Dietary Acid Load and the Risk of Pancreatic Cancer: A Prospective Cohort Study

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ABSTRACT

Background: Modern Western diets are rich in acidogenic foods. Human and *in vitro* studies suggest a potential link between dietary acid load and cancer risk. However, no epidemiologic studies have investigated the association of dietary acid load with the risk of pancreatic cancer. Therefore, we conducted a prospective cohort study to fill this gap.

Methods: A population-based cohort of 95,708 American adults was identified. Potential renal acid load (PRAL) and net endogenous acid production (NEAP) were used to assess dietary acid load of each subject, with greater values indicating greater dietary acid load. Cox regression was used to estimate risk estimates for pancreatic cancer incidence. Predefined subgroup analysis was used to identify the potential effect modifiers.

Results: A total of 337 pancreatic cancer cases were observed during 848,534.0 person-years of follow-up. PRAL score was found to be positively associated with the risk of pancreatic cancer [fully adjusted $HR_{quartile\ 4\ vs.\ 1}$: 1.73; 95% confidence interval (95% CI), 1.21–2.48; $P_{trend} = 0.001$] in a nonlinear dose–response pattern ($P_{nonlinearity} = 0.012$). Subgroup analysis found that the positive association of PRAL score with the risk of pancreatic cancer was more pronounced in subjects aged <65 years than in those ≥65 years ($P_{interaction} = 0.018$). Similar results were obtained for NEAP score.

Conclusions: Higher dietary acid load is associated with a higher risk of pancreatic cancer. Future studies should validate our findings in other populations and settings.

Impacts: This is the first epidemiologic study suggesting that reducing dietary acid load may be useful in primary prevention of pancreatic cancer.

Introduction

Pancreatic cancer is a highly lethal malignancy, with a mortality-incidence ratio of nearly 1 (1). In the United States, it is the fourth leading cause of cancer-related death, with estimated deaths of 47,050 in 2020 (2). Hence, it is of paramount importance to identify modifiable risk factors for improving primary prevention of this cancer. One of such candidate factors is dietary intake, as it has been implicated to play a critical role in the etiology of pancreatic cancer (3).

Dietary intake can significantly affect the acid-base balance of human body through supplying acid or base precursors (4, 5). Observational studies found that dietary acid load, a measure reflecting the intake of acidogenic foods, was positively associated with risks of metabolic syndrome (6) and type 2 diabetes (7), two well-established cancer risk factors (8, 9). Also, experimental studies found that increasing the acidity of tumor microenvironment would promote the invasion or metastasis of cancer cells (10–12). These findings together suggest a potentially detrimental role of increasing dietary acid load in cancer development (13). Indeed, a large-scale prospective study showed that higher dietary acid load was associated with a higher risk of breast cancer (14). However, to our knowledge, whether such a positive association is also observed for pancreatic cancer has not been determined previously.

A Western dietary pattern is characterized by the richness of acidogenic foods (e.g., meat and fish), resulting in chronic metabolic acidosis (15). Thus, clarifying the potential association between dietary acid load and the risk of pancreatic cancer will have important public health implications. Hence, we performed a prospective study of 95,708 American adults to examine the hypothesis that higher dietary acid load is associated with an increased risk of pancreatic cancer.

Materials and Methods

We reported this study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (16).

Study population

Our study population was identified from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a multicenter clinical trial that was designed to examine whether screening for prostate, lung, colorectal, and ovarian cancers could decrease mortality due to these cancers. Study design of the PLCO Cancer Screening Trial has been reported elsewhere (17). Briefly, individuals aged 55 to 74 years were invited to participate in this trial in ten U.S. screening centers (Minneapolis, Denver, Salt Lake City, Marshfield, Detroit,

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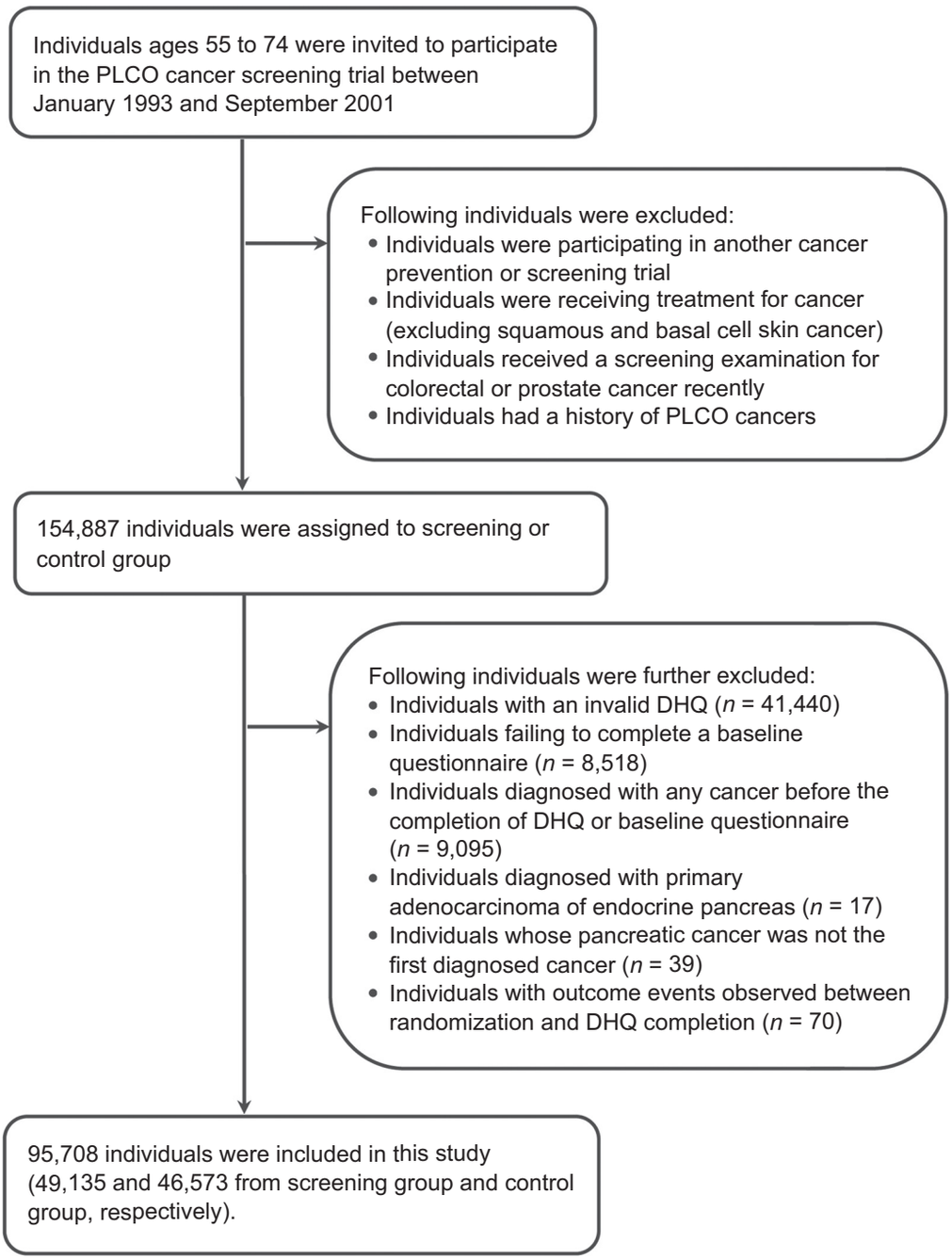

Figure 1.
The study flow chart of identifying eligible subjects. DHQ, diet history questionnaire.

Birmingham, St Louis, Pittsburgh, Washington, and Honolulu) from November 1993 to September 2001. After exclusions (see **Fig. 1** for the relevant exclusion criteria), a total of 154,887 eligible individuals (76,678 men and 78,209 women) were randomized into screening group and control group in equal proportions.

In this study, the following individuals were further excluded: (i) individuals with an invalid diet history questionnaire [DHQ; the invalid DHQ refers to the absence of DHQ completion date, death date before DHQ completion date, ≥8 missing DHQ items, or the presence of extreme energy intakes (top 1% or bottom 1%); n = 41,440]; (ii) individuals failing to complete a baseline questionnaire (n = 8,518); (iii) individuals diagnosed with any cancer before the completion of DHQ or baseline questionnaire (n = 9,095); (iv) individuals diagnosed with primary adenocarcinoma of endocrine pancreas (n = 17); (v) individuals receiving a diagnosis of pancreatic cancer following the diagnosis of other cancers during the trial

($n = 39$); and (vi) individuals with outcome events observed between randomization and DHQ completion ($n = 70$). Finally, a total of 95,708 individuals were included in this study (**Fig. 1**). Written informed consents were obtained from all participants. The PLCO Cancer Screening Trial was approved by the Institutional Review Boards of the NCI and each screening center.

Assessment of dietary acid load

We used potential renal acid load (PRAL; ref. 18) and net endogenous acid production (NEAP; ref. 4) to assess dietary acid load of each participant. These two scores were calculated by the following formulas:

PRAL score:

PRAL (mEq/d) = 0.4888 × protein intake (g/d) + 0.0366 × phosphorus (mg/d) – 0.0205 × potassium (mg/d) – 0.0125 × calcium (mg/d) – 0.0263 × magnesium (mg/d)

NEAP score:

NEAP (mEq/d) = [54.5 × protein intake (g/d) potassium intake (mEq/d)] – 10.2

For PRAL score, a negative value indicates an alkaline-forming potential, while a positive value indicates an acid-forming potential; for NEAP score, greater values indicate greater acid-forming potentials. Serval studies had confirmed the validity of PRAL and NEAP scores estimated from the above formulas and suggested that these scores yielded appropriate estimates to predict urine pH (4, 18–20). Notably, dietary nutrient intakes used for the calculation of PRAL and NEAP scores were adjusted for energy intake from diet using residual method (21).

The information of nutrient intakes was collected via the above-mentioned DHQ, a self-administered 137-item food frequency questionnaire, which is developed by the NCI for evaluating serving size and frequency of food consumption of each participant over the past 12 months. Of note, the DHQ was administered across both screening and control groups of the PLCO Cancer Screening Trial approximately three years after trial entry. The validity of the DHQ had been confirmed in the Eating at America's Table Study (22). Daily gram amounts of each food were approximated by multiplying serving size by food frequency; daily nutrient intake was approximated on the basis of national dietary data [USDA's 1994–96 Continuing Survey of Food Intakes by Individuals (23) or the Nutrition Data Systems for Research (24)].

Assessment of pancreatic cancer

In the PLCO Cancer Screening Trial, incident pancreatic cancer was ascertained mainly via a mailed annual study update form that required each participant to report whether they were diagnosed with any cancer, the date of cancer diagnosis, as well as the type and the site of cancer. For participants who did not return the form, they were contacted repeatedly via telephone or e-mail. Pancreatic cancer reported on the annual study update form was further confirmed by carefully checking the relevant medical records. Family reports and death certificates were used as additional sources for the ascertainment of pancreatic cancer. Of note, in this study, pancreatic cancer referred to primary adenocarcinoma of the exocrine pancreas only (ICD-O-2 code: C25.0-C25.3 and C25.7-C25.9).

Assessment of covariates

Sex, race, educational level, body height and weight, aspirin use, history of diabetes, history of hepatitis or cirrhosis, history of emphysema, family history of pancreatic cancer, and smoking status were assessed through a self-administrated baseline questionnaire. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). Physical activity level, which was defined as total time of moderate-to-vigorous activity per week in this study, was assessed through a self-administrated supplemental questionnaire. Healthy Eating Index 2015, a measure reflecting an individual's diet quality, with higher values indicating higher diet quality, was calculated using the method described in the literature (25). Remaining covariates, including age at DHQ completion, single or multivitamin supplement use, energy intake from diet, alcohol intake, food consumption, and nutrient intake, were assessed through the aforementioned DHQ.

Statistical analysis

Continuous variables were expressed as mean (SD), and categorical variables were expressed as numbers (percentage). To maximize statistical power and minimize selection bias, we used multiple imputation with chained equations to impute 24,148 missing values (25.2% of sample size) of the variable "physical activity level" under an assumption that these values were missing at random, with the number of imputations set at 25 (26). All variables involved in statistical analyses were included in the imputation model.

HRs and 95% confidence intervals (CI) were estimated for the association between PRAL and NEAP scores and the risk of pancreatic cancer using Cox proportional hazards regression, with person-year as time metric. In this study, person-year was calculated from DHQ completion to the date of pancreatic cancer diagnosis, the end of follow-up (i.e., December 31, 2009), the date of death, or loss to follow-up, whichever came first. No evidence indicating the violation of proportional hazards assumption was found using Schoenfeld residuals. PRAL and NEAP scores of the entire study population were split into sex-specific quartiles, as the distribution of these scores possibly differ by sex. Results for each of sex-specific quartiles were combined for overall results. The first quartile was used as the reference group in all Cox regression analyses. To examine a linear trend across quartiles of PRAL or NEAP score, the median of each quartile was first assigned to each participant in the quartile, and then treated as a continuous variable in Cox regression model for testing its statistical significance. Covariate inclusion for multivariable Cox regression was determined according to our knowledge of existing literature and the change-in-estimate strategy (27). Specifically, model 1 (the basic model) was adjusted for age and sex; model 2 (the model that included known pancreatic cancer risk factors) was further adjusted for smoking status, history of diabetes, alcohol intake, BMI, and family history of pancreatic cancer; model 3 additionally included factors that were confounders (energy-adjusted intakes of dietary fiber and carbohydrate) and energy intake from diet.

We used restricted cubic spline functions (28) with three knots placed at the 10th, 50th, and 90th percentiles to visually inspect the shape of the association of PRAL and NEAP scores with the risk of pancreatic cancer. For comparison with the results from Cox regression, the reference level was set at the median of first quartile (i.e., -26.8 and 21.3 mEq/day for PRAL and NEAP, respectively). To decrease the potential influence of extreme values on the results, individuals in the top 2.5% or bottom 2.5% of PRAL or NEAP score were excluded from the dose–response analysis. A P for nonlinearity was calculated by testing the null hypothesis that the regression coefficient of the second spline was equal to zero (28).

To identify the potential effect modifiers of the association of PRAL and NEAP scores with the risk of pancreatic cancer, we performed several predefined subgroup analyses after stratifying for age (≥ 65 vs. < 65 years), follow-up length (≥ 6 vs. < 6 years), BMI (≥ 25 vs. < 25 kg/m^2), single or multivitamin supplement use (yes vs. no), smoking status (current or former vs. never), and physical activity level (≥ median vs. < median). A $P_{interaction}$ was calculated by comparing models with and without interaction terms prior to performing the above subgroup analyses to avoid spurious subgroup differences.

Table 1. Baseline characteristics of the study population by sex-specific quartiles of the PRAL score.

Characteristics	Overall	Sex-specific quartiles of PRAL score			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Number of participants	95,708	23,928	23,926	23,926	23,928
Age at DHQ completion (years)	65.4 ± 5.7	66.0 ± 5.8	66.0 ± 5.8	65.5 ± 5.7	64.3 ± 5.5
Male	46,638 (48.7)	11,660 (48.7)	11,659 (48.7)	11,659 (48.7)	11,660 (48.7)
Race					
Non-Hispanic white	87,302 (91.2)	21,847 (91.3)	22,155 (92.6)	21,864 (91.4)	21,436 (89.6)
Non-Hispanic black	3,037 (3.2)	762 (3.2)	567 (2.4)	732 (3.1)	976 (4.1)
Hispanic	1,394 (1.5)	337 (1.4)	325 (1.4)	365 (1.5)	367 (1.5)
Others[a]	3,975 (4.2)	982 (4.1)	879 (3.7)	965 (4.0)	1,149 (4.8)
Educational level					
Below college	60,733 (63.5)	14,889 (62.2)	15,165 (63.4)	15,162 (63.4)	15,517 (64.8)
College graduate	16,952 (17.7)	4,132 (17.3)	4,233 (17.7)	4,342 (18.1)	4,245 (17.7)
Postgraduate	18,023 (18.8)	4,907 (20.5)	4,528 (18.9)	4,422 (18.5)	4,166 (17.4)
Body mass index (kg/m^2)	27.2 ± 4.8	26.5 ± 4.5	26.9 ± 4.6	27.2 ± 4.7	28.2 ± 5.2
Physical activity (minutes/week)[b]	124.7 ± 124.1	137.5 ± 131.8	125.5 ± 122.4	119.4 ± 120.0	116.3 ± 120.9
Aspirin use	45,153 (47.2)	11,786 (49.3)	11,391 (47.6)	11,071 (46.3)	10,905 (45.6)
Single or multivitamin supplement use	79,812 (83.4)	20,188 (84.4)	20,090 (84.0)	19,879 (83.1)	19,655 (82.1)
History of diabetes	6,268 (6.5)	1,296 (5.4)	1,418 (5.9)	1,548 (6.5)	2,006 (8.4)
History of hepatitis or cirrhosis	3,418 (3.6)	918 (3.8)	790 (3.3)	877 (3.7)	833 (3.5)
History of emphysema	1,996 (2.1)	572 (2.4)	479 (2.0)	474 (2.0)	471 (2.0)
Family history of pancreatic cancer	2,471 (2.6)	642 (2.7)	613 (2.6)	618 (2.6)	598 (2.5)
Energy intake from diet (kcal/day)	1,742.6 ± 735.8	1,768.6 ± 705.9	1,599.6 ± 650.6	1,636.6 ± 679.9	1,965.5 ± 836.7
Healthy Eating Index-2015	66.6 ± 9.7	70.3 ± 9.0	68.2 ± 9.0	65.9 ± 9.2	61.8 ± 9.4
Alcohol intake (g/day)	9.8 ± 25.7	11.5 ± 30.7	10.1 ± 25.2	9.2 ± 23.5	8.5 ± 22.5
Smoking status					
Current	8,870 (9.3)	2,622 (11.0)	2,114 (8.8)	2,020 (8.4)	2,114 (8.8)
Former	41,578 (43.4)	11,073 (46.3)	10,773 (45.0)	10,125 (42.3)	9,607 (40.1)
Never	45,260 (47.3)	10,233 (42.8)	11,039 (46.1)	11,781 (49.2)	12,207 (51.0)
Trial group					
Screening	49,135 (51.3)	11,963 (50.0)	12,274 (51.3)	12,481 (52.2)	12,417 (51.9)
Control	46,573 (48.7)	11,965 (50.0)	11,652 (48.7)	11,445 (47.8)	11,511 (48.1)
Food consumption					
Fruits (g/day)	273.3 ± 216.7	419.8 ± 303.8	271.7 ± 159.7	219.9 ± 139.6	181.8 ± 133.5
Vegetables (g/day)	284.0 ± 185.4	373.4 ± 244.7	269.0 ± 155.3	244.1 ± 142.0	249.6 ± 149.5
Red meat (g/day)	61.7 ± 52.4	46.0 ± 36.8	51.0 ± 37.9	59.3 ± 43.7	90.7 ± 71.3
Dairy (cups/day)	1.4 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	1.5 ± 1.2
Coffee (g/day)	640.5 ± 782.9	1,088.8 ± 1,011.0	687.5 ± 694.4	466.4 ± 588.4	319.3 ± 514.1
Whole grains (servings/day)	1.2 ± 0.8	1.2 ± 0.9	1.1 ± 0.8	1.1 ± 0.8	1.2 ± 0.9
Fish (g/day)	15.6 ± 18.6	14.1 ± 16.1	13.2 ± 14.2	14.5 ± 15.8	20.5 ± 25.2
Nutrient intake[c]					
Carbohydrate (g/day)	221.6 ± 91.2	248.0 ± 97.6	209.1 ± 81.4	204.5 ± 82.5	224.8 ± 97.4
Total protein (g/day)	66.8 ± 30.3	62.1 ± 26.1	59.2 ± 25.3	63.1 ± 27.0	82.7 ± 37.4
Total fat (g/day)	62.6 ± 33.5	55.4 ± 29.3	55.2 ± 28.4	60.0 ± 30.5	79.7 ± 40.4
Dietary fiber (g/day)	18.0 ± 8.5	22.0 ± 10.9	17.2 ± 8.1	16.0 ± 7.7	16.9 ± 8.5
Folate (mcg/day)	378.5 ± 166.7	436.8 ± 191.1	357.1 ± 148.8	344.4 ± 145.6	375.7 ± 164.9
Calcium (mg/day)	750.9 ± 405.6	785.3 ± 407.3	702.8 ± 377.1	708.7 ± 388.5	806.9 ± 439.3
Magnesium (mg/day)	323.3 ± 128.0	382.9 ± 131.1	309.4 ± 112.4	289.6 ± 114.5	311.2 ± 134.7
Iron (mg/day)	14.4 ± 6.2	15.6 ± 7.2	13.6 ± 6.3	13.4 ± 6.3	15.2 ± 7.3
Potassium (mg/day)	3,256.4 ± 1,256.5	4,012.6 ± 1,284.0	3,136.1 ± 1,046.1	2,879.4 ± 1,086.7	2,997.3 ± 1,265.5
Phosphorus (mg/day)	1,152.5 ± 505.0	1,139.4 ± 478.6	1,053.3 ± 450.4	1,089.2 ± 466.4	1,328.2 ± 572.7

Note: Data are mean (SD) or number (percentage) as indicated.
Abbreviation: DHQ, diet history questionnaire.
[a]"Others" refers to Asian, Pacific Islander, or American Indian.
[b]Total time of moderate-to-vigorous physical activity per week.
[c]Nutrient intake is not adjusted for energy intake from diet.

We performed the following sensitivity analyses to examine the robustness of our results: (i) excluded individuals with extreme energy intake values, which refer to <800 or >4,000 kcal/day for men and <500 or >3,500 kcal/day for women (29); (ii) excluded pancreatic cancer cases diagnosed within the first two years of follow-up to examine the potential impacts of reverse causation; (iii) excluded individuals with history of diabetes, liver comorbidity, or emphysema, as these conditions could lead to acid–base disturbance (30); (iv) repeated the main analyses in individuals with complete data; and (v) additional adjusted for Healthy Eating Index-2015 to determine whether the observed associations were mediated by diet quality.

Statistical analyses were performed using STATA software (version 12.0, StataCorp). The results were regarded to be statistically significant when a two-tailed P value was less than 0.05.

Table 2. The risk of pancreatic cancer by sex-specific quartiles of PRAL and NEAP scores.

Quartile of dietary acid load score	Number of cases	Person-years	Incidence per 10,000 person-years	HR (95% CI)		
				Model 1[a]	Model 2[b]	Model 3[c]
PRAL (mEq/day)[d]						
Overall						
Quartile 1	69	213,485.6	3.23	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	77	212,869.6	3.62	1.12 (0.81–1.55)	1.13 (0.82–1.57)	1.16 (0.83–1.62)
Quartile 3	94	212,151.8	4.43	1.40 (1.03–1.91)	1.42 (1.04–1.94)	1.48 (1.06–2.06)
Quartile 4	97	210,026.9	4.62	1.56 (1.15–2.13)	1.54 (1.13–2.11)	1.73 (1.21–2.48)
P_{trend}				0.002	0.003	0.001
Men						
Quartile 1	40	102,876.2	3.89	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	42	102,494.3	4.10	1.05 (0.68–1.61)	1.06 (0.69–1.63)	1.09 (0.70–1.70)
Quartile 3	53	102,386.5	5.18	1.35 (0.90–2.04)	1.36 (0.90–2.06)	1.45 (0.94–2.24)
Quartile 4	56	101,371.2	5.52	1.57 (1.04–2.35)	1.50 (1.00–2.27)	1.79 (1.12–2.87)
P_{trend}				0.016	0.029	0.008
Women						
Quartile 1	29	110,608.3	2.62	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	35	110,378.5	3.17	1.22 (0.74–1.99)	1.23 (0.75–2.01)	1.23 (0.74–2.05)
Quartile 3	41	109,798.6	3.73	1.46 (0.91–2.35)	1.48 (0.92–2.39)	1.50 (0.89–2.50)
Quartile 4	41	108,620.5	3.77	1.56 (0.96–2.51)	1.57 (0.97–2.54)	1.62 (0.93–2.84)
P_{trend}				0.051	0.049	0.068
NEAP (mEq/day)[e]						
Overall						
Quartile 1	75	213,485.6	3.51	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	81	212,869.6	3.81	1.10 (0.80–1.50)	1.10 (0.81–1.51)	1.17 (0.85–1.62)
Quartile 3	86	212,151.8	4.05	1.20 (0.88–1.64)	1.20 (0.88–1.64)	1.34 (0.96–1.86)
Quartile 4	95	210,248.5	4.52	1.43 (1.05–1.94)	1.39 (1.02–1.90)	1.64 (1.14–2.36)
P_{trend}				0.016	0.028	0.006
Men						
Quartile 1	47	102,164.9	4.60	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	46	102,995.6	4.47	1.00 (0.66–1.50)	1.00 (0.66–1.50)	1.07 (0.70–1.62)
Quartile 3	43	102,409.8	4.20	0.97 (0.64–1.46)	0.96 (0.63–1.45)	1.07 (0.69–1.68)
Quartile 4	55	101,557.8	5.42	1.34 (0.90–1.98)	1.27 (0.85–1.89)	1.52 (0.95–2.44)
P_{trend}				0.148	0.246	0.083
Women						
Quartile 1	28	110,117.6	2.54	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2	35	110,501.1	3.17	1.27 (0.77–2.08)	1.27 (0.77–2.10)	1.34 (0.81–2.23)
Quartile 3	43	110,129.8	3.90	1.60 (0.99–2.58)	1.61 (1.00–2.60)	1.76 (1.05–2.93)
Quartile 4	40	108,657.3	3.68	1.59 (0.97–2.58)	1.58 (0.97–2.59)	1.81 (1.02–3.23)
P_{trend}				0.046	0.049	0.034

[a]Adjusted for age (years) and sex (male, female; only for overall results).
[b]Adjusted for age (years), sex (male, female) (only for overall results), smoking status (current, former, and never), history of diabetes (yes, no), alcohol intake (g/day), body mass index (kg/m^2), and family history of pancreatic cancer (yes, no).
[c]Adjusted for age (years), sex (male, female) (only for overall results), smoking status (current, former, and never), history of diabetes (yes, no), alcohol intake (g/day), body mass index (kg/m^2), family history of pancreatic cancer (yes, no), energy-adjusted intakes of dietary fiber (g/day) and carbohydrate (g/day), and energy intake from diet (kcal/day).
[d]PRAL score was categorized into sex-specific quartiles. For men, quartile 1, quartile 2, quartile 3, and quartile 5 were <−17.8 mEq/day, −17.8 to −7.3 mEq/day, −7.4 to 2.5 mEq/day, and >2.5 mEq/day, respectively; for women, quartile 1, quartile 2, quartile 3, and quartile 5 were <−19.8 mEq/day, −19.8 to −10.7 mEq/day, −10.8 to −2.5 mEq/day, and >−2.5 mEq/day, respectively.
[e]NEAP score was categorized into sex-specific quartiles. For men, quartile 1, quartile 2, quartile 3, and quartile 5 were < 27.6 mEq/day, 27.7 to 34.6 mEq/day, 34.7 to 42.6 mEq/day, and >42.6 mEq/day, respectively; for women, quartile 1, quartile 2, quartile 3, and quartile 5 were < 24.3 mEq/day, 24.3 to 30.6 mEq/day, 30.7 to 38.1 mEq/day, and >38.1 mEq/day, respectively.

Ethics approval and consent to participate

The PLCO Screening Trial concept was approved by the Institutional Review Board of the NCI and each screening center. Written informed consent was obtained from all individuals.

Results

Participant characteristics

In the whole study population, the mean value (SD) was -9.8 (16.4) for PRAP score and 33.8 (11.7) for NEAP score. **Table 1** shows baseline characteristics of study population by sex-specific quartiles of PRAL score. Compared with participants in the lowest quartile of PARL score, those in the highest quartile were more likely to have a history of diabetes and be never smokers, had higher BMI and higher energy intake from diet, but had a lower physical activity level, lower Healthy Eating Index-2015, and lower alcohol consumption. In addition, participants in the highest versus the lowest quartiles of PRAL score had higher intakes of red meat, fish, total protein, total fat, calcium, and phosphorus but lower intakes of fruits, vegetables, coffee, carbohydrate, dietary fiber, folate, magnesium, and potassium.

PRAP and NEAP scores and the risk of pancreatic cancer

During 848,534.0 person-years of follow-up, a total of 337 incident pancreatic cancer cases were observed, with the overall incidence rate of 3.97 cases per 10,000 person-years. The mean (SD) follow-up duration was 8.87 (1.90) years. In the fully adjusted model, the highest versus the lowest quartiles of PRAL score was found to be associated with an increased risk of pancreatic cancer ($HR_{quartile\ 4\ vs.\ 1}$: 1.73; 95% CI, 1.21–2.48; $P_{trend} = 0.001$; **Table 2**) in the whole study population. A similar association was observed for NEAP score (fully adjusted $HR_{quartile\ 4\ vs.\ 1}$: 1.64; 95% CI: 1.14–2.36; $P_{trend} = 0.006$). When conducting Cox regression analyses in men and women separately, we found that the positive association of PRAL score with the risk of pancreatic cancer did not change materially in men and in women,

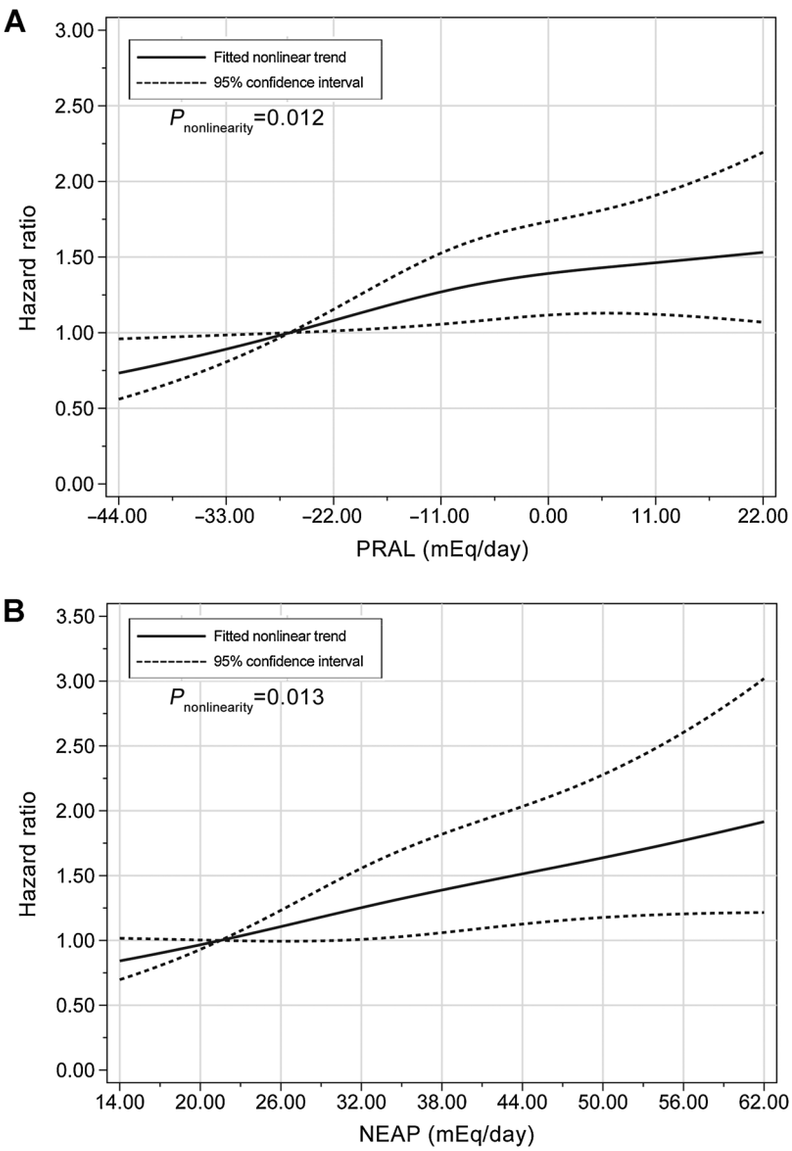

Figure 2.
Nonlinear dose–response analyses on the association of PRAL and NEAP scores with the risk of pancreatic cancer. The reference level was set at −26.8 mEq/day for PRAL score and 21.3 mEq/day for NEAP score. HR was adjusted for age, sex, smoking status, history of diabetes, alcohol intake, body mass index, and family history of pancreatic cancer. The solid line represents the fitted nonlinear trend, and the dashed line represents corresponding 95% CI.

Table 3. Subgroup analyses on the association of PRAL and NEAP scores with the risk of pancreatic cancer.

Subgroup variable	Sex-specific quartiles of dietary acid load score				$P_{interaction}$
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
PRAL (mEq/day)					
Age (years)					
≥65					**0.018**
Cases (person-years)	55 (121,591.8)	50 (121,280.3)	61 (114,528.5)	48 (93,502.1)	
HR (95% CI)	1.00 (reference)	0.90 (0.62–1.33)	1.17 (0.81–1.69)	1.13 (0.76–1.67)	
<65					
Cases (person-years)	14 (91,891.0)	27 (91,589.0)	33 (97,641.0)	49 (116,510.4)	
HR (95% CI)	1.00 (reference)	2.03 (1.07–3.88)	2.37 (1.27–4.43)	2.98 (1.64–5.42)	
Follow-up length (years)					
≥6					<**0.001**
Cases (person-years)	21 (207,058.4)	39 (207,113.1)	36 (205,564.3)	52 (202,326.3)	
HR (95% CI)	1.00 (reference)	1.47 (0.87–2.51)	1.60 (0.94–2.71)	2.79 (1.71–4.56)	
<6					
Cases (person-years)	47 (6,557.8)	42 (6,243.4)	58 (6,393.7)	42 (7,276.9)	
HR (95% CI)	1.00 (reference)	0.99 (0.66–1.50)	1.30 (0.89–1.92)	0.84 (0.54–1.29)	
Body mass index (kg/m^2)					
≥25					0.855
Cases (person-years)	41 (128,353.8)	50 (133,755.2)	65 (140,126.8)	69 (151,618.7)	
HR (95% CI)	1.00 (reference)	1.18 (0.78–1.79)	1.51 (1.02–2.24)	1.59 (1.07–2.35)	
<25					
Cases (person-years)	28 (85,122.4)	27 (79,122.4)	29 (72,033.8)	28 (58,400.8)	
HR (95% CI)	1.00 (reference)	1.05 (0.62–1.78)	1.24 (0.74–2.08)	1.52 (0.89–2.57)	
Single or multivitamin supplement use					
Yes					0.745
Cases (person-years)	57 (180,702.8)	62 (179,122.4)	77 (176,764.1)	76 (172,848.3)	
HR (95% CI)	1.00 (reference)	1.11 (0.78–1.60)	1.42 (1.01–2.01)	1.49 (1.05–2.12)	
No					
Cases (person-years)	12 (32,777.4)	15 (33,753.0)	17 (35,391.0)	21 (37,175.1)	
HR (95% CI)	1.00 (reference)	1.23 (0.57–2.63)	1.38 (0.66–2.90)	1.77 (0.86–3.63)	
Smoking status					
Current or former					0.882
Cases (person-years)	40 (120,392.7)	46 (113,109.2)	53 (106,280.9)	52 (101,530.1)	
HR (95% CI)	1.00 (reference)	1.21 (0.79–1.85)	1.49 (0.99–2.25)	1.57 (1.03–2.38)	
Never					
Cases (person-years)	29 (93,079.4)	31 (99,770.5)	41 (105,887.6)	45 (108,483.6)	
HR (95% CI)	1.00 (reference)	1.00 (0.60–1.66)	1.27 (0.79–2.05)	1.46 (0.91–2.35)	
Physical activity level					
≥Median					0.376
Cases (person-years)	30 (116,725.1)	36 (110,632.5)	37 (105,346.9)	45 (99,473.41)	
HR (95% CI)	1.00 (reference)	1.27 (0.78–2.06)	1.38 (0.85–2.23)	1.85 (1.16–2.96)	
<Median					
Cases (person-years)	39 (96,760.2)	41 (102,236.8)	57 (106,818.9)	52 (110,540.1)	
HR (95% CI)	1.00 (reference)	1.02 (0.66–1.59)	1.40 (0.93–2.11)	1.30 (0.85–1.98)	
NEAP (mEq/day)					
Age (years)					
≥65					**0.018**
Cases (person-years)	59 (126,140.3)	56 (120,663.3)	54 (111,929.5)	45 (92,155.7)	
HR (95% CI)	1.00 (reference)	1.00 (0.69–1.44)	1.04 (0.72–1.50)	1.05 (0.71–1.55)	
<65					
Cases (person-years)	16 (86,141.7)	25 (92,834.4)	32 (100,606.4)	50 (118,062.6)	
HR (95% CI)	1.00 (reference)	1.50 (0.80–2.80)	1.81 (0.99–3.31)	2.40 (1.36–4.25)	
Follow-up length (years)					
≥6					<**0.001**
Cases (person-years)	19 (206,023.3)	36 (207,540.6)	39 (206,008.4)	54 (202,487.3)	
HR (95% CI)	1.00 (reference)	2.31 (1.34–3.96)	1.72 (0.97–3.05)	3.25 (1.91–5.52)	
<6					
Cases (person-years)	54 (6,833.1)	37 (6,109.8)	54 (6,245.7)	44 (7,285.6)	
HR (95% CI)	1.00 (reference)	0.80 (0.53–1.21)	1.12 (0.77–1.63)	0.75 (0.50–1.14)	
Body mass index (kg/m^2)					
≥25					0.944
Cases (person-years)	46 (124,515.4)	54 (134,520.5)	55 (142,104.6)	70 (152,714.9)	
HR (95% CI)	1.00 (reference)	1.12 (0.76–1.67)	1.12 (0.76–1.67)	1.41 (0.96–2.06)	

(Continued on the following page)

Table 3. Subgroup analyses on the association of PRAL and NEAP scores with the risk of pancreatic cancer. (Cont'd)

Subgroup variable	Sex-specific quartiles of dietary acid load score				$P_{interaction}$
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
<25					
Cases (person-years)	29 (87,758.2)	27 (78,975.9)	31 (70,429.1)	25 (57,515.5)	
HR (95% CI)	1.00 (reference)	1.05 (0.62–1.77)	1.35 (0.81–2.25)	1.36 (0.79–2.33)	
Single or multivitamin supplement use					
Yes					0.657
Cases (person-years)	61 (178,944.0)	66 (180,143.1)	72 (177,879.8)	73 (172,471.1)	
HR (95% CI)	1.00 (reference)	1.10 (0.78–1.56)	1.24 (0.88–1.75)	1.34 (0.95–1.89)	
No					
Cases (person-years)	14 (33,336.2)	15 (33,367.0)	14 (34,648.0)	22 (37,744.8)	
HR (95% CI)	1.00 (reference)	1.15 (0.55–2.38)	1.05 (0.50–2.21)	1.63 (0.82–3.23)	
Smoking status					
Current or former					0.625
Cases (person-years)	44 (116,185.0)	49 (111,562.1)	46 (107,947.5)	52 (105,618.0)	
HR (95% CI)	1.00 (reference)	1.17 (0.78–1.75)	1.14 (0.75–1.73)	1.34 (0.89–2.02)	
Never					
Cases (person-years)	31 (96,090.4)	32 (101,936.8)	40 (104,576.6)	43 (104,617.5)	
HR (95% CI)	1.00 (reference)	1.01 (0.61–1.65)	1.27 (0.79–2.03)	1.46 (0.91–2.33)	
Physical activity level					
≥ Median					0.325
Cases (person-years)	33 (112,925.3)	34 (111,398.5)	37 (108,284.3)	44 (99,565.1)	
HR (95% CI)	1.00 (reference)	1.06 (0.65–1.71)	1.20 (0.75–1.92)	1.60 (1.01–2.54)	
< Median					
Cases (person-years)	42 (99,357.9)	47 (102,105.1)	49 (104,245.4)	51 (110,652.3)	
HR (95% CI)	1.00 (reference)	1.13 (0.75–1.72)	1.19 (0.79–1.80)	1.22 (0.80–1.85)	

Note: Bold type indicates statistical significance ($P < 0.05$).

[a]HRs were adjusted for age (years), sex (male, female), smoking status (current, former, and never), history of diabetes (yes, no), alcohol intake (g/day), body mass index (kg/m^2), and family history of pancreatic cancer (yes, no). In subgroup analyses stratified by smoking status, HRs were not adjusted for this stratification factor.

although the association in women did not reach statistical significance (**Table 2**). Similar results were obtained for NEAP score when Cox regression analyses were conducted in men and women separately.

Additional analyses

Restricted cubic spline functions revealed that both PRAL ($P_{nonlinearity} = 0.012$) and NEAP ($P_{nonlinearity} = 0.013$) scores were positively related to the risk of pancreatic cancer in a nonlinear dose–response fashion (**Fig. 2**). Subgroup analyses revealed that the positive associations of PRAL ($P_{interaction} = 0.018$) and NEAP ($P_{interaction} = 0.018$) scores with the risk of pancreatic cancer were more pronounced in participants aged <65 years than in those ≥65 years. In addition, the positive associations with PRAL ($P_{interaction}<0.001$) and NEAP ($P_{interaction}<0.001$) scores were more pronounced among individuals with follow-up length of ≥6 years. The initial associations did not alter materially in a series of sensitivity analyses, including sensitivity analyses excluding pancreatic cancer cases observed within the first two years of follow-up (i.e., two-year lagged analysis; **Table 4**).

Discussion

On the basis of prospective data of 95,708 American adults, we found that higher dietary acid load, as assessed by PRAL and NEAP scores, was associated with a higher risk of pancreatic cancer, even after controlling for the potential confounders; this positive association was more pronounced in participants aged <65 years than in those aged ≥65 years. Moreover, we found that the positive association of dietary acid load with the risk of pancreatic cancer was nonlinear, suggesting that with changes in dietary acid load, the risk of pancreatic cancer would change in a nonparallel fashion.

Previously, diet-induced acidosis has been suggested to be capable of promoting tumor initiation and progression through modulating molecular and cellular activities (13). However, only two epidemiologic studies had investigated the association of dietary acid load with the risk of developing cancer to date (14, 31). A prospective study of 27,096 male smokers found that the highest versus the lowest quintiles of dietary acid load score was not associated with the risk of bladder cancer (446 bladder cancer cases; fully adjusted $HR_{quintile\ 5\ vs.\ 1}$: 1.15; 95% CI, 0.86–1.55; $P_{trend} = 0.38$; ref. 31). In contrast, a prospective study of 43,570 women found that compared with those in the lowest quartile of dietary acid load score, women in the highest quartile were found to be at an increased risk of breast cancer (1,614 breast cancer cases; fully adjusted $HR_{quartile\ 4\ vs.\ 1}$: 1.21; 95% CI, 1.04–1.41; $P_{trend} = 0.04$; ref. 14). On the basis of prospective data from the PLCO Cancer Screening Trial, we found that higher dietary acid load scores were associated with a higher risk of pancreatic cancer. On the one hand, this finding can contribute to our understanding of the role of diet-induced acidosis in the etiology of pancreatic cancer. On the other hand, it indicates that encouraging consumption of more alkaline foods (e.g., fruit and vegetables) and decreasing consumption of acidogenic foods (e.g., meat and cheese) may represent an attractive approach to reduce the risk of pancreatic cancer, which is particularly relevant in the context that modern Western diets are gradually shifting toward more acidifying (32).

Intriguingly, our subgroup analysis observed that the positive association of PRAL and NEAP scores with the risk of pancreatic cancer was more pronounced in subjects aged <65 years than in those aged ≥65 years. In fact, Akter and colleagues also observed a stronger positive association of PRAL score with all-cause mortality in subjects aged <55 years than in those aged ≥55 years ($P_{interaction} = 0.005$; ref. 33). The exact reasons for these observations are unclear. One

Table 4. Sensitivity analyses on the association of PRAL and NEAP scores with the risk of pancreatic cancer.

Categories	Sex-specific quartiles of dietary acid load score[a]				P_{trend}
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
PRAL (mEq/day)					
Excluded subjects with extreme values of energy intake[b]	1.00 (reference)	1.14 (0.82–1.60)	1.49 (1.08–2.05)	1.59 (1.15–2.19)	0.002
Excluded cases observed within the first 2 years of follow-up	1.00 (reference)	1.23 (0.86–1.76)	1.47 (1.04–2.08)	1.80 (1.28–2.53)	<0.001
Excluded subjects with history of diabetes, liver comorbidity, or emphysema[c]	1.00 (reference)	1.10 (0.77–1.56)	1.27 (0.90–1.79)	1.54 (1.09–2.16)	0.010
Restricted the analysis to subjects with complete data	1.00 (reference)	1.62 (0.93–2.84)	1.56 (0.88–2.74)	2.73 (1.61–4.62)	<0.001
Additional adjustment for Healthy Eating Index-2015[d]	1.00 (reference)	1.13 (0.82–1.57)	1.41 (1.03–1.94)	1.54 (1.11–2.13)	0.005
NEAP (mEq/day)					
Excluded subjects with extreme values of energy intake[b]	1.00 (reference)	1.19 (0.86–1.64)	1.27 (0.92–1.75)	1.46 (1.06–2.02)	0.019
Excluded cases observed within the first 2 years of follow-up	1.00 (reference)	1.30 (0.92–1.84)	1.32 (0.93–1.88)	1.70 (1.21–2.40)	0.003
Excluded subjects with history of diabetes, liver comorbidity, or emphysema[c]	1.00 (reference)	1.20 (0.85–1.69)	1.20 (0.85–1.70)	1.47 (1.05–2.08)	0.031
Restricted the analysis to subjects with complete data	1.00 (reference)	2.22 (1.20–4.09)	2.60 (1.43–4.75)	3.34 (1.84–6.04)	<0.001
Additional adjustment for Healthy Eating Index-2015[d]	1.00 (reference)	1.10 (0.80–1.51)	1.19 (0.87–1.64)	1.37 (0.99–1.89)	0.049

[a]Data are expressed as HR (95% CI). HRs were adjusted for the following variables unless otherwise specified: age (years), sex (male, female), smoking status (current, former, and never), history of diabetes (yes, no), alcohol intake (g/day), body mass index (kg/m^2), and family history of pancreatic cancer (yes, no).
[b]Extreme values of energy intake are defined as <800 or >4,000 kcal/day for men and <500 or >3,500 kcal/day for women.
[c]HRs were not adjusted for history of diabetes.
[d]Healthy Eating Index-2015 was treated as the continuous variable in the multivariable Cox regression.

straightforward explanation is that dietary acid load has some interactions with age in biological pathways, resulting in that younger subjects are more susceptible to diet-induced acidosis than older subjects. An alternative explanation is that older subjects are more likely to use diuretics, given that chronic kidney disease is more common in older subjects than in younger subjects (34); thus, acids from diet can be quickly excreted by the kidneys among older subjects, which can weaken or even eliminate the potential influence of diet acid load on human body. Indeed, a cross-sectional study of 30,528 subjects found that the prevalence of acidosis (defined as bicarbonate <22 mEq/L) was decreased in older compared with younger subjects (8% vs. 12%), especially in subgroup with estimated glomerular filtration rate of <45 ml/min per 1.73 m^2 (15% vs. 54%; ref. 35). Unfortunately, we cannot confirm whether the latter explanation is the case in our study because of the unavailability of data on diuretic use in the PLCO Cancer Screening Trial. In addition, it should be reminded that we cannot rule out the possibility that age difference in the association of dietary acid load with the risk of pancreatic cancer we observed is a chance finding, despite that it may be explained by the abovementioned facts. In addition, our subgroup analyses found that the positive associations with PRAL and NEAP scores were more pronounced among individuals followed-up ≥ 6 years than those followed-up <6 years. This finding supports the notion that the positive association between dietary acid load scores and the risk of pancreatic cancer we observed is not due to reverse causation, which is actually consistent with the results from the two-year lagged analyses.

The positive association of dietary acid load with the risk of pancreatic cancer is biologically plausible. Diet-induced acidosis can lead to the increase in serum levels and the bioactivity of cortisol (36, 37), which has been found to promote insulin resistance (38). Meanwhile, low-grade metabolic acidosis resulting from long-term consumption of high protein is found to be associated with increased levels of serum insulin-like growth factor 1 (13). Of note, insulin resistance and insulin-like growth factor 1 have been demonstrated to promote the development and progression of pancreatic cancer (39, 40). In addition, metabolic acidosis is found to reduce circulating adiponectin levels through inhibiting the transcription of adiponectin gene (41); both experimental and epidemiologic studies have suggested the protective role of adiponectin against the occurrence of pancreatic cancer (42, 43). Furthermore, emerging evidence indicates that microenvironmental acidity can inhibit antitumor immunity and eventually promotes immune escape and cancer progression (44), which may also explain the positive association of dietary acid load with the risk of pancreatic cancer, at least in part.

The strengths of our study mainly include the prospective study design, the large sample size, the robustness of results in sensitivity analyses, and the long duration of follow-up. However, our study also has several limitations. First, we had adjusted for a wide range of possible confounders, but our results could be still subject to residual confounding because of unrecognized or unmeasured confounders. For example, it is well known that kidney function plays a critical role in maintaining the acid–base balance of human body; hence, the association of dietary acid load with the risk of pancreatic cancer could be confounded by this factor. However, we could not control this potential confounding effect as the data on kidney function were not collected in the PLCO Cancer Screening Trial. Nevertheless, the positive association of dietary acid load with the risk of pancreatic cancer is expected to be stronger in individuals with impaired kidney function than in those with normal kidney function. Likewise, PRAL and NEAP scores may be correlated to other exposures that are associated with the risk of pancreatic cancer, such as insulin resistance (45, 46). Unfortunately, we could not control the potential impacts of these exposures on the association between dietary acid load score and the risk of pancreatic cancer due to the unavailability of the relevant data. Second, our results were originated from a U.S. population ages 55 to 74 years with a relatively alkaline diet, and thus might not be generalized to other age groups or other populations with different dietary habits. Third, nutrient data used for the calculation of PRAL and NEAP scores were collected at baseline in the PLCO Cancer Screening Trial. The assessment of dietary intake at one time point may

lead to nondifferential bias, as dietary behaviors could change over time. Nonetheless, a classic assumption in nutritional epidemiology is that an adult's dietary habits would not change dramatically during a short period. Moreover, it has been suggested that the method only using baseline diet generally yields a weaker association than that using the cumulative averages (47). Finally, in subgroup analyses, it was found that the positive association of PRAL and NEAP scores with the risk of pancreatic cancer could not be modified by follow-up length, BMI, single or multivitamin supplement use, smoking status, and physical activity level. However, it should be reminded that these findings were based on a small number of pancreatic cancer cases, resulting in that likelihood ratio test may have inability to detect the potential interactions between PRAL and NEAP scores and the above stratification factors due to the insufficient power. Therefore, our findings from subgroup analyses should be treated with caution and need to be confirmed by future studies.

In conclusion, dietary acid load, as reflected by PRAL and NEAP scores, is found to be positively associated with the risk of pancreatic cancer in this population. These findings suggest that reducing dietary acid load may be beneficial in decreasing the risk of pancreatic cancer. As contemporary Western diets are rich in acidogenic foods, our findings could have substantial public health implications. Future studies should validate our results in other populations and settings.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

L.-W. Shi: Writing–original draft. **Y.-L. Wu:** Resources. **J.-J. Hu:** Writing–review and editing. **P.-F. Yang:** Writing–original draft. **W.-P. Sun:** Writing–review and editing. **J. Gao:** Software, formal analysis, methodology. **K. Wang:** Software, formal analysis, methodology. **Y. Peng:** Writing–review and editing. **J.-J. Wu:** Validation, methodology, writing–review and editing. **G.-C. Zhong:** Conceptualization, data curation, supervision, project administration, writing–review and editing.

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