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Fatty Acids Found in Dairy, Protein, and Unsaturated Fatty Acids Are Associated with Risk of Pancreatic Cancer in a Case-Control Study

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Abstract

Although many studies have investigated meat and total fat in relation to pancreatic cancer risk, few have investigated dairy, fish and specific fatty acids. We evaluated the association between intake of meat, fish, dairy, specific fatty acids and related nutrients and pancreatic cancer. In our American-based Mayo Clinic case-control study 384 cases and 983 controls frequency matched on recruitment age, race, sex, and residence area (Minnesota, Wisconsin, or Iowa, United States) between 2004 and 2009. All subjects provided demographic information and completed 144-item food frequency questionnaire. Logistic regression calculated odds ratios (OR) and 95% confidence intervals (95% CI) were adjusted for age, sex, cigarette smoking, body mass index, and diabetes mellitus. Significant inverse association (trend p-value < 0.05) between pancreatic cancer and the groupings (highest vs. lowest consumption quintile OR [95% CI]): meat replacement (0.67 [0.43–1.02]), total protein (0.58 [0.39–0.86]), vitamin B12 (0.67 [0.44, 1.01]), zinc (0.48 [0.32, 0.71]), phosphorus (0.62 [0.41, 0.93]), vitamin E (0.51 [0.33, 0.78]), polyunsaturated fatty acids (0.64 [0.42, 0.98]), and Linoleic Acid (fatty acid 18:2) (0.62 [0.40–0.95]). Increased risk associations were observed for saturated fatty acids (1.48 [0.97–2.23]), Butyric Acid (fatty acid 4:0) (1.77 [1.19–2.64]), Caproic Acid (fatty acid 6:0) (2.15 [1.42–3.27]), Caprylic Acid (fatty acid 8:0) (1.87 [1.27–2.76]), and Capric Acid (fatty acid 10:0) (1.83 [1.23–2.74]). Our study suggests that eating a diet high in total protein and certain unsaturated fatty acids is associated with decreased risk of developing pancreatic cancer in a dose dependent manner whereas fats found in dairy increase risk.

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Impact: Many studies have investigated meat and total fat in relation to pancreatic cancer risk; however, less have investigated the relation with intake of dairy and fish and few specific dietary fatty acids. Although the exact mechanism is uncertain, our results suggest that eating a diet high in protein and certain unsaturated fatty acids maybe associated with decreased risk of developing pancreatic cancer in a dose dependent manner whereas consumption of fats found in high or full fat dairy increase risk.

Conflicts of interest: none declared.

Keywords

Pancreatic Cancer; Meat Consumption; Fat Consumption; Dairy Consumption; Case-control Study

INTRODUCTION

In the United States, the rate of pancreatic cancer is among the highest in the world with 45,220 new cases and 38,480 deaths in 2013.[1] The prognosis is extremely poor with 1-year and 5-year survival rates of 25% and 4%, respectively.[2] Generally, the disease is diagnosed at a late stage[3] resulting in the nearly identical incidence and mortality rates. Early detection methods are still in an exploratory stage with cigarette smoking, diabetes, and body fatness as the only established risk factors. Therefore, an important approach is to focus on prevention by identifying additional modifiable risk factors.

The Continuous Update Project for Pancreatic Cancer from the World Cancer Research Fund evaluated literature on pancreatic cancer and food, nutrition, and physical activity risk factors concluded that the strength of the evidence supported body fatness and greater childhood growth are a cause of pancreatic cancer, with suggestive evidence for red and processed meat, alcohol use and saturated fatty acids (World Cancer Research Fund/ American Institute for Cancer Research. Continuous Update Project Summary. Food, Nutrition, Physical Activity, and the Prevention of Pancreatic Cancer. 2012),. Many studies have investigated meat and total fat in relation to pancreatic cancer risk; however, less have investigated the relation with intake of dairy and fish and few specific dietary fatty acids. In our literature search, we found positive associations with dietary fat were observed in 4 of 6 [5–10] case-control studies, and 4 of 6 [11–16] cohort studies. Positive associations with meat intake were observed in 3 of 3 [7, 17, 18] case-control and 3 of 5 [12, 14, 19–21] cohort studies. There are three studies that report null results between dairy intake and pancreatic cancer.[12, 14, 15] One case-control study showing an increased association between fish intake and pancreatic cancer risk[17] and two cohort study reported a null result[11, 14] while one cohort study showed an increased risk with non-fried fish.[22]

Our objective was to evaluate the association between meat, dairy products, fat, and specific fatty acids intake and pancreatic cancer using an American clinic-based case-control study. Our hypotheses were that high consumption of red meat, saturated fat, and high-fat dairy would be associated with increased risk of pancreatic cancer while fish intake (specifically those high in omega-3) would be associated with reduced risk. To minimize issues that may bias dietary based case-control studies, in this study we rapidly identified and enrolled cases who received care at Mayo Clinic and excluded those who reported changing their diet within the last five years.

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.[23] Briefly, 1,648 (66.6%) of the cases who received care and were approached at Mayo Clinic (Rochester, MN) from May 2004 to December 2009 consented to participate in a prospective registry at time of their visit using a rapid ascertainment method.[24] Over 99% of cases were confirmed with pathology or medical record. Controls were patients who received primary care at Mayo Clinic and were frequency-matched to cases on age at recruitment (in 5-year increments), race, sex, and region of residence (Olmsted County; three-state (Minnesota, Wisconsin, Iowa); or outside

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of area). Controls with prior diagnoses of cancer, except non-melanoma skin cancer, were excluded.

Dietary data from FFQ

Participants were asked to complete a 144-item food frequency questionnaire (FFQ) which is a modified version of a previous National Cancer Institute (NCI) developed FFQ. Details are given in our previous report.[23] Briefly, the NCI software DietCalc[25] was used to estimate an average for all the food and nutrient categories including fat, dairy, and meat intake from the survey questions with a meat module section for the five years prior to enrollment. FFQs were returned by 816 cases of pancreatic adenocarcinoma and 1,290 controls. To reduce disease related dietary change, 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 five 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). In total, 384 cases and 983 controls composed the final study sample.

Several “total” and combination categories were used to give a summary of intake in specific categories. The total dairy category includes intake of milk, cheese, butter, sour cream, cream cheese, margarine, and yoghurt; total meat category includes intake of beef, pork, lamb, eggs, fish, franks, luncheon meat, organs, poultry, and seafood; total white meat category includes intake of chicken\poultry, and fish; and total red meat category includes intake of beef, pork, lamb, eggs, franks, luncheon meats, organs; and meat replacements category includes intake of nuts/seeds, tofu, soy meats, soy milk, and peanut butter/nut butters.

Statistical analysis

Median, mean and range of intake of dietary food categories were separately calculated for cases and controls. Energy-adjusted food categories were created using the density method[26] to investigate associations with pancreatic cancer. A logistic regression model was used to calculate odds ratios (OR) for pancreatic cancer and 95% confidence intervals (95% CIs) adjusting for age, sex, cigarette smoking (current, former, never), usual adult body mass index (BMI), diabetes mellitus (DM) (no, diagnosis < 3 years prior, or diagnosis 3+ years prior), energy intake (per 1000 kcal), number of drinks of alcohol per week, and daily servings of total fruit and vegetable consumption. Potential confounders were chosen based on previously published evidence and an apriori causal diagram was constructed. All confounder variables determined to be associated with both dietary intake and pancreatic cancer were included as adjustments. All tests of statistical significance were 2-sided, and trend p-values < 0.05 were considered significant. Analyses were generated using SAS® software (Version (9.2)). [27]

RESULTS

In our study on average cases were more likely to be male, older, and have ever smoked (and if a past smoker, had quit more recently) with the percentage of current smokers among cases almost 4 times the percentage seen among controls. Cases were also more likely to have a personal history of diabetes (especially recent (< 3 years) onset; Table 1) compared to controls. Usual BMI was similar. When comparing male and female cases (not shown), males were on average younger, had a higher usual adult BMI, were more likely to have ever smoked (difference seen mostly among ex-smokers), and were more likely to have a personal history of diabetes (especially in the category diagnosed greater than 3 years before

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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.[23]

Several of the fat, dairy and meat categories were highly correlated (Pearson's correlation coefficient ≥ 0.80 and p-values < 0.0001). Total white meat with Clupanodonic Acid (fatty acid 22:5) (0.80); dairy with calcium (0.96), milk (0.95), vitamin D (0.89), and phosphorus (0.81); total protein with methionine (0.97); cholesterol with Arachidonic Acid (fatty acid 20:4) (0.87); monounsaturated fatty acids with Vaccenic Acid (fatty acid 18:1) (1.00) and total fat (0.95); polyunsaturated fatty acids with Linoleic Acid (fatty acid 18:2) (1.00) and fatty acid 20:1 (0.83); total fat with Vaccenic Acid (fatty acid 18:1) (0.94), and fatty acid 16:0 (0.86); Linoleic Acid (fatty acid 18:2) with fatty acid 20:1 (0.84); Eicosapentaenoic Acid (fatty acid 20:5) with Docosahexaenoic Acid (fatty acid 22:6) (0.94); and Clupanodonic Acid (fatty acid 22:5) with Docosahexaenoic Acid (fatty acid 22:6) (0.81).). The high correlation among the variables in these categories suggests that determining which item or combination of items in a category may be responsible for the association is difficult in this study. These, along with additional correlations > 0.50, are shown in the appendix (Appendix Table 1) and suggest result should be interpreted with caution.

Table 2–4 shows the number of cases and median value ranges of select groupings, OR, 95% CI, and trend test p-values across quintiles (which were constructed using the control population values). Significance was declared if the highest quintile consumption group was significantly different compared to the lowest quintile, or test for trend p-value was <0.05. In Table 2, inverse associations between pancreatic cancer and selected food categories (OR [95% CI]) included meat replacement (0.67 [0.43–1.02]). In Table 3, inverse association between pancreatic cancer and selected fat and fatty acids included polyunsaturated fatty acids (0.64 [0.42, 0.98]), Linoleic Acid (fatty acid 18:2) (0.62 [0.40–0.95]); an increased risk association was observed for saturated fatty acids (1.48 [0.97–2.23]), Butyric Acid (fatty acid 4:0) (1.77 [1.19–2.64]), Caproic Acid (fatty acid 6:0) (2.15 [1.42–3.27]), Caprylic Acid (fatty acid 8:0) (1.87 [1.27–2.76]), and Capric Acid (fatty acid 10:0) (1.83 [1.23–2.74]). In Table 4, inverse association between pancreatic cancer and selected nutrients found in meat, dairy, and oil included total protein (0.58 [0.39–0.86]), vitamin B12 (0.67 [0.44–1.01]), zinc (0.48 [0.32–0.71]), phosphorus (0.62 [0.41–0.93]), and vitamin E (0.51 [0.33–0.78]). Appendix Table 2 shows additional related food categories with significant results. An inverse relationship with pancreatic cancer was observed for fatty acid 20:1 (0.55 [0.36–0.84])and beta-tocopherol (0.49 [0.33–0.73]). Increased risk was observed for Myristic Acid (fatty acid 14:0)(1.96 [1.29–2.98]), Stearic Acid (fatty acid 18:0)(1.36 [0.90–2.07]), and 18:2 trans-octadecadienoic acid (1.78 [1.19–2.66]).

Since many of these fatty acids (4:0-14:0) and 18:2 trans-octadecadienoic acid are associated with high fat dairy foods, we ran our multivariable adjusted logistic regression model with intake of high-fat milk, butter, margarine, sour cream, cream cheese, ice cream, and cream pie. There were non-significant increased associations between butter, ice cream and cream pie (Appendix Table 3).

A sensitivity analysis was conducted to determine the impact of failure to exclude those who reported a diet change within the last five 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. We found changes in significance for vitamin B12 (from 0.67 [0.44–1.01] to 0.85 [0.65–1.19]), fatty acid 16:0 (from 1.47 [0.98–2.20] to 1.33 [0.98–1.82]), Eicosapentaenoic Acid (fatty acid 20:5) (from 0.80 [0.53–1.20] to 0.80 [0.59–1.08]), Clupanodonic Acid (fatty acid 22:5) (from 0.88 [0.62–1.24] to 0.74 [0.56–0.98]), delta-tocopherol (from 1.27 [0.87–1.86] to 1.42 [1.06–1.90]), total trans fatty acids (from 1.46

[0.97–2.18] to 1.63 [1.20–2.22]), 18:1 trans-octadecenoic acid (from 1.38 [0.92–2.07] to 1.69[1.24–2.31]), and total white meat (from 0.76 [0.50–1.15] to 0.71 [0.51–0.98]). These observed changes reinforce our decision to exclude those participants reporting a recent change from our final sample.

An additional sensitivity analysis was conducted running the logistic regression model for males and females separately. The results were generally similar for men and women in stratified analyses with no significant interactions by sex (p-value>0.05). Therefore we show only the combined results.

DISCUSSION

Our study suggests that eating a diet high in total protein and certain unsaturated fatty acids is associated with decreased risk of developing pancreatic cancer in a dose dependent manner whereas consumption of saturated fatty acids and fatty acids found in dairy increases risk.

No significant associations were found between pancreatic cancer and consumption of eggs, poultry, or fish in a meta-analysis and the observation that red meat was associated with increased risk was mostly limited to the case-control studies.[28] In the meta-analysis, positive associations for beef/lamb and higher fat, meat, and meat items with pancreatic cancer risk were observed. In our study, we observed a significant increased risk with total saturated fatty acids and many individual saturated fatty acids (between 4:0 – 14:0), which are found in high fat dairy foods. Also, we observed significant protective associations with a few polyunsaturated fatty acids groupings, total protein, and meat substitutes. Research regarding these categories is inconsistent with most of studies showing null results with a few increased risk associations for total protein and polyunsaturated fatty acids as well as decreased risk for polyunsaturated fatty acids and meat substitutes.[7, 14] There were non-significant increased risk associations between pancreatic cancer and butter, ice cream, and cream pies. The associations seen with vitamin B12, phosphorus, zinc, and copper (Table 4 and Appendix Table 2) are consistent, as all can be obtained from a variety of meat/seafood sources.

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, [29] insulin, [30] and plasma C-peptide levels [31] 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. [30, 32] 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, [32] potentially leading to pancreatic tumor promotion. [33] Furthermore, recent case-control studies of pancreatic cancer suggest that glucose intolerance, insulin resistance, and high insulin concentrations may play a role in carcinogenesis, [34] even without a diagnosis of diabetes mellitus. [29, 30] Because insulin is secreted into the blood in response to elevated blood glucose concentrations and the pancreas is exposed to much higher insulin concentrations, pancreatic cancer risk may increase by consumption of dietary factors that create insulin spikes.

Saturated fatty acids has been shown to be associated with insulin resistance.[35] Some, but not all, animal models have suggested a connection between high fat intake and pancreatic carcinogenesis[36] by demonstrating that an insulin sensitizer, metformin, can eliminate the association.[37] In most human studies, saturated fat and simple sugars (e.g., glucose, sucrose) promote insulin resistance, whereas monounsaturated fat, n-3 polyunsaturated fat, fiber, fruits, and vegetables improve insulin resistance.[38] This potential increased risk associated with saturated fatty acids and a protective effect of polyunsaturated fatty acids is suggested in our study. Trans unsaturated fatty acids also may impair insulin sensitivity[39] and has been associated with type 2 diabetes[40] and cancers.[41] A significant association between pancreatic cancer and 18:2 trans-octadecadienoic acid was observed in our study, supporting an increased risk hypothesis.

A second main hypothesis linking dietary intake with pancreatic cancer suggests that dietary components influence DNA damage/mutations through oxidative stress, inflammation, or consumption of pre-carcinogenic compounds. A closely related disease, pancreatitis, has demonstrated oxidative stress during early stages of disease.[42] Reactive oxygen species (ROS) have been involved in inflammation and DNA damage, resulting in p53 accumulation and apoptosis of pancreatic acinar cells.[4318, 19] Suggested explanations for meat as a source of ROS and associated increased risk of pancreatic cancer revolve around the creation of carcinogens during preparation.[18, 19, 44] This hypothesis is beyond the scope of this paper and will be evaluated in future research.

Fats and fatty acids stimulate pancreatic enzyme secretion and pancreatic hypertrophy and hyperplasia, which may increase susceptibility to carcinogens[45] in ways such as stimulating the tumor promoter, cyclooxygenase-2 (COX2).[46] In animal models, inhibitors of COX-2 and/or lipoxygenase have been shown to significantly reduce tumor formation, [47, 48] and omega-3 supplementation has reduced cancer growth.[49, 50]. The ratio of n-3 to n-6 polyunsaturated fatty acids (PUFAs) has been investigated since they compete in the COX driven biosynthesis of eicosanoids, such as prostaglandins.[51] Among the presented common n-3 and n-6 FAs in our study, intake of n-6 FA was much higher than n-3, and the only significant association (reduced risk) was seen for n-6 FA (FA 18:2).

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. To address reverse causation, we elected to exclude those individuals who reported a diet change in the 5 years prior to study entry, although there may have been unintentional dietary adjustment or earlier important dietary modifications among cases.

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. Within this study, cases were rapidly enrolled at the time of diagnosis and completed the FFQ shortly thereafter, potentially reducing the effect of such bias. Among the cases there could be unintended dietary modification (e.g. avoiding foods that adversely affect digestion or comfort) which could bias results. 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.[23] Given our reduced sample size after exclusions, the power to detect associations is reduced.

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In conclusion, our study suggests that eating a diet high in total protein and certain unsaturated fatty acids are associated with decreased risk of developing pancreatic cancer in a dose dependent manner, whereas, eating a diet high in saturated fatty acids and fatty acids found in dairy increases risk of pancreatic cancer. While this analysis of specific fatty acids and nutrients obtained from foods can provide potential targeted intervention and pathways to investigate, we emphasize that single dietary items are generally not consumed in isolation. Although the exact mechanism still needs to be determined, our results suggest that eating a diet containing specific unsaturated fatty acids and nutrients associated with high protein foods may reduce the risk of developing pancreatic adenocarcinoma while consuming high-fat dairy increases risk in certain populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
FFQ	food frequency questionnaire
NCI	National Cancer Institute
OR	odds ratios
ROS	Reactive oxygen species

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Table 1

Characteristics of pancreatic adenocarcinoma cases and controls used in the analysis (no recent diet change). Reproduced from [52] with permission.

	Cases (N=384)	Controls (N=983)
Sex		
Female	163 (42.4%)	500 (50.9%)
Male	221 (57.6%)	483 (49.1%)
Region[a]		
MN, WI, or IA	193 (50.4%)	675 (68.7%)
Other US	189 (49.4%)	305 (31.1%)
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 (21.0%)	43 (63.2%)
Onset < 3 years ago	120 (71.9%)	21 (30.9%)
Missing	12 (7.1%)	4 (5.9%)
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%)	1 (0.1%)
White/Caucasian	373 (97.0%)	966 (98.3%)
Multiracial	4 (1.1%)	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[b]		
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)		

	Cases (N=384)	Controls (N=983)
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]For case participants: 1 missing and 1 other country; for control participants: 3 other country.

[b]Only obtained data on: cases = 379(98.7%) and controls = 954(97.1%).

Table 2

Number of Cases and Select Median Intake (Range) of Meat, Fish, and Dairy Foods, and Odds Ratios With 95% Confidence Interval for Pancreatic Cancer Risk Generated by Constructing Quintiles of Intakes Based on Controls.

	Quintile 1	2	3	4	5	Trend p-value
Total Meat (g/1000 kcal)[b]						Adjusted[a]
Cases (M/F)	74 (36/38)	82 (47/35)	85 (46/39)	65 (43/22)	78 (49/29)	0.2
Odds Ratio (95% CI)	1.00 (ref)	1.02 (0.69,1.50)	1.04 (0.70,1.53)	0.80 (0.53,1.20)	0.83 (0.55,1.26)	Unadjusted
Median (Range)	27.83 (1.35–34.57)	41.52 (34.65–46.74)	53.48 (46.81–59.37)	65.64 (59.37–74.25)	88.7 (74.26–170.83)	0.77
Total Red Meat (g/1000 kcal)[c]						Adjusted[a]
Cases (M/F)	64 (27/37)	75 (33/42)	69 (45/24)	97 (64/33)	79 (52/27)	0.67
Odds Ratio (95% CI)	1.00 (ref)	1.05 (0.70,1.57)	0.90 (0.59,1.36)	1.15 (0.77,1.72)	0.86 (0.56,1.31)	Unadjusted
Median (Range)	13.3 (0.8–19.4)	24.21 (19.46–28.96)	32.88 (28.98–37.63)	42.6 (37.67–50.9)	63 (50.97–158.47)	0.11
Total White Meat (g/1000 kcal)[d]						Adjusted[a]
Cases (M/F)	90 (68/22)	90 (53/37)	80 (41/39)	69 (30/39)	55 (29/26)	0.1
Odds Ratio (95% CI)	1.00 (ref)	1.17 (0.80,1.70)	0.98 (0.67,1.44)	0.93 (0.62,1.38)	0.76 (0.50,1.15)	Unadjusted
Median (Range)	6.31 (0–8.82)	10.82 (8.86–12.92)	15.54 (12.93–19.07)	23.04 (19.11–29.08)	38.85 (29.1–107.22)	0.004
Total Meat Replacements (g/1000 kcal)[e]						Adjusted[a]
Cases (M/F)	94 (64/30)	96 (53/43)	74 (44/30)	70 (35/35)	50 (25/25)	0.03
Odds Ratio (95% CI)	1.00 (ref)	1.11 (0.77,1.59)	0.86 (0.59,1.27)	0.87 (0.59,1.29)	0.67 (0.43,1.02)	Unadjusted
Median (Range)	1.75 (0–2.84)	3.75 (2.85–4.83)	6.26 (4.83–7.93)	10.53 (7.94–13.43)	18.46 (13.47–68.71)	0.0004
Dairy (svg/1000 kcal)[f]						Adjusted[a]
Cases (M/F)	73 (36/37)	76 (49/27)	88 (58/30)	81 (43/38)	66 (35/31)	0.87
Odds Ratio (95% CI)	1.00 (ref)	1.11 (0.75,1.65)	1.21 (0.82,1.78)	1.20 (0.81,1.78)	1.00 (0.67,1.49)	Unadjusted
Median (Range)	0.31 (0.02–0.43)	0.55 (0.43–0.68)	0.81 (0.68–0.95)	1.14 (0.95–1.4)	1.76 (1.4–3.38)	0.74
Yogurt (svg/1000 kcal)						Adjusted[a]
Cases (M/F)	147 (109/38)	46 (34/12)	48 (22/26)	74 (29/45)	69 (27/42)	0.86
Odds Ratio (95% CI)	1.00 (ref)	0.85 (0.56,1.29)	0.51 (0.35,0.76)	0.90 (0.62,1.29)	0.94 (0.64,1.36)	Unadjusted
Median (Range)	0	0.01 (0–0.01)	0.02 (0.01–0.03)	0.05 (0.03–0.12)	0.23 (0.12–0.88)	0.03
Cheese (svg/1000 kcal)						Adjusted[a]

	Quintile 1	2	3	4	5	Trend p-value
Cases (M/F)	81 (48/33)	82 (50/32)	60 (33/27)	99 (52/47)	62 (38/24)	0.81
Odds Ratio (95% CI)	1.00 (ref)	0.98 (0.67,1.44)	0.76 (0.50,1.14)	1.29 (0.88,1.87)	0.92 (0.61,1.39)	Unadjusted
Median (Range)	0.05 (0–0.07)	0.09 (0.07–0.11)	0.13 (0.11–0.16)	0.19 (0.16–0.24)	0.3 (0.24–1)	0.43
Eggs (g/1000 kcal)						Adjusted[a]
Cases (M/F)	59 (32/27)	79 (48/31)	78 (48/30)	91 (50/41)	77 (42/34)	0.36
Odds Ratio (95% CI)	1.00 (ref)	1.20 (0.80,1.80)	1.18 (0.79,1.78)	1.38 (0.93,2.05)	1.15 (0.76,1.73)	Unadjusted
Median (Range)	1.63 (0–2.56)	3.52 (2.56–4.46)	5.52 (4.47–6.86)	8.9 (6.86–11.55)	17.07 (11.56–73.86)	0.13
Fish with Low Omega-3 (oz/1000 kcal)						Adjusted[a]
Cases (M/F)	226: 61/165	250: 86/164	286: 78/208	319: 95/224	247: 58/189	0.57
Odds Ratio (95% CI)	1.00 (ref)	0.69 (0.46, 1.05)	0.92 (0.61, 1.39)	0.81 (0.54, 1.21)	1.05 (0.68, 1.63)	Unadjusted
Median (Range)	(0,0.11)	(0.11,0.18)	(0.18,0.26)	(0.26,0.43)	(0.43,2.98)	0.15
Fish with High Omega-3 (oz/1000 kcal)						Adjusted[a]
Cases (M/F)	145: 42/103	340: 111/229	312: 89/223	263: 71/192	268: 65/203	0.36
Odds Ratio (95% CI)	1.00 (ref)	0.76 (0.48, 1.18)	0.89 (0.56, 1.41)	0.95 (0.59, 1.53)	1.01 (0.62, 1.63)	Unadjusted
Median (Range)	(0,0.02)	(0.02,0.05)	(0.05,0.08)	(0.08,0.14)	(0.14,1.38)	0.04

Abbreviations: g = grams; svg = servings; kcal = kilocalories; oz = ounces.

[a]Using a logistic model adjusted for age (continuous), sex (male/female), cigarette smoking (current, former, never), usual adult body mass index (continuous), diabetes mellitus (DM) (no, diagnosis < 3 years prior, or diagnosis 3+ years prior), energy intake (per 1000 kcal), number of drinks of alcohol per week, and daily servings of total fruit and vegetable consumption.

[b]Total meat includes beef, pork, lamb, eggs, fish, franks, luncheon meat, organs, poultry, and seafood

[c]Total red meat includes beef, pork, lamb, eggs, franks, luncheon meats, organs.

[d]Total white meat includes chicken\poultry, and fish

[e]The meat replacements includes nuts/seeds, tofu, soy meats, soy milk, and peanut butter/nut butters.

[f]Total dairy includes milk, cheese, butter, sour cream, cream cheese, margarine, and yoghurt

Table 3

Number of Cases and Select Median Fat, and Fatty Acid Intake (Range), and Odds Ratios With 95% Confidence Interval for Pancreatic Cancer Risk Generated by Constructing Quintiles of Intakes Based on Controls.

	Quintile 1	2	3	4	5	Trend p-value
Total Fat (g/1000 kcal)						Adjusted[a]
Cases (M/F)	63 (34/29)	91 (46/45)	61 (29/32)	91 (62/29)	78 (49/28)	0.84
Odds Ratio (95% CI)	1.00 (ref)	1.52 (1.02,2.24)	1.00 (0.66,1.53)	1.42 (0.95,2.12)	1.08 (0.71,1.64)	Unadjusted
Median (Range)	24.44 (12.11–27.9)	30.05 (27.91–32.07)	33.65 (32.08–35.36)	37.31 (35.38–39.26)	41.99 (39.27–54.5)	0.33
Saturated Fatty Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	55 (26/29)	61 (33/28)	81 (41/40)	88 (55/33)	99 (65/33)	0.03
Odds Ratio (95% CI)	1.00 (ref)	1.07 (0.70,1.64)	1.29 (0.86,1.95)	1.42 (0.94,2.14)	1.48 (0.97,2.23)	Unadjusted
Median (Range)	7.48 (3.82–8.58)	9.27 (8.58–10.05)	10.65 (10.05–11.36)	12.21 (11.36–13.01)	14.27 (13.02–27.56)	0.0004
Monounsaturated Fatty Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	58 (27/31)	99 (47/52)	68 (34/34)	71 (51/20)	88 (62/26)	0.64
Odds Ratio (95% CI)	1.00 (ref)	1.71 (1.15,2.54)	1.22 (0.80,1.86)	1.15 (0.75,1.77)	1.36 (0.90,2.06)	Unadjusted
Median (Range)	9.23 (4.79–10.75)	11.75 (10.75–12.51)	13.26 (12.51–14.04)	14.96 (14.05–15.78)	17.15 (15.78–24.76)	0.24
Polyunsaturated Fatty Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	90 (56/34)	85 (50/35)	93 (50/43)	66 (42/24)	50 (23/27)	0.01
Odds Ratio (95% CI)	1.00 (ref)	1.04 (0.72,1.51)	1.14 (0.79,1.64)	0.78 (0.52,1.15)	0.64 (0.42,0.98)	Unadjusted
Median (Range)	4.53 (1.18–5.08)	5.53 (5.08–5.95)	6.36 (5.96–6.83)	7.24 (6.83–7.85)	8.71 (7.86–16.19)	0.002
Total TRANS Fatty Acids (g/1000 kcal)						Adjusted[a]
Cases (M/F)	61 (31/30)	69 (36/33)	75 (37/38)	79 (50/29)	100 (67/33)	0.08
Odds Ratio (95% CI)	1.00 (ref)	1.17 (0.77,1.76)	1.24 (0.82,1.86)	1.24 (0.82,1.86)	1.46 (0.97,2.18)	Unadjusted
Median (Range)	1.26 (0.35–1.49)	1.67 (1.49–1.82)	1.97 (1.82–2.14)	2.31 (2.14–2.52)	2.86 (2.52–4.91)	0.008
Fatty Acids Associated with Dairy Foods						
Fatty Acid 4:0 – Butyric Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	57 (33/24)	68 (37/31)	66 (33/33)	89 (54/35)	104 (63/39)	0.003
Odds Ratio (95% CI)	1.00 (ref)	1.18 (0.78,1.79)	1.12 (0.73,1.70)	1.50 (1.00,2.25)	1.77 (1.19,2.64)	Unadjusted
Median (Range)	0.07 (0.01–0.1)	0.12 (0.1–0.14)	0.15 (0.14–0.18)	0.2 (0.18–0.24)	0.31 (0.24–1.25)	0.0006

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	Quintile 1	2	3	4	5	Trend p-value
Fatty Acid 6:0 – Caproic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	47 (27/20)	68 (37/31)	68 (35/33)	94 (55/40)	107 (66/38)	0.0002
Odds Ratio (95% CI)	1.00 (ref)	1.48 (0.96,2.29)	1.43 (0.92,2.21)	1.82 (1.19,2.77)	2.15 (1.42,3.27)	Unadjusted
Median (Range)	0.03 (0.01–0.04)	0.05 (0.04–0.06)	0.07 (0.06–0.09)	0.1 (0.09–0.13)	0.17 (0.13–0.7)	<0.0001
Fatty Acid 8:0 – Caprylic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	61 (44/17)	58 (29/29)	76 (37/39)	79 (51/28)	110 (60/50)	0.001
Odds Ratio (95% CI)	1.00 (ref)	1.00 (0.65,1.53)	1.28 (0.85,1.93)	1.27 (0.85,1.91)	1.87 (1.27,2.76)	Unadjusted
Median (Range)	0.04 (0.01–0.05)	0.06 (0.05–0.06)	0.07 (0.06–0.08)	0.09 (0.08–0.11)	0.14 (0.11–0.69)	0.0005
Fatty Acid 10:0 – Capric Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	53 (33/20)	63 (36/27)	80 (38/42)	82 (53/29)	106 (60/45)	0.002
Odds Ratio (95% CI)	1.00 (ref)	1.10 (0.72,1.70)	1.40 (0.93,2.12)	1.37 (0.91,2.08)	1.83 (1.23,2.74)	Unadjusted
Median (Range)	0.08 (0.02–0.1)	0.11 (0.1–0.13)	0.15 (0.13–0.16)	0.19 (0.16–0.22)	0.28 (0.22–0.97)	0.0002
Common Omega-3 Fatty Acids						
Fatty Acid 18:3 – Linolenic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	73 (47/26)	76 (36/40)	82 (50/32)	69 (41/28)	84 (46/37)	0.94
Odds Ratio (95% CI)	1.00 (ref)	1.09 (0.74,1.61)	1.14 (0.77,1.68)	0.95 (0.63,1.41)	1.09 (0.74,1.61)	Unadjusted
Median (Range)	0.37 (0.13–0.41)	0.44 (0.41–0.46)	0.49 (0.46–0.52)	0.55 (0.52–0.58)	0.65 (0.58–1.13)	0.67
Fatty Acid 20:5 – Eicosapentaenoic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	85 (55/30)	83 (48/35)	78 (41/37)	76 (42/34)	62 (35/27)	0.22
Odds Ratio (95% CI)	1.00 (ref)	1.05 (0.72,1.53)	1.00 (0.68,1.47)	0.93 (0.63,1.38)	0.80 (0.53,1.20)	Unadjusted
Median (Range)	0	0.01 (0–0.01)	0.01	0.01 (0.01–0.02)	0.03 (0.02–0.2)	0.1
Fatty Acid 22:6 – Docosahexaenoic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	85 (55/30)	85 (50/35)	80 (47/33)	65 (34/31)	69 (35/34)	0.22
Odds Ratio (95% CI)	1.00 (ref)	0.97 (0.66,1.41)	0.97 (0.66,1.42)	0.78 (0.52,1.16)	0.84 (0.56,1.26)	Unadjusted
Median (Range)	0.01 (0–0.01)	0.02 (0.01–0.02)	0.02 (0.02–0.03)	0.03 (0.03–0.04)	0.05 (0.04–0.3)	0.11
Common Omega-6 Fatty Acids						
Fatty Acid 18:2 – Linoleic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	89 (56/33)	86 (49/37)	91 (49/42)	71 (44/27)	47 (23/24)	0.01

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	Quintile 1	2	3	4	5	Trend p-value
Odds Ratio (95% CI)	1.00 (ref)	1.10 (0.76,1.60)	1.12 (0.77,1.62)	0.87 (0.59,1.28)	0.62 (0.40,0.95)	Unadjusted
Median (Range)	3.96 (1.02–4.49)	4.88 (4.5–5.29)	5.68 (5.29–6.1)	6.56 (6.1–7.12)	7.98 (7.13–15.26)	0.001
Fatty Acid 20:4 – Arachidonic Acid (g/1000 kcal)						Adjusted[a]
Cases (M/F)	62 (32/30)	97 (55/42)	69 (40/29)	81 (49/32)	75 (45/30)	0.84
Odds Ratio (95% CI)	1.00 (ref)	1.61 (1.09,2.38)	1.09 (0.72,1.65)	1.26 (0.84,1.90)	1.08 (0.71,1.64)	Unadjusted
Median (Range)	0.03 (0–0.04)	0.04 (0.04–0.05)	0.05 (0.05–0.06)	0.07 (0.06–0.08)	0.090.08–0.23)	0.64

Abbreviations: g = grams; kcal = kilocalories.

[a]Using a logistic model adjusted for age (continuous), sex (male/female), cigarette smoking (current, former, never), usual adult body mass index (continuous), diabetes mellitus (DM) (no, diagnosis < 3 years prior, or diagnosis 3+ years prior), energy intake (per 1000 kcal), number of drinks of alcohol per week, and daily servings of total fruit and vegetable consumption.

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Table 4

Number of Cases and Select Median Intake (Range) for Nutrients found in Meats, Dairy, and Oils, and Odds Ratios With 95% Confidence Interval for Pancreatic Cancer Risk Generated by Constructing Quintiles of Intakes Based on Controls.

	Quintile 1	2	3	4	5	Trend p-value
Correlated with animal foods and meat						
Protein (g/1000 kcal)						Adjusted[a]
Cases (M/F)	108 (63/45)	68 (43/25)	72 (43/29)	69 (33/36)	67 (39/28)	0.02
Odds Ratio (95% CI)	1.00 (ref)	0.67 (0.46,0.97)	0.69 (0.47,1.01)	0.66 (0.45,0.98)	0.58 (0.39,0.86)	Unadjusted
Median (Range)	33.03 (14.61–36.06)|	38.17 (36.14–39.79)	41.5 (39.8–43.09)	44.94 (43.12–47.22)	50.78 (47.24–67.2)	0.03
Methionine (g/1000 kcal)						Adjusted[a]
Cases (M/F)	100 (57/43)	64 (48/16)	76 (36/40)	76 (39/37)	68 (41/27)	0.15
Odds Ratio (95% CI)	1.00 (ref)	0.63 (0.43,0.93)	0.84 (0.58,1.23)	0.76 (0.52,1.11)	0.66 (0.44,0.98)	Unadjusted
Median (Range)	0.67 (0.33–0.75)	0.8 (0.75–0.84)	0.89 (0.84–0.94)	0.99 (0.94–1.04)	1.15 (1.04–1.6)	0.16
Cholesterol (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	54 (27/27)	69 (41/28)	90 (50/40)	88 (50/38)	83 (53/30)	0.17
Odds Ratio (95% CI)	1.00 (ref)	1.26 (0.83,1.92)	1.53 (1.01,2.30)	1.45 (0.96,2.20)	1.29 (0.85,1.97)	Unadjusted
Median (Range)	69.93 (15.37–84.78)	97.36 (84.81–108.33)	118.95 (108.58–130.6)	145.61 (130.75–166.68)	202.26 (166.74–641.89)	0.01
Vitamin B12 (mcg/1000 kcal)						Adjusted[a]
Cases (M/F)	75 (36/39)	95 (62/33)	68 (38/30)	87 (52/35)	59 (33/26)	0.05
Odds Ratio (95% CI)	1.00 (ref)	1.23 (0.84,1.79)	0.84 (0.56,1.25)	1.08 (0.73,1.59)	0.67 (0.44,1.01)	Unadjusted
Median (Range)	1.72 (0.53–2.05)	2.3 (2.05–2.49)	2.7 (2.49–2.91)	3.17 (2.91–3.53)	4.11 (3.53–12.88)	0.2
Iron (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	99 (63/36)	86 (52/34)	56 (30/26)	77 (43/34)	66 (33/33)	0.09
Odds Ratio (95% CI)	1.00 (ref)	0.94 (0.65,1.36)	0.62 (0.42,0.93)	0.85 (0.58,1.24)	0.72 (0.48,1.06)	Unadjusted
Median (Range)	6.58 (2.67–7.32)	7.83 (7.33–8.36)	8.79 (8.37–9.26)	9.97 (9.26–10.8)	12.22 (10.81–32.89)	0.03
Zinc (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	108 (68/40)	74 (43/31)	82 (45/37)	63 (32/31)	57 (33/24)	0.0001
Odds Ratio (95% CI)	1.00 (ref)	0.77 (0.53,1.12)	0.79 (0.55,1.15)	0.58 (0.39,0.86)	0.48 (0.32,0.71)	Unadjusted
Median (Range)	5.19 (2.36–5.65)	6.01 (5.65–6.32)	6.58 (6.32–6.93)	7.33 (6.93–7.88)	9.13 (7.88–26.28)	0.0009

	Quintile 1	2	3	4	5	Trend p-value
Correlated with dairy foods						
Calcium (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	83 (47/36)	79 (51/28)	85 (52/33)	80 (42/38)	57 (29/28)	0.47
Odds Ratio (95% CI)	1.00 (ref)	0.94 (0.64,1.38)	1.10 (0.76,1.61)	1.09 (0.74,1.59)	0.79 (0.52,1.18)	Unadjusted
Median (Range)	288.89 (121.78–328.39)	368.2 (329.14–406.49)	447.61 (406.65–497.39)	548.76 (497.39–627.12)	728.1 (627.26–1230.81)	0.09
Vitamin D (mcg/1000 kcal)						Adjusted[a]
Cases (M/F)	72 (33/39)	86 (53/33)	75 (51/24)	73 (41/32)	78 (43/35)	0.81
Odds Ratio (95% CI)	1.00 (ref)	1.15 (0.78,1.69)	0.95 (0.64,1.42)	0.95 (0.64,1.41)	1.04 (0.70,1.54)	Unadjusted
Median (Range)	1.17 (0.24–1.49)	1.77 (1.49–2.09)	2.4 (2.1–2.72)	3.16 (2.73–3.7)	4.54 (3.71–9.06)	0.99
Riboflavin (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	75 (42/33)	87 (50/37)	88 (61/27)	73 (38/35)	61 (30/31)	0.32
Odds Ratio (95% CI)	1.00 (ref)	1.29 (0.88,1.88)	1.19 (0.81,1.76)	1.04 (0.70,1.54)	0.89 (0.59,1.33)	Unadjusted
Median (Range)	0.82 (0.29–0.91)	0.98 (0.91–1.05)	1.11 (1.05–1.19)	1.28 (1.19–1.39)	1.55 (1.39–3.51)	0.19
Phosphorus (mg/1000 kcal)						Adjusted[a]
Cases (M/F)	100 (62/38)	84 (51/33)	73 (40/33)	74 (41/33)	53 (27/26)	0.03
Odds Ratio (95% CI)	1.00 (ref)	0.94 (0.65,1.35)	0.86 (0.59,1.26)	0.87 (0.60,1.27)	0.62 (0.41,0.93)	Unadjusted
Median (Range)	586.32 (202.34–627.08)	662.84 (627.85–692.65)	727.3 (692.69–761.7)	805.26 (761.82–855.71)	925.4 (856.73–1296.79)	0.002
Correlated with Polyunsaturated fatty acid						
Vitamin E (mg ATE/1000 kcal)						Adjusted[a]
Cases (M/F)	106 (80/27)	82 (49/32)	95 (55/40)	57 (24/33)	44 (13/31)	0.001
Odds Ratio (95% CI)	1.00 (ref)	0.76 (0.53,1.10)	1.04 (0.73,1.50)	0.62 (0.41,0.93)	0.51 (0.33,0.78)	Unadjusted
Median (Range)	3.04 (0.59–3.41)	3.7 (3.41–3.97)	4.34 (3.98–4.74)	5.28 (4.74–6.05)	7.9 (6.09–36.52)	<0.0001

Abbreviations: g = grams; kcal = kilocalories; mg = milligrams; ATE = alpha-tocopherol equivalents; and mcg = micrograms.

[a] Using a logistic model adjusted for age (continuous), sex (male/female), cigarette smoking (current, former, never), usual adult body mass index (continuous), diabetes mellitus (DM) (no, diagnosis < 3 years prior, or diagnosis 3+ years prior), energy intake (per 1000 kcal), number of drinks of alcohol per week, and daily servings of total fruit and vegetable consumption.

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