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Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area

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Abstract

There are no well-established modifiable risk factors for pancreatic cancer except smoking. Some dietary factors have been associated with pancreatic cancer risk and require further study. We examined the associations among intake of specific fatty acids and antioxidants and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. Unconditional logistic regression models were used to compute odds ratios (OR) and 95% confidence intervals (CI) as estimates of relative risk. Positive associations were observed for high levels of the eight individual saturated fatty acids (4^{th} vs. 1^{st} quartile: ORs ranged from 1.6 to 2.6; all P_{trend}<0.001), monounsaturated palmitoleic and oleic fatty acids [OR=1.6 (95%CI: 1.2-2.1) and 1.4 (95%CI: 1.1-1.9); both P_{trend} <0.01], and polyunsaturated linolenic acid [OR=1.5 (95%CI: 1.1-2.0); P_{trend}=0.02]. Inverse associations were observed for high levels of gadolic acid [4^{th} vs. 1^{st} quartile: OR=0.68 (95%CI: 0.50-0.92); P_{trend}=0.007] and omega-3 fatty acids [≥0.85g/day vs. 1^{st} quartile: OR=0.47 (95%CI: 0.25-0.90)]. An inverse association also was observed for high total intake of vitamin C [4^{th} vs. 1^{st} quartile: OR=0.69 (95%CI: 0.51-0.94); P_{trend}=0.004] and of vitamin E [OR=0.67 (95%CI: 0.49-0.92); P_{trend}=0.01]. Although similar decreased risks also were observed for high supplemental intake of these two vitamins (both P_{trend}<0.01), no association was observed for intake from food alone. These results support the hypotheses that a high intake of saturated and certain monounsaturated fatty acids may increase the risk of pancreatic cancer, whereas greater intake of omega-3 fatty acids, vitamins C and E may reduce the risk.

Keywords

Pancreatic neoplasms; nutrients; fatty acids; antioxidants; case-control studies

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Two brief statements: Few studies have examined pancreatic cancer risk associated with specific fatty acids and antioxidant nutrients, and their results have been inconclusive. The large study size (532 cases, 1,701 controls) and availability of extensive risk factor and food frequency questionnaire data in this population-based study provide an opportunity to evaluate these associations and to assess the effect of potential confounders and effect modifiers.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in U.S. men and women with an estimated 42,470 new cases and 35,240 deaths in 2009 (1). Because there are no early disease-specific symptoms and no effective screening diagnostics, most patients have metastatic or locally advanced disease with poor prognosis at the time of diagnosis (2). Also, with few effective treatment options, pancreatic cancer has one of the highest mortality rates of all cancers and a median survival of 3-6 months (3). The 5-year relative survival is less than 5% (3). Thus, primary prevention is critical to reduce the incidence of this highly fatal cancer.

Epidemiologic studies have identified few risk factors for pancreatic cancer and the etiology remains largely unknown. Family history and cigarette smoking are among the few established risk factors, but account for a relatively small proportion of all pancreatic cancer cases (4,5). Obesity, diabetes mellitus and chronic pancreatitis also have been frequently associated with risk of pancreatic cancer although reverse causation may play a role for the latter two conditions (6-10). Results from the studies that have investigated dietary factors and risk of pancreatic cancer have been inconclusive (5,11,12). More work is needed to clarify the association between modifiable dietary factors and pancreatic cancer given the integral role of dietary nutrients in tumor promoting or tumor preventive biologic pathways.

In animal models, dietary fat has been shown to promote pancreatic carcinogenesis (13). Results from epidemiologic studies that have evaluated dietary fat and pancreatic cancer have been mixed (14-22). Specific fatty acids have been associated with insulin resistance (23,24), altered insulin gene expression and apoptosis of pancreatic β-cell with effects varying by fatty acid length and unsaturatedness (25-29). Insulin resistance can result in diabetes and both conditions have been positively linked with pancreatic cancer risk (8,30). However, epidemiologic studies, including our previous analyses (21), mainly have examined the macronutrient effects of dietary fat, e.g. the quantity (total fat), source (animal fat, vegetable fat), or major type of fat (saturated fat, monounsaturated fat, polyunsaturated fat), rather than specific fatty acids. Results from the few epidemiological studies that have investigated specific fatty acids have been inconsistent (17-20,22).

In recent years, there also has been an increasing interest in the potential preventive effects of antioxidants on the development of various cancers. Because antioxidant vitamins and minerals such as vitamin C, vitamin E, selenium, and zinc can reduce oxidative DNA damage and genetic mutations (31-35), they may protect against pancreatic carcinogenesis. Although associations between pancreatic cancer risk and some antioxidants (e.g., vitamin C, E) have been reported, most studies have focused on nutrient intake from food alone and results have been inconclusive (16,18,20,22,36-44).

In this large population-based case-control study using rapid case ascertainment and in-person interviews, we examined pancreatic cancer risk associated with intake of specific fatty acids and the antioxidant nutrients vitamins C and E, and zinc and selenium, both from food and from supplements. We hypothesized that antioxidants may be inversely related to risk of pancreatic cancer, whereas specific fatty acids may increase risk.

Materials and Methods

Study population

Details of study methods and population characteristics have been described previously (21,45,46). In brief, cases with incident adenocarcinoma of the exocrine pancreas diagnosed between 1995 and 1999 were identified using rapid case ascertainment. Eligible cases were

21–85 years old, residents of one of six San Francisco Bay Area counties, alive at first contact, and able to complete an interview in English. Pancreatic cancer diagnoses were confirmed by participants' physicians and by Surveillance, Epidemiology and End Results (SEER) abstracts. Among the 798 eligible cases, 532 completed the interview for a response rate of 67%. Control participants were frequency-matched to cases by sex and 5-year age group and were selected from the target population using random digit dial methods. Recruitment of controls ≥65 years of age was supplemented by random selection from the Health Care Finance Administration (now Center for Medicare and Medicaid Services) lists. Among the 2,525 eligible controls, 1,701 completed the interview for a response rate of 67%.

Data collection

Detailed data including age, race, education, medical history, history of smoking, alcohol consumption, physical activity, and anthropometric measures were collected during in-person interviews by trained interviewers. No proxy interviews were conducted. Written informed consent was obtained from each participant. The study was reviewed and approved by the University of California San Francisco Committee on Human Research.

Participants were asked to report their average intake and portion size of specific foods one year before their diagnosis for cases, or interview for controls using a previously validated 131-item semi-quantitative food-frequency questionnaire (FFQ) (47-50). Relevant to analyses presented here, correlation was good between mean intake of nutrients computed from FFQ data and from one-week diet records (r = 0.7; range: 0.3-0.9) (48) as well as between repeat FFQs (range of 0.5 for vitamin E without supplements to 0.8 for vitamin C with supplements) (48). Nutrient intake was computed by multiplying the frequency of each food item by the nutrient content of the standard portion size specified for each food item. Food nutrient content values were obtained from the Harvard School of Public Health Department of Nutrition's food-composition relational database that is updated over time with data from the U.S. Department of Agriculture (51). Dietary supplement use included commonly used multivitamin and single vitamin or mineral supplements. Supplement intake of individual nutrients was computed by summing the amounts contributed from single and multivitamin supplements. However, because dietary selenium in food varies widely depending upon where the food is grown, assessment of intake based on food questionnaire data may be inaccurate (52). Thus, for these analyses, we examined the effect of selenium from supplement only, whereas intake of antioxidant nutrients other than selenium was examined as “total (food and supplement)”, “from food only”, and “from supplement only.”

Statistical methods

Adjusted unconditional logistic regression models were used to compute odds ratios (OR) and 95% confidence intervals (CI) as estimates of the relative risk of pancreatic cancer. Results are presented for men and women combined as they were similar when stratified by sex. Linear trends in odds ratios were based on the chi-square statistic for nutrient intake when included as an ordinal variable in multivariable unconditional logistic regression models.

Nutrient intake was adjusted for total energy intake using the residual method (53), and categorized into quartiles based on the distribution of the nutrient among controls. Specific supplement use also was analyzed as a categorical variable, and the distribution of observed values was used to define the cut points. Multivariable analyses included age in 5-year groups, race (White, Black/African American, Asian/Pacific Islanders, or others), total energy in quartiles, education level (less than high school, high school, 1-4 years college, and graduate work), usual adult body mass index (BMI: <25, 25-<30, and ≥30 kg/m^2),

smoking status (never smoker, former cigarette smoker who had quit >15 years previously, former cigarette smoker who had quit 1-15 years previously, current cigarette smoker or former smoker who had quit <1 year previously, and pipe and/or cigar smoker), history of diabetes, frequency of leisure time physical activity (30-minutes: <1/month, 1-4/month, 2-3/week, and ≥4/week), and alcohol consumption (never drinkers, ≤7, 8-14, 15-21, and >21 drinks/week).

Because smoking causes oxidative stress and may modify the association between antioxidant nutrients and pancreatic cancer risk, analyses were stratified by smoking status (never vs. ever) to evaluate potential effect modification. Given some antioxidants are fat soluble, *e.g.* vitamin E, and polyunsaturated fatty acids may have pro-oxidant effects (54), we also examined whether the effect of antioxidant nutrients on pancreatic cancer was modified by levels of polyunsaturated fat (low vs. high). Two-way statistical interaction between dietary factors and the dichotomously grouped variables was determined using a chi-square test for the difference in the −2 log-likelihood ratio statistics computed from the multivariable models with and without the cross-product terms.

All statistical tests were two-sided and considered statistically significant for $p<0.05$. Statistical analyses were conducted using SAS software V9.2 (SAS Institute, Inc., Cary, NC).

Results

Demographic and other selected factors of study participants were presented in Table I. Cases and controls were similar except that cases were more likely to be current smokers and heavy drinkers, and were less well educated compared with controls.

Results showed associations between individual fatty acid intake and risk of pancreatic cancer (Table II). In the multivariable analyses, ORs increased with increased intake of each of the eight saturated fatty acids investigated (all P_{trend} except one ≤ 0.0001). ORs ranged from 1.6 (lauric acid) to 2.6 (butyric acid) for the highest versus lowest quartiles of intake. For monounsaturated fatty acid, an increased risk of pancreatic cancer was observed for those in the highest quartiles of palmitoleic acid (OR=1.6, P_{trend} =0.0005) and oleic acid (OR=1.4, P_{trend} =0.008) intake, whereas there was a decreased risk observed for those with the highest gadolic acid intake (OR=0.68, P_{trend} =0.007). Among polyunsaturated fatty acids, participants with the highest linolenic acid intake had an increased risk of pancreatic cancer compared with those with the lowest intake (OR=1.5, P_{trend} =0.02). Although there was evidence of a decreased pancreatic cancer risk for those with the highest intake of eicosapentaenoic acid and of omega-3 fatty acids in the age, sex and energy adjusted models, the estimates were not different from unity after adjustment for multiple factors (Table II). Because the intake of omega-3 fatty acids was quite low in this study population, we examined the effect of omega-3 fatty acids by further categorizing the data in the 4th quartile of intake into three categories. Results showed that individuals in the ‘new’ highest category (≥0.85g/day) had a lower risk of pancreatic cancer compared with those in the first quartile (OR=0.47, 95% CI: 0.25-0.90).

Analyses of antioxidant nutrients, vitamins C and E, and zinc, showed several associations with pancreatic cancer risk (Table III). In multivariable analyses, risk of pancreatic cancer decreased with increased total intake of vitamin C and of vitamin E (4th versus 1st quartile, OR=0.69 and 0.67, respectively; both P_{trend} ≤0.01). In age, sex and energy adjusted models, increased intake of vitamin C from food alone was associated with a reduced pancreatic cancer risk (P_{trend}=0.009). However, the association was greatly attenuated and no longer different from unity after adjustment for multiple confounders in the full multivariable

model (P_{trend} =0.56). Vitamin E intake from food alone was not associated with pancreatic cancer risk (multivariable P_{trend} =0.66). There also was no association between pancreatic cancer risk and zinc intake (total or food alone). Results from analyses restricted to participants who did not take that specific nutrient supplement were similar to results that included supplement users (data not shown).

Due to the correlated use of multivitamins and single supplements within our study population, it is difficult to separate nutrient contributions from the two sources. Therefore, in analyses of supplement use of these antioxidants, supplemental intake was computed as the total dose from both multivitamin and single-supplement sources. Our results have shown that risk of pancreatic cancer decreased with increased intake level of supplemental vitamin C (P_{trend} =0.002) or E (P_{trend} =0.003; Table III). Increased intake of supplemental zinc was associated with a somewhat reduced pancreatic cancer risk (P_{trend} =0.08). There was no evidence of risk associated with use of supplemental selenium.

In smoking-stratified analyses, smoking status did not modify the effect of intake of any antioxidant nutrient on risk of pancreatic cancer (all $P_{interaction}$ >0.22; data not shown) with the exception of vitamin E intake ($P_{interaction}$=0.09; Table IV). Our results showed that the reduced risk of pancreatic cancer associated with vitamin E intake was stronger among never smokers. There were no significant interactions between antioxidant nutrients and polyunsaturated fat (all $P_{interaction}$>0.56; data not shown)

Discussion

In this large population-based case-control study, our results provided evidence that the saturated fatty acids, monounsaturated palmitoleic and oleic fatty acids, and polyunsaturated linolenic acid may increase the risk of pancreatic cancer, whereas gadolic acid (monounsaturated) and high intake of omega-3 fatty acids (polyunsaturated) may decrease risk. Pancreatic cancer risk also was decreased with increased intake of vitamin C or vitamin E, and we uniquely showed that the effect was largely due to intake from supplements rather than from food. Our results also suggested that the decreased pancreatic cancer risk associated with high intake of total vitamin E may be limited to or greater among never smokers, but should be interpreted with caution.

In our study, all individual saturated fatty acids were associated with an increased risk of pancreatic cancer independent of total energy intake. In contrast, a Canadian case-control study reported a decreased risk with increased intake of palmitic acid and of stearic acid, and no association with butyric acid and lauric acid (17). In the Nurses' Health Study cohort, no association was reported with stearic acid (19). Palmitic acid is the most common saturated fatty acid in the U.S. diet and is largely from consumption of red meat or processed meat, whereas dietary stearic, butyric, and lauric acids are less common and come mainly from dairy sources. Our saturated fatty acid results are consistent with results from our earlier analyses that showed a positive association between pancreatic cancer and foods containing high amounts of saturated fat such as ice cream, cheese, butter, beef, lamb, or certain processed meat (e.g., sausage, bacon) (21). Two cohort studies also reported increased risk with higher intake of saturated fat (20), high-fat dairy products (20), and with higher intake of saturated fat from red meat or processed meat (14). However, cohort study results also have reported no association with dairy products (14,19), or with any type of fat or meat (19).

We found a modest increase in pancreatic cancer risk with higher intake of the monounsaturated palmitoleic acid and oleic acid, and with the polyunsaturated linolenic acid. Results from three case-control and two cohort studies that assessed fatty acid intake

(17-20,22) are somewhat inconsistent with our findings. Overall, these results are inconclusive showing decreased risk with higher intake of oleic acid (17) and linoleic acid (22), and no association with any individual polyunsaturated fatty acids (17), or with oleic acid, linoleic acid, or α-linolenic acid (18-20). It is possible that small sample size (19,20) and use of proxy data (22) in some studies contributed to the discrepant results. The inconsistency of our results with the two large case-control studies (17,18) may be due to other study design-related differences including use of different measurement tools, unmeasured confounding, and differences in the range, average and median amount of fatty acid intake across the studied populations. For example, although vegetable oils and nuts have among the highest concentration of these fatty acids, the common sources for these fatty acids in European and U.S. populations are animal products (meat, dairy products) or foods prepared with cooking oils (e.g., potato chips, French fries) (55-57). As these food sources of fatty acid have been associated with increased risk of cancer, it may be difficult to separate the fatty acid effects from effects of other food components in populations with high consumption of animal products or processed foods.

In our study, there was some evidence of a decreased pancreatic cancer risk with high intake of the monounsaturated gadolic acid and the polyunsaturated long-chain omega-3 fatty acid. The reported association between pancreatic cancer and gadolic acid intake is unique to our study and the association with the long-chain omega-3 fatty acid was limited to participants with the highest intake (≥0.85 g/day, n=98). The dietary sources of these fatty acids are mainly fish and other seafood, especially fatty cold-water fish. Evidence from experimental studies indicates that long-chain omega-3 fatty acids (e.g., eicosapentaenoic acid, docosahexaenoic acid), that are present in fatty cold-water fish and fish oils can inhibit pancreatic carcinogenesis (25,28,58). Epidemiologic studies have shown mixed results for the association between fish intake and pancreatic cancer (14,19,21,36,44,59-61), and no association was found in the one published study among smokers that investigated the relationship between intake of marine omega-3 fatty acids and pancreatic cancer risk (20). The inconsistent or null findings in these studies could be related to the low intake of fish or long-chain omega-3 fatty acids in the studied populations. In our study, the inverse association was among participants who had the highest intake, suggesting that the low within-population variability in the intake of fish or long-chain omega-3 fatty acids also may contribute to the null findings. Although there are compelling data attributing positive health effects with intake of omega-3 fatty acids, the literature to support a chemopreventive effect in pancreatic cancer is limited. Further large studies or pooled studies that are designed to assess markers of nutrient intake, e.g. clinical, biological and epidemiological, are needed to confirm these findings and to elucidate the associated biologic mechanisms.

Results from our study provide support for the hypothesis that antioxidants may reduce the risk of pancreatic cancer. Total vitamin C or E intake was associated with a greater than 30% decreased risk of pancreatic cancer among those with the highest intake and was largely due to intake from supplements rather than from food. We found no association for vitamin C or E intake from food alone and the median values for the highest quartiles of total intake of vitamin C or E were increased ~5 to 40-fold over that from food alone. Our results showed that the decreased risk with total intake was driven by those with a high supplemental intake of these vitamins. Similar to our study, six case-control and three cohort studies reported no association with increased intake of vitamin C or E from food (18,20,36,37,39,41-43,62). However, the overall results have been mixed, as five other case-control studies have reported a decreased risk with vitamin C intake (16,22,38,40,44) and with vitamin E intake (44). The two studies that have published results of supplemental vitamin C use and pancreatic cancer risk suggested that ever use of vitamin C supplements was associated with a decreased risk of pancreatic cancer (18,63). Discrepancies in results may be partly explained by the narrow range of foods rich in dietary vitamin C (citrus fruits

and drinks), and in vitamin E (vegetable oils and nuts), differences in the range, average and median amount of antioxidant nutrient intake across populations, use of inadequate dietary assessment tools and small sample size. It is also possible that unmeasured variation in vitamin E transport genes or other antioxidant metabolism genes (e.g. SOD2) could partially explain apparent discrepancies in results. Given our results and the increasing prevalence of supplement use in the U.S. population (64), continued assessment of these nutrients is warranted and it will be important for future studies to collect supplement use data to clarify the association between these nutrients and pancreatic cancer risk.

Our results suggesting that the reduced risk of pancreatic cancer associated with high intake of total vitamin E may be limited to or greater among never smokers is somewhat supported by results from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study that showed no risk reduction with high intake of vitamin E among male smokers (62), although this study recently reported that high serum α-tocopherol concentration was associated with a lower pancreatic cancer risk in this population (54). There also is some evidence that smokers have lower plasma concentrations of vitamin E than nonsmokers due to the effect of oxidative stress from cigarette smoke (65,66). Although intriguing and biologically plausible, the differences across smoking strata could be due to chance and continued investigation is needed to confirm and clarify our results.

The biologic mechanisms to explain how dietary fat may affect risk for pancreatic cancer remain to be elucidated. However, studies have shown that high fat and certain fatty acids can promote excretion of bile acids resulting in increased bile reflux into the head of the pancreas that then may act as a tumor promoter (67). In addition, saturated fat and some monounsaturated fatty acids also can increase insulin resistance (23,24), a suggested risk factor for the development of pancreatic cancer (8,30). The association between pancreatic cancer and vitamins C and E is biologically plausible given their strong antioxidant properties that are known to have anti-carcinogenic effects. Vitamins C and E can block reactive oxygen species, reducing oxidative stress and thus reducing cancer-causing mutations (34,35). Vitamins C and E also may alter pancreatic cancer risk through their ability to stimulate immune function (68,69). Additional studies are needed to confirm and clarify these associations.

In this large population-based study, in-person interviews were conducted by trained and experienced interviewers. Rapid case ascertainment with a goal to identify eligible cases within one month of diagnosis was used to reduce selection bias and to minimize the effects of the short survival and high mortality rates on patient recruitment. No proxy interviews were conducted and props and photos were used for portion sizes to help reduce reporting and information bias. For most factors, participants were asked to report their exposure prior to the one year before their cancer diagnosis (cases) or interview (controls), to diminish potential effects related to reverse causation. Dietary data collected in the FFQ pertained to average intake of foods in the one year prior to diagnosis/interview. To assess whether cases were more likely to have recently changed their diets, possibly related to their cancer, we analyzed dietary changes over the past 10 years. We found that controls were more likely than cases to report dietary changes and these changes were toward ‘healthier diets’ *e.g.* more fruits and vegetables, less red meat (45). Our use of rapid case ascertainment to identify and interview patients shortly after diagnosis combined with few commonly known risk factors for pancreatic cancer, also would have helped to diminish recall bias and resultant misclassification of exposures. Any non-differential misclassification would have biased our results toward the null. However, if recall and thus misclassification of diet were related to case-control status in our study then the effect estimates may be biased either away from or toward the null. Also, given the high fatality rate of pancreatic cancer, if cases who were interviewed were healthier and more likely to have had better diets with resultant

higher levels of nutrient intake compared with not interviewed cases, then our results may be biased toward the null. The large sample size and extensive dataset allowed us to assess multiple lifestyle factors and exposures as potential confounders and effect modifiers of diet. However, more than 80% of the study population was non-Hispanic white and our results may not be generalizable to non-white populations, especially blacks/African-Americans who have high pancreatic cancer incidence and mortality rates.

In conclusion, results from this large population-based case-control study provide additional evidence that dietary factors and use of supplements may affect risk of pancreatic cancer. Our results showing increased risk of pancreatic cancer with increased saturated fatty acid intake and decreased risk with high intake of long-chain omega-3 fatty acid and of vitamin C and E from supplements contribute new data to the epidemiologic literature on pancreatic cancer. Future large studies are needed to confirm our findings and to clarify the role of specific nutrients from food and from supplements in pancreatic cancer development.

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Table I

Demographic, health, and lifestyle characteristics of 532 cases and 1701 controls in a population-based case-control study for pancreatic cancer, San Francisco Bay Area, California

Characteristics	Cases (n=532)[1] n (%)	Controls (n=1701)[1] n (%)
Age (yrs)		
<50	46 (9)	164 (10)
50-59	120 (23)	438 (26)
60-69	172 (32)	473 (28)
70-79	158 (30)	498 (29)
≥80	36 (7)	128 (8)
Sex		
Male	291 (55)	883 (52)
Female	241 (45)	818 (48)
Race		
White	442 (83)	1471 (86)
Black/African American	46 (9)	78 (5)
Asian or Pacific Islander	35 (7)	119 (7)
Others	9 (2)	33 (2)
Education		
< High-school graduate	71 (13)	162 (10)
High-school graduate	164 (31)	372 (22)
1-4 years college	200 (38)	754 (44)
Graduate work	97 (18)	413 (24)
History of diabetes		
Yes	76 (14)	161 (10)
Body mass index (kg/m^2)		
<25	281 (53)	999 (59)
25-<30	197 (37)	553 (33)
≥30	54 (10)	149 (9)
Smoking		
Non-smoker	163 (31)	652 (38)
Former smoker, quit >15 yrs	133 (25)	508 (30)
Former smoker, quit 1-15 yrs	89 (17)	260 (15)
Current smoker & quit <1 yr	131 (25)	208 (12)
Pipe/cigar smoker	16 (3)	73 (4)
Alcohol consumption		
Never	85 (16)	305 (18)
≤7 drinks/wk	231 (43)	804 (47)
8-14 drinks/wk	83 (16)	293 (17)
15-21 drinks/wk	39 (7)	138 (8)
>21 drinks/wk	91 (17)	161 (9)
Physical activity (30 min.)		

Characteristics	Cases (n=532)[1] n (%)	Controls (n=1701)[1] n (%)
<1/month	194 (37)	552 (32)
1-4/month	127 (24)	400 (24)
2-3/week	105 (20)	372 (22)
≥4/week	99 (19)	377 (22)

[1]Numbers may not add up to the total number of participants because of missing values

Table II

Odds Ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and intake of specific fatty acids in a population-based case-control study, San Francisco Bay Area, California

Nutrients Quartiles (range), g/day	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
Saturated fatty acids				
Butyric acid				
Q1 (<0.19)	77 (15)	425 (25)	1.0	1.0
Q2 (0.19-<0.30)	132 (25)	426 (25)	1.7 (1.2-2.2)	1.8 (1.3-2.5)
Q3 (0.30-<0.44)	128 (24)	424 (25)	1.6 (1.2-2.2)	1.7 (1.3-2.4)
Q4 (≥0.44)	188 (36)	426 (25)	2.5 (1.8-3.3)	2.6 (1.9-3.5)
P-trend			<.0001	<.0001
Caproic acid				
Q1 (<0.10)	85 (16)	425 (25)	1.0	1.0
Q2 (0.10-<0.16)	124 (24)	426 (25)	1.4 (1.1-2.0)	1.5 (1.1-2.1)
Q3 (0.16-<0.24)	126 (24)	424 (25)	1.5 (1.1-2.0)	1.6 (1.1-2. 1)
Q4 (≥0.24)	190 (36)	426 (25)	2.2 (1.7-3.0)	2.3 (1.7-3.2)
P-trend			<.0001	<.0001
Caprylic acid				
Q1 (<0.06)	87 (16)	426 (25)	1.0	1.0
Q2 (0.06-<0.10)	132 (25)	424 (25)	1.5 (1.1-2.1)	1.6 (1.2-2.2)
Q3 (0.10-<0.14)	127 (24)	425 (25)	1.5 (1.1-2.0)	1.5 (1.1-2.1)
Q4 (≥0.14)	179 (34)	426 (25)	2.1 (1.6-2.8)	2.1 (1.6-2.9)
P-trend			<.0001	<.0001
Capric acid				
Q1 (<0.18)	91 (17)	425 (25)	1.0	1.0
Q2 (0.18-<0.26)	113 (22)	425 (25)	1.2 (0.91-1.7)	1.3 (0.94-1.8)
Q3 (0.26-<0.36)	128 (24)	425 (25)	1.4 (1.1-1.9)	1.5 (1.1-2.0)
Q4 (≥0.36)	193 (37)	426 (25)	2.2 (1.6-2.9)	2.2 (1.6-2.9)
P-trend			<.0001	<.0001
Lauric acid				
Q1 (<0.27)	100 (19)	426 (25)	1.0	1.0
Q2 (0.27-<0.38)	127 (24)	425 (25)	1.3 (0.96-1.7)	1.3 (0.98-1.8)
Q3 (0.38-<0.54)	134 (26)	424 (25)	1.4 (1.0-1.8)	1.4 (1.0-1.9)
Q4 (≥0.54)	164 (31)	426 (25)	1.7 (1.3-2.2)	1.6 (1.2-2.1)
P-trend			.0004	.004
Myristic acid				
Q1 (<1.1)	92 (18)	426 (25)	1.0	1.0
Q2 (1.1-<1.5)	110 (21)	425 (25)	1.2 (0.89-1.7)	1.2 (0.90-1.7)
Q3 (1.5-<2.0)	127 (24)	425 (25)	1.4 (1.1-1.9)	1.4 (0.99-1.9)
Q4 (≥2.0)	196 (37)	425 (25)	2.2 (1.6-2.9)	2.1 (1.6-2.9)
P-trend			<.0001	<.0001
Palmitic acid				

Nutrients Quartiles (range), g/day	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
Q1 (<9)	98 (19)	426 (25)	1.0	1.0
Q2 (9-<11)	111 (21)	425 (25)	1.1 (0.81-1.5)	1.0 (0.76-1.4)
Q3 (11-<13)	114 (22)	425 (25)	1.2 (0.85-1.6)	1.1 (0.78-1.5)
Q4 (≥13)	202 (38)	425 (25)	2.1 (1.6-2.7)	1.8 (1.3-2.4)
P-trend			<.0001	<.0001
Stearic acid				
Q1 (<4)	88 (17)	425 (25)	1.0	1.0
Q2 (4-<5)	121 (23)	425 (25)	1.4 (1.0-1.9)	1.3 (0.95-1.8)
Q3 (5-<6)	116 (22)	426 (25)	1.3 (0.95-1.8)	1.2 (0.84-1.6)
Q4 (≥6.0)	200 (38)	425 (25)	2.3 (1.7-3.1)	2.0 (1.4-2.7)
P-trend			<.0001	<.0001
Monounsaturated fatty acids				
Palmitoleic acid				
Q1 (<0.92)	94 (18)	426 (25)	1.0	1.0
Q2 (0.92-<1.2)	124 (24)	424 (25)	1.3 (0.95-1.7)	1.2 (0.89-1.7)
Q3 (1.2-<1.4)	129 (24)	425 (25)	1.3 (1.0-1.8)	1.2 (0.90-1.7)
Q4 (≥1.4)	178 (34)	426 (25)	1.9 (1.4-2.5)	1.6 (1.2-2.1)
P-trend			<.0001	.0005
Oleic acid				
Q1 (<18)	107 (20)	425 (25)	1.0	1.0
Q2 (18-<21)	114 (22)	425 (25)	1.1 (0.78-1.4)	0.99 (0.73-1.3)
Q3 (21-<25)	130 (25)	426 (25)	1.2 (0.87-1.6)	1.1 (0.81-1.5)
Q4 (≥25)	174 (33)	425 (25)	1.6 (1.2-2.1)	1.4 (1.1-1.9)
P-trend			.0004	.008
Gadolic acid				
Q1 (<0.11)	159 (30)	426 (25)	1.0	1.0
Q2 (0.11-<0.16)	149 (28)	425 (25)	0.89 (0.68-1.2)	0.92 (0.70-1.2)
Q3 (0.16-<0.21)	114 (22)	425 (25)	0.72 (0.54-0.95)	0.78 (0.58-1.0)
Q4 (≥0.21)	103 (20)	425 (25)	0.64 (0.48-0.85)	0.68 (0.50-0.92)
P-trend			.0007	.007
Polyunsaturated fatty acids				
Linoleic acid				
Q1 (<8)	112 (21)	426 (25)	1.0	1.0
Q2 (8-<10)	143 (27)	424 (25)	1.3 (1.0-1.8)	1.3 (0.96-1.7)
Q3 (10-<12)	139 (26)	425 (25)	1.3 (0.94-1.7)	1.2 (0.86-1.6)
Q4 (≥12)	131 (25)	426 (25)	1.2 (0.89-1.6)	1.1 (0.80-1.5)
P-trend			.34	.83
Linolenic acid				
Q1 (<0.85)	97 (18)	426 (25)	1.0	1.0
Q2 (0.85-<1.1)	138 (26)	424 (25)	1.4 (1.1-1.9)	1.4 (1.0-1.9)
Q3 (1.1-<1.4)	145 (28)	426 (25)	1.5 (1.1-2.0)	1.4 (1.0-1.9)

Nutrients Quartiles (range), g/day	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
Q4 (≥1.4)	145 (28)	425 (25)	1.5 (1.1-2.0)	1.5 (1.1-2.0)
P-trend			.008	.02
Arachidonic acid				
Q1 (<0.09)	137 (26)	426 (25)	1.0	1.0
Q2 (0.09-<0.12)	126 (24)	424 (25)	0.90 (0.68-1.2)	0.92 (0.69-1.2)
Q3 (0.12-<0.16)	142 (27)	426 (25)	1.0 (0.78-1.3)	1.0 (0.75-1.3)
Q4 (≥0.16)	120 (23)	425 (25)	0.89 (0.67-1.2)	0.80 (0.59-1.1)
P-trend			.62	.23
Eicosapentaenoic acid (EPA)				
Q1 (<0.04)	158 (30)	425 (25)	1.0	1.0
Q2 (0.04-<0.08)	134 (26)	426 (25)	0.80 (0.61-1.0)	0.90 (0.68-1.2)
Q3 (0.08-<0.12)	123 (23)	424 (25)	0.76 (0.58-1.0)	0.90 (0.68-1.2)
Q4 (≥0.12)	110 (21)	426 (25)	0.68 (0.52-0.91)	0.83 (0.62-1.1)
P-trend			.008	.24
Docosahexaenoic acid (DHA)				
Q1 (<0.09)	152 (29)	425 (25)	1.0	1.0
Q2 (0.09-<0.14)	118 (22)	426 (25)	0.75 (0.56-0.99)	0.81 (0.61-1.1)
Q3 (0.14-<0.21)	138 (26)	425 (25)	0.92 (0.70-1.2)	0.98 (0.80-1.4)
Q4 (≥0.21)	117 (22)	425 (25)	0.95 (0.57-1.0)	0.88 (0.66-1.2)
P-trend			.15	.83
Long-chain omega-3 fatty acids (DHA+EPA)				
Q1 (<0.12)	149 (28)	425 (25)	1.0	1.0
Q2 (0.12-<0.22)	135 (26)	425 (25)	0.85 (0.65-1.1)	0.96 (0.72-1.3)
Q3 (0.22-<0.33)	130 (25)	426 (25)	0.88 (0.67-1.2)	1.0 (0.77-1.4)
Q4[3] (≥0.33)	111 (21)	426 (25)	0.73 (0.55-0.98)	0.88 (0.65-1.2)
P-trend			.049	.52
Q4 groups				
Q4a (0.33-<0.58)	74 (14)	256 (15)	0.83 (0.60-1.2)	1.0 (0.72-1.4)
Q4b (0.58-<0.85)	25 (5)	83 (5)	0.77 (0.47-1.3)	0.91 (0.54-1.5)
Q4c (≥0.85)	12 (2)	86 (5)	0.40 (0.21-0.76)	0.47 (0.25-0.90)
P-trend			.01	.20

[1] Residual model; adjusted for age in 5-year groups, sex, and total energy intake (quartiles)

[2] Residual model; additionally adjusted for race, education, body mass index, history of diabetes, smoking, physical activity, and alcohol consumption.

[3] Because intake of omega-3 fatty acid was low in the study population, the 4th quartile of intake was regrouped. We partitioned these participants into 3 groups reflecting the 90th percentile (Q4b) and 95th percentile (Q4c: ≥0.85 g/day) of intake in the controls as the new cutpoints.

Table III

Odds Ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and intake of vitamins C, E, zinc and selenium in a population-based case-control study, San Francisco Bay Area, California

Nutrients	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
Vitamin C intake, mg/day				
Total (food and supplement)[3]				
Q1 (<142)	161 (31)	426 (25)	1.0	1.0
Q2 (142-<235)	161 (31)	424 (25)	0.96 (0.74-1.2)	1.1 (0.82-1.4)
Q3 (235-<712)	112 (21)	426 (25)	0.66 (0.49-0.87)	0.79 (0.59-1.1)
Q4 (≥712)	91 (17)	425 (25)	0.58 (0.43-0.77)	0.69 (0.51-0.94)
P-trend			<.0001	.004
From food only[4]				
Q1 (<102)	157 (30)	425 (25)	1.0	1.0
Q2 (102-<144)	140 (27)	425 (25)	0.87 (0.66-1.1)	1.0 (0.77-1.3)
Q3 (144-<191)	117 (22)	425 (25)	0.74 (0.56-0.98)	0.91 (0.68-1.2)
Q4 (≥191)	111 (21)	426 (25)	0.71 (0.54-0.95)	0.94 (0.70-1.3)
P-trend			.009	.56
From supplement only[5]				
0	259 (49)	683 (40)	1.0	1.0
0.1-150	107 (20)	324 (19)	0.84 (0.65-1.1)	0.91 (0.70-1.2)
150.1-450	87 (17)	380 (22)	0.62 (0.39-1.0)	0.69 (0.43-1.1)
>450	72 (14)	314 (18)	0.61 (0.48-0.78)	0.68 (0.52-0.87)
P-trend			<.0001	.002
Vitamin E intake, mg/day				
Total (food and supplement) [3]				
Q1 (<6.9)	149 (28)	425 (25)	1.0	1.0
Q2 (6.9-<24)	152 (29)	425 (25)	0.86 (0.65-1.1)	1.0 (0.75-1.3)
Q3 (24-399)	137 (26)	425 (25)	0.84 (0.59-1.0)	0.89 (0.66-1.2)
Q4 (≥399)	87 (17)	426 (25)	0.57 (0.43-0.79)	0.67 (0.49-0.92)
P-trend			.0004	.01
From food only[4]				
Q1 (<5.5)	140 (27)	426 (25)	1.0	1.0
Q2 (5.5-<6.6)	133 (25)	425 (25)	0.96 (0.73-1.3)	1.1 (0.80-1.4)
Q3 (6.6-<8.1)	124 (24)	424 (25)	0.88 (0.66-1.2)	1.1 (0.79-1.4)
Q4 (≥8.1)	128 (24)	426 (25)	0.91 (0.69-1.2)	1.1 (0.80-1.4)
P-trend			.42	.66
From supplement only[5]				
0	267 (51)	705 (41)	1.0	1.0
0.1-150	124 (24)	391 (23)	0.83 (0.64-1.1)	0.90 (0.70-1.2)
150.1-450	105 (20)	463 (27)	0.60 (0.46-0.78)	0.66 (0.50-0.86)
>450	29 (6)	142 (8)	0.53 (0.34-0.81)	0.56 (0.36-0.87)

Nutrients	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
P-trend			<.0001	.003
Zinc intake, mg/day				
Total (food and supplement) [3]				
Q1 (<9)	135 (26)	425 (25)	1.0	1.0
Q2 (9-<11)	117 (22)	425 (25)	0.80 (0.59-1.2)	0.86 (0.64-1.2)
Q3 (11-<18)	155 (30)	426 (25)	1.1 (0.59-1.3)	1.1 (0.82-1.4)
Q4 (≥18)	118 (22)	425 (25)	0.83 (0.74-1.6)	0.89 (0.66-1.2)
P-trend			.59	.85
From food only[4]				
Q1 (<9)	135 (26)	425 (25)	1.0	1.0
Q2 (9-<10)	109 (21)	425 (25)	0.79 (0.59-1.1)	0.86 (0.64-1.2)
Q3 (10-<11)	135 (26)	425 (25)	0.97 (0.74-1.3)	1.1 (0.81-1.4)
Q4 (≥11)	146 (28)	426 (25)	1.1 (0.82-1.4)	1.1 (0.85-1.5)
P-trend			.33	.20
From supplement only[5]				
0	398 (76)	1235 (73)	1.0	1.0
0.1-15	78 (15)	254 (15)	0.95 (0.72-1.3)	0.98 (0.74-1.2)
>15	49 (9)	212 (12)	0.68 (0.49-0.96)	0.71 (0.50-1.0)
P-trend			.04	.08
Selenium from supplement, mcg/day[5,6]				
0	414 (79)	1348 (79)	1.0	1.0
0.1-20	73 (14)	218 (13)	1.1 (0.80-1.4)	1.1 (0.83-1.5)
>20	38 (7)	135 (8)	0.88 (0.60-1.3)	0.86 (0.58-1.3)
P-trend			.75	.79

[1] Residual model; adjusted for age in 5-year groups, sex and total energy intake (quartiles)

[2] Residual model; additionally adjusted for race, education, body mass index, history of diabetes, smoking, physical activity, and alcohol consumption

[3] Total (food and supplement) and nutrient from food only were categorized into quartiles based on the distribution of the nutrient among controls

[4] Nutrient intake from food only also included use of each specific vitamin supplement (yes/no) in the fully adjusted model

[5] Nutrient intake from supplements only was classified into 3or 4 categories based on the distribution of observed values

[6] Because dietary selenium in food varies widely depending upon where the food is grown, assessment of intake based on food questionnaire data may be inaccurate. Therefore we only present intake of selenium from supplements.

Table IV

Odds Ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and intake of vitamin E by smoking status in a population-based case-control study, San Francisco Bay Area, California

Nutrients Quartiles	Cases n (%)	Controls n (%)	OR (95% CI)[1]	OR (95% CI)[2]
Total Vitamin E intake, mg/day				
Never smokers				
Q1 (<6.9)	50 (31)	145 (22)	1.0	1.0
Q2 (6.9-<24)	48 (29)	168 (26)	0.77 (0.47-1.2)	0.76 (0.46-1.3)
Q3 (24-399)	38 (23)	159 (24)	0.64 (0.39-1.1)	0.69 (0.41-1.2)
Q4 (≥399)	27 (17)	180 (28)	0.41 (0.29-0.70)	0.43 (0.25-0.75)
P-trend			.0008	.003
Ever smokers[3]				
Q1 (<6.9)	99 (27)	280 (27)	1.0	1.0
Q2 (6.9-<24)	104 (29)	257 (25)	0.91 (0.64-1.3)	1.0 (0.73-1.5)
Q3 (24-399)	99 (27)	266 (25)	0.86 (0.60-1.2)	0.97 (0.68-1.4)
Q4 (≥399)	60 (9)	246 (23)	0.69 (0.48-1.0)	0.76 (0.52-1.1)
P-trend			.05	. 18
P for interaction			.12	.09

[1] Residual model; adjusted for age in 5-year groups, sex, and total energy intake (quartiles)

[2] Residual model; additionally adjusted for race, education, body mass index, history of diabetes, physical activity, and alcohol consumption.

[3] included 89 cigar or pipe smokers