Associations between Intake of Calcium, Magnesium, and Phosphorus and Risk of Pancreatic Cancer: A Population-Based, Case-Control Study in Minnesota

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Abstract

Experimental studies suggest that abnormal levels of calcium, magnesium, and phosphorus are implicated in pancreatic carcinogenesis. We investigated the associations between intakes of these minerals and the risk of pancreatic cancer in a case-control study conducted in 1994-1998. Cases of pancreatic cancer (n=150) were recruited from all hospitals in the metropolitan area of the Twin Cities and Mayo Clinic, Minnesota. Controls (n=459) were randomly selected from the general population and frequency matched to cases by age, sex, and race. All dietary variables were adjusted for energy intake using the residual method prior to data analysis. Logistic regression was performed to evaluate the associations between intake of three nutrients examined and the risk of pancreatic cancer. Total intake of calcium (936 vs. 1026 mg/day) and dietary intake of magnesium (315 vs. 331 mg/day) and phosphorus (1350 vs. 1402 mg/day) were significantly lower in cases than in controls. After adjustment for confounders, there were not significant associations of total and dietary intakes of calcium, magnesium, and phosphorus with the risk of pancreatic cancer. In addition, no significant interactions exist between intakes of these minerals and total fat on pancreatic cancer risk. In conclusion, the present study does not suggest that intakes of calcium, magnesium, and phosphorus were significantly associated with the risk of pancreatic cancer.

Introduction

Pancreatic cancer is the third leading cause of cancer-related death in the US [1]. In 2019, approximately 56,770 subjects developed pancreatic cancer and an estimated 45,750 subjects died from the disease [1]. Pancreatic cancer has been projected to become the second leading cause of cancer-related death by 2030 for the US population [2] despite improvements in five-year cancer survival in the past decades [3]. Early detection is an effective approach to reduce cancer mortality, but an accurate screening test is not yet available for pancreatic cancer. The etiology of pancreatic cancer remains elusive as cigarette smoking, family history, chronic pancreatitis, and obesity are the only well-established risk factors [4]. Therefore, it is important to identify modifiable risk factors for the primary prevention of pancreatic cancer.

Calcium, magnesium, and phosphorus are essential minerals that are metabolically correlated and are crucial for many biologic and cellular functions [5], including bone turnover, energy metabolism, and inflammation [6-10]. A growing body of evidence from experimental and human studies suggests that these minerals, particularly calcium, play a pivotal role in pancreatic carcinogenesis. Randomized trials showed that an increased intake of calcium significantly promoted fecal fat excretion and reduced levels of total cholesterol and low density lipoprotein (LDL)-cholesterol due to calcium soap formation and binding of bile acids in the intestine [6, 8]. Animal studies revealed that high calcium diets induced weight loss through inhibiting lipogenesis, accelerating lipolysis, and enhancing thermogenesis [11]. These findings offer a firm biological basis for the observation that dietary intake of calcium and the ratio of dietary calcium to phosphorus (Ca:P ratio) were inversely associated with obesity risk [12]. Obesity and diabetes have been linked to an increased risk of pancreatic cancer in many epidemiological studies [13, 14].

The essential roles of these elements in cellular functions suggest potential mechanisms

related to carcinogenesis. Intracellular Ca^{+2} concentrations modulate the proliferation and apoptosis of immune cells and cancer cells, and the rise of cytosolic Ca^{+2} is necessary for efficient targeting and killing of tumor cells by cytotoxic T lymphocytes and natural killer cells [15]. Magnesium deficiency is commonly found in patients with diabetes [7]. In a human experimental study, mild magnesium depletion significantly lowered serum levels of calcium and 1,25-(OH)2D [7]. Despite sound biological plausibility, the associations between intake of calcium, magnesium, and phosphorus and risk of pancreatic cancer have been inconsistent across previous epidemiological studies, with reports of a significant inverse association with intake of calcium [16] and magnesium [17], a significant positive association with calcium intake [18], and a nonsignificant association with intake of calcium [19], magnesium [20], and phosphorus [21]. Therefore, the present study sought to investigate these associations in a population-based, case-control study in Minnesota.

Materials and methods

Study population

The design and methodology of the case-control study of pancreatic cancer conducted from April 1994 to September 1998 in Minnesota have been described in detail elsewhere [22, 23]. Briefly, cases were patients recently diagnosed with pancreatic ductal adenocarcinoma (International Classification of Disease for Oncology, 3rd ed., code C25) and were 20 years or older, English-speaking, and mentally competent. The source cohort was residents of the Upper Midwest and cases were recruited from all hospitals in the seven-county metropolitan area of Minneapolis and Saint Paul, Minnesota and the Mayo Clinic. Given the high fatality of pancreatic cancer, a rapid case-ascertainment system was adopted for case enrollment. The median number of days between diagnosis and first contact for the study was only 13 days for

the cases recruited to the study.

Eligibility criteria for controls were the same as those for cases, disallowing a diagnosis of pancreatic cancer. Controls were randomly recruited from the source population of cases. Controls aged 20 to 64 years of age were identified from drivers' licenses and state identity card database, while those aged 65 years or older were obtained from U.S. Health Care Financing Administration (now Centers for Medicare & Medicaid Services) records. Controls were frequency matched to cases by age (within 5 years), sex, and race.

A total of 460 cases were identified and met the eligibility criteria. Of these, 202 were excluded due to death prior to being contacted or interviewed (n=85), refusal to participate (n=79), disallowance by their physician (n=31), and inability to be reached or contacted (n=7). After these exclusions, 258 participated in the study, yielding a response rate of 56.1%. A total of 1141 eligible controls were ascertained and 676 of them agreed to participate in the study, giving a response rate of 59.2%. Dietary and alcohol intake data were not collected from 108 cases and 217 controls largely because cases were too frail to endure the interview process or because controls declined to respond to the food frequency questionnaire. Finally, data from 150 cases and 459 controls were available for the present analysis.

Data collection

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the institutional review boards of the University of Minnesota and the Mayo Clinic. Written informed consent was obtained from all subjects prior to the interview. A general questionnaire was used to solicit information regarding demographic characteristics (e.g. age, sex, and race), socioeconomic measures (e.g. education), family history of cancer, physical activity, and cigarette smoking. A

slightly modified version of the Willett food frequency questionnaire (FFQ) was employed to assess the usual diet of the subjects. The Willett FFQ has been validated against dietary records, and validation studies showed that it had a reasonable level of reproducibility and validity for assessing individual nutrients and foods [24-26]. Specifically, the average de-attenuated correlation coefficient between the energy-adjusted nutrient intakes measured by the FFQ and diet records among 127 men was 0.65, with de-attenuated correlation coefficients of 0.61, 0.71, and 0.63 for calcium, magnesium, and phosphorus, respectively [25]. In the present study, we used a 131-item Willett FFQ (HarvardSSFQ.5/93) that had been modified for Minnesota Cancer Prevention Research Unit studies to include additional vegetables, fruits, and low-fat foods [26]. These modifications might have somewhat changed the reproducibility and validity of the Willet FFQ. The FFQ used in this case-control study has 153 individual foods or food groups (including alcohol consumption) commonly consumed in the USA and questions on use of nutrient supplements.

The general questionnaire and the FFQ were administered to study subjects by trained interviewers during face-to-face interviews. During the dietary survey, subjects were asked to recall how frequently they consumed each of the food items included in the FFQ in the year preceding pancreatic cancer diagnosis for cases or the referent date for controls. Dietary intake of total energy and nutrients were estimated by multiplying the portion size amount in each food item by the recalled frequency of consumption and summed over all food items. The amounts of energy and nutrients contained in portion sizes of all food items listed in the FFQ were derived from the Minnesota Colon Cancer Prevention Research Unit Studies database. Supplemental intake of calcium, magnesium, and phosphorus was also obtained from the responses of study subjects to the FFQ. Therefore, data on both total and dietary intakes of all three nutrients were

available for the present analysis.

Statistical analysis

All dietary variables were adjusted for energy intake using the residual method prior to data analysis [27]. Differences in categorical and continuous variables were examined with chi-square test and t-test, respectively. Pancreatic cancer risk, in relation to total and dietary intake of calcium, magnesium, and phosphorus, was estimated by performing unconditional logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by comparing the second, third, and fourth with the first quartile of total and dietary intakes of calcium, magnesium, and phosphorus. Cutoff points for creating the quartiles of each of the selected nutrients were based on their distributions among controls. Three regression models were constructed for each dietary variable. The first model estimated the effects of nutrients on pancreatic cancer risk without considering confounders. The second model was adjusted for age, sex, race, education (three levels), physical activity (hour/week), cigarette smoking (never, former and current), and alcohol consumption (serving/week). The third model was additionally adjusted for intake of total energy, total fat, fiber, fruits, and vegetables. The aforementioned covariates were adjusted as they are suspected or established confounders for the associations between dietary factors of interest and the risk of pancreatic cancer [4]. The statistical significance of the linear trend across quartiles of each of the nutrients examined was tested by assigning a median intake value to each quartile and then treating these as values of a continuous variable.

As high calcium intake promotes fecal fat excretion and lowers levels of total cholesterol and LDL-cholesterol [6, 8], the potential interactions on pancreatic cancer risk between each selected nutrient and total fat were evaluated with the likelihood ratio test. All statistical analyses

were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC), and a p-value of <0.05 was considered statistically significant.

Results

The mean ages of cases and controls were 65.8 and 66.3 years, respectively. Approximately 59.3% of cases and 56.9% of controls were male. Study subjects was predominately white (91.3% for cases and 98.0% for controls). Compared with controls, cases had a lower level of education and physical activity. Cases were more likely than controls to be former or current smokers and to report a history of diabetes (Table 1). Total intake of calcium (936 vs. 1026 mg/day) and dietary intake of magnesium (315 vs. 331 mg/day) and phosphorus (1350 vs. 1402 mg/day) were significantly lower in cases than in controls (Table 2).

After adjustment for confounders, total and dietary intakes of calcium, magnesium, and phosphorus were not statistically significantly associated with the risk of pancreatic cancer (Table 3). In addition, no significant associations were observed for the ratio of total intake of calcium to phosphorus or the ratio of dietary intakes of calcium to phosphorus (data not shown). There were no significant interactions of total and dietary intakes of calcium, magnesium, and phosphorus with total fat intake in relation to pancreatic cancer risk (all p-interaction values >0.05). The analyses stratified by the median of total fat intake (72.2 grams/day) did not reveal any clear patterns of differences in the associations between total and dietary intakes of nutrients considered and the risk of pancreatic cancer (Table A2 in the Appendix).

Discussion

The present study found no evidence that there were statistically significant associations between total and dietary intakes of calcium, magnesium, and phosphorus and the risk of pancreatic cancer after adjustment for suspected and established confounders.

A number of cellular, animal, and human studies have suggested that low levels of calcium are involved in pancreatic carcinogenesis. Experimental studies have shown that intracellular Ca^{+2} concentrations play a crucial role in the regulation of proliferation and apoptosis of immune and tumor cells and in the elimination of tumor cells by the innate immune system [15]. In addition, physiological intranuclear concentrations of calcium regulate DNA conformation and replication [28]. Animal studies have consistently demonstrated the anti-obesity effect of dietary calcium. Transgenic mice fed on high-calcium diets exhibited an accelerated loss of fat and weight [11]. The results of animal studies have been partially replicated in human intervention trials where high calcium intake promoted fecal fat excretion and favorably influenced insulin resistance biomarkers [6, 8]. Although it is biologically plausible that calcium intake protects against pancreatic cancer, epidemiological studies evaluating the association between calcium intake and pancreatic cancer risk have yielded conflicting results.

In 1990, Farrow et al. reported a reduced risk of pancreatic cancer associated with calcium intake in a small case-control study conducted in western Washington State [16]. However, this potential beneficial effect was not replicated in a large case-control study performed in the San Francisco Bay area. In the latter study, dietary intake of calcium was associated with an elevated risk of pancreatic cancer among men [OR (95% CI) for ≥1200 mg/day vs. <500 mg/day: 2.8 (1.2, 6.4)] [18]. A pooled analysis of 14 prospective cohort studies in western countries showed inverse but nonsignificant associations of total and dietary intakes of calcium with the risk of pancreatic cancer [OR (95% CI) for dietary calcium intake of ≥1100 mg/day vs. <500 mg/day: 0.86 (0.69, 1.07)] [19]. Likewise, the present study found an inverse, but not statistically significant, association between total and dietary intakes of calcium and pancreatic cancer risk [OR (95% CI): 0.72 (0.38, 1.37) when comparing subjects with a median dietary intake of 1300 mg/day

with those with a median dietary intake of 541 mg/day].

It is possible that the discrepant findings in the studies discussed above are due to differences in methods of case ascertainment, quality of calcium intake data, between-person variation in calcium intake, and control of confounding in those studies. Of note, scarce data on the association between calcium intake and pancreatic cancer are available from Asian populations which have relatively low intake of calcium (e.g. the median intake of calcium was only 328 mg/day for 11,937 Chinese adults residents) [29]. Therefore, epidemiological analyses in Asian countries may help us better understand the association between a wide range of calcium intake and the occurrence of pancreatic cancer.

Magnesium is involved in inflammatory cytokine excretion, immune response, DNA replication, and cell cycle regulation [30-33]. Randomized trials have revealed that magnesium supplementation optimized circulating vitamin D levels [34]. In addition, low intake of magnesium has been associated with an elevated risk of diabetes and metabolic syndrome, which are both risk factors for pancreatic cancer [35]. Although the findings of these studies suggest that low magnesium intake may also play a role in pancreatic carcinogenesis, few epidemiological studies have investigated this hypothesis. In the Vitamins and Lifestyle Study (VITAL), subjects whose magnesium intake was <75% of the Recommended Dietary Allowances (RDA) (420 mg/day for men and 320 mg/day for women) had a significantly increased risk of pancreatic cancer, compared with those who met the RDA for magnesium intake [17, 36]. However, this potential protective effect of magnesium on pancreatic cancer was not found in the European Prospective Investigation into Cancer and Nutrition study (EPIC) [20] and the US male Health Professionals Follow-up Study (HPFS) [37]. The present study showed inverse but nonsignificant associations between total and dietary intakes of magnesium with pancreatic cancer risk after

adjustment for confounders, which is largely consistent with findings from the EPIC and the HPFS.

It has been reported that mice fed a diet high in phosphorus exhibited an increased number and size of carcinogen-induced lung epithelial tumors [38]. The underlying mechanisms for this promoting effect could be that elevated intracellular phosphorus modulates active phosphorylated protein kinase B that stimulates cell cycle progression and other cellular events [38]. Although cigarette smoking that emitted diverse carcinogens is a risk factor shared by lung cancer and pancreatic cancer [39], it remains unclear whether an increased risk of chemically-induced lung tumor associated with high phosphorus intake in animals can be observed for pancreatic cancer in humans. To our knowledge, only one epidemiological study has investigated the association between phosphorus intake and pancreatic cancer risk [21]. In that Italian population-based case-control study, phosphorus intake was not associated with an altered risk of pancreatic cancer [21], which is in agreement with the results of the present study.

A major advantage of the present study is that a rapid case-ascertainment system was used to recruit all cases, which was necessary to maximize case enrollment due to the rapidly fatal nature of pancreatic cancer. As a result, all cases were interviewed in person and no proxy interviews, which are prone to recall bias, were used. To enhance the validity of dietary intake data collected from the FFQ, food models were provided to participants to help them estimate serving sizes for foods they consumed [40].

There are some limitations in our study. The response rates were less than 60% for both cases and controls. Although the case response rate is relatively high among population-based case-control studies of pancreatic cancer that do not rely on proxy interviews [41, 42], the generalizability of our results might have been limited as subjects who agreed to participate in

the study may be different from those who declined with regard to demographic, socioeconomic, and lifestyle factors. In addition, lack of complete dietary and alcohol intake data from some individuals who participated in the study reduced the number of cases and controls included in the present analysis and thus the power. Of note, however, our analysis showed that there were no significant differences in age, sex, race, education, smoking status, alcohol intake, and physical activity between all subjects considered in the present analysis and most subjects excluded from the analysis (69.4% of excluded cases and 56.7% of excluded controls) due to lack of data on dietary and alcohol intake. A sample size of 150 cases and 459 controls may not offer adequate power for us to detect the potential moderate associations between intakes of minerals examined and risk of pancreatic cancer. Dietary measurement error, arising from intentional or unintentional misreporting of individual food intake, might have led to misclassification of some subjects with regard to intake of the nutrients examined and consequently attenuated the risk estimates if such measurement error were non-differential and substantial.

Reverse causality should be considered in any case-control studies of diet and cancer as patients may change their dietary habits in response to clinical symptoms and medical treatments after diagnosis. Although we assessed diet history for the period prior to diagnosis to avoid this bias, the illness may affect recall as well. Overweight and obesity have been linked to pancreatic cancer [43], but we were unable to adjust for body mass index in our analysis because body height and weight were not measured due to an oversight. This limitation was in part overcome by adjustment for energy intake and physical activity, the two main determinants of body mass index [40]. Overweight and obesity are associated with an increased risk of diabetes [44]. In a sensitivity analysis, we adjusted for diabetes in regression models, with the exclusion of nine

patients with diabetes diagnosed within two years of cancer diagnosis to minimize the possibility of diabetes induced by subclinical pancreatic tumor. This sensitivity analysis revealed that an additional adjustment for diabetes did not materially alter our original results. Nevertheless, failure to adjust for body mass index might have distorted our findings. This case-control study was conducted 22-24 years ago. As there is still no screening test available for pancreatic cancer, most cases continue to be diagnosed at late stages. Survival from pancreatic cancer has improved slightly over the period since this study was conducted primarily due to improved treatment. For example, 1-year relative survival was 18.5% for 1990-1994 and 37.3% in 2016 [45]. Since our study was focused on etiology and the cases in our study were recruited very soon after diagnosis, the trends in survival are unlikely to have affected the relevance of our findings.

In conclusion, there were not significant associations between total and dietary intakes of calcium, magnesium, and phosphorus, and the risk of pancreatic cancer in this Upper Midwestern population of the U.S. More epidemiological studies are warranted to evaluate whether calcium, magnesium, and phosphorus confer an altered risk of pancreatic cancer in populations with a relatively low intake of these minerals (e.g. Eastern Asian populations). As dietary intake of energy and nutrients are subject to the measurement error derived from recall bias, urinary biomarkers of calcium, magnesium, and phosphorus should be considered in future studies [46]. A clear understanding of the roles of these nutrients in pancreatic cancer etiology may offer innovative practical avenues for its primary prevention.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study has been approved by the institutional review boards of the University of Minnesota and the Mayo Clinic and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All study subjects provided written informed consents prior to their inclusion in the study.

Authors' Contributions K. E. A. and J. Z. designed research; H. F., Y. Y., K. E. A., and J. Z. conducted research; H. F., Y. Y., and J. Z. performed statistical analysis; all authors drafted and/or revised it critically for important intellectual content; J.Z. is responsible for final content of manuscript. All authors read and approved the final manuscript.

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Table 1. Characteristics of cases and controls in a population-based, case-control study of pancreatic cancer in Minnesota, 1994–1998[a]

Characteristics[b]	Cases (n=150)	Controls (n=459)	P-value
Age (year)	65.8 (10.9)	66.3 (12.1)	0.64
Sex			0.48
Male	89 (59.3%)	261 (56.9%)	
Female	59 (39.3%)	198 (43.1%)	
Missing	2 (1.3%)	N/A	
Race			<0.001
White	137 (91.3%)	450 (98.0%)	
Black	7 (4.7%)	3 (0.7%)	
Other	6 (4%)	6 (1.3%)	
Education			<0.001
High school graduate	56 (37.3%)	116 (25.3%)	
Some college or more	76 (50.7%)	319 (69.5%)	
Some high school or less	18 (12.0%)	24 (5.2%)	
Cigarette smoking			0.12
Former smoker	63 (42.0%)	196 (42.7%)	
Never smoker	57 (38.0%)	215 (46.8%)	
Current smoker	23 (15.3%)	48 (10.5%)	
Missing	7 (4.7%)	N/A	
Alcohol intake (Serving/week)	3.4 (6.9)	4.6 (8.5)	0.065
Diabetes mellitus			<0.001
Yes	31 (20.7%)	33 (7.2%)	
No	101 (67.3%)	426 (92.8%)	
Missing	18 (12.0%)	N/A	
Physical activity (h/week)[c]			
Light	23.0 (17.0)	27.1 (16.2)	0.013
Moderate	15.2 (13.1)	18.1 (12.7)	0.022
Heavy	5.1 (11.8)	3.9 (5.5)	0.27

[a] Some variables have missing data.
[b] Values shown are mean (SD) for continuous variables and number (%) for categorical variables. T-test and Chi-square test were used to compare differences in continuous and categorical variables between cases and controls, respectively.
[c] Data were missing from 26 cases and 1 control.

Table 2. Difference in intake of calcium, magnesium, and phosphorus (mean and SD) between cases and controls in a population-based, case-control study of pancreatic cancer in Minnesota, 1994–1998[a]

Characteristics[b]	Cases (n=150)	Controls (n=459)	P-value
Calcium (mg/day)			
Total Calcium	936 (448)	1026 (448)	0.033
Dietary Calcium	835 (390)	883 (344)	0.17
Magnesium (mg/day)			
Total Magnesium	333 (89)	348 (85)	0.077
Dietary Magnesium	315 (75)	331 (75)	0.026
Phosphorus (mg/day)			
Total Phosphorus	1368 (281)	1417 (274)	0.062
Dietary Phosphorus	1350 (262)	1402 (271)	0.040

[a] Some variables have missing data.
[b] T-test was used to compare differences in intake of nutrients examined between cases and controls.

Table 3. Risk of pancreatic cancer in relation to intake of nutritional factors in a population-based, case-control study of pancreatic cancer in Minnesota, 1994–1998

Nutrients	Quartile				*p*- trend
	First	Second	Third	Fourth	
Total Calcium					
Median (mg/day)	575	789	1148	1532	
Cases/Controls	43/114	49/115	30/115	28/115	
Crude OR (95% CI)	1.00	1.13 (0.70, 1.83)	0.70 (0.41, 1.18)	0.65 (0.38, 1.11)	0.030
Adjusted OR1 (95% CI)[a]	1.00	1.01 (0.58, 1.73)	0.60 (0.33, 1.11)	0.70 (0.38, 1.29)	0.10
Adjusted OR2 (95% CI)[b]	1.00	1.01 (0.58, 1.77)	0.60 (0.32, 1.12)	0.69 (0.37, 1.28)	0.10
Dietary Calcium					
Median (mg/day)	541	716	941	1300	
Cases/Controls	40/114	57/116	26/115	27/114	
Crude OR (95% CI)	1.00	1.40 (0.87, 2.26)	0.64 (0.37, 1.12)	0.67 (0.39, 1.17)	0.022
Adjusted OR1 (95% CI)[a]	1.00	1.42 (0.83, 2.44)	0.70 (0.37, 1.31)	0.75 (0.40, 1.40)	0.087
Adjusted OR2 (95% CI)[b]	1.00	1.45 (0.82, 2.57)	0.70 (0.37, 1.34)	0.72 (0.38, 1.37)	0.074
Total Magnesium					
Median (mg/day)	264	316	364	434	
Cases/Controls	56/114	28/116	35/114	31/115	
Crude OR (95% CI)	1.00	0.49 (0.29, 0.83)	0.62 (0.38, 1.02)	0.55 (0.33, 0.91)	0.038
Adjusted OR1 (95% CI)[a]	1.00	0.58 (0.33, 1.04)	0.69 (0.40, 1.20)	0.59 (0.32, 1.07)	0.10
Adjusted OR2 (95% CI)[b]	1.00	0.58 (0.31, 1.06)	0.68 (0.38, 1.23)	0.59 (0.30, 1.16)	0.17
Dietary Magnesium					
Median (mg/day)	256	311	344	399	
Cases/Controls	54/114	33/115	35/115	28/115	
Crude OR (95% CI)	1.00	0.61 (0.37, 1.00)	0.64 (0.39, 1.06)	0.51 (0.30, 0.87)	0.013
Adjusted OR1 (95% CI)[a]	1.00	0.60 (0.34, 1.07)	0.75 (0.43, 1.32)	0.65 (0.36, 1.17)	0.16
Adjusted OR2 (95% CI)[b]	1.00	0.60 (0.33, 1.11)	0.73 (0.40, 1.34)	0.73 (0.36, 1.50)	0.38
Total Phosphorus					
Median (mg/day)	1124	1298	1475	1759	
Cases/Controls	50/115	32/114	41/116	27/114	
Crude OR (95% CI)	1.00	0.65 (0.39, 1.08)	0.81 (0.50, 1.32)	0.54 (0.32, 0.93)	0.055
Adjusted OR1 (95% CI)[a]	1.00	0.58 (0.32, 1.05)	0.85 (0.49, 1.49)	0.59 (0.32, 1.08)	0.19

Adjusted OR2 (95% CI)[b]	1.00	0.60 (0.33, 1.10)	0.93 (0.52, 1.63)	0.63 (0.34, 1.16)	0.29
Dietary Phosphorus					
Median (mg/day)	1116	1293	1452	1731	
Cases/Controls	48/114	36/115	43/115	23/115	
Crude OR (95% CI)	1.00	0.74 (0.45, 1.23)	0.89 (0.55, 1.44)	0.47 (0.27, 0.83)	0.019
Adjusted OR1 (95% CI)[a]	1.00	0.73 (0.41, 1.31)	0.92 (0.52, 1.61)	0.57 (0.31, 1.05)	0.12
Adjusted OR2 (95% CI)[b]	1.00	0.80 (0.44, 1.43)	1.02 (0.57, 1.80)	0.61 (0.32, 1.15)	0.19

Abbreviations: OR, odds ratio; CI, confidence interval

[a] Adjusted for age, sex, race, education, physical activity, cigarette smoking, and alcohol consumption per week

[b] Additionally adjusted for intake of energy, total fat, fiber, fruits, and vegetables

APPENDIX

Table A1. Characteristics of subjects in a population-based, case-control study of pancreatic cancer in Minnesota, stratified by quartiles of total calcium intake, total magnesium intake, and total phosphorus intake, 1994–1998[a]

	Quartile of total calcium intake				Quartile of total magnesium intake				Quartile of total phosphorus intake			
	First	Second	Third	Fourth	First	Second	Third	Fourth	First	Second	Third	Fourth
Median (mg/day) / Characteristics	575	789	1148	1532	264	316	364	434	1124	1298	1475	1759
Age (year)	64.3 (12.3)	66.5（11.5)	66.1 (12.7)	68.1 (10.4)	65.0 (13.0)	66.7 (12.2)	64.4 (11.2)	66.0 (10.5)	64.0 (12.6)	66.8 (11.3)	67.6 (11.5)	66.6 (11.4)
Sex												
Male	112 (71.3)	108 (65.9)	73 (50.3)	57 (40.0)	109 (64.1)	91 (63.2)	87 (58.4)	63 (43.1)	107 (64.9)	86 (58.9)	86 (54.8)	71 (50.3)
Female	44 (28.1)	55 (33.5)	72 (49.7)	86 (60.1)	59 (34.7)	53 (36.8)	62 (41.6)	83 (56.9)	57 (34.5)	59 (40.4)	71 (45.2)	70 (49.7)
Missing	1 (0.6)	1 (0.6)	0 (0)	0 (0)	2 (1.2)	0(0)	0(0)	0(0)	1 (0.6)	1 (0.7)	0 (0)	0 (0)
Race												
White	150 (95.5)	158 (96.3)	139 (95.9)	140 (97.9)	161 (94.7)	142 (98.6)	144 (96.6)	140 (95.9)	161 (97.6)	141 (96.6)	149 (94.9)	136 (96.6)
Black	5 (3.2)	1 (0.6)	1 (0.7)	3 (2.1)	4 (2.4)	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.2)	1 (0.7)	4 (2.5)	2 (1.4)
Other	2 (1.3)	5 (3.1)	5 (3.4)	0 (0)	5 (2.9)	0 (0)	3 (2.0)	4 (2.7)	2 (1.2)	4 (2.7)	4 (2.6)	2 (1.4)
Education												
High school graduate	47 (29.9)	51 (31.1)	30 (20.7)	44 (30.8)	66 (38.8)	37 (25.7)	37 (24.9)	32 (21.9)	54 (32.7)	46 (31.5)	36 (22.9)	36 (255)
Some college or more	93 (59.3)	100 (61.0)	105 (72.4)	97 (67.8)	88 (51.8)	94 (65.3)	103 (69.1)	110 (75.4)	96 (58.2)	88 (60.3)	112 (71.3)	99 (70.2)
Some high school or less	17 (10.8)	13 (7.9)	10 (6.9)	2 (1.4)	16 (9.4)	13 (9.0)	9 (6.0)	4 (2.7)	15 (9.1)	12 (8.2)	9 (5.7)	6 (4.3)
Cigarette smoking												
Former smoker	71 (45.3)	77 (47.0)	53 (36.6)	58 (40.6)	69 (40.6)	62 (43.1)	66(44.3)	62 (42.5)	76 (46.0)	63 (43.2)	55 (35.0)	65 (46.1)
Never smoker	58 (36.9)	69 (12.0)	74 (51.0)	71 (49.7)	70 (41.1)	66 (45.8)	65 (43.6)	71 (48.6)	60 (36.4)	65 (44.5)	85 (54.1)	62 (44.0)
Current smoker	28 (17.8)	15 (9.2)	16 (11.0)	12 (8.3)	30 (17.7)	16 (11.1)	17 (11.4)	8 (5.5)	28 (17.0)	17 (11.6)	15 (9.6)	11 (7.8)
Missing	0 (0)	3 (1.8)	2 (1.4)	2 (1.4)	1 (0.6)	0 (0)	1 (0.7)	5 (3.4)	1 (0.6)	1 (0.7)	2 (1.3)	3 (2.1)
Alcohol intake (serving/week)	6.9 (11.9)	4.0 (6.8)	3.5 (6.2)	2.8 (5.3)	4.3 (7.9)	5.3 (10.0)	4.5 (8.5)	3.3 (5.7)	7.9 (12.4)	3.7 (6.3)	3.0 (5.1)	2.4 (4.3)
Diabetes mellitus												
Yes	8 (5.1)	21 (12.8)	20 (13.8)	15 (10.5)	12 (7.1)	13 (9.0)	18 (12.1)	21 (14.4)	9 (5.5)	12 (8.2)	25 (15.9)	18 (12.8)
No	145 (92.4)	138 (84.2)	119 (82.1)	125 (87.4)	155 (91.2)	126 (87.5)	127 (85.2)	119 (81.5)	148 (89.6)	129 (88.4)	129 (82.2)	121 (85.8)
Missing	4 (2.5)	5 (3.0)	6 (4.1)	3 (2.1)	3 (1.7)	5 (3.5)	4 (2.7)	6 (4.1)	8 (4.9)	5 (3.4)	3 (1.9)	2 (1.4)
Physical activity (hour/week)[b]												
Light	27.2 (17.1)	25.3 (15.6)	26.6 (15.8)	25.8 (17.2)	25.0 (16.4)	27.7 (16.9)	26.5 (17.4)	26.2 (15.9)	26.6 (15.9)	27.3 (16.7)	25.3 (16.1)	25.8 (28.2)
Moderate	18.4 (14.1)	17.2 (12.0)	17.3 (12.6)	17.0 (12.6)	15.1 (11.7)	19.3 (12.8)	16.7 (12.9)	19.4 (13.7)	16.7 (12.5)	18.6 (13.1)	17.5 (13.9)	17.3 (11.8)
Heavy	4.6 (6.1)	4.2 (6.8)	4.4 (10.3)	3.4 (5.2)	4.3 (7.5)	4.7 (6.9)	3.2 (4.6)	4.4 (9.5)	4.4 (7.0)	3.9 (5.8)	4.8 (10.5)	3.3 (4.3)

[a] Some variables have missing data.
[b] Data were missing from 26 cases and 1 control.

Table A2. Risk of pancreatic cancer in relation to total and dietary intakes of calcium, magnesium, and phosphorus, stratified by the median intake of total fat, in a population-based, case-control study of pancreatic cancer in Minnesota, 1994–1998

	lower total fat intake (<72.2 g/day) Quartile					Higher total fat intake (≥72.2 g/day) Quartile				
Nutrients	First	Second	Third	Fourth	p- trend	First	Second	Third	Fourth	p- trend
Total Calcium										
Median (mg/day)	582	847	1211	1569		571	746	1029	1473	
Cases/Controls	24/60	19/59	14/59	10/59		21/56	24/55	21/56	17/55	
Crude OR (95% CI)	1.00	0.81 (0.40, 1.62)	0.59 (0.28, 1.26)	0.42 (0.19, 0.96)	0.027	1.00	1.16 (0.58, 2.33)	1.00 (0.49, 2.03)	0.82 (0.39, 1.73)	0.47
Adjusted OR1 (95% CI)[a]	1.00	1.09 (0.48, 2.48)	0.78 (0.32, 1.91)	0.53 (0.20, 1.38)	0.13	1.00	1.02 (0.48, 2.16)	0.86 (0.40, 1.88)	0.74 (0.33, 1.67)	0.41
Adjusted OR2 (95% CI)[b]	1.00	1.20 (0.50, 2.88)	0.79 (0.31, 1.99)	0.56 (0.21, 1.50)	0.17	1.00	0.94 (0.42, 2.06)	0.79 (0.35, 1.78)	0.71 (0.31, 1.63)	0.38
Dietary Calcium										
Median (mg/day)	551	767	1060	1319		538	695	862	1253	
Cases/Controls	19/59	23/59	10/60	15/59		22/55	27/56	18/56	16/55	
Crude OR (95% CI)	1.00	1.21 (0.60, 2.45)	0.52 (0.22, 1.21)	0.79 (0.37, 1.70)	0.20	1.00	1.20 (0.61, 2.37)	0.80 (0.39, 1.66)	0.73 (0.35, 1.53)	0.24
Adjusted OR1 (95% CI)[a]	1.00	1.52 (0.66, 3.53)	0.74 (0.28, 1.94)	1.02 (0.40, 2.57)	0.57	1.00	1.06 (0.50, 2.23)	0.77 (0.34, 1.72)	0.70 (0.31, 1.59)	0.30
Adjusted OR2 (95% CI)[b]	1.00	1.69 (0.67, 4.22)	0.73 (0.27, 2.00)	1.08 (0.41, 2.81)	0.59	1.00	0.87 (0.39, 1.95)	0.68 (0.29, 1.59)	0.63 (0.27, 1.47)	0.26
Total Magnesium										
Median (mg/day)	284	335	384	452		247	304	336	407	
Cases/Controls	24/59	19/59	13/59	11/60		29/56	16/55	15/55	23/56	
Crude OR (95% CI)	1.00	0.79 (0.39, 1.60)	0.54 (0.25, 1.16)	0.45 (0.20, 1.00)	0.031	1.00	0.56 (0.27, 1.15)	0.53 (0.25, 1.09)	0.79 (0.41, 1.54)	0.51
Adjusted OR1 (95% CI)[a]	1.00	0.92 (0.41, 2.09)	0.69 (0.29, 1.63)	0.54 (0.21, 1.38)	0.16	1.00	0.68 (0.31, 1.09)	0.48 (0.21, 1.09)	0.87 (0.40, 1.87)	0.65
Adjusted OR2 (95% CI)[b]	1.00	1.02 (0.43, 2.39)	0.85 (0.33, 2.15)	0.68 (0.23, 2.00)	0.45	1.00	0.53 (0.23, 1.23)	0.36 (0.14, 0.88)	0.70 (0.30, 1.66)	0.45
Dietary Magnesium										
Median (mg/day)	279	327	365	415		240	297	325	373	
Cases/Controls	22/59	13/59	18/59	14/59		27/56	22/55	16/56	18/55	
Crude OR (95% CI)	1.00	0.59 (0.27, 1.28)	0.82 (0.40, 1.68)	0.63 (0.29, 1.34)	0.32	1.00	0.83 (0.42, 1.63)	0.59 (0.29, 1.22)	0.68 (0.34, 1.37)	0.19
Adjusted OR1 (95% CI)[a]	1.00	0.86 (0.35, 2.11)	1.29 (0.56, 2.95)	0.85 (0.34, 2.10)	0.94	1.00	0.94 (0.44, 1.99)	0.71 (0.32, 1.56)	0.78 (0.34, 1.78)	0.45
Adjusted OR2 (95% CI)[b]	1.00	0.90 (0.35, 2.29)	1.77 (0.72, 4.37)	1.23 (0.43, 3.49)	0.44	1.00	0.74 (0.32, 1.71)	0.54 (0.22, 1.31)	0.61 (0.23, 1.62)	0.24
Total Phosphorus										
Median (mg/day)	1135	1344	1536	1773		1117	1274	1431	1709	
Cases/Controls	23/60	18/59	16/59	10/59		25/56	18/55	20/56	20/55	
Crude OR (95% CI)	1.00	0.80 (0.39, 1.62)	0.71 (0.34, 1.47)	0.44 (0.19, 1.01)	0.052	1.00	0.73 (0.36, 1.49)	0.80 (0.40, 1.60)	0.81 (0.41, 1.63)	0.66
Adjusted OR1 (95% CI)[a]	1.00	0.83 (0.35, 1.99)	1.13 (0.47, 2.72)	0.56 (0.21, 1.49)	0.36	1.00	0.68 (0.31, 1.49)	0.88 (0.40, 1.92)	0.81 (0.37, 1.77)	0.75
Adjusted OR2 (95% CI)[b]	1.00	1.02 (0.40, 2.58)	1.28 (0.52, 3.16)	0.66 (0.24, 1.82)	0.55	1.00	0.64 (0.29, 1.43)	0.86 (0.38, 1.93)	0.82 (0.37, 1.83)	0.82
Dietary Phosphorus										
Median (mg/day)	1125	1332	1514	1753		1101	1267	1417	1657	
Cases/Controls	23/59	18/59	15/60	11/59		24/55	19/56	23/55	17/56	
Crude OR (95% CI)	1.00	0.78 (0.38, 1.60)	0.64 (0.31, 1.35)	0.48 (0.21, 1.07)	0.059	1.00	0.78 (0.38, 1.58)	0.96 (0.48, 1.90)	0.70 (0.34, 1.43)	0.42
Adjusted OR1 (95% CI)[a]	1.00	0.75 (0.31, 1.79)	1.03 (0.42, 2.51)	0.59 (0.23, 1.53)	0.39	1.00	0.70 (0.32, 1.52)	1.02 (0.48, 2.19)	0.69 (0.31, 1.54)	0.52
Adjusted OR2 (95% CI)[b]	1.00	0.96 (0.38, 2.43)	1.15 (0.46, 2.86)	0.73 (0.27, 1.98)	0.63	1.00	0.62 (0.28, 1.41)	1.01 (0.46, 2.23)	0.70 (0.31, 1.58)	0.59

Abbreviations: OR, odds ratio; CI, confidence interval

[a] Adjusted for age, sex, race, education, physical activity, cigarette smoking, and alcohol consumption per week

[b] Additionally adjusted for intake of energy, total fat, fiber, fruits, and vegetables