Intake of calcium, magnesium, and phosphorus and risk of pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Margaret Hoyt[a], Yiqing Song[a], Sujuan Gao[b], Jacquelynn O'Palka[c], and Jianjun Zhang[ad*]

[a]*Department of Epidemiology, Indiana University Richard M. Fairbanks School of Public Health, Indianapolis, IN, USA*

[b]*Department of Biostatistics, Indiana University Richard M. Fairbanks School of Public Health and School of Medicine, Indianapolis, IN, USA*

[c]*Department of Nutrition and Dietetics, Indiana University School of Health and Human Sciences, Indianapolis, IN, USA*

[d]*Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN, USA*

*Jianjun Zhang, MD , PhD
Department of Epidemiology
Indiana University Fairbanks School of Public Health
1050 Wishard Boulevard, RG5118
Indianapolis, IN 46202
Phone: (317) 274-4287
Fax: (317) 274-3443
Email: JZ21@iu.edu

Abstract: Few epidemiological studies have investigated the associations between calcium, magnesium, and phosphorus intake and pancreatic cancer. We examined these associations in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Diet was assessed using the Dietary Questionnaire (DQX) at baseline in the intervention arm and the Dietary History Questionnaire (DHQ) in 1999 or around the third anniversary of randomization in both the intervention and control arms. During a median follow-up of 12.2 years, 279 cases of pancreatic cancer occurred from 58,477 participants who completed DQX; 380 cases arose from 101,622 participants who responded to DHQ over a median follow-up of 8.9 years. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Total calcium intake was inversely associated with pancreatic cancer [HR (95% CI) for the fourth vs. the first quartiles in the DHQ cohort: 0.67 (0.47, 0.96); p-trend: 0.035]. An inverse association was also observed for total magnesium intake [HR (95% CI) for the fourth vs. the first quartiles in the DQX cohort: 0.61 (0.37, 1.00); p-trend: 0.023]. Reduced risk associated with total calcium intake was confined to subjects with a high fat intake (>73 g/day) in the DHQ cohort (p-interaction: 0.16). There was not a significant association between dietary phosphorus intake and pancreatic cancer risk in both cohorts. Total intake of calcium and magnesium are associated with a lower pancreatic cancer risk. The effect of total calcium intake was modified by fat intake.

Keywords: calcium; magnesium; phosphorus; fat; pancreatic cancer

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Introduction

Pancreatic cancer is the third leading cause of cancer-related death in both men and women in the US and has been projected to become the second leading cause by 2030 (1). The disproportionately high mortality of this disease is primarily attributable to the late diagnosis of most cases and the lack of an effective screening test (2). Relatively little is known about the etiology of pancreatic cancer, with cigarette smoking and excess adiposity as established modifiable risk factors and red/processed meats, alcohol consumption, and sugary drinks as potential risk factors (2, 3). Therefore, it is critical to identify more modifiable risk factors (e.g. diet) for the primary prevention of this disease.

Obesity has been associated with an increased risk of developing several sites of cancer (4-6) . The biological mechanisms behind this association are not completely understood, but proposed mechanisms include increased chronic inflammation, altered growth factor signaling, and decreased immunity in response to increased adiposity (4, 5, 7-9). Obesity has been closely linked to type 2 diabetes (10), a metabolic disorder that confers an elevated risk of pancreatic cancer (2, 4, 6). It has been found that progression of early pancreatic neoplasia was significantly accelerated in mice fed a high-fat, high-energy diet, compared with those fed a control diet (11, 12). Such a promoting effect on pancreatic carcinogenesis was considered to occur due to a reduced autophagy of cancer cells and sustained inflammation induced by the high-fat diet and resultant obesity (13). The metabolic changes observed in the animal models are similar to those seen in obese humans, which suggests that obesity plays a critical role in pancreatic carcinogenesis. Epidemiological studies have shown a positive association between obesity and pancreatic cancer risk, although this association is not consistent across all previous studies (4, 6, 14-17).

Calcium, magnesium, and phosphorus are metabolically correlated and share some biological functions (18). Experimental and human studies have demonstrated that these mineral nutrients are involved in energy metabolism, glucose/insulin homeostasis, obesity, diabetes, and carcinogenesis (19-23). Changes in intracellular calcium are partially controlled by sulfonylurea receptors on the pancreas and are considered to modulate the development of adiposity and obesity (22). It was found that high intake of calcium protected against weight gain through increasing lipolysis, decreasing lipogenesis, and promoting fecal fat excretion (19, 21, 22). In a Brazilian cross-sectional study, dietary intake of calcium and the ratio of dietary calcium to phosphorus (Ca:P ratio) were inversely correlated with the risk of central obesity (24). Magnesium deficiency is common in diabetes (20). Emerging evidence indicates that high magnesium intake from diet or supplements may favorably affect a cluster of metabolic abnormalities including insulin resistance, systemic inflammation, obesity, hypertension, and dyslipidemia. Magnesium may also regulate cell proliferation, differentiation, apoptosis, and angiogenesis through its role in nucleic acid metabolism, protein synthesis, and energy production (25). In a human experimental study, magnesium deficiency induced low levels of serum calcium and vitamin D (20). Of particular interest is that intracellular calcium participates in the targeting and killing of cancer cells through optimizing the function and efficiency of cytotoxic T lymphocytes and natural killer cells (26).

There are scant data on the role of micronutrients in pancreatic cancer etiology, particularly data generated from prospective cohort studies. It has been reported that high intake of calcium and magnesium was associated with a reduced risk of other sites of gastrointestinal cancer (27, 28). These observations suggest that intake of these minerals may also modulate the risk of pancreatic cancer.

Despite substantial experimental and human evidence supporting the potential effects of calcium, magnesium, and phosphorus on pancreatic carcinogenesis, relatively few case-control studies have evaluated the associations between intake of these nutrients and risk of pancreatic cancer, with inverse (29-31), null (32-34), and positive associations reported (35). Even fewer cohort studies have been conducted that revealed inverse (29) and null (33) associations of interest. Therefore, the present study was thereby conducted to investigate whether total and/or dietary intakes of calcium, magnesium, and phosphorus are associated with pancreatic cancer risk and whether these associations are modified by total fat intake or types of fat among participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Methods

Study Population

The design and methodology of the PLCO trial have been described in detail elsewhere (36). A total of 76,682 men and 78,215 women, aged 55-74 years, were recruited from 10 screening centers across the U.S. from 1993 to 2001. Study participants were randomly assigned to the intervention arm (n=38,340 men and 39,104 women) and control arm (n=38,342 men and 39,111 women). The Dietary Questionnaire (DQX) was administered to participants in the intervention arm only at baseline (T0), while the Dietary History Questionnaire (DHQ) was provided to participants in both the intervention and control arms. Participants who were recruited before December 1995 were asked to complete the DHQ in 1999 and those who were enrolled at or after that time were invited to respond to the DHQ generally around their third anniversary of randomization (T3).

Of the 77,444 participants assigned to the intervention arm, we sequentially excluded 16,047 subjects, including 1833 for not completing baseline questionnaire, 40 for personal history of pancreatic cancer prior to the administration of baseline questionnaire, 12,405 for not completing the DQX, and 1809 for providing invalid DQX [missing ≥8 food items or extreme energy intake values (i.e., lowest or highest 1%)]. We further excluded 2770 participants for personal history of cancer prior to DQX and 110 subjects for loss to follow-up, leaving 58,477 participants available for DQX analysis. During a median follow-up of 12.2 years, 58,477 participants gave rise to 279 cases of pancreatic cancer (including 56 early-stage cases). When similar exclusion criteria described above were used, 101,622 participants in both the intervention and control arms remained in the cohort and provided valid DHQ data for statistical analysis. A total of 380 cases of pancreatic cancer (including 74 early-stage disease) were diagnosed over the median follow-up of 8.9 years after DHQ completion. Written informed consent was obtained from all participants and the study protocol was approved by the institutional review boards of all participating institutions.

Ascertainment of Pancreatic Cancer

The diagnosis of pancreatic cancer (ICD-O-02: C250-259) in both intervention and control arms of the PLCO trial was confirmed primarily through the review of medical records of participants with self-reported pancreatic cancer on annual study update or indication of pancreatic cancer in death certificates. Based on pathology reports, pancreatic cancer was classified into three stages: 1) localized and surgically resectable, 2) locally advanced, surgically unresectable, but not metastatic, and 3) metastatic. Only incident cases of pancreatic cancer were considered in the present study.

Data Collection

Information on age, sex, race, height, weight, marital status, education, physical activity, cigarette smoking, diabetes, family history of pancreatic cancer, and other variables was collected for participants in both intervention arm and control arms by using a sex-specific Baseline Questionnaire (37). As previously described, two food frequency questionnaires (FFQ) were used to assess usual diet of PLCO participants. Food items (including alcohol beverages) commonly consumed by the general U.S. population are listed in both the DQX (n=137 items) and the DHQ (n=124 items). While the DQX was modified from the validated Willett and Block FFQs (38), the DHQ have been validated against four 24-hour recalls, one in each season (39). During the dietary survey, participants were asked to recall the average frequency of consumption of each food item included in the DQX or the DHQ in the past year. Dietary intake of energy and nutrients was calculated by multiplying the amount of energy and nutrients in a standard portion size of each food item by the reported frequency of consumption and summing over all reported food items. The nutrient contents of foods were based on values from the USDA's 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII) and the University of Minnesota's Nutrition Data Systems for Research (37).

Both DQX and DHQ also solicit information on supplemental use of calcium, magnesium, other minerals, and vitamins (37). Calcium and magnesium supplements are available in multivitamin or single nutrient preparations in the US. The prevalence of calcium supplement use was 55.2% for the DQX cohort and 51.5% for the DHQ cohort at the time of or in the past year prior to the dietary survey. The corresponding prevalence of magnesium supplement use was 44.7% for the DQX cohort and 54.0% for the DHQ cohort. The supplemental intake of calcium and magnesium (mg/day) was calculated by using the same method as for dietary intake. The dose values for calcium and magnesium supplements were derived from the nutrient composition of commercial products.

Statistical Analysis

Demographic, anthropometric, and lifestyle characteristics of study participants were compared across the quartiles of total calcium intake using chi-square tests for categorical variables and analysis of variance for continuous variables. Intakes of total calcium, dietary calcium, total magnesium, dietary magnesium, and dietary phosphorus were compared between individuals who developed any or early-stage pancreatic cancer and those who were free from this malignancy during follow-up. As the dietary variables considered were not normally distributed, the two-sided Wilcoxon rank-sum test was used for these comparisons.

Cox proportional hazards regression analysis was performed to calculate hazard ratio (HR) and 95% confidence intervals (CI) for pancreatic cancer risk in relation to total and/or dietary intakes of calcium, magnesium, and phosphorus. Time-to-event was calculated from the date of cohort entry to date of diagnosis with pancreatic cancer for individuals who developed the disease. Time-to-event was censored at date of death, study dropout, or study end date (December 31, 2009), whichever came earlier, for those without pancreatic cancer. Time-to-event was also censored for persons who were diagnosed with another cancer (except non-melanoma skin cancer) prior to pancreatic cancer. The date of entry to the DQX cohort was defined as the date of randomization, baseline questionnaire completion, or dietary survey completion, whichever occurred later. The date of entry to the DHQ cohort was determined as the date of completion of this dietary assessment instrument.

Intakes of total and dietary calcium, total and dietary magnesium, and dietary phosphorus were each divided into FFQ-specific quartiles, and the HRs (95% CIs) for subjects in the second quartile through the fourth (highest) quartile were calculated with those in the first (lowest) quartile as reference. Linear trends across quartiles of each of these dietary variables were tested by modeling median value for each quartile as a continuous variable in Cox regression. Age, sex, race, BMI, cigarette smoking (pack-years), family history of pancreatic cancer, diabetes status, and intake of total energy, fruits, and vegetables were adjusted as confounders because they are consistently or potentially associated with dietary intake of calcium, magnesium, and/or phosphorus and the risk of pancreatic cancer. The randomization variable was also included in the cox regression analyses of dietary data derived from the DHQ to control for potential confounding due to study assignment. Other dietary factors, alcohol consumption, and physical activity were not adjusted because they were not potential or true confounders for the associations of interest. The likelihood ratio test was used to test the potential interactions of the aforementioned variables and fat intake with calcium, magnesium, or phosphorus in relation to pancreatic cancer risk.

Separate analyses were conducted for early stage, resectable pancreatic cancer and total pancreatic cancer. Stratified analyses were performed for the associations of total calcium intake and total magnesium intake with risk of pancreatic cancer by tertiles of total fat intake. In the stratified analysis, total calcium intake and total magnesium intake were each divided into tertiles (instead of quartiles) to avoid a small number of cases in some categories. Habitual high intake of fat is an established risk factor for obesity and diabetes (40). The potential effect modification of fat intake on the associations examined was evaluated because calcium, magnesium, and phosphorus play a critical role in energy metabolism, fecal fat excretion, metabolic syndrome, and obesity, which were discussed in the Introduction and Discussion sections. Additionally, risk of pancreatic cancer was assessed by comparing individuals meeting the respective recommended daily allowances (RDA) of total calcium, total magnesium, and dietary phosphorus with those meeting 75%-<100% and <75% of those RDAs. To account for potential reverse causality, cases of pancreatic cancer diagnosed within two years of enrollment (n=27 for the DQX cohort; n=8 for the DHQ cohort) were excluded from data analysis. The proportional hazards assumption was graphically tested for all the models constructed, and none of them violated the assumption. SAS version 9.4 (Cary, NC) was used for statistical analysis, and a p-value of <0.05 (2-sided) was considered statistically significant.

Results

Characteristics of study participants by total calcium intake quartile are shown in Table 1. Significant differences were observed for sex, race, BMI, physical activity, cigarette smoking, family history of pancreatic cancer, diabetes status, total energy intake, and dietary intake of fat, magnesium, and phosphorus. Participants in the highest quartile of total calcium intake were more likely to be white, non-Hispanic female, leaner, and more physically active and to have a higher intake of fat, magnesium, and phosphorus than those in other quartiles.

Total and/or dietary intakes [median and interquartile range (IQR)] of calcium, magnesium, phosphorus, and total fat by pancreatic cancer diagnosis are presented in Table 2. Individuals with pancreatic cancer tended to have consistently lower intakes of all nutrients (except total fat) than those without pancreatic cancer, although significant differences existed only for total calcium (p=0.034 for the DQX; p=0.0067 for the DHQ). Similar patterns of differences in nutrients of interest were observed between individuals with early-stage pancreatic cancer and those free of this malignancy during follow-up.

Risk estimates of pancreatic cancer in relation to intakes of total and dietary calcium, total and dietary magnesium, and dietary phosphorus are displayed in Table 3. After adjustment for established and suspected confounders mentioned above, an inverse association was observed between total calcium intake and total pancreatic cancer; HRs (95% CIs) for the second, third, and fourth quantiles vs. the first quartile were 0.93 (0.70, 1.24), 0.96 (0.71, 1.29), and 0.67 (0.47, 0.96) (p-trend: 0.035) for the DHQ cohort. This inverse association remained largely unchanged after additional adjustment for total magnesium intake (p-trend: 0.0082). No significant associations were observed between intakes of calcium and magnesium from diet and supplements alone (data not shown) and pancreatic cancer risk. In the DQX cohort, pancreatic cancer risk decreased with increasing intake of total magnesium intake [HRs (95% CIs) for the second, third, and fourth quantiles vs. the first quartile were 0.95 (0.68, 1.32), 0.66 (0.45, 0.97), and 0.61 (0.37, 1.00), p-trend: 0.023]. A similar pattern of the association persisted after additional adjustment for total calcium intake (p-trend: 0.061). A reduced risk of pancreatic cancer across the quartiles of total calcium intake (p-trend: 0.0089) and total magnesium intake (p-trend: 0.045) remained virtually unaltered after patients diagnosed with the disease within two years of baseline were excluded from the analysis. Intakes of total calcium, total magnesium, and dietary phosphorus, assessed using both the FFQs, were not significantly associated with the risk of early-stage pancreatic cancer (data not shown). No significant interactions existed between intakes of calcium, magnesium, and phosphorus on risk of total and early-stage pancreatic cancer.

Table 4 shows pancreatic cancer risk estimated in terms of whether and to what extent each individual met the RDAs of calcium, magnesium, and phosphorus. In the DHQ cohort, HRs (95% CIs) for the individuals whose total calcium intake met 75-<100% and <75% of RDA, compared with the those whose total intake met or exceeded the RDA, were 1.11 (0.83, 1.50) and 1.25 (0.97, 1.62), respectively. The corresponding HRs (95% CIs) for total magnesium were 1.15 (0.88, 1.51) and 1.36 (1.00, 1.84).

The results of stratified analysis of pancreatic cancer risk in relation to total calcium intake and total magnesium intake by tertiles of total fat intake are displayed in Table 5. In the DHQ cohort, total calcium intake was significantly associated with a reduced risk of pancreatic cancer only among participants in the highest tertile of total fat intake [HR (95% CI) for the second and third tertiles vs. the first tertile of total calcium intake: 0.56 (0.35, 0.90) and 0.50 (0.30, 0.84, respectively; p-trend: 0.031] (p-interaction: 0.16). No clear patterns of interaction existed between total intake of magnesium and total intake of fat on pancreatic cancer risk. When total fat was replaced by types of fat (saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and ratio of omega-6 to omega-3 fatty acids) in the above stratified analyses, there were no apparent interactions between type of fatty acids and total intake of calcium and magnesium to modulate pancreatic cancer risk (data not shown).

Discussion

In the present study, we found that total calcium intake from both dietary and supplemental sources was associated with a reduced risk of pancreatic cancer independent of established and suspected confounders. This association was largely confirmed when risk was estimated by comparing total calcium intake of less than 75% of the RDA with intake of equal to or greater than the RDA. Furthermore, the inverse association between total calcium intake and pancreatic cancer risk was confined to subjects with high total fat intake. A significant linear inverse association was observed between total magnesium intake and pancreatic cancer risk.

Our observed reduction in pancreatic cancer risk associated with high intake of total calcium was consistent with a population-based case-control study conducted in western Washington (29, 30). In that study, persons in the highest quartile of calcium intake experienced a 70% lower risk of pancreatic cancer than those in the lowest quartile of intake. However, both total and dietary intakes of calcium were not associated with an altered risk of pancreatic cancer in the Health Professionals Follow-up Study and the Nurses' Health Study in which a high proportion of individuals regularly took multivitamin and mineral supplements (including calcium) (29, 30). Although biological mechanisms linking calcium intake to pancreatic carcinogenesis remain elusive, experimental studies have revealed that intracellular Ca (2+) concentrations are modulatory of cancer cell proliferation and apoptosis and thus are critical for efficient functioning of natural killer cells and cytotoxic T lymphocytes, immune cells that eliminate tumorigenic cells (26).

We detected an interaction between total calcium intake and total fat intake (estimated from the DHQ) in relation to pancreatic cancer risk. Significantly inverse association between total calcium intake and pancreatic cancer was only observed among participants in the highest tertile of total fat intake. To our knowledge, this effect modification has been not reported in any previous studies. Several biological mechanisms may account for this interaction. Randomized trials have found that dietary calcium increases fecal fat excretion primarily due to calcium soap formation in the gut (19). Increased fecal loss of fat subsequently mitigates the detrimental effects of dysregulated autophagy, insulin resistance, and sustained inflammation, abnormal physiological conditions associated with elevated fat intake (13, 41). In addition, our finding has gained indirect support from animal studies showing that the promoting effect of high fat diet on chemically-induced mammary and colon tumorigenesis in rodents were modulated by dietary calcium intake (42, 43). Another piece of indirect supporting evidence is that the potential protective effect of total calcium intake (assessed with the DHQ) on pancreatic cancer risk was restricted to obese individuals [HR 95% CI) for the highest vs. lowest tertiles: 0.47 (0.23-0.94); p-interaction: 0.06] (data not shown).

A significant reduction in pancreatic cancer risk associated with total magnesium intake was observed with a significant linear trend across the quartiles of total magnesium intake. Such an inverse association was virtually replicated when risk estimates were obtained by comparing subjects with total magnesium intake that was less than <75% of the RDA with those with the intake that met or exceeded the RDA. Some epidemiological studies have reported a reduced risk associated with increased magnesium intake (44, 45), but results are inconsistent across previous studies (46). Two prospective cohort studies identified an inverse association between magnesium intake and pancreatic cancer risk only among overweight men (47, 48). This inverse association may be mediated through the favorable effect of magnesium intake on risk of type 2 diabetes (49, 50), a disease that is likely to exist in the intermediate pathogenic pathway between overweight and pancreatic cancer (2). Nevertheless, the precise mechanisms underlying the relation between magnesium metabolism and carcinogenesis are far from clear. There is some evidence from experimental studies that magnesium is involved in maintaining genomic stability, inhibiting c-*myc* oncogene expression in colon cancer cells, and reducing toxic effects of bile acids on colonic epithelial cells (51, 52).

We identified a significantly reduced risk of pancreatic cancer associated with an increased total intake of calcium and magnesium, but such an inverse association was not observed for intake of these two minerals from diet or supplemental use alone (data not shown). It remains unclear why these different results occurred. One possible reason is that total intakes of calcium and magnesium reflect the actual amounts of these nutrients from all sources that are available for the absorption and metabolism of study individuals. In the DQX cohort, supplemental calcium intake accounted for 6.4%, 14.6%, 22.5%, and 31.1% of total calcium intake in quartiles 1 to 5, respectively. The corresponding proportions were 6.0%, 10.9%, 12.3%, and 11.3% for total magnesium intake in quartiles 1 to 5. Supplement users were enriched in quartiles 3 and 4 of total intakes of calcium (DQX: Q3: 22.5% and Q4: 31.1%) and magnesium (DQX: Q3: 12.3% and Q4: 11.3%). Similar supplemental data were obtained from participants in the DHQ cohort. In spite of the prevalence and amounts of supplemental use, the findings of the present study suggest that total intake values, rather than sources, of calcium and magnesium are important and relevant for the potential beneficial effects of these minerals on pancreatic cancer risk.

The present study revealed an inverse but insignificant association between dietary phosphorus intake and pancreatic cancer risk. Our results are not consistent with those of a Mayo Clinic case-control study in which dietary phosphorus intake was associated with a significantly reduced risk of pancreatic cancer (31). Although epidemiological data on the potential influence of phosphorus intake on risk of pancreatic cancer are relatively scarce, it is biologically plausible that phosphorus is implicated in pancreatic carcinogenesis. Phosphorus is essential to adenosine triphosphate (ATP) production in the human body. Therefore, it is possible that an increase in dietary intake of phosphorus could lead to an increase in availability of energy for physical activity and a subsequent reduction in overweight and obesity (53). As mentioned above, a significant inverse correlation between Ca:P ratio and risk of central obesity defined by waist-to-height ratio was found among an adult Brazilian population (24).

No significant associations between intakes of calcium, magnesium, and phosphorus and early-stage pancreatic cancer were observed in this study. However, caution should be exercised as only a small number of early-stage pancreatic cancer (n= 56 in DQX cohort and n=74 in DHQ cohort) were available for the present analysis. There is a substantial difference in 5-year survival rate between localized, regional, and metastatic pancreatic cancer (54). It is thereby interesting and warranted to further investigate the effects of these nutrients on risk of early-stage pancreatic cancer among a consortium of prospective cohort studies that can offer an adequate power for such an analysis.

Some different results were obtained from the two dietary questionnaires used in the PLCO trial. The underlying reasons for these different observations are largely unclear but may be primarily related to differences in study participants who completed the DQX (in the intervention arm only) and those who responded to the DHQ (in both the intervention and control arm), the point in time in which the DQX (at baseline) and the DHQ (generally around the third anniversary of randomization) were administered, and the number of food items that were included in the DQX (n=137) and the DHQ n=124).

The present study has some advantages. The associations of interest were evaluated in a large prospective cohort study. Such a prospective study design substantially reduced the probability of reverse causality, a methodological issue that often occurs in case-control studies of nutrition and disease. Exclusion of patients diagnosed with pancreatic cancer within two years of enrollment from the analysis did not substantially change our risk estimates, which offers additional evidence that the findings of the present study are virtually free from reverse causality. It is unlikely that differential recall bias has materially distorted our obtained results because subjects were not diagnosed with pancreatic cancer at the time of dietary assessment. In the PLCO trial, the diet of participants was assessed at two time points (i.e., baseline and 3 years after entry into the cohort), which might have somewhat reduced the likelihood of chance findings on the associations between three minerals considered and pancreatic cancer risk.

There are several limitations in the present study. A small number of individuals with early-stage pancreatic cancer precluded us from adequately investigating the effects of selected nutrient intake on the occurrence of the disease at a critical stage when it is potentially curable by surgical intervention (55). Dietary intake of calcium, magnesium, and phosphorus was estimated using dietary questionnaires. Measurement error that arises from recall bias is common with this type of dietary assessment. Such a measurement error, if non-differential and substantial, might have resulted in a misclassification of subjects with regard to their intake levels of calcium, magnesium, and phosphorus, consequentially leading to attenuated risk estimates of the true associations (56). As calcium, magnesium, and phosphorus share some food sources, it would be difficult to tease out the independent effect of each nutrient from one another or from other dietary nutrients such as fiber, folate, and potassium. In addition, we cannot completely rule out the possibility of residual confounding due to some lifestyle and dietary factors. The generalization of obtained results might have been somewhat compromised due to statistically significant differences in sex, race, BMI, cigarette smoking, vigorous physical activity, family history of pancreatic cancer, and history of diabetes between study participants with and without dietary data.

In summary, the present study found that total calcium intake was associated with a reduced risk of pancreatic cancer among participants in the PLCO trial and that this potential beneficial effect was restricted to those with high fat intake. In addition, there is an inverse association between total magnesium intake and pancreatic cancer risk. It is important to further evaluate the role of calcium, magnesium, and phosphorus in the etiology of pancreatic cancer in other prospective epidemiological studies conducted in populations with different dietary habits. It is expected that the findings of these studies could provide novel and effective dietary modification and intervention strategies for the primary prevention of pancreatic cancer.

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Table 1. Baseline characteristics of study participants by total calcium intake in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993-2009

	Quartiles (Q) of Total Calcium Intake (mg/day)[1]				
Characteristics[2]	Q1 (<784) n= 14, 619	Q2 (784-1135) n= 14,619	Q3 (1136-1589) n= 14,620	Q4 (>=1589) n= 14,619	p-value[3]
Age (year)	62.6 (5.3)	62.6 (5.3)	62.6 (5.3)	62.5 (5.3)	0.97
Sex (%)					<0.0001
Male (n= 30,095)	56.5	59.1	50.9	39.4	
Female (n= 28,382)	43.5	40.9	49.1	60.6	
Race/Ethnicity (%)					<0.0001
White (n= 53,101)	84.8	90.7	93.0	94.8	
Black (n= 2,243)	7.1	3.8	2.7	1.8	
Hispanic (n= 886)	1.9	1.5	1.4	1.2	
Asian (n= 1,860)	5.2	3.3	2.4	1.8	
Other (n= 387)	1.0	0.6	0.6	0.5	
Body Mass Index (BMI) (kg/m^2)	27.5 (4.8)	27.4 (4.6)	27.5 (4.8)	27.1 (4.9)	<0.0001
Vigorous Physical Activity (%)					<0.0001
None (n= 8,906)	20.3	15.6	13.8	11.5	
<1 hour per week (n= 10,482)	20.2	18.7	17.2	15.8	
1-3 hours per week (n=25,235)	39.8	43.3	45.0	45.2	
≥4 hours per week (n= 13,648)	19.6	22.5	24.0	27.5	
Family History of Pancreatic Cancer (%)					0.003
Yes (n= 1,453)	2.6	2.5	2.4	2.6	
No (n= 54,939)	94.2	94.5	95.1	94.8	
Possible (n= 1,662)	3.3	3.0	2.5	2.6	
Diabetes (%)					<0.0001
Yes (n= 4,179)	7.8	7.7	7.1	6.1	
No (n= 54,140)	92.2	92.3	92.9	93.9	
Cigarette Smoking (%)					<0.0001
Never Smokers (n=27,394)	42.6	44.8	47.8	52.2	
Former Smokers (n= 25,341)	44.7	44.8	43.3	40.5	
Current Smokers (n= 5,737)	12.6	10.4	8.9	7.4	
Cigarette smoking (pack-year)	19.8 (27.5)	18.8 (27.0)	17.0 (26.1)	15.7 (25.9)	<0.0001
Energy Intake (kcal/d)	1524 (482)	1982 (625)	2215 (758)	2474 (929)	<0.0001
Fat Intake (g/d)	50 (20)	66 (27)	74 (33)	80 (41)	<0.0001
Total Calcium Intake (mg/d)	580 (140)	958 (100)	1342 (129)	2075 (459)	<0.0001
Total Magnesium Intake (mg/d)	301 (93)	409 (116)	472 (137)	556 (178)	<0.0001
Dietary Phosphorus Intake (mg/d)	921 (255)	1284 (337)	1529 (459)	1895 (717)	<0.0001

[1] Intake of energy, calcium, and other nutrients were calculated from the Dietary Questionnaire (DQX).
[2] Values shown are mean (SD) for continuous variables and percentages for categorical variables.
[3] p-values were calculated using chi-square for categorical variables and ANOVA for continuous variables.

Table 2. Differences in intake of calcium, magnesium, phosphorus, and fat between subjects who did and did not develop pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993-2009[a]

Cohorts	Total Pancreatic Cancer (1)	Early-stage Pancreatic Cancer (2)	Non-Pancreatic Cancer (3)	p-value (1) vs. (3)	p-value (2) vs. (3)
DQX	n=279	n= 56	n= 58,198		
Total Calcium (mg/d)	1054 (723-1447)	1026 (624-1516)	1135 (785-1590)	**0.034**	0.11
Dietary Calcium (mg/d)	830 (621-1105)	749 (593-1026)	857 (617-1189)	0.26	0.07
Total Magnesium (mg/d)	389 (311-511)	361 (298-464)	413 (318-525)	0.12	**0.033**
Dietary Magnesium (mg/d)	359 (276-453)	340 (269-392)	364 (280-468)	0.25	0.08
Dietary Phosphorus (mg/d)	1253 (984-1650)	1212 (1014-1468)	1307 (982-1720)	0.41	0.10
Total Fat (g/d)	61(43-82)	57 (41-75)	60 (44-83)	0.95	0.20
DHQ	n= 380	n= 74	n= 101,341		
Total Calcium (mg/d)	845 (554-1230)	903 (571-1263)	923 (601-1337)	**0.0067**	0.63
Dietary Calcium (mg/d)	642 (460-871)	646 (446-876)	662 (466-939)	0.19	0.20
Total Magnesium (mg/d)	349 (270-436)	329 (254-416)	354 (274-446)	0.33	0.15
Dietary Magnesium (mg/d)	294 (233-391)	279 (217-349)	303 (233-389)	0.46	0.054
Dietary Phosphorus (mg/d)	1035 (785-1367)	997 (794-1344)	1065 (790-1416)	0.24	0.20
Total Fat (g/d)	54 (39-78)	50 (35-72)	55 (39-78)	0.63	0.19

a. Values shown are medians (25^{th}–75^{th} percentiles).

Table 3. Hazard ratio (HR) [95% confidence interval (CI)] for pancreatic cancer in relation to intake of calcium, magnesium, and dietary phosphorus in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993-2009

	DQX					DHQ			
Nutrient (mg/d)	No. of Cases	Person-years	HR (95% CI)[a]	HR (95% CI)[b]		No. of Cases	Person -years	HR (95% CI)[a]	HR (95% CI)[b,c]
Dietary Calcium					Dietary Calcium				
Q1 (<617)	69	160,792	Reference	Reference	Q1 (<466)	99	212,167	Reference	Reference
Q2 (617-856)	78	163,066	1.11 (0.80, 1.53)	1.07 (0.76, 1.50)	Q2 (466-661)	100	213,581	1.01 (0.77, 1.34)	0.97 (0.72, 1.30)
Q3 (857-1188)	73	163,894	1.03 (0.74, 1.43)	0.87 (0.66, 1.42)	Q3 (662-938)	101	213,253	1.01 (0.77, 1.34)	0.99 (0.72, 1.35)
Q4 (>1188)	59	164,073	0.83 (0.59, 1.18)	0.77 (0.49, 1.23)	Q4 (>938)	80	212,949	0.81 (0.60, 1.09)	0.73 (0.49, 1.07)
p-trend			0.20	0.19				0.14	0.086
Total Calcium					Total Calcium				
Q1 (<784)	82	161,289	Reference	Reference	Q1 (<601)	110	211,374	Reference	Reference
Q2 (784-1134)	76	163,119	0.91 (0.67, 1.25)	0.90 (0.65, 1.25)	Q2 (601-922)	101	212,970	0.90 (0.69, 1.18)	0.93 (0.70, 1.24)
Q3 (1135-1589)	68	164,084	0.81 (0.59, 1.12)	0.82 (0.57, 1.17)	Q3 (923-1336)	100	213,620	0.90 (0.68, 1.18)	0.96 (0.71, 1.29)
Q4 (>1589)	53	163,333	0.64 (0.45, 0.90)	0.67 (0.45 1.02)	Q4 (>1336)	69	213,986	0.61 (0.45, 0.82)	**0.67 (0.47 0.96)**
p-trend			0.0075	0.056				0.0017	**0.035**
Dietary Magnesium					Dietary Magnesium				
Q1 (<279)	72	160,744	Reference	Reference	Q1 (<233)	95	211,868	Reference	Reference
Q2 (279-363)	73	162,934	1.00 (0.72, 1.38)	0.93 (0.65, 1.32)	Q2 (233-302)	106	213,619	1.10 (0.84, 1.46)	1.11 (0.83, 1.49)
Q3 (363-467)	73	164,540	0.98 (0.71, 1.36)	0.83 (0.56, 1.25)	Q3 (303-389)	83	213,560	0.84 (0.63, 1.14)	0.81 (0.57, 1.16)
Q4 (>467)	61	163,608	0.83 (0.59, 1.16)	0.64 (0.37, 1.11)	Q4 (>389)	96	212,903	1.01 (0.76, 1.33)	1.01 (0.64, 1.59)
p-trend			0.26	0.10				0.69	0.76
Total Magnesium					Total Magnesium				
Q1 (<318)	78	161,555	Reference	Reference	Q1 (<274)	100	212,102	Reference	Reference
Q2 (318-412)	79	163,137	1.00 (0.73, 1.37)	0.95 (0.68, 1.32)	Q2 (274-353)	97	213,310	0.95 (0.72, 1.26)	0.96 (0.72, 1.28)
Q3 (412-525)	61	163,723	0.77 (0.55, 1.08)	**0.66 (0.45, 0.97)**	Q3 (354-446)	95	213,603	0.93 (0.70, 1.23)	0.92 (0.67, 1.26)
Q4 (>525)	61	163,410	0.77 (0.55, 1.08)	**0.61 (0.37, 1.00)**	Q4 (>446)	88	212,935	0.88 (0.66, 1.17)	0.89 (0.59, 1.33)
p-trend			0.062	**0.023**				0.36	0.54
Dietary Phosphorus					Dietary Phosphorus				
Q1 (<982)	69	161,175	Reference	Reference	Q1 (<790)	97	212,210	Reference	Reference
Q2 (982-1306)	81	163,015	1.16 (0.84, 1.59)	1.02 (0.72, 1.44)	Q2 (790-1064)	104	213,784	1.06 (0.81, 1.40)	1.01 (0.75, 1.36)
Q3 (1307-1720)	71	163,855	1.01 (0.72, 1.40)	0.81 (0.54, 1.23)	Q3 (1065-1415)	97	213,276	0.98 (0.74, 1.30)	0.88 (0.63, 1.24)
Q4 (>1720)	58	163,780	0.82 (0.58, 1.17)	0.59 (0.33, 1.06)	Q4 (>1415)	82	212,680	0.83 (0.62, 1.12)	0.68 (0.43, 1.10)
p-trend			0.15	0.050				0.16	0.088

DQX, dietary questionnaire; DHQ, dietary history questionnaire; Q, quartile.

a. Crude HR.

b. Adjusted for age, sex, race, BMI, family history of pancreatic cancer, diabetes status, cigarette pack-years, and dietary intake of energy, fruits, and vegetables.

c. DHQ was additionally adjusted for randomization.

Table 4. Hazard ratio (HR) [95% confidence interval (CI)] for pancreatic cancer associated with intake of total calcium, total magnesium, and dietary phosphorus by percentage of recommended daily allowance (RDA) in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993-2009[1]

	DQX[a]			DHQ[a,b]		
Nutrients[c]	Person-years	No. of cases	HR (95% CI)	Person-years	No. of Cases	HR (95% CI)
Total Calcium						
≥100% RDA	344,340	138	Reference	321,149	126	Reference
75-<100% RDA	131,197	49	0.88 (0.62, 1.23)	168,204	73	1.11 (0.83, 1.50)
<75% RDA	176,287	92	1.24 (0.91, 1.69)	362,597	181	1.25 (0.97, 1.62)
Total Magnesium						
≥100% RDA	406,379	155	Reference	401,828	155	Reference
75-<100% RDA	145,260	72	1.32 (0.97, 1.79)	239,512	113	1.15 (0.88, 1.51)
<75% RDA	100,185	52	1.44 (0.98, 2.09)	210,610	112	**1.36 (1.00, 1.84)**
Dietary Phosphorus						
≥100% RDA	604,253	257	Reference	703,910	318	Reference
75-<100% RDA	36,181	16	1.04 (0.61, 1.78)	94,114	42	0.95 (0.67, 1.35)
<75% RDA	11,391	6	1.22 (0.53, 2.83)	53,926	20	0.75 (0.46, 1.23)

DQX, dietary questionnaire; DHQ, dietary history questionnaire.

a. Adjusted for age, sex, race, BMI, family history of pancreatic cancer, diabetes status, cigarette pack-years, and dietary intake of energy, fruits, and vegetables.
b. DHQ was additionally adjusted for randomization.
c. RDA cut-off points: total calcium: ≥100% RDA: male age 50-70: ≥1000 mg/d; male age >70 or female age>50: ≥1200 mg/d; 75-<100% RDA: male age 50-70: 750-<1000 mg/d; male age >70 or female age>50: 900-<1200 mg/d; <75% RDA: male age 50-70: <750 mg/d; male age >70 or female age>50: <900 mg/d. total magnesium: ≥100% RDA: male age>30: ≥420 mg/d; female age>30: ≥320 mg/d; 75-<100% RDA: male age>30: 315-<420 mg/d; female age>30: 240-<320 mg/d; <75% RDA: male age>30: <315 mg/d; female age>30: <240 mg/d. dietary phosphorus: ≥100% RDA: age≥19: ≥700 mg/d; 75-<100% RDA: age≥19: 525-<700 mg/d; <75% RDA: age≥19: <525 mg/d.

Table 5. Hazard ratio (HR) [95% confidence interval (CI)] for pancreatic cancer in relation to total intake of calcium and magnesium, stratified by tertiles (T) of fat intake, in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 1993-2009

DQX					DHQ				
Total Fat Intake (g/d)	Nutrient Intake (mg/d)	No. of Cases	Person-years	HR (95% CI)[a]	Total Fat Intake (g/d)	Nutrient Intake (mg/d)	No. of Cases	Person -years	HR (95% CI)[b]
	Total Calcium					Total Calcium			
T1 (<49)	T1 (<900)	49	87,255	Reference	T1 (<44)	T1 (<702)	60	129,235	Reference
	T2 (900-1409)	25	48,548	0.94 (0.56, 1.58)		T2 (702-1186)	36	80,018	1.09 (0.71, 1.70)
	T3 (≥1409)	18	42,180	0.89 (0.49, 1.64)		T3 (>=1186)	27	74,834	0.96 (0.57, 1.62)
	p- trend			0.71		p-trend			0.94
T2 (49-73)	T1 (<900)	37	54,736	Reference	T2 (44-68)	T1 (<702)	49	100,079	Reference
	T2 (900-1409)	38	60,985	1.07 (0.67, 1.73)		T2 (702-1186)	45	94,109	0.99 (0.65, 1.51)
	T3 (≥1409)	20	53,382	0.71 (0.38, 1.31)		T3 (>=1186)	39	90,329	0.94 (0.57, 1.51)
	P-trend			0.27		p-trend			0.79
T3 (>73)	T1 (<900)	19	19,298	Reference	T3 (69- 332)	T1 (<702)	38	53,014	Reference
	T2 (900-1409)	35	53,586	0.79 (0.45, 1.41)		T2 (702-1186)	45	110,272	**0.56 (0.35, 0.90)**
	T3 (≥1409)	38	68,521	0.71 (0.38, 1.33)		T3 (>=1186)	41	120,061	**0.50 (0.30, 0.84)**
	p-trend			0.93		p-trend			**0.031**
p for interaction = 0.82						p for interaction = 0.16			
	Total Magnesium					Total Magnesium			
T1 (<49)	T1 (<350)	58	126,897	Reference	T1 (<44)	T1 (<301)	70	161,437	Reference
	T2 (350-481)	22	65,625	0.73 (0.42, 1.27)		T2 (301-411)	35	89,981	1.01 (0.64, 1.58)
	T3 (≥481)	12	24,857	1.08 (0.50, 2.34)		T3 (>=411)	18	32,668	1.44 (0.72, 2.88)
	p- trend			0.78		p-trend			0.44
T2 (49-73)	T1 (<350)	35	68,498	Reference	T2 (44-68)	T1 (<301)	52	91,924	Reference
	T2 (350-481)	40	87,064	0.78 (0.48, 1.28)		T2 (301-411)	44	111,341	**0.62 (0.41, 0.94)**
	T3 (≥481)	20	62,355	0.53 (0.26, 1.04)		T3 (>=411)	37	81,252	0.66 (0.39, 1.11)
	P-trend			0.066		p-trend			0.087
T3 (>73)	T1 (<350)	11	20,211	Reference	T3 (69- 332)	T1 (<301)	13	29,765	Reference
	T2 (350-481)	31	65,693	0.83 (0.41, 1.68)		T2 (301-411)	51	83,369	1.26 (0.68, 2.35)
	T3 (≥481)	50	130,625	0.64 (0.30, 1.38)		T3 (>=411)	60	170,213	0.81 (0.42, 1.60)
	p-trend			0.21		p-trend			0.16
p for interaction = 0.59					p for interaction =0.073				

DQX, dietary questionnaire; DHQ, dietary history questionnaire.

a. Adjusted for age, sex, race, BMI, family history of pancreatic cancer, diabetes status, cigarette pack-years, and dietary intake of energy, fruits, and vegetables.

b. DHQ analysis is additionally adjusted for randomization.