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Brief communication

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

Hannah Arem PhD [a,b,*], Susan T. Mayne PhD [a,c], Joshua Sampson PhD [b], Harvey Risch PhD, MD [a,c], Rachael Z. Stolzenberg-Solomon PhD [b]

[a] Department of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, CT
[b] Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD
[c] Yale Cancer Center, New Haven, CT

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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.
Methods: 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 Cancer Screening Trial. We used Cox proportional hazards regression to examine associations between fat intake and pancreatic cancer risk.
Results: Over 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 nonsignificant when individuals with fewer than 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, whereas 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 owing to undetected disease may explain the observed inverse association with saturated fat.

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Identification of pancreatic cancer risk factors is of great importance because few individuals survive long after diagnosis. Pancreatic cancer is the fourth leading cause of cancer death in the United States [1]. Although some animal studies report a detrimental effect of high 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 prediagnostic but increasingly symptomatic period [19]. Studies that account for changes in dietary practices in the years before 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 with extended follow-up time.

Methods

Study population

The Prostate, Lung, Colorectal and Ovarian 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

* Corresponding author. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Nutritional Epidemiology Branch, 9609 Medical Center Drive, Room 6E324, Bethesda, MD 20892. Tel.: +1 240-276-7204; fax: +1 240-276-7837.
E-mail address: aremhe2@mail.nih.gov (H. Arem).

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participating institutional review boards and the National Cancer Institute [21]. At baseline, men and women aged 55 to 74 years 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 eight or more 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 (maximum 11.3).

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 because 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 (December 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 more than 10% were included in models. The final models were adjusted for age at DHQ completion and the following baseline covariates: Gender, smoking status (never, former, current), body mass index (BMI; <18.5, $18.5-<25$, $25-<30$, and ≥ 30 kg/m^2, or 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 nonlinear association between dietary fat and pancreatic cancer risk nonparametrically with restricted cubic splines [24]. Tests for nonlinearity 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 gender, BMI, and time. Only the time proved significant, and examining Wald test statistics in 2-year increments across follow-up suggested that differences in risk apparent between two distinct intervals, 0 to 4 and more than 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 (SAS, Institute, Inc., Cary, NC) 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 gender are reported 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

Table 1
Characteristics of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort by quintile of fat intake*

	Men (n = 53,670)			Women (n = 57,746)		
	Q1	Q3	Q5	Q1	Q3	Q5
Baseline characteristics						
Mean age (SD) at baseline (y)	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 DHQ						
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)
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)

DHQ = diet history questionnaire; Q = quintile; SD = standard deviation.
* Column percentages may not sum to 100 owing to rounding or missing values.

have 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 vs. Q1: HR, 0.64 [95% CI, 0.46–0.88]), although the association became nonsignificant when 4406 individuals (162 cases) with fewer than 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 fewer than 4 years of follow-up the total fat HR was 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 seemed 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 for the trend = 0.034), although the HRs comparing extreme quintiles were not statistically different. Formal tests for interaction with follow-up time were not significant, but in analyses excluding those with fewer than 4 years of follow-up, each of these associations was nonsignificant (data not shown).

Discussion

In our study population, no association was observed between dietary fat intake and pancreatic cancer incidence after excluding subjects with fewer than 4 years of follow-up. Eliminating cases diagnosed within the first 4 years is intended to exclude those who may have changed dietary intake before baseline owing to latent disease. Dyspepsia or impaired digestion are common symptoms 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 are 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], and four reported no significant association [10,11,13,29]; 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 to 18 years and number of cases ranged from 83 to 1337. Associations with saturated fat are also mixed, with some studies reporting positive risk estimates in the range of 30% to 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 owing to differences in food frequency questionnaires, 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

Table 2
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

	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*	Ref	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†	Ref	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†	Ref	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†	Ref	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*	Ref	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†	Ref	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†	Ref	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†	Ref	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*	Ref	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†	Ref	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
Polyunsaturated fat							
Cases (n)	94	94	63	84	76		
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*	Ref	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†	Ref	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

Q = quintile; SD = standard deviation.

* Model 1 is adjusted for age, gender, and calories.

† Model 2 hazard ratio (95% confidence intervals) are adjusted for age, gender, calories, diabetes (yes/no), BMI (<18.5, 18.5–25, 25–30, and ≥30 kg/m^2, or missing), and smoking status (never, former, current).

Table 3
Energy and multivariable-adjusted hazard ratios and 95% confidence intervals* for pancreatic cancer risk in association with dietary fats by intake source in the Prostate, Lung, Colorectal and Ovarian cancer screening cohort

Fat intake sources	Q1	Q2, HR (95% CI)	Q3, HR (95% CI)	Q4, HR (95% CI)	Q5, HR (95% CI)	*p* trend
Total fat from						
Animals†	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†	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†	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†	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
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

Q = quintile.
* Multivariate models are adjusted for age, gender, calories, diabetes (yes/no) BMI (<18.5, 18.5–<25, 25–<30, ≥30 kg/m^2, or missing), and smoking status (never, former, current).
† Animal sources include contributions from meat, dairy, eggs and fish.

energy than carbohydrates and proteins, are not efficiently oxidized for energy, and increase the expression of genes associated with adipocyte proliferation [31]. As described, although some epidemiologic 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. In addition, 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 follow-up.

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