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Nutrients from Fruit and Vegetable Consumption Reduce the Risk of Pancreatic Cancer

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Abstract

Purpose—Pancreatic cancer is a devastating disease for which the role of dietary factors remains inconclusive. Our objective was to evaluate the risk of pancreatic cancer associated with nutrients found in fruits and vegetables and nutrient supplementation using a clinic-based case-control design.

Methods—Our study included 384 rapidly ascertained cases and 983 controls frequency-matched on age at time of recruitment (in 5-year increments), race, sex, and region of residence. All subjects provided demographic information and completed a 144-item food frequency questionnaire in which they reported no change to their diet within 5 years prior to entering the study. Logistic regression was used to calculate odds ratios (OR) and 95% CIs, adjusted for age, sex, smoking, body mass index, energy intake, and alcohol consumption.

Results—Results show a significant (trend p-value < 0.05) inverse association between pancreatic cancer and nutrient/supplement groupings in a dose-dependent manner including magnesium, potassium, selenium, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin, niacin, total alpha-tocopherol, total vitamin A activity, vitamin B6, and vitamin C. Adjusting for diabetes or total sugar intake did not result in significant changes.

Conclusion—We conclude that most nutrients obtained through consumption of fruits and vegetables may reduce the risk of developing pancreatic cancer.

Keywords

Pancreatic Cancer; Diet; Nutrients; Case-control; Fruits; Vegetables

Worldwide, the age-standardized incidence rate of pancreatic cancer is $4.5/10^5$ for males and $3.3/10^5$ for females, with the age-standardized mortality rate of $4.3/10^5$ and $3.1/10^5$, respectively. [1] In the United States, the estimates are higher with 43,920 new cases of pancreatic cancer and 37,390 deaths are predicted for 2012. [2] Generally, the disease is

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diagnosed at a late stage [3] and prognosis is extremely poor with 1-year and 5-year survival rates of 25% and 4%, respectively. [4] Given the rarity of disease, general population screening for pancreatic cancer is unfeasible. Therefore, one important strategy at present is to focus on modifiable risk factor identification as a prevention strategy.

For macronutrients, the evidence from both case-control and adequately powered cohort studies remains inconclusive. Several case-control studies [5–8] and one cohort study [9] have reported decreased risk of pancreatic cancer associated with nutrients commonly found in fruits and vegetables (e.g., vitamin C and carotenoids). Antioxidant vitamins and minerals such as vitamin C, selenium, and beta-carotene have been proposed to have many potential modes of action, including reducing oxidative DNA damage and genetic mutation, [10, 11] suggesting their protective potential. Reports of associations between pancreatic cancer and nutrient intake from food alone have been inconsistent, [7, 12, 13] with high supplemental (not food derived) intake (e.g., vitamin C [14, 15]) of these vitamins being associated with a reduced risk.

Our objective was to evaluate nutrients obtained from fruit and vegetable consumption along with supplementation for their association with pancreatic cancer using a clinic-based case-control design. The method of rapid ascertainment of cases used in this study is advantageous as the questionnaire was self-completed around the time of recruitment, which was usually at the time of diagnosis of cancer. This contrasts with population-based case-control studies that often experience a 6-month delay between diagnosis and study enrollment, during which as many as 40% of patients may succumb to the cancer. Therefore, our study likely captures a more representative sample of newly diagnosed pancreatic cancer patients.

MATERIALS AND METHODS

Study population description

This study was approved by the Mayo Clinic Institutional Review Board. The study population is described in detail elsewhere. [16] Briefly, 1,648 (66.6%) of the cases approached from May 2004 to December 2009 were consented to participate in a prospective registry at the time of their Mayo Clinic visit using a rapid ascertainment method described elsewhere. [17] Controls from Mayo Clinic primary care were frequency-matched to cases on age at time of recruitment (in 5-year increments), race, sex, and region of residence (Olmsted County; three-state (MN, WI, IA); or outside of area). Controls with prior diagnoses of cancer except non-melanoma skin cancer were excluded.

Dietary data from FFQ

Participants were also asked to complete a 144-item food frequency questionnaire (FFQ) to address possible dietary causes of pancreatic cancer. Details are given in our previous report. [16] Briefly, the National Cancer Institute (NCI) software DietCalc [18] was used to estimate average nutrient intake and average supplement use was gathered from the survey questions for the 5 years prior to enrollment. FFQs were returned by 816 cases of adenocarcinoma pancreatic cancer and 1,290 controls. Individuals were excluded from this analysis if they answered affirmatively or failed to answer the question, “Have you recently changed your diet?” and if the change occurred within the previous 5 years (cases: n=420; controls n=286). No individuals were found to have an extreme daily energy intake requiring exclusion; however, we excluded individuals who did not answer 17 or more items (cases: n=12; controls n=21). Therefore, 384 cases and 983 controls composed the final study sample.

Statistical analysis

Median, mean and range of intake of nutrients were separately calculated for cases and controls. In general, sex-specific quintiles based on the control population were calculated using the density method for energy-adjusted nutrients [19] to investigate associations with pancreatic cancer and nutrient categories are presented as per 1,000 kcal. Logistic regression was used to calculate odds ratios (OR) and 95% CIs adjusting for age, sex, smoking (ever/never), BMI, energy intake (per 1000 kcal) and number of drinks of alcohol per week. In order to test the null hypothesis of no linear trend in pancreatic cancer risk across quintiles of intake, an appropriate linear contrast vector (i.e. -2,-1,0,1,2) was used within the logistic regression model. All tests of statistical significance were 2-sided and *P*-values< 0.05 were considered significant. All analyses were generated using SAS® software (Version (9.2)). [20]

RESULTS

In our study, cases were more likely to be male, be slightly older, and have ever smoked (and if a past smoker, had quit more recently). Cases were more likely to have a personal history of pancreatitis or diabetes (especially recent onset (< 3 years); Table 1) compared to controls. Usual BMI was similar between cases and controls. When comparing male and female cases (not shown), males were slightly younger, had a higher usual BMI, were more likely to have ever smoked (difference seen mostly among ex-smokers), and were more likely to have a personal history of pancreatitis or diabetes (especially in the category diagnosed greater than 3 years before pancreatic cancer). We have previously compared the demographic characteristics of those who did and did not complete the questionnaire after recruitment and determined the two groups were similar.[16]

Several of the nutrient categories were highly correlated (Pearson's $r^2 \geq 0.80$) such as, Magnesium and Potassium (0.85), Beta-Carotene and Lutein and Zeaxanthin (0.82), Beta-Cryptoxanthin and Vitamin C, and, Thiamin and Vitamin B6 (0.82). The high correlation among these categories suggests that determining which nutrient (or what combination) may be responsible for the association is difficult in this study.

Table 2 shows the number of cases and median value ranges of nutrients for each sex, OR and 95% CI, along with trend test of OR across quintiles which were constructed using the control population values for each sex. Associations between nutrient groupings and pancreatic cancer were determined using a multivariable logistic regression model that adjusted for age, sex, energy (per 1000 kcal), BMI, cigarette smoking status (ever/never smoked), and drinks of alcohol per week, and compared each quintile to the reference (low consumption). Significant results (whether highest quintile was significantly different from low consumption (first quintile) and/or test for trend, p-value <0.05) for an inverse association between pancreatic cancer and nutrients (OR [95% CI]) were: magnesium (0.30[0.19,0.46]), potassium (0.36[0.23,0.55]), selenium (0.65[0.45,0.95]), alpha-carotene (0.52[0.35,0.77]), beta-carotene (0.42[0.28,0.63]), beta-cryptoxanthin (0.55[0.37,0.82]), lutein and zeaxanthin (0.46[0.31,0.70]), niacin (0.52[0.35,0.77]), total alpha-tocopherol (0.52[0.34,0.79]), total vitamin A activity (0.55[0.37,0.81]), vitamin B6 (0.49[0.33,0.72]), and vitamin C (0.51[0.34,0.76]).

We examined eight nutrient supplements for associations with pancreatic cancer using a multivariable logistic regression model with adjustments as stated above. Table 3 lists the number of cases and median supplement value ranges of supplements for each sex, OR and 95% CI, along with trend test of OR for zero and non-zero categories. Most of the supplements investigated were significantly associated with a decreased risk of pancreatic cancer (p-trend < 0.05) including: beta-carotene, niacin, thiamin, vitamin A, and vitamin B6.

Because diabetes is a known risk factor for pancreatic cancer and because diabetics are advised to modify their diet, we investigated whether adding diabetes (categorized as no diabetes, diabetes diagnosis less than 3 years prior to completing questionnaire, or diabetes diagnosis 3 years or more prior to questionnaire) to our logistic model would significantly change our results. We did not find any nutrient categories which changed in significance for trend p-value (results not shown).

Total sugar intake was considered as a possible confounder for our fruit and vegetable food groupings and was adjusted for in a version of the presented model. This adjustment only resulted in two changes in significance to the trend p-value for the nutrients total vitamin A activity (from 0.0280 to 0.0628) and selenium (from 0.0050 to 0.0971; results not shown).

A sensitivity analysis was conducted (not shown) to determine the impact of failure to exclude those who reported a diet change within the last 5 years. When trying to identify risk factors that cause disease, it could be important to exclude those with a diet change likely related to pancreatic adenocarcinoma. There was one nutrient which changed significance when we included those reporting a recent diet change in the analysis (total alpha-tocopherol: from 0.03 to 0.09). Among male cases who reported a recent diet change, the median values for total energy intake and all nutrients except lycopene, potassium, and magnesium increased or remained the same; among controls the median values for every category but selenium, lycopene, and total vitamin A activity increased or remained the same. Among female cases, the median values decreased for all nutrients except magnesium, lycopene, niacin, and thiamin; among controls the median values for every category increased except magnesium, potassium, beta-carotene, beta-cryptoxanthin, and thiamin. These observed changes reinforce our decision to exclude those who reported a recent diet change.

DISCUSSION

In this study, we found that most of the nutrients contained in fruits and vegetables and their supplements are associated with a reduced risk of pancreatic cancer. Cases were on average more likely to be older, male, have ever smoked, and have a personal history of pancreatitis or diabetes compared to controls. While some of these risk factors have been consistently associated with risk of pancreatic cancer across different study designs (smoking, BMI, diabetes, and age), others such as dietary intake have been largely inconsistent. Variable study designs and ascertainment bias may partially explain the inconsistencies.

Currently, one of the main hypotheses as to how an individual's dietary intake could influence pancreatic cancer development and progression involves dietary components affecting insulin insensitivity or insulin resistance pathways. Pre-diagnostic plasma glucose, [21, 22] insulin, [23, 24] and plasma C-peptide levels [25] have also been associated with increased risk of pancreatic cancer. Hyperinsulinemia, a result of insulin insensitivity, has been shown to increase local circulation and cell division within the pancreas. [22, 23] Pancreatic exocrine cells are estimated to be exposed to very high insulin concentrations and evidence indicates that insulin acts as a growth promoter and mutagen in the pancreas, [26, 27] potentially leading to pancreatic tumor promotion. [28] Furthermore, recent observational studies of pancreatic cancer suggest that glucose intolerance, insulin resistance, and high insulin concentrations (which increase insulin-like growth factor (IGF) levels by reducing levels of IGF-binding proteins or activating IGF receptors) may play a role in carcinogenesis, [29] even without a diagnosis of diabetes mellitus. [23] Because insulin is secreted into the blood in response to elevated blood glucose concentrations and the fact that the pancreas is exposed to much higher insulin concentrations compared to the blood, pancreatic cancer risk may increase due to dietary factors that create insulin spikes.

In animal studies, a magnesium–deficient diet has been shown to cause impaired insulin secretion and action [30] and elevated C-reactive protein concentrations. [31] Also, magnesium supplementation has been shown to lower type 2 diabetes [32] and systemic inflammation. [33] Human studies have supported the observations for benefit of supplementation on glucose metabolism and/or insulin sensitivity [34, 35] and high magnesium intake has been inversely associated with risk of type 2 diabetes. [30, 36] This suggests a possible indirect mechanism for reduced risk of pancreatic cancer and is reflected in our data. Additionally, there is a relationship between magnesium and type 2 diabetes after adjusting for type 2 diabetes; we found that the OR for dietary magnesium intake remained consistent and significantly inversely associated with pancreatic risk.

A second main hypothesis linking dietary intake with pancreatic cancer suggests that dietary components reduce DNA damage/mutations by reducing oxidative stress and inflammation. Overall, results of studies evaluating pancreatic cancer risk and nutrient intake from food have been mixed and limited. Although several case-control studies have reported a decreased risk associated with vitamin C intake, [5, 7, 12] other nutrients like beta-carotene and total carotenoids, [37] or high serum alpha-tocopherol concentration [38] have been inversely associated with risk only among never smokers, while carotenoid and lycopene were associated with a decreased risk of pancreatic cancer only in men. [6] The present study is consistent with evidence for a protective effect of nutrients associated with fruits and vegetables, as the intake of most nutrients indicate a dose-dependent risk reduction of pancreatic cancer development. Several nutrient supplements also showed a significant association with a reduced risk of pancreatic cancer, although sample size and intake variation were very restricted.

A possible suggested explanation for inconsistencies in reported dietary associations with pancreatic cancer could be unmeasured variation in inflammation genes or antioxidant metabolism genes (e.g., mitochondrial manganese superoxide dismutase (SOD2)). While significant inflammation gene results were not replicated in additional populations, [39] variation in genes of antioxidant pathways have been shown to be associated with pancreatic cancer risk. [40] Potential mechanisms of action of these nutrients include: 1) antioxidant protection against free-radical damage to DNA; 2) apoptosis (e.g., indole-3 carbinol in cruciferous vegetables); 3) enhancing immune function (e.g., carotenoids and vitamin C), [41]; 4) enhancing insulin-like growth factor (e.g., lycopene); 5) inhibiting cellular proliferation (e.g., carotenoids); and 6) ensuring proper DNA methylation and gene expression. [6, 42]

Serum levels of antioxidants have been positively associated with fruit and vegetable intake, [43] and these food items have been inversely associated with pancreatic cancer risk. [44, 45] Nonenzymatic dietary antioxidants (e.g., vitamin C and selenium) work together with enzymatic mechanisms to provide defense against oxidative stress. [46] The enzymatic mechanisms mainly include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and a few other relevant enzymes and proteins. [47] Under *in vitro* and *in vivo* conditions, overexpression of SOD2 suppresses cell growth or can reverse the malignant phenotype of pancreatic cancer. [48]

This clinic based case-control study has over 99% of the adenocarcinoma cases confirmed with pathology or medical record, avoiding misclassification of the case population. The unique recruitment protocol enabled rapid ascertainment of cases, increasing the probability of self completion and enrollment of cases at all stages of disease. We wanted to avoided reverse causation so we elected to exclude those individuals who reported a diet change in the 5 years prior to study entry. There are limitations that affect retrospective designs requiring participant recall of past events and behavior. Differential misclassification and recall of dietary patterns between cases and controls could contribute to biased risk

estimates. In these situations, cases compared to controls may differentially recall past behaviors and consumption patterns given time after diagnosis. However within this study, cases were rapidly enrolled at the time of diagnosis and completed the FFQ shortly after, potentially reducing the effect of such bias. In retrospective population-based studies of rapidly fatal disease, bias can occur due to demise of eligible cases (with a higher proportion of later stage disease), possibly resulting in non-random non-response. Of those consented, FFQs were returned by 49.5% of the cases and 85.2% of the controls. The excluded groups could have a different dietary intake pattern than those included in the study which would change results reported here. However, distributions of the clinical characteristics in those with and those without an FFQ proportions were similar. [16] Given our reduced sample size after exclusions, the power to detect associations is reduced.

There were individuals who did not answer portions of the FFQ, which could have biased reported results if missing values differed by case status. However, we found the absolute difference in percent of missing responses between cases and controls averaged less than 1%. Since smoking was only crudely controlled for in our study, residual confounding is a possibility, although a sensitivity analysis we conducted (not shown) provides evidence against it.

In conclusion, our study suggests that nutrients obtained from eating a diet high in fruits and vegetables (and to a lesser degree nutrient supplements) are associated with decreased risk of developing pancreatic cancer, and that this reduction occurs in a dose dependent manner. While this analysis of specific nutrients can provide potential targeted intervention and pathways to investigate, it is important to remember that single dietary items are generally not consumed in isolation. Although the exact mechanism is uncertain, our results highly suggest that eating fruits and vegetables and their corresponding nutrients will reduce the risk of developing pancreatic adenocarcinomas. It is essential from a prevention standpoint to promote a diet rich fruits and vegetables which contain numerous potentially beneficial nutrients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OR	odds ratios
CI	confidence interval
FFQ	food frequency questionnaire
NCI	National Cancer Institute
IGF	insulin-like growth factor
SOD2	mitochondrial manganese superoxide dismutase
CAT	catalase

GPX glutathione peroxidase

References

1. Ferlay, J.; Shin, H.; Bray, F.; Forman, D.; Mathers, C.; Parkin, D. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr [accessed on 18/11/2011]
2. American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; [Accessed March 3, 2012]
3. Chari ST. Detecting early pancreatic cancer: problems and prospects. Seminars in oncology. 2007; 34:284–94. [PubMed: 17674956]
4. Klapman J, Malafa MP. Early detection of pancreatic cancer: why, who, and how to screen. Cancer Control. 2008; 15:280–7. [PubMed: 18813195]
5. Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, Simard A, Baillargeon J, de Waard F, Przewozniak K, et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. International journal of cancer. 1992; 51:365–72.
6. Nkondjock A, Ghadirian P, Johnson KC, Krewski D. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. The Journal of nutrition. 2005; 135:592–7. [PubMed: 15735099]
7. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. Cancer Causes Control. 1991; 2:291–7. [PubMed: 1932541]
8. Ghadirian P, Simard A, Baillargeon J, Maisonneuve P, Boyle P. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. International journal of cancer. 1991; 47:1–6.
9. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, Hartman TJ, Tangrea JA, Rautalahti M, Sehlub J, Virtamo J, Taylor PR. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. Journal of the National Cancer Institute. 1999; 91:535–41. [PubMed: 10088624]
10. Foksinski M, Gackowski D, Rozalski R, Siomek A, Guz J, Szpila A, Dziaman T, Olinski R. Effects of basal level of antioxidants on oxidative DNA damage in humans. European journal of nutrition. 2007; 46:174–80. [PubMed: 17265170]
11. Morales E, Porta M, Vioque J, Lopez T, Mendez MA, Pumarega J, Malats N, Crous-Bou M, Ngo J, Rifa J, Carrato A, Guarner L, et al. Food and nutrient intakes and K-ras mutations in exocrine pancreatic cancer. Journal of epidemiology and community health. 2007; 61:641–9. [PubMed: 17568059]
12. Lin Y, Tamakoshi A, Hayakawa T, Naruse S, Kitagawa M, Ohno Y. Nutritional factors and risk of pancreatic cancer: a population-based case-control study based on direct interview in Japan. Journal of gastroenterology. 2005; 40:297–301. [PubMed: 15830290]
13. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. American journal of epidemiology. 2002; 155:783–92. [PubMed: 11978580]
14. Anderson LN, Cotterchio M, Gallinger S. Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada. Cancer Causes Control. 2009; 20:825–34. [PubMed: 19194662]
15. Silverman DT, Swanson CA, Gridley G, Wacholder S, Greenberg RS, Brown LM, Hayes RB, Swanson GM, Schoenberg JB, Pottern LM, Schwartz AG, Fraumeni JF Jr, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. Journal of the National Cancer Institute. 1998; 90:1710–9. [PubMed: 9827525]
16. Jansen RJ, Robinson DP, Stolzenberg-Solomon RZ, Bamlet WR, de Andrade M, Oberg AL, Hammer TJ, Rabe KG, Anderson KE, Olson JE, Sinha R, Petersen GM. Fruit and vegetable

consumption is inversely associated with having pancreatic cancer. Cancer Causes Control. 2011; 22:1613–25. [PubMed: 21915615]

17. Wang L, Bamlet WR, de Andrade M, Boardman LA, Cunningham JM, Thibodeau SN, Petersen GM. Mitochondrial genetic polymorphisms and pancreatic cancer risk. Cancer Epidemiol Biomarkers Prev. 2007; 16:1455–9. [PubMed: 17627010]
18. Applied Research Program. National Cancer Institute; Nov. 2005 Diet*Calc Analysis Program, Version 1.4.3.
19. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. American journal of epidemiology. 1986; 124:17–27. [PubMed: 3521261]
20. SAS® software Version [] of the SAS System for Unix Version [] Cary, NC, USA: Copyright © [] SAS Institute Inc.:SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
21. Stattin P, Bjor O, Ferrari P, Lukanova A, Lenner P, Lindahl B, Hallmans G, Kaaks R. Prospective study of hyperglycemia and cancer risk. Diabetes care. 2007; 30:561–7. [PubMed: 17327321]
22. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. Jama. 2000; 283:2552–8. [PubMed: 10815119]
23. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. Jama. 2005; 294:2872–8. [PubMed: 16352795]
24. McCarty MF. Insulin secretion as a determinant of pancreatic cancer risk. Medical hypotheses. 2001; 57:146–50. [PubMed: 11461162]
25. Michaud DS, Wolpin B, Giovannucci E, Liu S, Cochrane B, Manson JE, Pollak MN, Ma J, Fuchs CS. Prediagnostic plasma C-peptide and pancreatic cancer risk in men and women. Cancer Epidemiol Biomarkers Prev. 2007; 16:2101–9. [PubMed: 17905943]
26. Fisher WE, Boros LG, Schirmer WJ. Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumors. The Journal of surgical research. 1996; 63:310–3. [PubMed: 8661216]
27. Kazakoff K, Cardesa T, Liu J, Adrian TE, Bagchi D, Bagchi M, Birt DF, Pour PM. Effects of voluntary physical exercise on high-fat diet-promoted pancreatic carcinogenesis in the hamster model. Nutrition and cancer. 1996; 26:265–79. [PubMed: 8910909]
28. Zagorsky JL. Health and wealth. The late-20th century obesity epidemic in the U. S. Economics and human biology. 2005; 3:296–313. [PubMed: 15941679]
29. Giovannucci E. Nutrition, insulin, insulin-like growth factors and cancer. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2003; 35:694–704. [PubMed: 14710348]
30. Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE, Hu FB. Magnesium intake and risk of type 2 diabetes in men and women. Diabetes care. 2004; 27:134–40. [PubMed: 14693979]
31. Guerrero-Romero F, Rodriguez-Moran M. Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. Int J Obes Relat Metab Disord. 2002; 26:469–74. [PubMed: 12075573]
32. Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL. Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. The American journal of physiology. 1995; 269:E745–52. [PubMed: 7485490]
33. Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. The American journal of clinical nutrition. 2007; 85:1068–74. [PubMed: 17413107]
34. Paolisso G, Scheen A, Cozzolino D, Di Maro G, Varricchio M, D'Onofrio F, Lefebvre PJ. Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. The Journal of clinical endocrinology and metabolism. 1994; 78:1510–4. [PubMed: 8200955]
35. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. Diabetes care. 2003; 26:1147–52. [PubMed: 12663588]

36. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. Journal of internal medicine. 2007; 262:208–14. [PubMed: 17645588]
37. Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. Cancer Epidemiol Biomarkers Prev. 2005; 14:2093–7. [PubMed: 16172215]
38. Stolzenberg-Solomon RZ, Sheffler-Collins S, Weinstein S, Garabrant DH, Mannisto S, Taylor P, Virtamo J, Albanes D. Vitamin E intake, alpha-tocopherol status, and pancreatic cancer in a cohort of male smokers. The American journal of clinical nutrition. 2009; 89:584–91. [PubMed: 19116326]
39. Reid-Lombardo KM, Fridley BL, Bamlet WR, Cunningham JM, Sarr MG, Petersen GM. Inflammation-related gene variants as risk factors for pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 20:1251–4. [PubMed: 21467233]
40. Wheatley-Price P, Asomaning K, Reid A, Zhai R, Su L, Zhou W, Zhu A, Ryan DP, Christiani DC, Liu G. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma. Cancer. 2008; 112:1037–42. [PubMed: 18205184]
41. Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Annals of nutrition & metabolism. 2006; 50:85–94. [PubMed: 16373990]
42. McCullough ML, Giovannucci EL. Diet and cancer prevention. Oncogene. 2004; 23:6349–64. [PubMed: 15322510]
43. Dauchet L, Peneau S, Bertrais S, Vergnaud AC, Estaquio C, Kesse-Guyot E, Czernichow S, Favier A, Faure H, Galan P, Hercberg S. Relationships between different types of fruit and vegetable consumption and serum concentrations of antioxidant vitamins. The British journal of nutrition. 2008; 100:633–41. [PubMed: 18279554]
44. Nkondjock A, Krewski D, Johnson KC, Ghadirian P. Dietary patterns and risk of pancreatic cancer. International journal of cancer. 2005; 114:817–23.
45. Inoue M, Tajima K, Takezaki T, Hamajima N, Hirose K, Ito H, Tominaga S. Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). International journal of epidemiology. 2003; 32:257–62. [PubMed: 12714546]
46. Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, oxidative stress, and antioxidants: a review. Journal of biochemical and molecular toxicology. 2003; 17:24–38. [PubMed: 12616644]
47. Cullen JJ, Mitros FA, Oberley LW. Expression of antioxidant enzymes in diseases of the human pancreas: another link between chronic pancreatitis and pancreatic cancer. Pancreas. 2003; 26:23–7. [PubMed: 12499913]
48. Ough M, Lewis A, Zhang Y, Hinkhouse MM, Ritchie JM, Oberley LW, Cullen JJ. Inhibition of cell growth by overexpression of manganese superoxide dismutase (MnSOD) in human pancreatic carcinoma. Free radical research. 2004; 38:1223–33. [PubMed: 15621700]

Table 1

Characteristics of pancreatic adenocarcinoma cases and controls used in the analysis (no recent diet change).

	Cases (N=384)	Controls (N=983)
Sex		
Female	163 (42.4%)	500 (50.9%)
Male	221 (57.6%)	483 (49.1%)
Age when approached		
Mean (SD)	67.0 (10.52)	65.8 (10.86)
Median	67.0	67.0
Q1, Q3	60.0, 75.0	59.0, 74.0
Range	(31.0–92.0)	(24.0–94.0)
Diabetes Mellitus Type 2		
Yes	167 (43.5%)	68 (6.9%)
Onset ≥ 3 years ago	35 (9.1%)	43 (4.4%)
Onset < 3 years ago	120 (31.3%)	21 (2.1%)
Missing	12 (3.3%)	4 (0.0%)
No	214 (55.7%)	914 (93.0%)
Missing	3 (0.8%)	1 (0.1%)
Race		
American Indian/Alaskan Native	0 (0%)	4 (0.4%)
Asian/Asian-American	3 (0.8%)	8 (0.8%)
Black/African American	4 (1%)	1 (0.1%)
White/Caucasian	373 (97.1%)	966 (98.3%)
Multiracial	4 (1%)	4 (0.4%)
Smoking		
Current	59 (15.4%)	37 (3.8%)
Former	163 (42.4%)	402 (40.9%)
Quit < 10 years ago	20 (12.3%)	34 (8.5%)
Quit 10+ years ago	141 (86.5%)	361 (89.8%)
Missing	2 (1.2%)	7 (1.7%)
Never	160 (41.7%)	539 (54.8%)
Missing	2 (0.5%)	5 (0.5%)
Usual BMI[a]		
Mean (SD)	27.6 (5.31)	26.7 (4.24)
Median	26.8	26.3
Q1, Q3	24.0, 30.3	23.7, 29.0
Range	(15.3–53.0)	(14.0–49.0)
Alcohol (drinks/week)		
Mean (SD)	0.8 (1.46)	0.8 (1.20)
Median	0.3	0.3
Q1, Q3	0.1, 1.0	0.1, 1.0
Range	(0.0–11.3)	(0.0–11.3)

Abbreviations: SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile; Range (minimum-maximum)

[a]Analyzed: cases = 379(98.7%) and controls = 954(97.1%).

Table 2

Number of Cases and Median Nutrient Intake (Range) for Each Sex. Odds Ratios With 95% Confidence Interval for Pancreatic Cancer Risk Generated by Constructing Quintiles of Intakes Based on Controls Within Each Sex.

	Quintile					
	1	2	3	4	5	Trend p-val*
Magnesium (mg/1000 kcal)						
Cases (M/F)	120 (65/55)	89 (53/36)	59 (27/32)	72 (50/22)	44 (26/18)	<.0001
Odds Ratio (95% CI)	1.00 (ref)	0.76 (0.53,1.08)	0.50 (0.34,0.73)	0.61 (0.42,0.89)	0.30 (0.19,0.46)	
Males: Median (Range)	149.6 (46.82–164.82)	178.26 (164.84–189.14)	197.59 (189.21–205.39)	218.39 (205.53–233.97)	254.44 (234.32–430.5)	
Female: Median (Range)	159.75 (64.39–178.02)	188.12 (178.21–197.87)	209 (198.08–221.27)	231.05 (221.39–242.7)	262.66 (242.77–629.09)	
Potassium (mg/1000 kcal)						
Cases (M/F)	103 (59/44)	90 (44/46)	67 (36/31)	74 (50/24)	50 (32/18)	<.0001
Odds Ratio (95% CI)	1.00 (ref)	0.91 (0.63,1.30)	0.63 (0.43,0.92)	0.65 (0.44,0.95)	0.36 (0.23,0.55)	
Males: Median (Range)	1428.95 (371.38–1573.24)	1685.2 (1573.85–1782.51)	1874.53 (1783.26–1956.03)	2062.73 (1958.1– 2234.83)	2466.87 (2236.52–4401.3)	
Female: Median (Range)	1541.74 (546.56–1694.34)	1804.99 (1699.29–1923.37)	2031.48 (1923.8– 2146.08)	2242.12 (2148.12–2390.96)	2589.44 (2395.28–6246.06)	
Selenium (mcg/1000 kcal)						
Cases (M/F)	117 (68/49)	73 (47/26)	69 (42/27)	49 (22/27)	76 (42/34)	0.005
Odds Ratio (95% CI)	1.00 (ref)	0.66 (0.46,0.96)	0.60 (0.42,0.88)	0.45 (0.30,0.68)	0.65 (0.45,0.95)	
Males: Median (Range)	42.1 (21.01–46.58)	49.55 (46.63–51.72)	54.41 (51.76–57.11)	59.14 (57.11–61.96)	66.45 (62.05–87.9)	
Female: Median (Range)	41.18 (19.58–45.39)	48.04 (45.43–50.32)	52.47 (50.35–54.25)	56.35 (54.31–59.06)	64.14 (59.1–88.66)	
Alpha-Carotene (mcg/1000 kcal)						
Cases (M/F)	115 (65/50)	89 (57/32)	68 (35/33)	56 (32/24)	56 (32/24)	0.0002
Odds Ratio (95% CI)	1.00 (ref)	0.74 (0.52,1.05)	0.61 (0.42,0.89)	0.51 (0.35,0.76)	0.52 (0.35,0.77)	
Males: Median (Range)	119.57 (14.99–163.08)	199.67 (163.43–244.31)	280.16 (244.37–322.05)	386.08 (322.39–464.26)	591.75 (466.3–1640.25)	
Female: Median (Range)	171.33 (38.98–213.55)	253.38 (213.87–295.96)	358.32 (296.26–415.51)	502.43 (417.64–616.4)	756.7 (616.91–4298.54)	
Beta-Carotene (mcg/1000 kcal)						
Cases (M/F)	116 (69/47)	96 (62/34)	62 (29/33)	66 (37/29)	44 (24/20)	<.0001
Odds Ratio (95% CI)	1.00 (ref)	0.83 (0.59,1.18)	0.55 (0.38,0.81)	0.60 (0.41,0.88)	0.42 (0.28,0.63)	
Males: Median (Range)	633.56 (96.53–786.75)	974.9 (787.43–1130.49)	1272.27 (1131.92–1436.65)	1750.77 (1438.54–2068.35)	2665.65 (2072.85–13001.63	
Female: Median (Range)	858.26 (325.73–1055.86)	1240.34 (1057.23–1384.12)	1635.69 (1387.77–1817.68)	2108.66 (1818.52–2525.26)	3411.53 (2533.31–11628.02	
Beta-Cryptoxanthin (mcg/1000 kcal)						
Cases (M/F)	113 (59/54)	71 (50/21)	67 (37/30)	70 (40/30)	63 (35/28)	0.01

	Quintile					
	1	2	3	4	5	Trend p-val*
Odds Ratio (95% CI)	1.00 (ref)	0.66 (0.45,0.96)	0.72 (0.49,1.05)	0.68 (0.46,0.99)	0.55 (0.37,0.82)	
Males: Median (Range)	28.33 (4.32–37.57)	46.9 (37.64–60.71)	72.99 (60.75–87.98)	105.73 (88.21–125.78)	152.38 (125.9–462.23)	
Female: Median (Range)	41.17 (4.52–53.94)	66.77 (54.17–78.37)	92.95 (78.92–107.82)	125.14 (108.73–149.71)	185.48 (150.31–501.81)	
Lutein and Zeaxanthin (mcg/1000 kcal)						
Cases (M/F)	112 (64/48)	95 (57/38)	70 (45/25)	61 (27/34)	46 (28/18)	<.0001
Odds Ratio (95% CI)	1.00 (ref)	0.90 (0.63,1.28)	0.70 (0.48,1.02)	0.59 (0.40,0.86)	0.46 (0.31,0.70)	
Males: Median (Range)	536.59 (67.23–656.04)	747.34 (656.17–877.85)	981.68 (880.28–1142.48)	1294.46 (1145.8–1628.47)	2323.18 (1628.52–15073.02	
Female: Median (Range)	674.23 (229.75–807.03)	914.44 (808.5–1031.48)	1138.82 (1035.63–1285.24)	1482.81 (1286.54–1841.91)	2692.03 (1842.56–15270.64	
Lycopene (mcg/1000 kcal)						
Cases (M/F)	80 (41/39)	77 (45/32)	84 (54/30)	79 (52/27)	64 (29/35)	0.24
Odds Ratio (95% CI)	1.00 (ref)	1.03 (0.70,1.51)	1.10 (0.75,1.62)	1.04 (0.71,1.54)	0.76 (0.51,1.13)	
Males: Median (Range)	1459.42 (352.79–1806.11)	2152.15 (1806.35–2466.99)	2843.29 (2469.69–3225.06)	3773.27 (3226.49–4764.45)	7021.8 (4774.28–59722.11)	
Female: Median (Range)	1662.35 (603.88–2053.85)	2358.49 (2060.72–2676.34)	3061.57 (2678.27–3389.31)	3825.05 (3393.41–4621.12)	6434.63 (4638.99–36818.75	
Niacin (mg/1000 kcal)						
Cases (M/F)	97 (52/45)	96 (56/40)	51 (29/22)	82 (53/29)	58 (31/27)	0.0005
Odds Ratio (95% CI)	1.00 (ref)	0.98 (0.68,1.41)	0.50 (0.33,0.75)	0.75 (0.52,1.09)	0.52 (0.35,0.77)	
Males: Median (Range)	9.78 (3.36–10.66)	11.47 (10.67–12.07)	12.66 (12.09–13.29)	14.17 (13.29–15.35)	16.85 (15.35–37.11)	
Female: Median (Range)	9.97 (6.61–10.88)	11.59 (10.9–12.19)	12.71 (12.19–13.54)	14.36 (13.54–15.39)	16.93 (15.4–40.08)	
Thiamin (mg/1000 kcal)						
Cases (M/F)	99 (60/39)	76 (43/33)	64 (36/28)	78 (39/39)	67 (43/24)	0.08
Odds Ratio (95% CI)	1.00 (ref)	0.80 (0.55,1.16)	0.70 (0.48,1.04)	0.81 (0.55,1.20)	0.66 (0.44,0.99)	
Males: Median (Range)	0.66 (0.23–0.72)	0.77 (0.72–0.81)	0.84 (0.81–0.88)	0.93 (0.88–0.99)	1.12 (0.99–2.5)	
Female: Median (Range)	0.7 (0.21–0.76)	0.82 (0.76–0.86)	0.89 (0.86–0.93)	0.98 (0.93–1.05)	1.17 (1.05–2.76)	
Total Alpha-Tocopherol (mg/1000 kcal)						
Cases (M/F)	101 (67/34)	83 (46/37)	83 (48/35)	69 (34/35)	48 (26/22)	0.004
Odds Ratio (95% CI)	1.00 (ref)	0.81 (0.56,1.18)	0.95 (0.65,1.37)	0.76 (0.52,1.11)	0.52 (0.34,0.79)	
Males: Median (Range)	2.78 (0.6–3.08)	3.3 (3.08–3.54)	3.81 (3.54–4.15)	4.48 (4.15–5)	5.9 (5–18.46)	
Female: Median (Range)	3.04 (1.29–3.39)	3.71 (3.41–4.03)	4.42 (4.04–4.83)	5.46 (4.83–6.29)	7.81 (6.3–20.83)	
Total Vitamin A Activity (mcg RAE/1000 kcal)						
Cases (M/F)	108 (61/47)	73 (44/29)	58 (39/19)	83 (38/45)	62 (39/23)	0.03

	Quintile					
	1	**2**	**3**	**4**	**5**	**Trend p-val***
Odds Ratio (95% CI)	1.00 (ref)	0.66 (0.45,0.96)	0.59 (0.40,0.87)	0.82 (0.57,1.18)	0.55 (0.37,0.81)	
Males: Median (Range)	247.04 (69.08–289.87)	322.46 (290.56–350.48)	379.04 (351.06–410.39)	441.05 (410.77–491.25)	580.14 (491.54–1491.48)	
Female: Median (Range)	261.64 (76.67–318.08)	363.06 (319.02–392.67)	429.54 (392.93–453.18)	493.64 (453.46–547.76)	623.54 (548.75–1284.03)	
Vitamin B6 (mg/1000 kcal)						
Cases (M/F)	121 (73/48)	67 (40/27)	74 (42/32)	60 (37/23)	62 (29/33)	0.0005
Odds Ratio (95% CI)	1.00 (ref)	0.55 (0.38,0.80)	0.63 (0.44,0.91)	0.49 (0.33,0.72)	0.49 (0.33,0.72)	
Males: Median (Range)	0.83 (0.26–0.93)	0.98 (0.93–1.04)	1.1 (1.04–1.18)	1.26 (1.18–1.35)	1.5 (1.35–3.71)	
Female: Median (Range)	0.86 (0.41–0.99)	1.06 (0.99–1.12)	1.18 (1.12–1.26)	1.34 (1.26–1.42)	1.61 (1.42–3.81)	
Vitamin C (mg/1000 kcal)						
Cases (M/F)	108 (65/43)	84 (54/30)	77 (44/33)	57 (26/31)	58 (32/26)	0.0001
Odds Ratio (95% CI)	1.00 (ref)	0.83 (0.57,1.19)	0.73 (0.50,1.07)	0.53 (0.36,0.80)	0.51 (0.34,0.76)	
Males: Median (Range)	32.79 (8.14–42.79)	51.7 (42.84–59.53)	68.09 (59.62–77.09)	86.98 (77.14–99.02)	116.58 (99.18–301.49)	
Female: Median (Range)	40.95 (11.82–52.32)	59.37 (52.36–68.72)	78.29 (69.35–87.49)	100.02 (87.95–114.75)	140.55 (115.07–284.64)	

g = grams; svg = servings; kcal = kilocalories; mg = milligrams; mcg = micrograms

*Using a logistic model adjusted for energy, smoking, BMI, age, sex, and drinks of alcohol per week

Table 3

Number of Cases and Median Supplement Intake (Range) for Each Sex and Odds Ratios With 95% Confidence Interval for Pancreatic Cancer Risk Generated by Constructing Zero and Non-zero Intakes Based on Controls Within Each Sex.

	Zero Intake	Non-zero Intake	Trend p-value*
Supplements: Magnesium (mg/day)			
Cases (M/F)	213 (134/79)	171 (87/84)	0.08
Odds Ratio (95% CI)	1.00 (ref)	0.80 (0.63–1.02)	
Males: Median (Range)	0	100.00 (1.64–100.00)	
Female: Median (Range)	0	100.00 (1.64–100.00)	
Supplements: Selenium (mcg/day)			
Cases (M/F)	373 (215/158)	11 (6/5)	0.14
Odds Ratio (95% CI)	1.00 (ref)	0.60 (0.31–1.19)	
Males: Median (Range)	0	42.86 (0.00–42.86)	
Female: Median (Range)	0	42.86 (0.00–42.86)	
Supplements: Beta-Carotene (mcg/day)			
Cases (M/F)	175 (108/67)	209 (113/96)	0.02
Odds Ratio (95% CI)	1.00 (ref)	0.75 (0.58–0.96)	
Males: Median (Range)	0	600.00 (8.21–3100.00)	
Female: Median (Range)	0	600.00 (9.86–3100.00)	
Supplements: Niacin (mg/day)			
Cases (M/F)	169 (106/63)	215 (115/100)	0.03
Odds Ratio (95% CI)	1.00 (ref)	0.76 (0.59–0.98)	
Males: Median (Range)	0	20.00 (0.33–84.29)	
Female: Median (Range)	0	20.00 (0.33–84.29)	
Supplements: Thiamin (mg/day)			
Cases (M/F)	171 (106/65)	213 (115/98)	0.04
Odds Ratio (95% CI)	1.00 (ref)	0.77 (0.60–0.98)	
Males: Median (Range)	0	1.50 (0.02–7.93)	
Female: Median (Range)	0	1.50 (0.02–7.93)	
Supplements: Vitamin A (mcg/day)			
Cases (M/F)	171 (105/66)	213 (116/97)	0.04
Odds Ratio (95% CI)	1.00 (ref)	0.79 (0.62–1.01)	
Males: Median (Range)	0	1500.00 (24.64–9000.00)	
Female: Median (Range)	0	1500.00 (24.64–9000.00)	
Supplements: Vitamin B6 (mg/day)			
Cases (M/F)	167 (104/63)	217 (117/100)	0.05
Odds Ratio (95% CI)	1.00 (ref)	0.78 (0.61–1.00)	
Males: Median (Range)	0	2.00 (0.03–66.29)	
Female: Median (Range)	0	2.00 (0.03–66.29)	

	Zero Intake	Non-zero Intake	Trend p-value*
Supplements: Vitamin C (mg/day)			
Cases (M/F)	135 (86/49)	249 (135/114)	0.05
Odds Ratio (95% CI)	1.00 (ref)	0.77 (0.59–1.00)	
Males: Median (Range)	0	60.00 (0.99–2102.86)	
Female: Median (Range)	0	60.00 (0.99–2085.71)	

mg = milligrams; mcg = micrograms

* Using a logistic model adjusted for energy, smoking, BMI, age, sex, and drinks of alcohol per week