Mendelian Randomization Analysis of n-6 Polyunsaturated Fatty Acid Levels and Pancreatic Cancer Risk

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ABSTRACT

Background: Whether circulating polyunsaturated fatty acid (PUFA) levels are associated with pancreatic cancer risk is uncertain. Mendelian randomization (MR) represents a study design using genetic instruments to better characterize the relationship between exposure and outcome.

Methods: We utilized data from genome-wide association studies within the Pancreatic Cancer Cohort Consortium and Pancreatic Cancer Case–Control Consortium, involving approximately 9,269 cases and 12,530 controls of European descent, to evaluate associations between pancreatic cancer risk and genetically predicted plasma n-6 PUFA levels. Conventional MR analyses were performed using individual-level and summary-level data.

Results: Using genetic instruments, we did not find evidence of associations between genetically predicted plasma n-6 PUFA levels and pancreatic cancer risk [estimates per one SD increase in each PUFA-specific weighted genetic score using summary statistics: linoleic acid odds ratio (OR) = 1.00, 95% confidence interval (CI) = 0.98–1.02; arachidonic acid OR = 1.00, 95% CI = 0.99–1.01; and dihomo-gamma-linolenic acid OR = 0.95, 95% CI = 0.87–1.02]. The OR estimates remained virtually unchanged after adjustment for covariates, using individual-level data or summary statistics, or stratification by age and sex.

Conclusions: Our results suggest that variations of genetically determined plasma n-6 PUFA levels are not associated with pancreatic cancer risk.

Impact: These results suggest that modifying n-6 PUFA levels through food sources or supplementation may not influence risk of pancreatic cancer.

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Introduction

Pancreatic cancer remains one of the deadliest cancers (1). Polyunsaturated fatty acids (PUFA), linked to the inflammatory process, may influence pancreatic cancer development (2). However, evidence from epidemiologic studies is inconsistent (3). For example, associations with n-3 PUFA intake were inverse, positive, or null, and associations with n-6 PUFA intake were positive or null across different studies. Conventional epidemiologic study designs may suffer from methodologic limitations, such as reverse causation, selection bias, and uncontrolled confounding (4). We, therefore, conducted a Mendelian randomization (MR) analysis using genetic variants as instrumental variables. Higher proportions of variance of n-6 PUFA levels were explained by variants compared with n-3 PUFA levels (5, 6). We thus focused on n-6 PUFA in our analysis.

Materials and Methods

Instrumental variables

We identified SNPs associated with plasma or red blood cell (RBC) levels of n-6 PUFAs [linoleic acid, arachidonic acid, adrenic acid, gamma linolenic acid (GLA), and dihomo-gamma-linolenic acid (DGLA)] from the genome-wide association studies (GWAS) catalog and from published literature (up to November 2018; ref. 6). We selected SNPs associated at $P < 5 \times 10^{-8}$ that were independent from each other ($r^2 < 0.1$). For correlated SNPs, the SNP with a lower P value was selected unless an independent association was reported, in which case both were selected. We used estimates of association with plasma PUFA levels for our analyses. For SNPs initially reported to be associated with RBC PUFA levels, we checked their associations with plasma levels in the GWAS conducted by the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE; ref. 6); if estimates were significant ($P < 0.05$) we included them in our analyses.

Genetic association datasets for pancreatic cancer risk

For evaluation of associations with pancreatic cancer risk, we used data from four GWASs conducted in the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case–Control Consortium (PanC4; ref. 7). Detailed information on quality control and imputation has been provided elsewhere (7). Data from approximately 9,269 cases and 12,530 controls of European ancestry were used. Only variants with imputation quality of $r^2 \geq 0.3$ were retained.

MR analysis

We performed separate MR analyses for each type of PUFA. On the basis of power estimation (https://shiny.cnsgenomics.com/mRnd/), the minimal detectable ORs per SD of genetically predicted PUFA levels at 80% power and alpha of 0.05 ranged from 1.08 to 1.13 for linoleic acid, 1.06 to 1.21 for arachidonic acid, 1.13 to 1.15 for adrenic acid, 1.17 to 1.27 for GLA, and 1.08 to 1.11 for DGLA. We created a weighted genetic score (wGRS) to represent the genetically estimated PUFA level using information from published GWASs of PUFA plasma levels and data from PanScan/PanC4 GWASs. For each subject, a wGRS was created as the weighted sum of the number of association alleles at each locus multiplied by the point estimate for the association with plasma PUFA level:

$$wGRS = \sum_{i=1}^{n} \beta_i SNP_i$$

where β_i is the regression coefficient of the ith SNP for the PUFA and SNP_i is the dosage of the association alleles (0, 1, 2) of the ith SNP. All association alleles were converted to correspond to increased PUFA

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levels. We used logistic regression models to assess the associations between wGRS and pancreatic cancer risk. Besides unadjusted analyses, we performed analyses adjusting for age, sex, and the top principal components. We stratified the data by age (<50 years, 50–70 years, and ≥70 years) and sex. We also used the summary statistics of the PanScan/PanC4 GWASs to estimate the MR associations using the fixed effects inverse variance-weighted approach (4).

Results

The instruments used for each of the n-6 PUFA are included in **Table 1**. There was no evidence of association (at $P < 0.01$) between any of the wGRS and common pancreatic cancer risk factors. We did not detect any statistically significant associations between genetically predicted plasma n-6 PUFA levels and pancreatic cancer risk (**Table 2**). The estimates for adrenic acid and GLA had wide confidence intervals, consistent with the estimated lower power for these. The associations remained virtually unchanged regardless of covariate adjustment, analyzing individual-level versus summary statistics data, or within strata of age or sex.

Discussion

We did not observe significant associations between genetically predicted n-6 PUFA levels and pancreatic cancer risk in the PanScan/PanC4 subjects. As the proportion of variance of n-6 PUFA that can be explained by the summed association magnitudes of these GWAS-identified loci is relatively high, there is reasonable statistical power to detect any meaningful associations. PUFA has been reported to be associated with colorectal cancer risk on the basis of MR analysis (8). Most dietary sources of n-6 PUFA are consumed infrequently. A limitation of this study is that there is no information for the genetic variants associated with total n-6 PUFA levels in previous literature, and thus, we could not determine the association between total n-6 PUFA levels and pancreatic cancer risk using genetic instruments. Alternative designs of a direct assessment of dietary sources and measurement of PUFA levels in blood at repeat timepoints can better characterize the relationship between PUFA and pancreatic cancer risk. Further studies are also needed to investigate the potential relationships in subjects of other populations.

Disclosure of Potential Conflicts of Interest

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Table 1. Genetic instruments for plasma phospholipid levels of n-6 PUFAs (% of total fatty acids) that were genome-wide significant ($P < 5 \times 10^{-8}$) in previous GWASs.

Chr	SNP	GRCh37/hg19 position	Allele[a]	EAF	β	SE	*P*	% VE[b] per allele	% VE per IV[c]	F-statistic per IV[d]
Linoleic acid (18:2n6)										
10	rs10740118	65101207	G/C	0.56	0.2484	0.0431	8.08×10^{-9}	0.2–0.7	9.4–25.1	452–1461
11	rs174547	61570783	C/T	0.32	1.4737	0.0417	4.98×10^{-274}	7.6–18.1		
11	rs2727270	61603237	T/C	0.44	0.69	0.07	2.60×10^{-21}	0.5–2.4		
16	rs16966952	15135943	A/G	0.31	0.3512	0.0439	1.23×10^{-15}	0.5–2.5		
16	rs2280018	15150833	A/C	0.38	0.38	0.05	3.60×10^{-14}	0.6–1.4		
Arachidonic acid (20:4n6)										
11	rs174547	61570783	T/C	0.68	1.6909	0.0253	3.30×10^{-971}	3.7–37.6	4.1–44	311–5708
11	rs102275	61557803	T/C	0.68	2.49	0.1	6.60×10^{-147}	0.3–5.8		
16	rs16966952	15135943	G/A	0.69	0.1989	0.0314	2.43×10^{-10}	0.1–0.6		
Adrenic acid (22:4,n6)										
11	rs174547	61570783	T/C	0.67	0.0483	0.0019	6.26×10^{-140}	7.8–10.9	7.8–10.9	1844–2667
GLA (18:3,n6)										
11	rs174547	61570783	T/C	0.67	0.0156	0.0009	2.29×10^{-72}	2.2–4.6	2.5–6.4	186–497
16	rs16966952	15135943	G/A	0.69	0.0061	0.0009	5.05×10^{-11}	0.3–1.8		
11	rs10899123[e]	75501207	C/G	0.91	0.0055	0.0014	9.97×10^{-5}	NA		
DGLA (20:3,n6)										
11	rs174547	61570783	C/T	0.33	0.3550	0.0136	2.63×10^{-151}	8.7–11.1	13.5–26.3	850–1944
11	rs968567	61595564	T/C	0.16	0.29	0.02	1.30×10^{-42}	1.4–7.9		
16	rs16966952	15135943	G/A	0.69	0.2204	0.013	7.55×10^{-65}	2.0–4.5		
16	rs2280018	15150833	C/A	0.61	0.16	0.02	4.50×10^{-25}	1.4–2.8		

Abbreviations: Chr, chromosome; EAF, effect allele frequency; IV, instrumental variable; VE, variation explained.

[a]The first listed allele represents the effect allele associated with an increased level of corresponding PUFA; the second allele represents the alternative allele.

[b]% VE = $[2 \times \beta^2 \times \text{EAF} \times (1 - \text{EAF})/\text{var(PUFA)}] \times 100$, unless indicated in article, such as in Guan and colleagues (6).

[c]% VE per IV = sum of the %VE per allele for each SNP included in the IV.

[d]F-statistic is a measure of the strength of the genetic instrument and is calculated as follows: $[R^2 \times (n - 1 - k)]/[(1 - R^2) \times k]$, where R^2 = % VE, n = sample size, k = total number of instrumental variables.

[e]Genetic variant, rs10899123, showed an association at $5 \times 10^{-8} < P < 0.05$ in the CHARGE studies (Guan and colleagues, 2014; ref. 6), although it showed a GWAS significant association in the study by Hu and colleagues (2016; ref. 9). It was included in the genetic instrument in sensitivity analyses while it did not significantly change the association. The analyses excluding it in the instrument are reported in **Table 2**.

Table 2. Associations between 1 SD increase in PUFA-specific wGRSs and pancreatic cancer risk in PanScan and PanC4 studies[a].

		Linoleic acid		Arachidonic acid		DGLA	
Subgroup	**Cases/controls**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Overall[b]	9,269/12,530	0.99 (0.97–1.01)	0.30	1.01 (1.00–1.02)	0.37	0.94 (0.87–1.01)	0.10
Overall[c]	9,206/12,525	1.00 (0.98–1.02)	0.89	1.00 (0.99–1.01)	0.53	0.94 (0.87–1.02)	0.13
Data source[c]							
PanScan1	1,746/1,812	1.03 (0.97–1.08)	0.31	0.99 (0.97–1.01)	0.35	0.97 (0.81–1.16)	0.72
PanScan2	1,768/1,841	0.99 (0.93–1.04)	0.59	1.01 (0.99–1.03)	0.47	0.97 (0.82–1.15)	0.73
PanScan3	1,528/5,080	0.99 (0.93–1.05)	0.66	1.01 (0.98–1.03)	0.56	0.91 (0.76–1.10)	0.34
PanC4	4,164/3,792	1.00 (0.96–1.03)	0.91	1.01 (0.99–1.02)	0.53	0.94 (0.83–1.06)	0.30
Overall[d]	9,040/12,496	1.00 (0.97–1.03)	0.95	1.00 (0.99–1.02)	0.73	0.95 (0.87–1.03)	0.21
Age[e]							
>70	3,494/3,385	1.02 (0.98–1.06)	0.42	1.00 (0.98–1.01)	0.68	1.02 (0.90–1.17)	0.73
50–70	3,917/6,916	0.99 (0.96–1.03)	0.74	1.01 (0.99–1.02)	0.55	0.91 (0.81–1.02)	0.11
≤50	1,795/2,224	0.98 (0.93–1.03)	0.42	1.01 (0.99–1.04)	0.32	0.90 (0.75–1.07)	0.24
Sex[f]							
Male	4,985/7,801	1.00 (0.97–1.03)	0.94	1.00 (0.99–1.02)	0.66	0.97 (0.87–1.08)	0.55
Female	4,221/4,225	1.00 (0.97–1.04)	0.99	1.00 (0.99–1.02)	0.71	0.99 (0.95–1.04)	0.77

Abbreviation: CI, confidence interval.

[a]Results for adrenic acid and GLA not shown; their associations were not significant, with relatively wide CIs.

[b]ORs and 95% CIs estimated using individual-level data without adjustment, and represent 1 SD increase in each PUFA-specific wGRS.

[c]ORs and 95% CIs estimated using individual-level data with adjustment of age (under 50, 50–60, 60–70, 70–80, and above 80), sex, and 10 or seven principal components for PanScan and PanC4 data, respectively, and represent 1 SD increase in each PUFA-specific wGRS.

[d]ORs and 95% CIs estimated using summary statistics data.

[e]ORs and 95% CIs estimated using individual-level data with adjustment of age, sex, and 10 or seven principal components for PanScan and PanC4 data, respectively, and represent 1 SD increase in each PUFA-specific wGRS.

[f]ORs and 95% CIs estimated using individual-level data with adjustment of age (under 50, 50–60, 60–70, 70–80, and above 80) and 10 or seven principal components for PanScan and PanC4 data, respectively, and represent 1 SD increase in each PUFA-specific wGRS.

submitted work; serves as a director for CytomX Therapeutics and owns unexercised stock options for CytomX Therapeutics and Entrinsic Health; is a cofounder of EvolveImmune Therapeutics and has equity in this private company; and has provided expert testimony for Amylin Pharmaceuticals and Eli Lilly. I-M. Lee reports grants from NIH during the conduct of the study. R.L. Milne reports grants from National Health and Medical Research Council during the conduct of the study. A.L. Oberg reports grants from NCI (P50 CA102701) during the conduct of the study. I.M. Thompson Jr reports grants from NCI, NIH (several grants in support of conduct and administration of SELECT and PCPT studies) during the conduct of the study. J. Wactawski-Wende reports grants from NIH/National Heart, Lung, and Blood Institute (funding for WHI) during the conduct of the study. A. Zeleniuch-Jacqotte reports grants from NIH/NCI during the conduct of the study. A.P. Klein reports grants from NCI during the conduct of the study. X.-O. Shu reports grants and personal fees from NCI (grant review) during the conduct of the study. L. Wu reports grants from NCI during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

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