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Dietary fat intake and risk of pancreatic cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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Abstract

Purpose—Epidemiologic and experimental studies suggest that dietary fat intake may affect risk of pancreatic cancer, but published results are inconsistent.

Method—We examined risk associations for specific types of dietary fat intakes and related food sources among 111,416 participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. We used Cox proportional hazards regression to examine associations between fat intake and pancreatic cancer risk.

Results—During a mean 8.4 years of follow-up 411 pancreatic cancer cases were identified. We observed an inverse association between saturated fat intake and pancreatic cancer risk (Hazard ratio (HR)=0.64 comparing extreme quintiles, 95% Confidence Interval (CI) 0.46–0.88), but the association became weaker and non-significant when individuals with <4 years of follow-up were excluded to avoid possible reverse causation: HR=0.88 (95% CI 0.58–1.33). Total fat intake showed a similar pattern of association, while intakes of monounsaturated and polyunsaturated fats and fats from animal or plant sources showed no associations with risk.

Conclusions—These results do not support the hypothesis of increased pancreatic cancer risk with higher fat consumption overall or by specific fat type or source. Dietary changes due to undetected disease may explain the observed inverse association with saturated fat.

Keywords

Dietary fats; Cohort studies; Pancreatic neoplasms; epidemiology

Introduction

Identification of pancreatic cancer risk factors is of great importance because few individuals survive long after diagnosis. Pancreatic cancer is the 4th leading cause of cancer death in the U.S. [1]. While some animal studies report a detrimental effect of high

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unsaturated fat consumption [2–4], epidemiologic literature on dietary fat intake and pancreatic cancer risk is inconsistent, with some studies finding an increased risk of pancreatic cancer with higher total fat or saturated fat consumption [5–7], and others showing an increased [8] or reduced [9] risk of pancreatic cancer with higher specific saturated and monounsaturated fatty acid intakes. Other studies show no association with pancreatic cancer risk [10–15]. Some studies have also shown a positive association for animal fat intake overall [16–17] and specifically for fat from red meat [5, 10] and dairy [5–6].

Dietary fat intake is particularly challenging to study in relation to pancreatic cancer given the extended undetectable phase of tumorigenesis [18] and the dietary changes that can occur during this pre-diagnostic, but increasingly symptomatic period [19]. Studies that account for changes in dietary practices in the years prior to diagnosis are needed to address the problem of reverse causation. We examined the association between fat intake and pancreatic cancer risk in a large, prospective cohort of men and women.

Methods

Study population

The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial was a randomized clinical trial (enrollment 1993–2001) designed to assess whether screening tests reduce mortality from these four cancers among 37,000 men and 37,000 women in a screened arm, and an equal number of control men and women [20]. The study has been previously described and was approved by all participating institutional review boards and the National Cancer Institute [21]. At baseline, men and women aged 55–74 years old completed questionnaires on demographic information and medical history. Three years after enrollment, 116,734 participants completed a self-administered Diet History Questionnaire (DHQ), reporting frequencies and portion sizes of 124 foods and supplements consumed over the previous year. The DHQ has been validated against four 24-hour dietary recalls (Spearman correlation coefficients for total fat=0.66 for men and 0.62 for women) [22].

We excluded from analyses participants who had 8 missing response items on the DHQ or who were in the top or bottom 1% of the distribution of total energy intake (n=5221), participants with a history of pancreatic cancer (n=76), and those without recorded follow-up time (n=21). After exclusions, our analytic cohort included 111,416 participants with average follow-up time of 8.4 years.

Ascertainment of pancreatic cancer cases

Incident pancreatic adenocarcinomas (n=411) were identified through annual mailed, self-administered study questionnaires or from periodic cohort linkages to the National Death Index. Diagnoses were confirmed by pathology reports and medical record abstractions. We excluded pancreatic endocrine tumors, sarcomas and lymphomas as these types of cancers likely differ etiologically from exocrine pancreatic cancer. Follow-up time began at completion of the dietary questionnaire and ended at pancreatic cancer diagnosis, death, study withdrawal or administrative cutoff date (12/31/2009 or 13 years from individual trial entry date), whichever happened first.

Statistical analysis

We used nutrient density energy-adjustment to account for differences in caloric intake [23]. Using gender-specific quintiles of fat intake, we first examined baseline characteristics and dietary data from the DHQ. We then used Cox proportional hazards models to calculate

hazard ratios (HRs) and 95% confidence intervals (CIs). Putative risk factors and those that changed the log HRs by >10% were included in models. The final models included age at DHQ completion and the following baseline covariates: sex, smoking status (never, former, current), body mass index (BMI; <18.5, 18.5–<25, 25–<30, 30+ kg/m², missing), and self-reported diabetes mellitus (yes/no). Adding educational attainment, family history of pancreatic cancer or red meat to the models did not alter parameter estimates. We also tested for the possibility of a non-linear association between dietary fat and pancreatic cancer risk non-parametrically with restricted cubic splines [24]. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and cubic spline terms. Furthermore, we considered effect modifiers of fat in stratified analyses and tested for interactions with sex, BMI and time. Only the latter proved significant, and examining Wald test statistics in two-year increments across follow-up suggested that differences in risk apparent between two distinct intervals, 0–4 and >4 years from baseline, sufficed. The proportional hazards assumption, which was tested by creating an interaction term with person time and using the Wald test for statistical significance, was met for all covariates in the model. All analyses were conducted in SAS version 9.2 and statistical significance was determined using a two-sided alpha level of 0.05.

Results

Baseline participant characteristics by alternate quintiles of total fat intake and by sex are given in Table 1. Participants who reported higher fat intake were more likely to be non-Hispanic white, less educated, current smokers, have a higher BMI, and higher percent energy intake from fat. Intake of fat from both animal (dairy, meat, fish and eggs) and plant sources was higher among those consuming more fat.

Multivariable-adjusted models showed that higher saturated fat intake was associated with reduced pancreatic-cancer risk (Q5 versus Q1 HR=0.64, 95% CI 0.46–0.88), although the association became non-significant when 4406 individuals (162 cases) with <4 years of follow-up time were excluded (HR=0.88, 95% CI 0.58–1.33) (Table 2). On average saturated fat was 31.7% of total fat intake, and the associations for total fat paralleled those observed for saturated fat; after exclusion of participants with <4 years of follow up the total fat HR=0.76 (95% CI 0.51–1.15). Monounsaturated and polyunsaturated fat intakes were not associated with pancreatic cancer.

After separating dietary fat by animal and plant sources (Table 3), saturated and monounsaturated fats from animal sources were associated with risk comparing the highest to lowest intake quintiles (HR=0.70, 95% CI 0.52–0.96 and HR=0.70, 95% CI 0.51–0.95, respectively). For saturated fat from animal sources the association appeared to be influenced by dairy intake (HR=0.61, 95% CI 0.44–0.84). Intake of polyunsaturated fat from plant sources was inversely associated with risk (p-trend=0.034), although the hazard ratios comparing extreme quintiles were not statistically different. Formal tests for interaction with follow up time were not significant, but in analyses excluding those with <4 years of follow-up each of these associations was non-significant (data not shown).

Discussion

In our study population no association was observed between dietary fat intake and pancreatic cancer incidence after excluding subjects with <4 years of follow-up. Eliminating cases diagnosed within the first four years is intended to exclude those who may have changed dietary intake prior to baseline due to latent disease. Dyspepsia, or impaired digestion, is a common symptom of pancreatic cancer and may be triggered by high fat intake [25–26].

Published data on the association between dietary fat intake and pancreatic cancer risk is limited and inconsistent [27]. Of seven identified prospective cohorts that examined the association between total fat intake and pancreatic cancer, two reported an increased risk with greater fat intake [5, 28], while four reported no statistically significant association [10–11, 13, 29] and a previous analysis in this cohort suggested an inverse association before exclusion of early cases [12]. In these studies follow-up time ranged from 6.5–18 years and number of cases ranged from 83–1337. Associations with saturated fat are also mixed, with some studies reporting positive risk estimates in the range of 30–40% [5, 28], and others finding no association [10–11, 13].

Prospective studies where the association between fat sources and risk of pancreatic cancer was examined have suggested positive associations with pancreatic cancer specifically from animal fat in red and processed meats [5, 10], dairy [5] or butter [6]. One of these studies detailed that positive patterns were observed for saturated fat and monounsaturated fat from animal sources, but not from vegetable food sources [5]. Our findings may differ from the results described above due to differences in FFQs, study population, or timing from data collection to diagnosis.

Mechanisms explaining a possible association between dietary fat and carcinogenesis are well documented [30]. Some animal studies have reported no effect of saturated fat on pancreatic cancer carcinogenesis but a detrimental effect of high unsaturated fat consumption [2–4]. This suggests that fat mechanisms may extend beyond caloric density. Saturated fats are more readily stored as energy than carbohydrate and protein, are not efficiently oxidized for energy, and increase the expression of genes associated with adipocyte proliferation [31]. As described above, while some epidemiological studies have associated higher saturated fat intake with increased pancreatic cancer risk, the present study showed no such association.

Strengths of our study include the prospective nature of the cohort, precluding differential recall between cases and non-cases. In addition, with 411 cases we were better powered to detect an association than previous studies in this cohort and the extended duration of follow-up allowed for more in-depth evaluation of the relationship between time from the DHQ to pancreatic cancer diagnosis. We also were able to examine fat by dietary source to further investigate differences in type of fat consumption and pancreatic cancer risk. Limitations of our study include the measurement error inherent to the DHQ. Also, demographic characteristics and medical history were collected only at baseline and we used only a single dietary questionnaire. However, these factors may have changed over the time from questionnaire completion to pancreatic cancer diagnosis.

In conclusion, our findings do not support a positive association between dietary fat intake and risk of pancreatic cancer. Instead, we observed an inverse association that was attenuated with exclusion of cases with shorter-term follow-up. Our results highlight the need to carefully examine possible reverse causation in studies of diet and pancreatic malignancy and the importance of basing conclusions on a body of evidence from studies with longer-term followup.

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List of abbreviations

BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
NIH	National Institutes of Health
PLCO	Prostate, Lung, Colorectal and Ovarian
DHQ	Diet History Questionnaire

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Table 1

Characteristics of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial cohort by quintile of fat intake^a

	Men (n=53,670)					Women (n=57,746)				
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q5
Baseline characteristics										
Mean age (SD) at baseline (years)	63.2 (5.8)	62.8 (5.3)	61.9 (5.1)	63.2 (5.4)	62.5 (5.4)	61.7 (5.2)				
Race (%)										
Non-Hispanic White	87.2	91.1	91.2	88.5	91.9	92.3				
Non-Hispanic Black	3.1	2.7	2.9	4.8	3.4	3.7				
Hispanic	1.4	1.7	2.0	1.3	1.0	1.5				
Other	8.2	4.5	2.9	5.5	3.7	2.5				
Education (%)										
Less than high school	6.0	6.7	8.1	4.3	4.8	6.5				
High school	15.6	18.1	20.9	24.3	27.6	30.5				
Post high school/ some college	29.7	32.6	35.3	35.4	36.8	37.2				
College or graduate	48.4	42.4	35.3	35.8	30.7	25.6				
Mean (SD) body mass index (kg/m ²)	26.7 (3.8)	27.5 (3.9)	28.4 (4.5)	25.8 (4.9)	27.1 (5.3)	28.0 (5.8)				
Smoking history (%)										
Never	38.3	39.2	33.1	58.3	57.9	51.7				
Former	54.5	52.2	51.7	35.7	34.6	35.1				
Current	7.2	8.6	15.1	6.0	7.6	13.2				
Self-reported diabetes (%)	6.5	7.5	10.3	4.4	5.4	6.6				
Family history of pancreatic cancer (%)	2.5	2.1	2.2	3.2	3.1	2.9				
Mean (SD) daily nutrient intake at time of Dietary History Questionnaire										
Calories (kcal)	1814 (856)	1945 (743)	2257 (876)	1353 (498)	1485 (526)	1656 (613)				
Energy adjusted fat (g/1000 kcal)	23.2 (4.2)	35.4 (1.2)	46.7 (4.1)	23.2 (3.5)	34.7 (1.2)	46.7 (4.7)				
Fat from animal sources (g/1000 kcal)	12.9 (4.0)	21.0 (4.5)	27.4 (6.7)	12.0 (3.6)	19.3 (4.3)	25.5 (6.9)				
Fat from dairy (g/1000 kcal)	4.9 (2.9)	8.8(4.2)	11.6 (5.6)	4.9(2.7)	8.6 (4.1)	12.0 (6.1)				
Fat from meat (g/1000 kcal)	6.4 (2.8)	9.6 (3.5)	12.3 (5.0)	5.6 (2.5)	8.2 (3.2)	9.9 (4.3)				
Fat from fish (g/1000 kcal)	0.7 (0.7)	0.8 (0.8)	0.8 (0.9)	0.6 (0.7)	0.8 (0.8)	0.9 (1.1)				
Fat from eggs (g/1000 kcal)	0.9 (1.0)	1.7 (1.5)	2.8 (2.5)	0.9 (0.9)	1.7 (1.5)	2.8 (2.6)				

	Men (n=53,670)			Women (n=57,746)		
	Q1	Q3	Q5	Q1	Q3	Q5
Fat from vegetable sources (g/1000 kcal)	10.5 (3.4)	14.6 (4.4)	19.1 (6.8)	10.8 (3.1)	14.9 (4.3)	20.7 (7.2)

^aColumn percentages may not sum to 100 due to rounding or missing values.

Energy and multivariable-adjusted hazard ratios and 95% confidence intervals for pancreatic cancer risk in association with total fat and fat subtype in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort

Table 2

	Q1	Q2	Q3	Q4	Q5	P-trend	P-interaction with time
Total fat							
Cases, N	100	86	80	74	71		
Mean (SD) intake	23.4 (3.9)	30.8 (1.5)	35.3 (1.2)	39.7 (1.4)	46.9 (4.4)		
Model 1 ^a	1.00	0.88 (0.66–1.18)	0.85 (0.63–1.14)	0.81 (0.63–1.14)	0.82 (0.60–1.09)	0.149	
Model 2 ^b	1.00	0.86 (0.64–1.14)	0.81 (0.60–1.09)	0.74 (0.54–1.00)	0.70 (0.51–0.95)	0.014	0.093
Cases with person years <4, N	45	39	30	21	27		
Model 2 ^b	1.00	0.86 (0.56–1.33)	0.68 (0.43–1.08)	0.53 (0.31–0.89)	0.64 (0.39–1.06)	0.015	
Cases with person years 4, N	55	47	50	53	44		
Model 2 ^b	1.00	0.85 (0.58–1.25)	0.91 (0.62–1.33)	0.94 (0.64–1.38)	0.76 (0.51–1.15)	0.349	
Saturated fat							
Cases, N	99	96	65	85	66		
Mean (SD) intake	6.8 (1.2)	9.3 (0.5)	11.0 (0.5)	12.8 (0.6)	16.0 (2.0)		
Model 1 ^a	1.00	1.00 (0.76–1.33)	0.70 (0.51–0.96)	0.94 (0.70–1.26)	0.76 (0.55–1.04)	0.080	
Model 2 ^b	1.00	0.97 (0.74–1.29)	0.66 (0.48–0.90)	0.85 (0.63–1.14)	0.64 (0.46–0.88)	0.005	0.030
Cases with person years <4, N	49	38	27	29	19		
Model 2 ^b	1.00	0.89 (0.58–1.37)	0.57 (0.35–0.92)	0.61 (0.38–0.98)	0.37 (0.21–0.63)	<0.001	
Cases with person years 4, N	50	58	38	56	47		
Model 2 ^b	1.00	1.17 (0.80–1.70)	0.76 (0.50–1.16)	1.09 (0.74–1.61)	0.88 (0.58–1.33)	0.491	
Monounsaturated fat							
Cases, N	94	89	71	83	74		
Mean (SD) intake	8.4 (1.5)	11.4 (0.6)	13.2 (0.5)	15.0 (0.6)	18.2 (2.0)		
Model 1 ^a	1.00	0.98 (0.73–1.30)	0.80 (0.59–1.09)	0.97 (0.72–1.31)	0.91 (0.67–1.24)	0.568	
Model 2 ^b	1.00	0.95 (0.71–1.27)	0.76 (0.56–1.04)	0.89 (0.66–1.21)	0.89 (0.66–1.21)	0.134	0.247
Polysaturated fat							
Cases, N	94	94	63	84	76		

	Q1	Q2	Q3	Q4	Q5	P-trend	P-interaction with time
Mean (SD) intake	5.1 (0.8)	6.7 (0.3)	7.8 (0.3)	9.0 (0.4)	11.7 (1.9)		
Model 1 ^a	1.00	1.02 (0.77–1.36)	0.70 (0.51–0.97)	0.96 (0.71–1.29)	0.87 (0.64–1.18)	0.305	
Model 2 ^b	1.00	1.02 (0.77–1.36)	0.69 (0.50–0.95)	0.92 (0.69–1.24)	0.83 (0.61–1.13)	0.162	0.323

^aModel 1 is adjusted for age, sex, and calories.

^bModel 2 HR(95% CIs) are adjusted for age, sex, calories, diabetes (yes/no), BMI (<18.5, 18.5–<25, 25–<30, 30+ kg/m², missing), and smoking status (never, former, current).

Energy and multivariable-adjusted hazard ratios and 95% confidence intervals^a for pancreatic cancer risk in association with dietary fats by intake source in the PLCO cancer screening cohort

Table 3

Fat intake sources	Q1	Q2	Q3	Q4	Q5	P-trend
Total fat from		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Animals ^b	Ref	0.79 (0.59–1.06)	0.62 (0.45–0.85)	0.83 (0.62–1.11)	0.76 (0.56–1.03)	0.137
Meat	Ref	0.85 (0.62–1.15)	1.08 (0.81–1.45)	0.82 (0.60–1.12)	0.91 (0.67–1.24)	0.543
Dairy	Ref	0.85 (0.63–1.14)	0.95 (0.71–1.27)	0.80 (0.59–1.08)	0.77 (0.57–1.05)	0.101
Eggs	Ref	1.21 (0.89–1.64)	0.84 (0.60–1.17)	1.13 (0.83–1.54)	1.17 (0.86–1.59)	0.498
Fish	Ref	0.91 (0.68–1.21)	0.86 (0.64–1.15)	0.77 (0.57–1.05)	0.82 (0.61–1.11)	0.101
Plants	Ref	1.14 (0.85–1.53)	1.04 (0.77–1.41)	0.90 (0.66–1.23)	0.89 (0.65–1.22)	0.194
Saturated fat from						
Animals ^b	Ref	0.92 (0.69–1.22)	0.61 (0.44–0.84)	0.84 (0.62–1.12)	0.70 (0.52–0.96)	0.022
Meat	Ref	0.91 (0.67–1.23)	1.02 (0.76–1.38)	0.89 (0.65–1.21)	0.89 (0.65–1.21)	0.456
Dairy	Ref	0.70 (0.51–0.95)	0.98 (0.74–1.30)	0.83 (0.62–1.11)	0.61 (0.44–0.84)	0.024
Eggs	Ref	1.17 (0.86–1.59)	0.87 (0.62–1.20)	1.07 (0.78–1.47)	1.19 (0.87–1.61)	0.457
Fish	Ref	0.91 (0.68–1.22)	0.93 (0.69–1.24)	0.80 (0.59–1.09)	0.80 (0.59–1.09)	0.106
Plants	Ref	1.05 (0.79–1.40)	0.85 (0.63–1.15)	0.85 (0.62–1.15)	0.80 (0.59–1.09)	0.061
Monounsaturated fat from						
Animals ^b	Ref	0.71 (0.53–0.96)	0.65 (0.48–0.88)	0.79 (0.59–1.06)	0.70 (0.51–0.95)	0.060
Meat	Ref	0.81 (0.60–1.11)	1.00 (0.75–1.34)	0.87 (0.64–1.19)	0.85 (0.62–1.16)	0.465
Dairy	Ref	0.95 (0.71–1.29)	0.96 (0.71–1.29)	0.82 (0.60–1.12)	0.80 (0.59–1.10)	0.105
Eggs	Ref	1.17 (0.87–1.59)	0.84 (0.60–1.17)	1.11 (0.82–1.51)	1.11 (0.81–1.50)	0.673
Fish	Ref	0.91 (0.68–1.21)	0.82 (0.61–1.11)	0.77 (0.57–1.05)	0.80 (0.59–1.08)	0.071
Plants	Ref	1.06 (0.79–1.42)	0.99 (0.73–1.33)	0.94 (0.69–1.27)	0.82 (0.59–1.12)	0.154
Polyunsaturated fat from						
Animals ^b	Ref	0.75 (0.54–1.03)	0.95 (0.70–1.28)	0.92 (0.68–1.25)	1.03 (0.77–1.39)	0.464
Meat	Ref	0.80 (0.59–1.09)	0.93 (0.69–1.25)	0.69 (0.50–0.95)	1.06 (0.79–1.41)	0.988
Dairy	Ref	0.99 (0.74–1.34)	0.96 (0.71–1.30)	0.74 (0.54–1.03)	1.02 (0.76–1.37)	0.534
Eggs	Ref	1.01 (0.74–1.38)	1.11 (0.81–1.50)	0.90 (0.66–1.24)	1.19 (0.88–1.61)	0.375
Fish	Ref	0.91 (0.68–1.23)	0.97 (0.72–1.30)	0.79 (0.58–1.08)	0.86 (0.63–1.16)	0.207

Fat intake sources	Q1	Q2	Q3	Q4	Q5	P-trend
Plants	Ref	0.90 (0.67–1.21)	0.94 (0.70–1.25)	0.76 (0.56–1.04)	0.75 (0.55–1.02)	0.034

^aMultivariate models are adjusted for age, sex, calories, diabetes (yes/no), BMI (<18.5, 18.5–<25, 25–<30, 30+ kg/m², missing), and smoking status (never, former, current).

^bAnimal sources includes contributions from meat, dairy, eggs and fish.