Dietary Fatty Acids and Pancreatic Cancer in the NIH-AARP Diet and Health Study

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Background Previous research relating dietary fat, a modifiable risk factor, to pancreatic cancer has been inconclusive.

Methods We prospectively analyzed the association between intakes of fat, fat subtypes, and fat food sources and exocrine pancreatic cancer in the National Institutes of Health–AARP Diet and Health Study, a US cohort of 308 736 men and 216 737 women who completed a 124-item food frequency questionnaire in 1995–1996. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models, with adjustment for energy intake, smoking history, body mass index, and diabetes. Statistical tests were two-sided.

Results Over an average follow-up of 6.3 years, 865 men and 472 women were diagnosed with exocrine pancreatic cancer (45.0 and 34.5 cases per 100 000 person-years, respectively). After multivariable adjustment and combination of data for men and women, pancreatic cancer risk was directly related to the intakes of total fat (highest vs lowest quintile, 46.8 vs 33.2 cases per 100 000 person-years, HR = 1.23, 95% CI = 1.03 to 1.46; P_{trend} = .03), saturated fat (51.5 vs 33.1 cases per 100 000 person-years, HR = 1.36, 95% CI = 1.14 to 1.62; P_{trend} < .001), and monounsaturated fat (46.2 vs 32.9 cases per 100 000 person-years, HR = 1.22, 95% CI = 1.02 to 1.46; P_{trend} = .05) but not polyunsaturated fat. The associations were strongest for saturated fat from animal food sources (52.0 vs 32.2 cases per 100 000 person-years, HR = 1.43, 95% CI = 1.20 to 1.70; P_{trend} < .001); specifically, intakes from red meat and dairy products were both statistically significantly associated with increased pancreatic cancer risk (HR = 1.27 and 1.19, respectively).

Conclusion In this large prospective cohort with a wide range of intakes, dietary fat of animal origin was associated with increased pancreatic cancer risk.

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Pancreatic cancer ranks fourth for cancer mortality in the United States and is one of the most rapidly fatal malignancies (1). Other than cigarette smoking, diabetes mellitus, and obesity, modifiable risk factors are not well established (2,3). Various dietary factors have been investigated as potential risk factors for pancreatic cancer (3). Consumption of fat overall and fat from animal products has been associated with elevated disease risk in some epidemiological studies [ecological (4,5), case–control (6–10), or prospective (11–13)] but not in others (14–25).

We analyzed the association between intakes of fat and pancreatic cancer risk in a large cohort of US men and women, the National Institutes of Health–AARP (NIH-AARP) Diet and Health Study. Because previous research showed an increase in pancreatic cancer risk with red meat consumption in this cohort (26), we also considered food sources of fat and individual fatty acids to better understand what aspects of fat may be important in pancreatic cancer etiology.

Materials and Methods

Study Population

Details of the NIH-AARP Diet and Health Study are given elsewhere (27). Briefly, the initial cohort consisted of 617 119 men and women who responded to a 124-item food frequency questionnaire (FFQ) in 1995–1996. All respondents were members of AARP,

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CONTEXT AND CAVEATS

Prior knowledge

Fat consumption has been linked to pancreatic cancer risk in some studies but not in others.

Study design

Information concerning diet and pancreatic cancer incidence was collected for a cohort of 525 473 American men and women, aged 50–71 years, from the National Institutes of Health–AARP Diet and Health Study. All participants were given a food frequency questionnaire in 1995–1996, and some were given two 24-hour dietary recall surveys within a year. Nutrient intakes were calculated from US Department of Agriculture databases, and pancreatic cancer data were collected from state cancer registries. Only cancers that occurred 1 year or more after the initial survey data until the end of 2003 were considered. Participants were divided into quintiles on the basis of percent energy from fat consumption, and hazard ratios (HRs) for risk of pancreatic cancer were estimated using Cox proportional hazards models.

Contribution

After a mean of 6.3 years of follow-up, men and women in the highest quintile of fat consumption had 53% and 23% higher incidence of pancreatic cancer, respectively, compared with the lowest quintiles for each sex. After multivariable adjustment, the combined risk of pancreatic cancer in the highest quintile, compared with the lowest quintile, was related to the intake of total fat, saturated fat, and monounsaturated fat, and particularly with the intake of saturated fat from animal sources (HR = 1.43).

Implications

Intake of saturated fats, particularly from meats and dairy products, can increase pancreatic cancer risk.

Limitations

These results are mostly based on self-reported food intakes on a food frequency questionnaire.

From the Editors

were 50–71 years old at baseline (when they completed the questionnaire), and resided in one of six US states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, Georgia, or Detroit, Michigan). Cancer incidence in the cohort was ascertained by linkage to cancer registries covering the eight states (28), as well as Arizona, Texas, and Nevada. Vital status was ascertained annually by linkage to the Social Security Administration Death Master File, as well as by cancer registry linkage. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI). All participants gave informed consent by virtue of completing the questionnaire.

From the initial respondents, we excluded 27 552 men and women who did not answer substantial portions of the questionnaire, 13 442 who indicated that they were not the intended respondent and did not complete the questionnaire, 8127 who had more than 10 recording errors or reported consuming fewer than 10 foods, 829 who later requested to be removed from the study, six who did not report whether they were male or female, 179 who completed duplicate questionnaires, 272 who died before study entry, 322 who moved out of the cancer registry ascertainment areas before study entry, 15 760 who indicated that they were not the intended respondent but completed the questionnaire, and 8584 who had a diagnosis of cancer before baseline (except for nonmelanoma skin cancer) as identified by cancer registry match. From the remaining 542 046 participants (319 484 men and 222 562 women), we excluded 132 subjects who were diagnosed with or died from pancreatic cancer within the first year of follow-up and 6663 other subjects whose follow-up lasted less than 1 year to avoid the influence of subclinical disease or reverse causation. We further excluded 9778 subjects who had reported extreme values (ie, more than two interquartile ranges above the 75th percentile or below the 25th percentile on the logarithmic scale) for total energy intake (n = 4205), total fat intake (n = 741), or percent energy from total fat (n = 4832). Our final analytic cohort consisted of 525 473 individuals (308 736 men and 216 737 women).

Dietary Data

The FFQ was a grid-based version of the NCI's Diet History Questionnaire (DHQ) (29,30). This questionnaire was designed to assess usual diet by inquiring about the frequency of consumption (in 10 categories that ranged from never to six or more times per day for beverages, and from never to two or more times per day for foods) and portion size (presented as three ranges based on national dietary data for adults representing less than the 25th, the 25th to the 75th, and greater than the 75th percentiles of intake) of 124 food items including alcohol use over the past year. In addition, the questionnaire included 21 questions about whether particular foods were consumed as versions that were sugar free, low fat, caffeine free, or whole grain, and details about the additions and types of fats, creamers, or sweeteners added to foods or used in food preparation. Portion size ranges and daily nutrient intakes were calculated using databases from the 1994–1996 US Department of Agriculture's (USDA) Continuing Survey of Food Intake by Individuals, a national dietary surveillance survey of nearly 10 000 respondents conducted at a time period consistent with administration of the NIH-AARP DHQ. Individual foods reported on 24-hour dietary recalls (24HDRs) were placed into food groups consistent with items found on the DHQ, and nutrient values for the foods listed on the DHQ were generated by calculating weighted means by food group, sex of participant, and portion size using the USDA survey nutrient database (31). The responses to the NIH-AARP DHQ were compared with two 24HDRs that were administered by telephone within a year from the baseline questionnaire and an average of 25 days apart to a stratified randomly chosen subset of the NIH-AARP participants (n = 2053) (27). The estimated energy-adjusted Pearson correlation coefficients for the DHQ and 24HDRs, adjusted for within-person random variation and total energy intake, were .72 and .62 for total fat, .76 and .69 for saturated fat, .71 and .62 for monounsaturated fat, and .53 and .56 for polyunsaturated fat in men and women, respectively (32).

Statistical Analysis

Person-years of follow-up were calculated from 1 year after the date of response to the baseline questionnaire to the date of pancreatic

cancer diagnosis or death, or to censoring at the date of another cancer diagnosis (except for nonmelanoma skin cancer), death, emigration out of the study area, or December 31, 2003, whichever occurred first. Our outcome of interest was incident adenocarcinoma of the exocrine pancreas [*International Classification of Diseases for Oncology*, third edition (33) code C250–C259]. Our case definition excluded pancreatic endocrine tumors, sarcomas, and lymphomas (*International Classification of Diseases* histology types, 8150, 8151, 8153, 8155, 8240) because the etiology of these cancers is thought to be different. Absolute rates for pancreatic cancer were standardized within 5-year age categories to the age distribution of person-years experienced by all study subjects. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models, with age as the primary time variable (34), and the Efron approximation method to handle ties (35). We verified that the proportional hazards assumption was not violated for our main exposure and other fixed covariates by including interaction terms with age (36). In a sensitivity analysis, we excluded one additional year of follow-up for all subjects (2 years in total) to reduce potential influence of subclinical cancer on dietary intake or reverse causation.

We considered intakes of total fat and fat subtypes (saturated, monounsaturated, and polyunsaturated fatty acids [PUFAs]), cholesterol, and individual fatty acids as our exposure of interest. We distinguished between n-6 and n-3 PUFAs, which arise from two distinct essential fatty acid precursors (respectively, linoleic [18:2] and α-linolenic [18:3] acids), because they tend to come from different food sources and they may have differing effects on carcinogenesis. Thus, we calculated total n-6 PUFA intake as the sum of 18:2 and 20:4 fatty acid intakes and total n-3 PUFA intake as the sum of 18:3, 18:4, 20:5, 22:5, and 22:6 fatty acid intakes. We also computed the ratio of total n-3 PUFA to total n-6 PUFA intakes. We further examined food sources of total, saturated, and monounsaturated fat, in particular red meat (beef, processed meat, red meat dishes, and sauces) and dairy products (milk, cream, yogurt, cheese, butter, ice cream, and cream soup). Together with poultry, fish, and eggs, these two groups contributed to the animal source food group, as opposed to the vegetable food group.

For each exposure variable (except n-3 to n-6 ratio), we used the multivariable density method to examine associations with fat intake independent of energy intake (37). In all models, the natural logarithm was used to transform total energy intake and fat exposure variables. We performed all analyses using the main exposure variable as either a continuous or a categorical variable. We conducted continuous analyses after examination of the spline regression terms showed no departure of the logarithm of the hazard ratio from linearity (38). Hazard ratios on the continuous scale were calculated for a twofold increase in fat intake, for example, from 20% to 40% energy from total fat. In categorical analyses, quintiles of fat intake were based on sex-specific distributions observed in the study population at baseline. Tests for linear trend were performed by using sex-specific median intake levels in each quintile. We tested for interaction by sex using the likelihood ratio test, with fat intake considered as a continuous variable. In most instances, the interaction test by sex was not statistically significant, so we present results from Cox models for men and women combined; in those models, adjustment for sex was performed by including sex as a strata variable, therefore allowing different baseline risks between men and women.

We selected a parsimonious model by including variables that were associated with pancreatic cancer risk and that changed the risk estimates for total fat intake by 10% or more (39). The final parsimonious model included smoking history (never smoked; quit ≥10 years ago; quit 5–9 years ago; quit 1–4 years ago; quit <1 year ago or current smoker with ≤20 cigarettes per day; quit <1 year ago or current smoker with >20 cigarettes per day; or missing), body mass index (BMI: <18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2, or missing), and self-reported history of diabetes (yes, no). Baseline alcohol use was not included because it did not confound the association between fat intake and pancreatic cancer in this cohort. In sensitivity analyses, we verified that both the complete case analysis [which excluded subjects with missing values in any adjustment covariates (40)] and analyses that used the Horvitz–Thompson inverse probability weighting method (41) yielded results similar to those of the main analysis. Only a small proportion of the study participants (6.2%) had missing values for at least one of the adjustment covariates included in the parsimonious models.

To correct for measurement error, we used data from the 1923 participants who were included in the calibration substudy (27,32) and met the inclusion criteria for the present analysis. We used the two-step linear regression calibration procedure (42) to adjust the hazard ratios observed in the parsimonious models on the continuous scale. First, we considered sex, smoking history, and diabetes as exactly measured covariates and corrected for measurement error in the assessment of fat and energy intakes. We took the average of the two 24HDRs as the reference instrument. We used all observations from the calibration substudy, that is, all 24HDRs regardless of whether a repeated measure was available, as well as repeated DHQ measures, by applying the Seemingly Unrelated Measurement Error Model method (43) to estimate attenuation factors and their standard errors for the assessment of fat and energy intakes only. Second, we corrected the hazard ratios using only the attenuation factors (44) because the residual confounding by energy intake was very small and not statistically significant for intakes of total fat and fat subtypes. The 95% confidence intervals for the corrected hazard ratios were calculated using the delta method to take into account uncertainties in the estimated attenuation factors (44).

We also investigated possible effect modification of fat intake and pancreatic cancer association by BMI (18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (never, quit ≥10 years ago, quit 1–9 years ago, current), and self-reported diabetes history (never, ever) with stratified analyses and likelihood ratio tests for interaction, with fat intake considered as a continuous variable. SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC) was used for all analyses. All statistical tests were two-sided, and *P* values less than .05 were considered to be statistically significant.

Results

Distributions in total fat intake expressed as a percentage of total energy intake were similar among men and women, with the median within the lowest quintile (10th percentile) being 20.8% and 20.3% of energy intake, respectively, and the median within

the highest quintile (90th percentile) being 40.0% of energy intake for both sexes. For both sexes, high consumers of total fat were more likely to have less education, to be non-Hispanic white, to have self-reported diabetes, or to be current smokers compared with low consumers (Table 1). They also had higher BMI, less physical activity, higher energy intake, and lower alcohol consumption than low consumers.

During up to 7.2 years of follow-up (mean ± SD = 6.3 ± 1.2 years), 865 men and 472 women were diagnosed with incident exocrine pancreatic cancer, reflecting incidence rates of 45.0 and 34.5 cases per 100 000 person-years, respectively. Men in the highest quintile of fat consumption (as a percentage of total energy intake) had a 53% higher incidence of pancreatic cancer than men in the lowest quintile (53.5 vs 35.0 cases per 100 000 person-years), and women in the highest quintile had a 23% higher incidence of pancreatic cancer than women in the lowest quintile (37.5 vs 30.5 cases per 100 000 person-years). After multivariable adjustment, pancreatic cancer risk was directly related to the intakes of total fat and major fat subtypes, except polyunsaturated fat (Table 2). Compared with those in the lowest quintile, men and women in the highest quintile of percent energy from fat had increased risks of pancreatic cancer associated with total fat consumption (46.8 vs 33.2 cases per 100 000 person-years, HR = 1.23, 95% CI = 1.03 to 1.46; P_{trend} = .03), with saturated fat consumption (51.5 vs 33.1 cases per 100 000 person-years, HR = 1.36, 95% CI = 1.14 to 1.62; P_{trend} < .001), and with monounsaturated fat consumption (46.2 vs 32.9 cases per 100 000 person-years, HR = 1.22, 95% CI = 1.02 to 1.46; P_{trend} = .05). Similar increases in pancreatic cancer risk were found for these three fat subgroups when we performed continuous analyses to estimate risks associated with a twofold increase in fat consumption (for total fat, HR = 1.20, 95% CI = 1.03 to 1.39; for saturated fat, HR = 1.25, 95% CI = 1.10 to 1.41; and for monounsaturated fat, HR = 1.11, 95% CI = 0.97 to 1.27). After we took dietary measurement error into account, these associations remained statistically significant for total fat (HR = 1.45, 95% CI = 1.07 to 1.97) and saturated fat (HR = 1.41, 95% CI = 1.16 to 1.72).

When we further adjusted for protein and alcohol intakes to estimate the effect of substituting calories from total fat for the same amount of calories from carbohydrates only while keeping total energy intake constant, the pancreatic cancer risk associated with total fat consumption remained virtually unchanged (HR = 1.26, 95% CI = 1.08 to 1.48) for the continuous analysis (data not shown). When we included all of the fat subtypes (saturated, monounsaturated, and polyunsaturated) with protein and alcohol intakes in the models to estimate the effect of substituting the intake of a given fat subtype for carbohydrate intake, the positive association between saturated fat intake and pancreatic cancer became more pronounced (for the continuous analysis, multivariable-adjusted HR = 1.63, 95% CI = 1.29 to 2.04), whereas monounsaturated fat intake showed a statistically significant negative relation to pancreatic cancer (for the continuous analysis, multivariable-adjusted HR = 0.66, 95% CI = 0.47 to 0.92). However, saturated

Table 1. Baseline characteristics by quintile of total fat intake as a percentage of energy among 308 736 men and 216 737 women in the National Institutes of Health–AARP Diet and Health Study*

	Men			Women		
Characteristic	**Quintile I**	**Quintile III**	**Quintile V**	**Quintile I**	**Quintile III**	**Quintile V**
Median total fat intake, % of total energy	20.8	30.8	40.0	20.3	30.0	40.0
Education, %						
≤11 y	17.9	21.2	25.3	25.5	31.4	37.4
High school	8.2	9.4	10.1	9.6	11.0	11.4
Post high school	20.4	22.0	24.1	25.0	24.3	24.9
College and postgraduate	51.1	45.0	37.5	36.7	30.2	22.6
Race/ethnicity, %						
Non-Hispanic white	91.2	92.9	93.7	88.8	89.6	90.5
Non-Hispanic black	2.8	2.6	2.7	5.2	5.7	5.3
Hispanic	2.4	1.8	1.3	2.3	1.9	1.4
Other	2.5	1.4	1.1	2.1	1.4	1.2
Mean age at baseline, y	62.5	62.3	62.0	62.0	61.9	61.8
Mean total energy intake, kcal/d	1926	1979	2207	1464	1568	1732
Mean carbohydrate intake, g/d	275.1	253.3	235.4	234.1	213.4	192.0
Mean protein intake, g/d	67.0	76.5	87.5	55.1	61.3	65.6
Mean alcohol intake, g/d	31.4	12.9	6.8	9.3	5.3	3.4
Mean body mass index, kg/m^2	26.4	27.3	28.1	25.5	27.0	27.9
Self-reported diabetes, %	6.9	9.7	14.8	4.7	7.6	10.7
Smoking history, %						
Never-smoker	30.6	30.0	25.6	44.6	44.9	39.5
Quit >10 years ago	47.1	44.5	39.5	30.0	26.1	21.4
Quit 1–9 years ago	10.5	11.1	12.3	10.8	10.9	11.4
Current smoker	7.9	10.7	18.5	10.9	14.5	24.2
Physical activity five or more times a week, %	28.6	20.0	16.6	23.3	15.0	11.2

* Sex-specific quintiles based on the distribution of total fat intake as a percentage of total energy intake observed separately for men and women in the study population at baseline.

Table 2. Energy- and multivariable-adjusted hazard ratios and 95% confidence intervals for pancreatic cancer risk in association with intakes of total fat and fat subtypes among 308 736 men and 216 737 women in the National Institutes of Health–AARP Diet and Health Study*

Fat intake	Quintile I	Quintile II	Quintile III	Quintile IV	Quintile V	P_{trend}†	Continuous‡
Total fat							
Cases/person-years	223/661 727	259/661 472	281/660 201	274/657 318	300/652 405		
Median % energy intake, men/women	20.8/20.3	26.7/25.9	30.8/30.0	34.7/34.1	40.0/40.0		
Energy-adjusted HR (95% CI)	1.00 (reference)	1.17 (0.98 to 1.40)	1.28 (1.07 to 1.52)	1.25 (1.05 to 1.50)	1.41 (1.18 to 1.67)	<.001	1.36 (1.18 to 1.58)
Multivariable-adjusted HR (95% CI)	1.00 (reference)	1.14 (0.96 to 1.37)	1.22 (1.02 to 1.45)	1.16 (0.97 to 1.39)	1.23 (1.03 to 1.46)	.03	1.20 (1.03 to 1.39)
Corrected HR§ (95% CI)							1.45 (1.07 to 1.97)
Saturated fat							
Cases/person-years	226/663 182	239/661 579	260/659 505	283/657 349	329/651 509		
Median % energy intake, men/women	5.9/5.8	7.9/7.6	9.4/9.0	11.0/10.6	13.3/13.2		
Energy-adjusted HR (95% CI)	1.00 (reference)	1.08 (0.90 to 1.29)	1.19 (0.99 to 1.42)	1.31 (1.10 to 1.57)	1.55 (1.31 to 1.84)	<.001	1.39 (1.23 to 1.56)
Multivariable-adjusted HR (95% CI)	1.00 (reference)	1.04 (0.87 to 1.25)	1.12 (0.94 to 1.34)	1.21 (1.01 to 1.45)	1.36 (1.14 to 1.62)	<.001	1.25 (1.10 to 1.41)
Corrected HR§ (95% CI)							1.41 (1.16 to 1.72)
Monounsaturated fat							
Cases/person-years	222/661 714	276/660 851	263/660 015	280/657 859	296/652 684		
Median % energy intake, men/women	7.6/7.2	10.0/9.5	11.7/11.1	13.3/12.8	15.5/15.2		
Energy-adjusted HR (95% CI)	1.00 (reference)	1.26 (1.05 to 1.50)	1.20 (1.01 to 1.44)	1.29 (1.08 to 1.54)	1.39 (1.17 to 1.66)	<.001	1.25 (1.09 to 1.43)
Multivariable-adjusted HR (95% CI)	1.00 (reference)	1.23 (1.03 to 1.46)	1.15 (0.96 to 1.37)	1.20 (1.00 to 1.43)	1.22 (1.02 to 1.46)	.05	1.11 (0.97 to 1.27)
Corrected HR§ (95% CI)							1.23 (0.95 to 1.59)
Polyunsaturated fat							
Cases/person-years	256/658 703	263/659 965	243/659 702	300/658 512	275/656 241		
Median % energy intake, men/women	4.5/4.5	5.7/5.8	6.7/6.9	7.8/8.1	9.6/10.2		
Energy-adjusted HR (95% CI)	1.00 (reference)	1.03 (0.87 to 1.22)	0.95 (0.79 to 1.13)	1.17 (0.99 to 1.38)	1.07 (0.90 to 1.27)	.21	1.11 (0.98 to 1.25)
Multivariable-adjusted HR (95% CI)	1.00 (reference)	1.02 (0.86 to 1.21)	0.92 (0.77 to 1.10)	1.13 (0.95 to 1.33)	1.00 (0.84 to 1.18)	.68	1.05 (0.93 to 1.19)
Corrected HR§ (95% CI)							1.17 (0.81 to 1.69)

* Energy-adjusted bivariate Cox regression models stratified by sex (sex-specific quintiles in the categorical analysis), adjusted for total energy intake (continuous), using age as the underlying time metric. Multivariable-adjusted Cox regression models stratified by sex, adjusted for total energy intake (continuous), smoking history (never smoked; quit ≥10 years ago; quit 5–9 years ago; quit 1–4 years ago; quit <1 year ago or current smoker with ≤20 cigarettes per day; quit <1 year ago or current smoker with >20 cigarettes per day; or missing), body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2, or missing), and self-reported history of diabetes (yes, no). HR = hazard ratio; CI = confidence interval.

† Two-sided Wald χ^2 test for linear trend using median intake in each quintile.

‡ HRs presented for a twofold increase in percent energy from fat.

§ Corrected for measurement error in assessment of fat and energy intakes, adjusted for smoking history, body mass index, and self-reported history of diabetes.

and monounsaturated fat intakes were highly correlated in this cohort (Spearman coefficient = .80).

When we considered food sources of fat, the positive association of total, saturated, and monounsaturated fat with pancreatic cancer that we observed was mostly determined by animal foods, especially red meat and dairy products, and was not determined by vegetable food sources (Table 3 and Figure 1 for saturated fat only). Unlike polyunsaturated fat intake, meat and dairy foods were the main food sources for total, saturated, and monounsaturated fat (45). A borderline statistically significant interaction by sex was observed for the relationship of pancreatic cancer to saturated fat intake from red meat ($P = .05$ for the multivariable-adjusted analysis), men showing a strong statistically significant association (for extreme quintile comparison, 58.9 vs 34.5 cases per 100 000 person-years, multivariable-adjusted HR = 1.49, 95% CI = 1.20 to 1.86; $P_{trend} = .001$), whereas no association was observed in women (data not shown). By contrast, the statistically significant positive association between saturated fat intake from dairy and pancreatic cancer was suggested in both men (for extreme quintile comparison, 52.1 vs 41.0 cases per 100 000 person-years, HR = 1.16, 95% CI = 0.94 to 1.43; $P_{trend} = .07$) and women (39.1 vs 29.5 cases per 100 000 person-years, HR = 1.26, 95% CI = 0.94 to 1.68; $P_{trend} = .03$). For men and women combined, we observed statistically significant positive associations of pancreatic cancer risk with saturated fat intake from both red meat (for extreme quintile comparison, 48.2 vs 33.4 cases per 100 000 person-years, HR = 1.27, 95% CI = 1.07 to 1.52; $P_{trend} = .02$) and dairy products (48.2 vs 33.4 cases per 100 000 person-years, HR = 1.19, 95% CI = 1.01 to 1.42; $P_{trend} = .005$). Altogether, saturated fat intake from animal food sources was associated with an increased risk of pancreatic cancer (52.0 vs 32.2 cases per 100 000 person-years, HR = 1.43, 95% CI = 1.20 to 1.70; $P_{trend} < .001$).

When we considered intakes of individual fatty acids, pancreatic cancer risk was consistently related to the types of fatty acids that primarily came from animal food sources (Table 4). We observed statistically significant positive associations for both the categorical and the continuous analyses with saturated palmitic (16:0) and stearic (18:0) acids, monounsaturated palmitoleic acid (16:1), polyunsaturated arachidonic acid (20:4), and *trans* 16:1 fatty acid; hazard ratios contrasting the highest to the lowest quintile were similar, ranging from 1.31 (95% CI = 1.10 to 1.56) for stearic acid to 1.38 (95% CI = 1.17 to 1.64) for *trans* 16:1 fatty acid. Conversely, monounsaturated oleic acid (18:1), its *trans* isomer, and *trans* 18:2-showed no association with pancreatic cancer. Of note, individual *trans* fatty acids differed in terms of food sources and estimated intakes, *trans* 16:1 (median, 0.02% energy) originating mainly from red meat, butter and margarines, and the other two (*trans* 18:1 at 1.8% energy and *trans* 18:2 at 0.2% energy) originating from likely sources of partially hydrogenated vegetable oils, including butter and margarines, cakes, and bread. Finally, pancreatic cancer risk was not related to long-chain n-3 eicosapentaenoic acid (20:5), but a statistically significant positive association was seen with docosahexaenoic acid (22:6) in the categorical analysis (for extreme quintile comparison, 44.1 vs 36.3 cases per 100 000 person-years, HR = 1.25, 95% CI = 1.05 to 1.49; $P_{trend} = .009$). With the addition of linolenic acid (18:3) and stearidonic acid (18:4), the sum of n-3 PUFA intakes was associated with an

Table 3. Multivariable-adjusted hazard ratios and 95% confidence intervals for pancreatic cancer risk in association with total, saturated, and monounsaturated fat intakes by food sources among 308 736 men and 216 737 women in the National Institutes of Health–AARP Diet and Health Study*

Fat intake	Quintile I	Quintile II	Quintile III	Quintile IV	Quintile V	P_{trend}†	Continuous‡
Total fat from							
Red meat, HR (95% CI)	1.00 (reference)	1.27 (1.07 to 1.51)	1.09 (0.91 to 1.31)	1.22 (1.02 to 1.46)	1.32 (1.11 to 1.58)	.01	1.06 (1.00 to 1.12)
Dairy products, HR (95% CI)	1.00 (reference)	0.96 (0.80 to 1.15)	1.09 (0.91 to 1.30)	1.21 (1.02 to 1.44)	1.19 (1.01 to 1.42)	.004	1.07 (1.01 to 1.12)
Animal food sources,§ HR (95% CI)	1.00 (reference)	1.00 (0.83 to 1.20)	1.12 (0.94 to 1.34)	1.28 (1.07 to 1.52)	1.33 (1.12 to 1.59)	<.001	1.23 (1.11 to 1.36)
Vegetable food sources, HR (95% CI)	1.00 (reference)	1.02 (0.86 to 1.21)	1.07 (0.90 to 1.27)	1.04 (0.88 to 1.23)	0.97 (0.82 to 1.15)	.83	1.00 (0.91 to 1.09)
Saturated fat from							
Red meat, HR (95% CI)	1.00 (reference)	1.18 (0.99 to 1.41)	1.09 (0.91 to 1.30)	1.17 (0.98 to 1.39)	1.27 (1.07 to 1.52)	.02	1.06 (1.00 to 1.12)
Dairy products, HR (95% CI)	1.00 (reference)	0.96 (0.81 to 1.16)	1.08 (0.91 to 1.29)	1.19 (1.01 to 1.42)	1.19 (1.01 to 1.42)	.005	1.06 (1.01 to 1.12)
Animal food sources,§ HR(95% CI)	1.00 (reference)	1.10 (0.92 to 1.32)	1.08 (0.90 to 1.29)	1.33 (1.11 to 1.58)	1.43 (1.20 to 1.70)	<.001	1.19 (1.09 to 1.30)
Vegetable food sources, HR (95% CI)	1.00 (reference)	1.03 (0.87 to 1.22)	1.04 (0.88 to 1.24)	0.91 (0.76 to 1.08)	1.06 (0.90 to 1.25)	.94	1.02 (0.94 to 1.11)
Monounsaturated fat from							
Red meat, HR (95% CI)	1.00 (reference)	1.21 (1.01 to 1.44)	1.09 (0.91 to 1.31)	1.19 (1.00 to 1.42)	1.29 (1.08 to 1.54)	.02	1.06 (1.00 to 1.12)
Dairy products, HR (95% CI)	1.00 (reference)	1.05 (0.88 to 1.26)	1.14 (0.95 to 1.36)	1.26 (1.06 to 1.50)	1.25 (1.05 to 1.48)	.002	1.07 (1.01 to 1.12)
Animal food sources,§ HR (95% CI)	1.00 (reference)	1.08 (0.90 to 1.30)	1.27 (1.06 to 1.52)	1.24 (1.03 to 1.48)	1.44 (1.21 to 1.72)	<.001	1.22 (1.11 to 1.35)
Vegetable food sources, HR (95% CI)	1.00 (reference)	1.10 (0.92 to 1.30)	1.06 (0.89 to 1.26)	1.11 (0.93 to 1.31)	0.96 (0.81 to 1.14)	.74	0.97 (0.90 to 1.05)

* Energy-adjusted bivariate Cox regression models stratified by sex (sex-specific quintiles in the categorical analysis), adjusted for total energy intake (continuous), using age as the underlying time metric. Multivariable-adjusted Cox regression models stratified by sex, adjusted for total energy intake (continuous), smoking history (never smoked; quit ≥10 years ago; quit 5–9 years ago; quit 1–4 years ago; quit <1 year ago or current smoker with ≤20 cigarettes per day; quit <1 year ago or current smoker with >20 cigarettes per day; or missing), body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2, or missing), and personal history of diabetes (yes, no).

† Two-sided Wald χ^2 test for linear trend using median intake in each quintile.

‡ HRs presented for a twofold increase in percent energy from fat.

§ Animal foods include red meat and dairy products, as well as other meat, fish, and eggs.

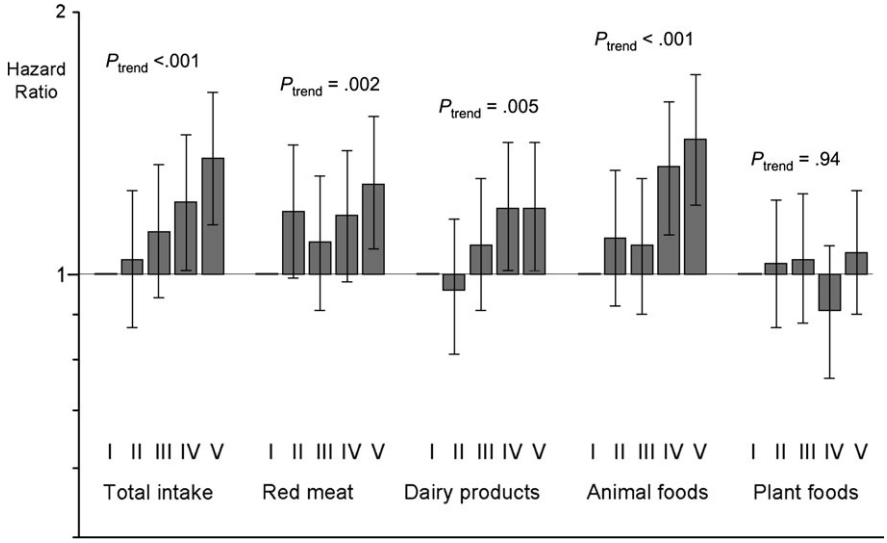

Figure 1. Multivariable-adjusted hazard ratios (**vertical bars**) and 95% confidence intervals (**vertical lines**) for pancreatic cancer risk in association with quintiles (I–V) of saturated fat intake according to food sources among 308736 men and 216737 women in the National Institutes of Health–AARP Diet and Health Study. Multivariable-adjusted Cox regression models were adjusted as in Table 3. Animal foods include red meat and dairy products, other meat, fish, and eggs. *P* values are from two-sided Wald χ^2 tests for linear trend using median intake in each quintile.

increased risk of pancreatic cancer (for extreme quintile comparison, 43.8 vs 34.8 cases per 100 000 person-years, HR = 1.21, 95% CI = 1.02 to 1.44; P_{trend} = .01), whereas the ratio of n-3 to n-6 PUFA did not show any association for the categorical analysis.

Because dietary cholesterol is found only in animal foods (mostly eggs, fish, and poultry in this cohort), we also examined cholesterol intake and pancreatic cancer. Compared with those in the lowest quintile, men and women in the highest quintile of cholesterol intake (expressed as milligrams per 1000 kcal) had an increased risk of pancreatic risk (49.5 vs 34.1 cases per 100000 person-years, HR = 1.28, 95% CI = 1.08 to 1.52; P_{trend} < .001). However, when adjusted for saturated fat intake, this association became non–statistically significant (HR = 1.15, 95% CI = 0.93 to 1.42; P_{trend} = .07).

The positive associations of pancreatic cancer with intakes of total, saturated, and monounsaturated fat; saturated fat from red meat, dairy products, and animal food sources; total n-3 PUFAs; and *trans* 16:1 fatty acids all remained statistically significant after we further excluded the second year of follow-up after baseline (1177 cases of pancreatic cancer left; data not shown). We did not find evidence of effect modification by BMI, self-reported diabetes, or smoking history ($P_{interaction}$ > .5 in most instances; data not shown). Among the limited number of lifelong never-smokers (359 cases), those in the highest quintile of saturated fat intake overall (compared with the lowest quintile; 35.6 vs 25.6 cases per 100000 person-years, HR = 1.33, 95% CI = 0.94 to 1.87; P_{trend} = .05) and those in the highest quintile of saturated fat intake from animal sources (39.7 vs 24.0 cases per 100000 person-years, HR = 1.45, 95% CI = 1.03 to 2.03; P_{trend} = .02) remained at increased risk of pancreatic cancer.

Discussion

In this large prospective study, we found statistically significant associations between intakes of total, saturated, and monounsaturated fat, but not polyunsaturated fat, and pancreatic cancer. Further examination of the food sources of fatty acids revealed positive associations with saturated fat from animal sources (especially red meat and dairy products), as well as with the individual fatty acids that originate mostly from these food sources.

Few prospective studies have examined associations between dietary fat and pancreatic cancer, and their findings have been inconsistent. This inconsistency may be due to the small number of patients diagnosed with pancreatic cancer and/or to the narrow range of fat intakes in these cohorts, either of which would limit the ability to observe associations if they existed. One cohort study among male smokers in Finland (12) provided suggestive evidence of a positive association of exocrine pancreatic cancer with total and saturated fat but not with other fat components. In the Finnish population, consumption of dairy products, in particular butter and to a lesser extent cream, likely contributed to those associations (12). Subsequent analyses in the Nurses' Health Study (24) and the Multiethnic Cohort Study (13) showed no association for overall fat intake and pancreatic cancer. However, when food sources of fat were examined in the latter cohort, total fat and saturated fat from red meat and processed meat were positively related to pancreatic cancer (13). Our finding of an association between dietary fat and pancreatic cancer mostly driven by animal food sources is consistent with reports from both the Finnish and the Multiethnic studies. In the NIH-AARP cohort, a positive association was seen for saturated and monounsaturated fat from dairy products, as well as from red meat, whereas pancreatic cancer was unrelated to fat from dairy products in the Multiethnic Cohort Study (13).

A larger number of case–control studies on dietary fat and pancreatic cancer have been published. A positive association of pancreatic cancer with total fat was found in four (6,8–10) of 12 studies (14,16–21,23). However, none of these studies examined associations with dietary fat by its food sources, although one US study reported an increased risk of pancreatic cancer with high consumption of high-fat foods, particularly bacon and sausages, as well as with high-fat foods other than meat or dairy, in both men and women (46). The failure to identify consistent risk factors likely reflects the methodological difficulties including reverse causation,

Table 4. Multivariable-adjusted hazard ratios and 95% confidence intervals for pancreatic cancer risk in association with individual fatty acid intakes among 308736 men and 216737 women in the National Institutes of Health–AARP Diet and Health Study*

Dietary variable	Quintile I	Quintile II	Quintile III	Quintile IV	Quintile V	P_{trend}†	Continuous‡
Saturated fatty acids							
Palmitic acid, 16:0, HR (95% CI)	1.00 (reference)	1.06 (0.88 to 1.27)	1.08 (0.91 to 1.30)	1.21 (1.02 to 1.44)	1.33 (1.11 to 1.58)	<.001	1.27 (1.10 to 1.46)
Stearic acid, 18:0, HR (95% CI)	1.00 (reference)	1.08 (0.91 to 1.30)	1.18 (0.99 to 1.41)	1.06 (0.89 to 1.27)	1.31 (1.10 to 1.56)	.008	1.22 (1.07 to 1.38)
Monounsaturated fatty acids							
Palmitoleic acid, 16:1, HR (95% CI)	1.00 (reference)	1.07 (0.89 to 1.28)	1.20 (1.00 to 1.43)	1.29 (1.08 to 1.54)	1.34 (1.12 to 1.59)	<.001	1.26 (1.13 to 1.41)
Oleic acid, 18:1, HR (95% CI)	1.00 (reference)	1.15 (0.97 to 1.38)	1.16 (0.97 to 1.39)	1.15 (0.96 to 1.37)	1.16 (0.97 to 1.39)	.12	1.09 (0.96 to 1.25)
n-6 Polyunsaturated fatty acids							
Linoleic acid, 18:2, HR (95% CI)	1.00 (reference)	1.00 (0.84 to 1.19)	0.96 (0.81 to 1.14)	1.04 (0.88 to 1.23)	0.99 (0.83 to 1.17)	.98	1.04 (0.92 to 1.16)
Arachidonic acid, 20:4, HR (95% CI)	1.00 (reference)	1.16 (0.98 to 1.38)	1.07 (0.90 to 1.28)	1.20 (1.01 to 1.43)	1.33 (1.12 to 1.58)	.002	1.10 (1.02 to 1.18)
Total, HR (95% CI)	1.00 (reference)	1.01 (0.85 to 1.20)	0.97 (0.82 to 1.16)	1.05 (0.89 to 1.25)	0.99 (0.84 to 1.18)	.91	1.04 (0.92 to 1.17)
n-3 Polyunsaturated fatty acids							
Linolenic acid, 18:3, HR (95% CI)	1.00 (reference)	1.13 (0.95 to 1.34)	0.99 (0.83 to 1.19)	1.17 (0.98 to 1.39)	1.13 (0.95 to 1.34)	.15	1.11 (0.98 to 1.25)
Eicosapentaenoic acid, 20:5, HR (95% CI)	1.00 (reference)	1.05 (0.88 to 1.25)	1.14 (0.96 to 1.36)	1.03 (0.86 to 1.22)	1.19 (1.00 to 1.41)	.35	1.00 (0.98 to 1.02)
Docosahexaenoic acid, 22:6, HR (95% CI)	1.00 (reference)	1.10 (0.92 to 1.31)	1.13 (0.95 to 1.35)	1.17 (0.98 to 1.39)	1.25 (1.05 to 1.49)	.009	1.02 (0.98 to 1.06)
Total n-3, HR (95% CI)	1.00 (reference)	1.13 (0.95 to 1.35)	1.10 (0.92 to 1.31)	1.29 (1.09 to 1.53)	1.21 (1.02 to 1.44)	.01	1.14 (1.01 to 1.29)
Ratio of n-3 to n-6 fatty acids, HR (95% CI)	1.00 (reference)	0.91 (0.76 to 1.08)	1.12 (0.95 to 1.32)	1.02 (0.86 to 1.21)	1.06 (0.89 to 1.25)	.28	1.20 (1.00 to 1.43)
Trans unsaturated fatty acids							
trans 16:1, HR (95% CI)	1.00 (reference)	1.02 (0.85 to 1.23)	1.15 (0.96 to 1.38)	1.17 (0.98 to 1.40)	1.38 (1.17 to 1.64)	<.001	1.06 (1.01 to 1.10)
trans 18:1, HR (95% CI)	1.00 (reference)	0.99 (0.83 to 1.17)	1.08 (0.91 to 1.28)	0.97 (0.82 to 1.16)	1.01 (0.85 to 1.20)	.98	1.02 (0.93 to 1.12)
trans 18:2, HR (95% CI)	1.00 (reference)	0.98 (0.82 to 1.17)	1.06 (0.89 to 1.26)	1.09 (0.92 to 1.30)	1.00 (0.84 to 1.19)	.69	1.06 (0.96 to 1.17)
Total, HR (95% CI)	1.00 (reference)	0.93 (0.78 to 1.10)	1.05 (0.89 to 1.25)	0.97 (0.81 to 1.15)	0.99 (0.83 to 1.17)	>.99	1.03 (0.94 to 1.13)

* Multivariable-adjusted Cox regression models using age as the underlying time metric, stratified by sex (sex-specific quintiles in the categorical analysis), adjusted for total energy intake (continuous), smoking history (never smoked; quit ≥10 years ago; quit 5–9 years ago; quit 1–4 years ago; quit <1 year ago or current smoker with ≤20 cigarettes per day; quit <1 year ago or current smoker with >20 cigarettes per day; or missing), body mass index (<18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2, or missing), and self-reported history of diabetes (yes, no). HR = hazard ratio; CI = confidence interval.

† Two-sided Wald χ^2 test for linear trend using median intake in each quintile.

‡ HRs presented for a twofold increase in percent energy from fat.

recall and surrogate reporting, selection, and survival biases associated with collecting data, particularly within case–control studies for this rapidly fatal gastrointestinal cancer. Cohort studies are less prone to these biases.

The associations of intakes of total, saturated, and monounsaturated fat with pancreatic cancer that we observed in this cohort were independent of energy intake. Moreover, neither consumption of meat nor methods of meat preparation alone appeared to explain our fat findings. Indeed, an association between saturated fat from red meat and pancreatic cancer was seen in men only—consistent with what was reported in this cohort for red meat consumption (26)—whereas the association with saturated fat overall and from dairy products did not differ between men and women. A general mechanism for a direct association between fat intake and pancreatic cancer could be related to the exocrine function of the pancreas, which excretes enzymes such as lipases that digest fat. Fats and fatty acids contained in chyme enter the duodenum, which releases cholecystokinin to stimulate pancreatic enzyme secretion and pancreatic hypertrophy and hyperplasia, which could in turn increase the susceptibility of the pancreas to other carcinogens (47). Dietary fat has generally been observed in animal experiments to promote pancreatic carcinogenesis, but it seems unclear whether this is mediated by cholecystokinin release or through other pathways (47). In addition, saturated fat has been associated with insulin resistance in several observational studies as well as in randomized controlled trials (48). Diabetes and insulin resistance are related to increased pancreatic cancer risk in both epidemiological and animal studies (49–51).

Studies relating pancreatic cancer to individual fatty acid intakes are scarce. High consumption of PUFAs and more specifically linoleic acid (18:2), the most common PUFA and the precursor of the n-6 family, has been associated with decreased risk in a few case–control studies (14,16–18) but not in cohort studies (12,24). Consistently, our study suggested no association between PUFA, total n-6, or linoleic acid intakes and pancreatic cancer. Only dietary arachidonic acid (20:4), an n-6 PUFA from mostly animal foods, was statistically significantly associated with an increased risk of pancreatic cancer. Previously published studies did not provide evidence for a protective effect of high consumption of n-3 PUFA (12,14,24,25,52) or fish, a major source for long-chain n-3 PUFAs (10,12,52–54). An increased risk of pancreatic cancer with high consumption of total fish was reported in one case–control study in the Netherlands (55), and an increased risk of pancreatic cancer in women, but not in men, with high consumption of seafood was reported in one case–control study in Louisiana (56). To our knowledge, the ratio of n-3 to n-6 fatty acid intakes has not been examined with respect to pancreatic cancer, although they have been related to cancer of other sites, including breast, colon, and prostate (57). Consideration of the ratio of n-3 PUFA to n-6 PUFA intakes is of interest because both categories of PUFAs compete in the biosynthesis of eicosanoids (58–60). Eicosanoids such as prostaglandins influence several biological processes, including inflammation, cell proliferation, apoptosis, and angiogenesis, and eicosanoids could play a role in pancreatic cancer as shown with other gastrointestinal cancers (60). In this study, we did not find any suggestion of an association between the n-3 to n-6 ratio and pancreatic cancer; however, total n-3 PUFA intake was associated with an increased risk of pancreatic cancer, regardless of n-6 PUFA intake. We note that in this cohort, as in other Western populations (61,62), red meat and poultry consumption, in addition to vegetable and fish or seafood sources, contributed to both linolenic acid and long-chain n-3 PUFA intake (63).

The consumption of *trans* fatty acids has been hypothesized to contribute to the risk of cancer, in addition to that of cardiovascular diseases (64). *Trans* unsaturated fatty acids have been linked to type 2 diabetes (65) and may impair insulin sensitivity, although the evidence for the latter seems to be less consistent than for saturated fat (66). High levels of *trans* fatty acids in blood have been associated with an increased risk of breast (67,68) and prostate (69,70) cancers, but studies based on estimated dietary intakes have been less conclusive. In our study, we found an increased risk of pancreatic cancer with high consumption of *trans* 16:1 fatty acid but not so consistently with other more common *trans* fatty acids. The null association for total *trans* fatty acids was consistent with previously published studies (24,25).

The strengths of our prospective cohort study include its large sample size and wide range of fat intake (27) from diverse food sources. Recall bias was precluded because information on exposure was collected before diagnosis of pancreatic cancer. Moreover, to avoid reverse causation, the first year of follow-up was discarded from the main analysis, and we found similar results when the second year of follow-up was further excluded in sensitivity analyses.

There are also limitations in the current study. First, we cannot exclude spurious associations in view of the large number of tests performed. However, we found some internal consistency in our results, with a positive association between pancreatic cancer from animal fat intake but not from vegetable fat. Second, spurious associations may also arise from unmeasured or insufficiently controlled confounding variables. However, the positive associations between saturated fat and pancreatic cancer seen among lifelong never-smokers suggest that residual confounding by smoking does not explain the direct associations in this cohort. Similarly, these associations held among self-reported nondiabetic participants and did not differ between leaner and heavier subjects, contrary to one recent case–control analysis (25). Finally, measurement error in reported dietary habits could have affected our results; although associations remained statistically significant after correction for measurement error, we should acknowledge the limitations of using another self-report (24HDRs) as a reference instrument (71). However, it seems likely that measurement error correction based on the 24HDRs is in the right direction but still underestimates the true hazard ratio (45).

In conclusion, we observed positive associations between pancreatic cancer and intakes of total, saturated, and monounsaturated fat overall, particularly from red meat and dairy food sources. We did not observe any consistent association with polyunsaturated, saturated, or monounsaturated fat from plant food sources. Altogether, these results suggest a role for animal fat in pancreatic carcinogenesis.

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