	166,344	164,427	166,411	167,114	
Age-adjusted	1.0	1.19 (0.84, 1.69)	0.87 (0.60, 1.28)	1.06 (0.73, 1.52)	0.92 (0.63, 1.34)	0.53
Multivariate-adjusted ³	1.0	1.25 (0.88, 1.77)	0.93 (0.63, 1.37)	1.14 (0.79, 1.65)	1.00 (0.68, 1.47)	0.88
NHS and HPFS ⁴						
Multivariate-adjusted ³	1.0	1.15 (0.91, 1.45)	0.99 (0.77, 1.26)	1.11 (0.87, 1.40)	1.05 (0.82, 1.34)	0.81
Dietary insulin index						
NHS						
Quintile median	34	38	40	42	46	
No. of cases	82	76	86	82	77	
Person-years	420,478	427,539	427,347	429,694	429,758	
Age-adjusted	1.0	0.94 (0.69, 1.29)	1.07 (0.79, 1.44)	1.01 (0.74, 1.37)	0.91 (0.67, 1.25)	0.69
Multivariate-adjusted ³	1.0	1.00 (0.73, 1.37)	1.15 (0.85, 1.57)	1.09 (0.80, 1.49)	1.00 (0.73, 1.37)	0.87
HPFS						
Quintile median	34	38	41	43	47	
No. of cases	64	65	54	55	50	
Person-years	160,574	165,038	165,752	167,477	166,352	
Age-adjusted	1.0	1.04 (0.73, 1.47)	0.90 (0.62, 1.29)	0.91 (0.63, 1.31)	0.85 (0.59, 1.24)	0.29
Multivariate-adjusted ³	1.0	1.08 (0.76, 1.53)	0.95 (0.66, 1.37)	0.97 (0.67, 1.41)	0.92 (0.63, 1.34)	0.54
NHS and HPFS ⁴						
Multivariate-adjusted ³	1.0	1.04 (0.82, 1.31)	1.06 (0.84, 1.35)	1.04 (0.82, 1.32)	0.96 (0.75, 1.23)	0.77

¹ Dietary insulin load and dietary insulin index were measured at baseline in 1980 for the Nurses' Health Study (NHS) and in 1986 for the Health Professionals Follow-Up Study (HPFS).

² RR; 95% CI in parentheses (all such values).

³ Adjusted for age, height (quintiles), BMI (kg/m² in quintiles), diabetes (yes or no), physical activity (quintiles), pack-years of smoking [never smoker or current smoker (1–9, 10–24, 25–44, or ≥45 pack-years)], and energy intake (quintiles).

⁴ NHS and HPFS were pooled by using random-effects models.

with pancreatic cancer (2). Furthermore, metformin (a drug that reduces insulin resistance but does not affect insulin secretion) completely inhibited the development of chemically induced pancreatic cancer in hamsters with peripheral insulin resistance (25). The importance of insulin resistance in the insulin-cancer relation is further supported by our finding that a diet with a high insulin load is associated with an increased risk of pancreatic cancer in individuals with greater insulin resistance, approximated by obesity and/or physical inactivity. Because insulin resistance amplifies the insulin response to insulinogenic foods, individuals with insulin resistance may be exposed to greater hyperinsulinemia after meals than are those with normal insulin sensitivity. Therefore, the effects of insulinogenic diets on cancer development may only become apparent in individuals who already have an underlying degree of insulin resistance. In a separate analysis of our cohorts, we found a positive association between dietary insulin scores and plasma triacylglycerol concentrations (a marker of insulin secretion), and this association was stronger in overweight individuals as well (26). This observation also indicated that individuals with some degree of insulin resistance are particularly susceptible to diets that induce increased insulin response.

Another possible explanation for the overall null association with insulin scores is that the frequency of insulinogenic food intake, rather than the total quantity of intake, might be more relevant to pancreatic carcinogenesis. Because food intake increases insulin demand on a short-term basis and induces high peaks and lower troughs in circulating insulin, temporary hyperinsulinemia triggered by foods may have a limited effect on cancer development. One may speculate that frequent fluctuations in blood insulin might increase exposure to hyperinsulinemia and therefore increase the subsequent risk of pancreatic cancer. A previous study showed that after adjustment for total energy intake, individuals who ate ≥3 meals/d doubled the risk of pancreatic cancer compared with that in those who ate 1 meal/d (27), which suggests that frequent stimulated hyperinsulinemia may be important.

Alternatively, given that the consumption of diets with high insulin scores was associated with a healthy lifestyle in this study, the observed lack of an overall association could have been due to residual confounding by some unknown lifestyle factors. However, such confounding factors would have to be relatively prevalent, highly correlated with insulin scores in this cohort and with strong risk factors for pancreatic cancer, to have a great effect. We also could not exclude the possibility that insulin might

TABLE 3

Dietary insulin load, dietary insulin index, and risk of pancreatic cancer by tertile (T), stratified by BMI (in kg/m²) and physical activity¹

	No. of cases	T1	T2	T3	P-trend	P-interaction
Dietary insulin load						
BMI <27.5	526	1.0	1.01 (0.82, 1.25) ²	1.02 (0.82, 1.26)	0.94	
BMI ≥27.5	155	1.0	1.26 (0.82, 1.92)	1.32 (0.86, 2.00)	0.19	0.34
High physical activity ³	336	1.0	0.99 (0.67, 1.48)	0.93 (0.65, 1.31)	0.63	
Low physical activity ³	289	1.0	1.18 (0.88, 1.59)	1.30 (0.97, 1.74)	0.08	0.10
BMI <27.5 and high physical activity	264	1.0	0.92 (0.49, 1.72)	0.95 (0.61, 1.48)	0.81	
Intermediate group ⁴	274	1.0	1.02 (0.73, 1.43)	1.02 (0.75, 1.37)	0.87	0.78
BMI ≥27.5 and low physical activity	77	1.0	1.72 (0.87, 3.38)	2.03 (1.05, 3.93)	0.04	0.05
Dietary insulin index						
BMI <27.5	526	1.0	1.01 (0.82, 1.25)	0.96 (0.77, 1.19)	0.68	
BMI ≥27.5	155	1.0	1.05 (0.56, 1.98)	1.05 (0.64, 1.71)	0.75	0.90
High physical activity ³	336	1.0	0.95 (0.51, 1.78)	0.85 (0.65, 1.12)	0.25	
Low physical activity ³	289	1.0	1.00 (0.59, 1.71)	1.09 (0.81, 1.45)	0.46	0.24
BMI <27.5 and high physical activity	264	1.0	0.88 (0.37, 2.06)	0.86 (0.61, 1.21)	0.40	
Intermediate group ⁴	274	1.0	1.02 (0.74, 1.42)	0.95 (0.70, 1.29)	0.83	0.79
BMI ≥27.5 and low physical activity	77	1.0	0.92 (0.31, 2.76)	1.24 (0.68, 2.26)	0.40	0.29

¹ Adjusted for age, height (quintiles), BMI (quintiles), diabetes (yes or no), physical activity (quintiles), pack-years of smoking [never smoker or current smoker (1–9, 10–24, 25–44, or ≥45 pack-years)], and energy intake (quintiles). The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) were pooled by using random-effects models. Dietary insulin load and dietary insulin index were measured at baseline in 1980 for the NHS and in 1986 for the HPFS.

² RR; 95% CI in parentheses (all such values).

³ Above or below the median (NHS: 3.0 h/wk; HPFS: 11.5 metabolic equivalent hours/wk).

⁴ BMI <27.5 and low physical activity or BMI ≥27.5 and high physical activity.

not influence the development of pancreatic cancer. Conditions that lead to insulin resistance and hyperinsulinemia could promote carcinogenesis through alternative mechanisms; for example, obesity may promote cancer development by increasing oxidative stress, independently of its effect on insulin resistance (4). None-

theless, in a previous study of our cohorts, circulating concentrations of C-peptide were significantly associated with the risk of pancreatic cancer (3).

Another possibility is that the insulin index, in the current study, was not measured accurately. However, the procedure for developing

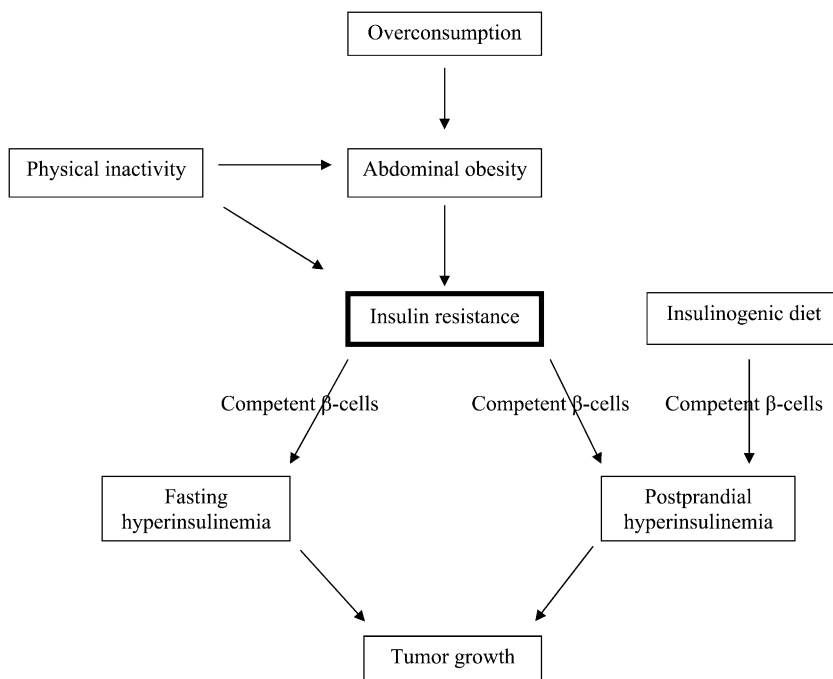


FIGURE 1. Proposed model whereby lifestyle and dietary factors affect pancreatic cancer risk through an influence on insulin dynamics.

the food insulin index was done under highly standardized conditions (15). Furthermore, a recent study showed that the insulin scores were significantly correlated with the actual serum insulin concentrations (16). Additionally, in the current study, insulin scores were significantly correlated with triacylglycerol concentrations, which indicated that summary estimates based on the food-frequency questionnaires were able to predict an expected biological response. One concern with the food insulin index values was that they were derived from lean university students (15), whose absolute insulin responses were likely to have been different from those of the older and heavier subjects. However, the method is valid if the increase in insulin concentrations induced by a food, ie, the relative insulin response, is comparable between the 2 groups. Actually, in the biomarker validation study (26), we observed that the positive association between the insulin index and triglyceride concentrations was much stronger in overweight individuals, which indicated that the general method used to develop the insulin index works in heavier subjects.

The strengths of this study included its prospective design, its large sample size, its long follow-up (≤ 26 y), its high follow-up rate, and the additional control for other known or suspected risk factors for pancreatic cancer. Moreover, with the availability of extensive covariate data, we were able to consider a series of sensitivity analyses to rule out the effect of subclinical cancers on dietary intake. Finally, the availability of repeated dietary measures in these cohorts reduced measurement error by updating dietary insulin scores biennially.

In summary, diets high in foods that increase postprandial insulin concentrations do not increase the overall risk of pancreatic cancer; however, a diet with a high insulin load may increase the risk in individuals with preexisting insulin resistance. These findings potentially offer insight concerning the relative role of insulin secretion and insulin resistance on pancreatic cancer risk. The significant findings from the subgroup analyses should be interpreted with caution because of the small sample size, and additional studies are needed to confirm these findings.

The authors' responsibilities were as follows—YB: performed the data analyses and interpretation and drafted the manuscript; KN: assisted with the data analyses and made substantial contributions to the manuscript; BMW and DSM: made substantial contributions to the manuscript; JCB-M and WCW: developed the insulin index database and made substantial contributions to the manuscript; and EG and CSF: discussed the study design and analyses and made substantial contributions to the manuscript. None of the authors had a conflict of interest.

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