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

Dalia H. Ghoneim[1], Jingjing Zhu[1], Wei Zheng[2], Jirong Long[2], Harvey J. Murff[3], Fei Ye[4], Veronica Wendy Setiawan[5], Lynne R. Wilkens[1], Nikhil K. Khankari[2], Philip Haycock[6], Samuel O. Antwi[7], Yaohua Yang[2], Alan A. Arslan[8], Laura E. Beane Freeman[9], Paige M. Bracci[10], Federico Canzian[11], Mengmeng Du[12], Steven Gallinger[13], Graham G. Giles[14,15,16], Phyllis J. Goodman[17], Charles Kooperberg[18], Loïc Le Marchand[1], Rachel E. Neale[19], Ghislaine Scelo[20], Kala Visvanathan[21,22], Emily White[23], Demetrius Albanes[9], Pilar Amiano[24], Gabriella Andreotti[9], Ana Babic[25], William R. Bamlet[26], Sonja I. Berndt[9], Lauren K. Brais[25], Paul Brennan[20], Bas Bueno-de-Mesquita[27,28,29,30], Julie E. Buring[31,32], Peter T. Campbell[33], Kari G. Rabe[26], Stephen J. Chanock[9], Priya Duggal[34], Charles S. Fuchs[35,36,37], J. Michael Gaziano[32,38], Michael G. Goggins[39], Thilo Hackert[40], Manal M. Hassan[41], Kathy J. Helzlsouer[42], Elizabeth A. Holly[10], Robert N. Hoover[9], Verena Katske[43], Robert C. Kurtz[44], I-Min Lee[31,32], Núria Malats[45], Roger L. Milne[14,15,16], Neil Murphy[46], Ann L. Oberg[26], Miquel Porta[47], Nathaniel Rothman[9], Howard D. Sesso[31,32], Debra T. Silverman[9], Ian M. Thompson Jr[48], Jean Wactawski-Wende[49], Xiaoliang Wang[23], Nicolas Wentzensen[9], Herbert Yu[1], Anne Zeleniuch-Jacquotte[50], Kai Yu[9], Brian M. Wolpin[25], Eric J. Jacobs[51], Eric J. Duell[52], Harvey A. Risch[53], Gloria M. Petersen[26], Laufey T. Amundadottir[54], Peter Kraft[55], Alison P. Klein[21,22,39], Rachel Z. Stolzenberg-Solomon[9], Xiao-Ou Shu[2], and Lang Wu[1]

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.

[1]Division of Cancer Epidemiology, Population Sciences in the Pacific Program, University of Hawaii Cancer Center, University of Hawaii at Manoa, Honolulu, Hawaii. [2]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee. [3]Division of General Internal Medicine, Department of Medicine, Vanderbilt University, Nashville, Tennessee. [4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee. [5]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California. [6]MRC Integrative Epidemiology Unit, University of Bristol, Bristol, England, United Kingdom. [7]Department of Health Sciences Research, Mayo Clinic, Jacksonville, Florida. [8]Departments of Obstetrics and Gynecology, Population Health and Environmental Medicine, NYU Perlmutter Comprehensive Cancer Center, New York, New York. [9]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. [10]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California. [11]Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. [12]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York. [13]Lunenfeld-Tanenbaum Research Institute, Sinai Health System and University of Toronto, Toronto, Ontario, Canada. [14]Division of Cancer Epidemiology, Cancer Council Victoria, Melbourne, Victoria, Australia. [15]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. [16]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. [17]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, Washington. [18]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington. [19]Department of Population Health, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [20]International Agency for Research on Cancer, Lyon, France. [21]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland. [22]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center,

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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

Johns Hopkins School of Medicine, Baltimore, Maryland. [23]Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington. [24]Ministry of Health of the Basque Government, Public Health Division of Gipuzkoa, Biodonostia Health Research Institute, Donostia-San Sebastian; CIBER Epidemiología y Salud Pública, Madrid, Spain. [25]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. [26]Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota. [27]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. [28]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, the Netherlands. [29]Department of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, London, United Kingdom. [30]Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [31]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [32]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts. [33]Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, Georgia. [34]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland. [35]Yale Cancer Center, New Haven, Connecticut. [36]Department of Medicine, Yale School of Medicine, New Haven, Connecticut. [37]Smilow Cancer Hospital, New Haven, Connecticut. [38]Boston Veteran Affairs Healthcare System, Boston, Massachusetts. [39]Department of Pathology, Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins School of Medicine, Baltimore, Maryland. [40]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany. [41]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [42]Epidemiology and Genomics Research Program, Division of Cancer Control and Population Science, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. [43]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [44]Gastroenterology, Hepatology, and Nutrition Service, Memorial Sloan Kettering Cancer Center, New York, New York. [45]Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Center, Madrid, Spain. [46]Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France. [47]Hospital del Mar Institute of Medical Research (IMIM), Universitat Autònoma de Barcelona, Barcelona, Spain. [48]CHRISTUS Santa Rosa Hospital – Medical Center, San Antonio, Texas. [49]Department of Epidemiology and Environmental Health, University of Buffalo, Buffalo, New York. [50]Departments of Population Health and Environmental Medicine, NYU Perlmutter Comprehensive Cancer Center, New York, New York. [51]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia. [52]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Bellvitge Biomedical Research Institute (IDIBELL), Catalan Institute of Oncology (ICO), Barcelona, Spain. [53]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut. [54]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. [55]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

Note: D.H. Ghoneim and J. Zhu contributed equally as co–first authors of this article.

Corresponding Authors: Lang Wu, University of Hawaii Cancer Center, 701 Ilalo Street, Building B, Room 520, Honolulu, HI 96813. Phone: 808-564-5965; Fax: 808-586-2982; E-mail: lwu@cc.hawaii.edu; and Xiao-Ou Shu, Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37232. Phone: 615-936-0713; E-mail: xiao-ou.shu@vanderbilt.edu

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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

P. Haycock reports grants from Cancer Research UK during the conduct of the study. M. Du reports grants from NCI (P30CA008748), Geoffrey Beene Foundation, Arnold and Arlene Goldstein Family Foundation, and Society of Memorial Sloan Kettering Cancer Center during the conduct of the study. G.G. Giles reports grants from National Health and Medical Research Council (paid to institution, Cancer Council Victoria) during the conduct of the study. L. Le Marchand reports grants from NCI during the conduct of the study. R.E. Neale reports grants from National Health and Medical Research Council during the conduct of the study. J.E. Buring reports grants from NIH during the conduct of the study. C.S. Fuchs reports personal fees from Agios, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho, and Unum Therapeutics outside the

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**.

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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.

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Disclaimer

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

Authors' Contributions

D.H. Ghoneim: Formal analysis, writing–review and editing. **J. Zhu:** Formal analysis, investigation, writing–original draft. **W. Zheng:** Methodology, writing–review and editing. **J. Long:** Writing–review and editing. **H.J. Murff:** Writing–review and editing. **F. Ye:** Writing–review and editing. **V.W. Setiawan:** Writing–review and editing. **L.R. Wilkens:** Writing–review and editing. **N.K. Khankari:** Resources, writing–review and editing. **P. Haycock:** Methodology, writing–review and editing. **S.O. Antwi:** Writing–review and editing. **Y. Yang:** Writing–review and editing. **A.A. Arslan:** Resources, data curation. **L.E. Beane Freeman:** Resources, data curation. **P.M. Bracci:** Resources, data curation. **F. Canzian:** Resources, data curation. **M. Du:** Resources, data curation. **S. Gallinger:** Resources, data curation. **G.G. Giles:** Resources, data curation. **P.J. Goodman:** Resources, data curation. **C. Kooperberg:** Resources, data curation. **L. Le Marchand:** Resources, data curation, writing–review and editing. **R.E. Neale:** Resources, data curation, writing–review and editing. **G. Scelo:** Resources, data curation. **K. Visvanathan:** Resources, data curation. **E. White:** Resources, data curation. **D. Albanes:** Resources, data curation. **P. Amiano:** Resources, data curation. **G. Andreotti:** Resources, data curation. **A. Babic:** Resources, data curation. **W.R. Bamlet:** Data curation. **S.I. Berndt:** Resources, data curation. **L.K. Brais:** Resources, data curation. **P. Brennan:** Resources, data curation. **B. Bueno-de-Mesquita:** Resources, data curation. **J.E. Buring:** Resources, data curation. **P.T. Campbell:** Resources, data curation. **K.G. Rabe:** Data curation. **S.J. Chanock:** Resources, data curation. **P. Duggal:** Resources, data curation. **C.S. Fuchs:** Resources, data curation. **J.M. Gaziano:** Resources, data curation. **M.G. Goggins:** Resources, data curation. **T. Hackert:** Resources, data curation. **M.M. Hassan:** Resources, data curation. **K.J. Helzlsouer:** Resources, data curation. **E.A. Holly:** Resources, data curation. **R.N. Hoover:** Resources, data curation. **V. Katzke:** Resources, data curation. **R.C. Kurtz:** Resources, data curation. **I-M. Lee:** Resources, data curation. **N. Malats:** Resources, data curation. **R.L. Milne:** Resources, data curation, writing–review and editing. **N. Murphy:** Resources, data curation. **A.L. Oberg:** Data curation. **M. Porta:** Resources, data curation. **N. Rothman:** Resources, data curation. **H.D. Sesso:** Resources, data curation. **D.T. Silverman:** Resources, data curation. **I.M. Thompson Jr:** Resources, data curation. **J. Wactawski-Wende:** Resources, data curation. **X. Wang:** Data curation. **N. Wentzensen:** Resources, data curation. **H. Yu:** Resources, writing–review and editing. **A. Zeleniuch-Jacqotte:** Resources, data curation. **K. Yu:** Data curation. **B.M. Wolpin:** Resources, data curation. **E.J. Jacobs:** Resources, data curation. **E.J. Duell:** Resources, data curation. **H.A. Risch:** Resources, data curation, writing–review and editing. **G.M. Petersen:** Resources, data curation. **L.T. Amundadottir:** Data curation. **P. Kraft:** Resources, data curation. **A.P. Klein:** Resources, data curation. **R.Z. Stolzenberg-Solomon:** Resources, data curation. **X.-O. Shu:** Conceptualization, resources, supervision, investigation, writing–review and editing. **L. Wu:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft, project administration.

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Dalia H. Ghoneim, Jingjing Zhu, Wei Zheng, et al.

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