Title

Dietary Patterns of Insulinemia, Inflammation and Glycemia, and Pancreatic Cancer Risk: Findings from the Women's Health Initiative

Journal

Cancer Epidemiology Biomarkers & Prevention, 30(6)

ISSN

1055-9965

Authors

Jin, Qi
Hart, Phil A
Shi, Ni
et al.

Publication Date

2021-06-01

DOI

10.1158/1055-9965.epi-20-1478

Peer reviewed

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2021 June ; 30(6): 1229–1240. doi:10.1158/1055-9965.EPI-20-1478.

Dietary Patterns of Insulinemia, Inflammation and Glycemia and Pancreatic Cancer Risk: Findings from the Women's Health Initiative

Qi Jin[1], **Phil A. Hart**[2], **Ni Shi**[3], **Joshua J. Joseph**[4], **Macarius Donneyong**[5], **Darwin L. Conwell**[2], **Steven K. Clinton**[1,3,6], **Zobeida Cruz-Monserrate**[1,2,3], **Theodore M. Brasky**[3,6,13], **Lesley F. Tinker**[7], **Simin Liu**[8], **Aladdin H. Shadyab**[9], **Cynthia A. Thomson**[10], **Lihong Qi**[11], **Thomas Rohan**[12], **Fred K. Tabung**[1,3,6,13]

[1]Interdisciplinary Ph.D. Program in Nutrition, The Ohio State University, Columbus, OH

[2]Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

[3]The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH

[4]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

[5]College of Pharmacy, The Ohio State University, Columbus, OH

[6]Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

[7]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[8]Department of Epidemiology, Brown University, Providence, R.I.

[9]Department of Family Medicine and Public Health, School of Medicine, University of California San Diego, La Jolla, CA

[10]Department of Health Promotion Sciences, Mel & Enid Zuckerman College of Public Health, The University of Arizona, Tucson, AZ

[11]School of Medicine, University of California Davis, Davis, CA

For correspondence: Fred K. Tabung: 410 West 12th Avenue, 302B Wiseman Hall/CCC, Columbus, OH, 43210; fred.tabung@osumc.edu.

Author's Contributions:

Conception and design: Tabung; Development of methodology: Tabung; Acquisition of data: Tabung and Jin; Analysis and interpretation of data: all authors; Original manuscript draft: Jin; Writing, review, and/or revision of the manuscript: all authors

Publisher's Disclaimer: Disclaimers: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Ethical approval: The institutional review boards (IRB) at the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) and at each Clinical Center approved the WHI protocol (10).

Previous presentations: American Pancreatic Association 2020 scientific conference, Oct 30, 2020 (ePoster presentation)

Disclosures of Potential Conflict of Interest: All authors declare that they have no conflicts of interest.

[12]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

[13]Division of Epidemiology, College of Public Health, The Ohio State University, Columbus, OH

Abstract

Background: Pancreatic cancer risk is increasing in countries with high consumption of Western dietary patterns and rising obesity rates. We examined the hypothesis that specific dietary patterns reflecting hyperinsulinemia (empirical dietary index for hyperinsulinemia-EDIH), systemic inflammation (empirical dietary inflammatory pattern-EDIP), and postprandial glycemia (glycemic index-GI, glycemic load-GL) are associated with pancreatic cancer risk, including the potential modifying role of type 2 diabetes (T2D) and body mass index (BMI).

Methods: We calculated dietary scores from baseline (1993–1998) food frequency questionnaires among 129,241 women, 50–79 years-old in the Women's Health Initiative. We used multivariable-adjusted Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) for pancreatic cancer risk.

Results: During a median 19.9 years of follow-up, 850 pancreatic cancer cases were diagnosed. We observed no association between dietary scores and pancreatic cancer risk overall. However, risk was elevated among participants with longstanding T2D (present >3 years before pancreatic cancer diagnosis) for EDIH. For each 1 standard deviation increment in dietary score, the HRs (95%CIs) were: EDIH, 1.33(1.06–1.66); EDIP, 1.26(0.98–1.63); GI, 1.26(0.96–1.67); and GL, 1.23(0.96–1.57); though interactions were not significant (all $P_{interaction}$ >0.05). Separately, we observed inverse associations between GI, 0.86(0.76–0.96), $P_{interaction}$=0.0068; and GL, 0.83 (0.73–0.93), $P_{interaction}$=0.0075, with pancreatic cancer risk among normal-weight women.

Conclusion: We observed no overall association between the dietary patterns evaluated and pancreatic cancer risk, although women with T2D appeared to have greater cancer risk.

Impact: The elevated risk for hyperinsulinemic diets among women with longstanding T2D and the inverse association among normal-weight women warrant further examination.

Keywords

Pancreatic cancer; Dietary patterns; empirical dietary index for hyperinsulinemia; empirical dietary inflammatory pattern; glycemic index; glycemic load; type 2 diabetes; obesity

INTRODUCTION

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States (1). Due to the non-specific nature and late onset of symptoms, early detection is challenging, and most patients are diagnosed at an advanced cancer stage. Combined with biological factors promoting treatment resistance, pancreatic cancer has a poor prognosis, with a five-year survival rate of only 9% (1). Therefore, it is crucial to identify modifiable risk factors for prevention.

Diet is a modifiable factor that may influence pancreatic cancer risk (2). In contrast to the reductionist strategies of single nutrients or single foods, the dietary pattern approach

accounts for the complex interactions between dietary variables and allows assessment of the cumulative effects of multiple dietary components on disease risk. Such efforts regarding pancreatic cancer risk are few (3), and have been conducted primarily as case-control studies, with inherent concerns of recall bias. Nevertheless, current literature suggests a greater risk with dietary patterns described as the Western dietary pattern rich in animal products while inverse associations have been noted for dietary patterns defined as “prudent” and rich in fruits, vegetables and fiber (3). Potential reverse causation by occult disease, which cannot be addressed in case-control studies, is a major limitation and it is imperative that additional studies of dietary patterns focus on large, prospective designs. It is also important to consider multiple strategies for defining dietary patterns. For example, one approach uses dietary guidelines or hypotheses (based on prevailing evidence) regarding a diet-disease relation to define a pattern, *a priori*, such as the healthy eating index. Another strategy is purely empirical (data-driven) and employs statistical approaches to group dietary variables into patterns, *a posteriori*, based on the explained variation in the diet. Our team utilized a hybrid approach to define empirical hypothesis-oriented dietary patterns that are data-driven yet based on a specific hypothesis (e.g., hyperinsulinemia, chronic systemic inflammation, etc.) relating diet with disease (4,5). We hypothesize that dietary patterns associated with hyperinsulinemia or a chronic systemic inflammatory state may increase risk of pancreatic cancer.

Dietary patterns have been associated with risk of obesity (6) and T2D (7,8), which interfaces with investigations of the association of dietary patterns with pancreatic cancer risk, yet the temporal relationships have not been clearly described. Further refinement in our understanding of the role of obesity and T2D in pancreatic cancer risk offers opportunities to define prevention strategies. The dietary glycemic index (GI) and dietary glycemic load (GL) are two dietary indices that are widely used for assessing the postprandial glycemic potential of the diet; however, these indices do not account for the intake of fat, protein, and the diverse array of phytochemicals that influence insulin secretion and glucose regulation (5). Our group previously developed the empirical dietary index for hyperinsulinemia (EDIH) score based on circulating C-peptide levels, for assessing the insulinemic potential of the dietary pattern (5), and the empirical dietary inflammatory pattern (EDIP) score, based on circulating inflammatory biomarkers, for evaluating the inflammatory potential of the dietary pattern (4). In the current study, we calculated the EDIH, EDIP, GI and GL scores to estimate the insulinemic, inflammatory and glycemic potentials, respectively, of the diet and examined associations with risk of developing pancreatic cancer in the Women’s Health Initiative (WHI). In addition, we investigated potential effect modification of these associations by T2D and BMI.

METHODS

Study Population:

Between 1993 and 1998, a total of 161,808 postmenopausal women aged 50–79 years were enrolled in the WHI (9) at 40 clinical centers across the U.S. Women were enrolled into either an observational study (n=93,676) or one or more of 4 overlapping clinical trials (n=68,132). The institutional review boards at the Clinical Coordinating Center at the Fred

Hutchinson Cancer Research Center (Seattle, WA) and at each Clinical Center approved the WHI protocol (10). The original WHI study completed data collection in 2005 but extension and ancillary studies have continued to collect long-term data. The current extension study is collecting annual health information from consenting WHI participants through 2020. Supplementary Table S1 contains a list of WHI investigators.

We sequentially excluded women with: implausible energy intake (<600 kcal/day and >5000 kcal/day; n=4,686) as these individuals may have filled out questionnaires incorrectly (11); extreme BMI (< 15 or >50 kg/m^2; n=6,476); prevalent cancer (except non-melanoma skin cancer) at baseline(n=11,840); baseline T2D (n=7,768), as dietary modifications usually occur after disease diagnosis; baseline pancreatitis (n=496); and those with missing information on pancreatic cancer status or those with a pancreatic cancer diagnosis and missing date of diagnosis (n=1,154) (Supplementary Figure S1). Early symptoms of undiagnosed pancreatic cancer may alter one's dietary pattern and body weight; hence we applied a 4-year lag (12) between dietary assessment and pancreatic cancer ascertainment, and excluded those who were diagnosed with pancreatic cancer within 4 years from baseline (n=147). Our final analytic sample included 129,241 women who had comparable baseline characteristics with the excluded participants for most variables (Supplementary Table S2), as well as with the entire WHI cohort (Supplementary Table S3).

Dietary assessment and calculation of dietary indices

Dietary scores were calculated using baseline habitual dietary data, assessed using the WHI food frequency questionnaire (FFQ), a 122-item semi-quantitative self-administered FFQ covering the dietary intake in the preceding three months (13). Nutrient intake from the FFQ was estimated using the University of Minnesota Nutrition Coordinating Center food and nutrient database (Nutrient data System for Research - NDSR) (14). The measurement characteristics of the WHI FFQ were evaluated by comparing the FFQ nutrient intake estimates with those from four 24-hour dietary recalls and 4-day food records (13). The mean intake of most nutrients estimated from the FFQ was found to be comparable to corresponding intakes estimated from dietary recalls and records (13).

The development and validation of the EDIP and EDIH scores have been described (4,5). Briefly, the EDIP is a weighted sum of 18 food groups most predictive of three circulating inflammatory biomarkers (IL6, CRP, TNFαR-2) measured from plasma, with more positive scores indicating more pro-inflammatory dietary patterns (4). EDIH is comprised of 18 food groups, selected from 39 food groups most predictive of plasma C-peptide concentrations, a marker of beta-cell secretory activity. More positive scores indicate hyperinsulinemic dietary patterns (5). The component foods of both scores are presented in Supplementary Table S4. A GI score estimates the quality of carbohydrates in the diet, and represents the percent incremental area under the 2-hour postprandial glucose response curve for consumption of a given carbohydrate-containing food relative to the corresponding area for consumption of a reference food (glucose or white bread) with equal amount of carbohydrates (15). The GL of each food is the product of the food's GI and the amount of carbohydrate in that food, summed across all foods for each individual (16).

Ascertainment of pancreatic cancer

The primary outcome, incident pancreatic cancer, was identified through medical record adjudication by study physicians following self-report of a diagnosis at semi-annual contact in the Clinical Trials (CT) and/or annual contact in the Observational Study (OS) and extension studies. A total of 850 pancreatic cancer cases were ascertained between 4 years from baseline and end of study on March 1st 2019. (17).

Assessment of covariates

Age, race/ethnicity, education, pack-years of cigarette smoking, family history of diabetes, gallbladder removal, and nonsteroidal anti-inflammatory drug (NSAIDs) use were assessed at baseline via self-administered questionnaires. Hormone use was the sum (yes=1/no=0 for each hormone) of 8 WHI hormone usage variables at baseline. Dietary supplement use was defined as the number of supplements taken and was the sum (yes=1/no=0 for each supplement) of 23 vitamin and/or mineral supplements (18). Physical activity was defined as total energy expended from recreational physical activity (MET-hours/week) and was assessed semi-annually (CT) or annually (OS) (19). The Hormone Therapy study arm and Dietary Modification study arm to which the participants were randomized were also included as covariates. We calculated a comorbidity score by summing the presence (yes=1/no=0) of hypercholesterolemia, high blood pressure, heart disease, stroke, and rheumatoid/other arthritis at baseline. Details regarding covariates are presented in Supplementary Table S5.

The T2D status and duration variable (No T2D, recent onset, and longstanding T2D) was defined as follows. First, we ascertained a T2D status variable: at each contact, incident T2D was ascertained if participants self-reported that they had received T2D treatment (i.e., oral medications, insulin, and/or diabetes diet/exercise) and/or had been hospitalized for diabetes (20). This was validated using diabetes medication inventories (19). Participants were followed from enrollment until T2D diagnosis, death, loss to follow-up, or the end of the study on March 1, 2019 to define the time-to-T2D diagnosis. Next, a case of longstanding T2D was defined as diabetes diagnosed more than 3 years before pancreatic cancer diagnosis, whereas recent onset T2D as a diabetes diagnosis less than or equal to 3 years from a pancreatic cancer diagnosis. Body mass index [BMI = weight (kg)/height $(m)^2$] was categorized as normal weight, 18.5 to <25; overweight 25 to <30; and obese 30 to 50.

Statistical analysis

We described participants' baseline characteristics using means ± standard deviations for continuous variables and frequencies for categorical variables, and adjusted dietary scores for total energy intake using the residual method (21). We created the dietary quintiles with cutpoints based on the entire final analytic sample. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of developing pancreatic cancer in higher dietary index quintiles using the lowest quintiles as reference categories. Participants were followed from enrollment to pancreatic cancer diagnosis, death, loss to follow-up, or end of study on March 1, 2019. We calculated p values for linear trend across dietary index quintiles by assigning the quintile medians of each quintile to all participants in the corresponding quintile as an ordinal variable in the

multivariable-adjusted models. In addition to the categorical analysis, we modeled the dietary indices as continuous variables (1-SD increment). We tested the proportional hazards (PH) assumption using the Schoenfeld residuals method and by running time-dependent covariate models. The multivariable adjusted models were stratified by hormone use, education, and age (covariates that violated the PH assumption), and further adjusted for family history of T2D, physical activity, race/ethnicity, pack-years of cigarette smoking, hormone therapy trial arms, NSAID use, supplement use, dietary modification trial arms, gallbladder removal status (22), and comorbidity score (3,23) (Supplementary Table S5). The multivariable plus BMI adjusted models were further stratified by BMI category. In subgroup analyses, we used the likelihood ratio test to test for potential effect modification (24) by diabetes status and duration categories and by BMI categories, by comparing the models with and without the interaction terms. For subgroup analyses, the dietary indices were categorized into quartiles.

We calculated multivariable-adjusted incidence rates of pancreatic cancer in quintiles of each dietary index. For incidence rate analyses, we used the residual method (21) to adjust the dietary indices for the same covariates that were adjusted in the corresponding Cox regression models. We further estimated the incidence rate in dietary index quintiles within each T2D and BMI categories. We conducted all statistical analyses using SAS 9.4 (SAS Institute, Cary, NC) and 2-sided $p<0.05$ was considered statistically significant.

RESULTS

Compared with those in the lowest quintiles, participants in the highest quintiles (reflecting higher potential of the dietary pattern to contribute to higher insulin, inflammation or postprandial glucose, respectively) for all four dietary indices (EDIH, EDIP, GI and GL) had higher proportions of black/African Americans, lower proportions of non-Hispanic white, and higher prevalence of cholecystectomy. Participants classified in the highest quintiles of EDIH, EDIP, and GI had higher BMI and were less physically active as compared to those in the lowest quintiles. In contrast, participants with higher GL scores had lower BMI and reported more physical activity (Table 1).

Compared with those in the lowest quintiles, participants in the highest quintiles of EDIH and EDIP had higher intakes of red meat, processed meat, sugar-sweetened beverages and lower intakes of whole grain, wine, fruit juice, dark-yellow vegetables, green-leafy vegetables and coffee/tea intake. Participants who were in the higher quintiles of GI had higher red meat, processed meat, sugar-sweetened beverages, and refined grain intake and had lower wine, fruit juice, dark-yellow vegetables, green-leafy vegetables, and coffee/tea intake. Regarding nutrient intakes, participants in higher quintiles of EDIH, EDIP and GI had lower total fiber and lycopene intake compared with the lowest quintiles (Table 2). In contrast, the trend of food and nutrient intakes in GL quintiles appeared inversely related to that for EDIH, which aligns with the inverse correlation between the two scores (Supplementary Table S6).

Over a median of 19.9 years of follow-up, 850 incident cases of pancreatic cancer were ascertained. Table 3 presents the hazard ratios (HRs) and 95% confidence intervals (CIs) for

the associations of each dietary index with pancreatic cancer risk. In multivariable-adjusted models, none of the four indices was associated with future development of pancreatic cancer, and the HRs (95%CI) for each 1 standard deviation (SD) increment in dietary index were as follows: EDIH 1.03 (0.96, 1.10); P-trend=0.83; EDIP 0.95 (0.89, 1.02); P-trend=0.07; GI 0.96 (0.89, 1.03); P-trend=0.28; GL 0.96 (0.89, 1.03); P-trend=0.19.

Although there was no statistical evidence of interaction between the dietary indices and T2D categories (interaction p values; EDIH: 0.96, EDIP: 0.41, GI: 0.94, GL: 0.28) (Table 4), HRs were modestly elevated among women with longstanding T2D. An increase in EDIH score by 1 SD was associated with a 33% higher risk of developing pancreatic cancer (HR 1.33; 95%CI 1.06, 1.66; P-trend=0.01). Similarly, we observed increased, but statistically non-significant, associations for 1 SD increments in the other three dietary indices with risk of pancreatic cancer among women with longstanding diabetes (EDIP: HR 1.26; 95%CI 0.98, 1.63; P-trend=0.07; GI: HR 1.26; 95%CI 0.96, 1.67; P-trend=0.10; GL: HR 1.23; 95%CI 0.96, 1.57; P-trend=0.10). No associations were observed between any of the dietary indices and pancreatic cancer risk among women with recent onset diabetes or among those with no diabetes (Table 4).

The BMI subgroup analysis is presented in Table 5. In general, we observed no significant associations within BMI categories, though we found an inverse association between higher GI and GL scores and pancreatic cancer risk among normal-weight women (GI: HR 0.86; 95% CI 0.76, 0.96; P-trend= 0.009; P-interaction=0.007; GL HR 0.83; 95%CI 0.73, 0.93; P-trend= 0.002; P-interaction=0.007).

Corresponding absolute risk estimates presented in Table 6 for the overall sample and in T2D and BMI subgroups, aligned well with the relative risks. For example, there was no excess absolute risk for any of the four dietary indices in the overall sample, whereas all four dietary indices resulted in modest excess risk of between 11 and 13 incident pancreatic cancer cases per 100,000 person-years among women with longstanding diabetes, but no excess risk in other subgroups.

DISCUSSION

We used several validated dietary indices to assess the association between habitual consumption of hyperinsulinemic (EDIH), pro-inflammatory (EDIP), and hyperglycemic (GI and GL) dietary patterns and future risk of pancreatic cancer in a large cohort of postmenopausal women. In the overall sample, we did not observe significant associations between these biologic domains of the diet and risk of pancreatic cancer. However, when stratified by diabetes categories, we observed a modestly elevated (though non-significant) risk of pancreatic cancer for higher scores of each dietary index among women with longstanding diabetes, and a corresponding excess absolute risk. We also observed significant inverse associations between dietary glycemic scores and pancreatic cancer risk among normal-weight women.

Previous epidemiological studies of the association of dietary inflammatory potential and risk of developing pancreatic cancer have used a literature-derived nutrient-based dietary

inflammatory index (DII) to assess the inflammatory potential of the diet and the results have been mixed (12,25,26). The DII, being nutrient-based, is heavily weighted towards nutritional supplements and therefore results based on the DII are difficult to directly compare with those obtained from the food-based EDIP score used in the current study, as it is hard to uncover the influence of diet when mixed with supplements. Investigators found significant associations between higher DII scores, reflecting more pro-inflammatory diets, and pancreatic cancer risk in an Italian case-control study (25), a finding that was later confirmed by pooling data from six case-control studies in the Pancreatic Cancer Case-Control Consortium (PanC4) but not in the Pancreatic Cancer Cohort Consortium studies (PanScan) (26). Also, when the DII was applied in a prospective study using data from the Prostate Lung, Colorectal and Ovarian (PLCO) cancer cohort, there was no association with pancreatic cancer risk (12), highlighting similar inconsistencies by study design that are evident when other dietary patterns have been examined in relation to pancreatic cancer risk (3). In addition, when effect modification by time was investigated, higher DII scores appeared to be inversely associated with pancreatic cancer risk in the first 4 years of follow-up and positively associated with pancreatic cancer risk when follow-up was at least 4 years (12). This highlights the potential reverse causation that we have addressed in the current study by including a 4-year lag as our primary analytic approach, to separate diet assessment from pancreatic cancer diagnosis, thus improving the internal validity of our findings. In the only previous study of the EDIH score in relation to pancreatic cancer risk, there was no association among women in the Nurses' Health Study (NHS) and among men in the Health Professionals Follow-up Study (HPFS) (27), consistent with our findings here.

Evidence regarding the glycemic potential of the diet in relation to pancreatic cancer risk has been mostly inconsistent. One meta-analysis that included both case-control (n=11) and cohort (n=9) studies observed no associations of pancreatic cancer with higher GI and GL scores (28). Another meta-analysis that included only cohort studies (n=13) found no association between GI or GL and pancreatic cancer risk. The summary RR per 10 GI units was 1.02; 95% CI, 0.93–1.12, and per 50 GL units was 1.03; 95% CI, 0.93–1.14 (29). Furthermore, a previous prospective study conducted in the WHI, examined associations of GI and GL with risk of pancreatic cancer and included only 287 cases with a median of 8 years of follow-up (30). This study did not support an association between dietary patterns high in GI or GL and elevated pancreatic cancer risk, findings that we have verified in the current study with almost three times the number of cases and longer follow-up.

We observed elevated, though non-significant, risk of pancreatic cancer for each of the four dietary indices among women with longstanding diabetes. To our knowledge, this is the first study to report on the association of dietary pattern and pancreatic cancer risk stratified by diabetes duration. The current study suggests that the observed diet-pancreatic cancer association is influenced by co-existing chronic hyperglycemia, hyperinsulinemia, and inflammation resulting from the longstanding diabetes. Unlike recent onset T2D which may be more related to pancreatic dysfunction associated with nascent pancreatic cancer not yet diagnosed, diet may directly influence the development of longstanding T2D (7,8,31). Longstanding T2D may then mediate pancreatic cancer development through prolonged insulin resistance, hyperinsulinemia, hyperglycemia, and progressive deterioration in beta-cell function, combined with a pro-inflammatory state (32). A recent prospective cohort

study conducted in the NHS and HPFS cohorts, reported a non-linear relationship between T2D duration and pancreatic cancer risk, where the risk peaked around 8 years after T2D diagnosis and gradually decreased afterwards (33). Also, the study found a higher C-peptide level (reflecting higher beta-cell secretory activity) among participants with prevalent T2D of ≤8 years, whereas HbA1c levels were found to be higher among those with prevalent T2D of up to 15 years (33). In the current study, the median duration of T2D was 7.22 (mean 8.19 years) years for the longstanding T2D category. This may indicate that diet may influence pancreatic cancer development among those with longstanding diabetes via sustained hyperinsulinemia and insulin resistance.

Multiple studies suggest an interrelationship between obesity and type 2 diabetes (T2D), both characterized by insulin resistance, hyperinsulinemia, hyperglycemia, and the promotion of a chronic inflammatory state which may promote greater risk of pancreatic cancer (34–37). Conceptually, two different types of associations between glucose dysregulation and pancreatic cancer likely exist (38,39). First, developing diabetes mellitus in the months prior to a pancreatic cancer diagnosis is common and likely due to dysregulation of endocrine and exocrine functions of the pancreas due to the developing malignancy in the organ, often described as a paraneoplastic process and referred to as “pancreatogenic” diabetes (40). This scenario is supported by preclinical studies and the observation that recent onset diabetes immediately prior to detection of pancreatic cancer often resolves following successful treatment of the cancer (41–43). In contrast, obesity promotes the metabolic syndrome and sustained insulin hypersecretion leading to type 2 diabetes (34), while also promoting chronic systemic inflammation (44). The hyperglycemia and hyperinsulinemia of obesity and T2D may also act upon premalignant and malignant pancreatic ductal epithelial cells to support cancer stem cell functions linked to epithelial-mesenchymal-transition and the carcinogenesis cascade (45).

The finding suggesting a protective association between higher dietary GI and GL and pancreatic cancer risk in normal-weight women is intriguing. It may suggest that in the absence of obesity and insulin resistance, higher glycemic exposures do not elevate insulin, inflammation or glucose, the mechanisms proposed to drive cancer risk. In addition, this finding may suggests that the composition of the diet was low in fat, as lower fat intake has previously been shown to be associated with lower pancreatic cancer risk (46), although early evaluation in WHI did not show protection of a low-fat dietary pattern in normal-weight women nor in a recent meta-analysis (47,48). Furthermore, higher GL scores were associated with lower fat intake in the current study. Also, the inverse associations may be partially explained by the properties of the dietary indices, especially the GL, as we found that higher GL scores were associated with lower BMI and with higher physical activity and higher total fiber intake.

A strength of the current study is the application of novel food-based empirical hypothesis-oriented dietary patterns in a large, multiethnic sample. The prospective design allowed us to account for potential reverse causation bias that is not possible in the case-control design. The large sample size and long duration of follow-up allowed us to conduct subgroup analyses though the overall incidence of pancreatic cancer cases among women with recent onset and longstanding diabetes was low and power may have been limited. We were able to

calculate the absolute risk of pancreatic cancer, which aligned well with the relative risks, and is more reflective of the clinical utility of the dietary pattern. Also, the self-reported T2D had been validated against diabetes medication use (19). However, our study has limitations as well. Though the measurement characteristics of the FFQ were previously assessed, it is appreciated that there is measurement error in diet assessment (49,50), and that dietary patterns may change during the subjects' lifetime, though our group has shown that dietary intake was relatively stable in WHI (51). Data regarding pancreatic cancer subgroups (e.g., adenocarcinoma or pancreatic neuroendocrine tumor) were unavailable, but considering the relative preponderance of pancreatic ductal adenocarcinoma compared to other types of pancreatic cancer, this is expected to have a small effect, if any. We adjusted for a large number of potential confounding variables in the estimation of both the relative and absolute risk, but potential residual confounding and confounding by unmeasured variables remain possible.

In summary, our study does not support an overall association between the insulinemic, inflammatory, or glycemic potential of diet and risk of developing pancreatic cancer in this large cohort of postmenopausal women in the United States. However, these dietary patterns may influence pancreatic cancer development among women with longstanding diabetes. Future studies are warranted to confirm these associations in a larger sample of patients with longstanding diabetes and a larger number of pancreatic cancer cases. Also, the finding of a protective association for GI and GL in normal weight women warrants additional investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Funding/Support:

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30 doi 10.3322/caac.21590. [PubMed: 31912902]
2. Tognon G, Nilsson LM, Lissner L, Johansson I, Hallmans G, Lindahl B, et al. The Mediterranean diet score and mortality are inversely associated in adults living in the subarctic region. J Nutr 2012;142(8):1547–53 doi 10.3945/jn.112.160499. [PubMed: 22739377]
3. Zheng J, Guinter MA, Merchant AT, Wirth MD, Zhang J, Stolzenberg-Solomon RZ, et al. Dietary patterns and risk of pancreatic cancer: a systematic review. Nutr Rev 2017;75(11):883–908 doi 10.1093/nutrit/nux038. [PubMed: 29025004]
4. Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs CS, Hu FB, et al. Development and Validation of an Empirical Dietary Inflammatory Index. J Nutr 2016;146(8):1560–70 doi 10.3945/jn.115.228718. [PubMed: 27358416]

5. Tabung FK, Wang W, Fung TT, Hu FB, Smith-Warner SA, Chavarro JE, et al. Development and validation of empirical indices to assess the insulinaemic potential of diet and lifestyle. Br J Nutr 2016:1–12 doi 10.1017/S0007114516003755.
6. Tabung FK, Satija A, Fung TT, Clinton SK, Giovannucci EL. Long-Term Change in both Dietary Insulinemic and Inflammatory Potential Is Associated with Weight Gain in Adult Women and Men. J Nutr 2019;149(5):804–15 doi 10.1093/jn/nxy319. [PubMed: 31004153]
7. Lee DHL, Jun Li, Yanping, Liu Gang, Wu Kana, Bhupathiraju Shilpa, Rimm Eric B, Rexrode Kathryn M, Manson JoAnn E, Willett Walter C, Hu Frank B, Tabung Fred K, Giovannucci Edward. Dietary Inflammatory and Insulinemic Potential and Risk of Type 2 Diabetes: Results from Three Prospective U.S. Cohort Studies. Diabetes Care 2020 doi 10.2337/dc20-0815.
8. Jin Q, Shi N, Aroke D, Lee DH, Joseph JJ, Donneyong M, et al. Insulinemic and Inflammatory Dietary Patterns Show Enhanced Predictive Potential for Type 2 Diabetes Risk in Postmenopausal Women. Diabetes Care 2021(Epub ahead of print. doi:10.2337/dc20–2216) doi 10.2337/dc20-2216.
9. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials 1998;19(1):61–109 doi 10.1016/s0197-2456(97)00078-0. [PubMed: 9492970]
10. Ma Y, Hebert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, et al. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. Nutrition 2008;24(10):941–9 doi 10.1016/j.nut.2008.04.005. [PubMed: 18562168]
11. Petimar J, Smith-Warner SA, Fung TT, Rosner B, Chan AT, Hu FB, et al. Recommendation-based dietary indexes and risk of colorectal cancer in the Nurses' Health Study and Health Professionals Follow-up Study. Am J Clin Nutr 2018;108(5):1092–103 doi 10.1093/ajcn/nqy171. [PubMed: 30289433]
12. Zheng J, Merchant AT, Wirth MD, Zhang J, Antwi SO, Shoaibi A, et al. Inflammatory potential of diet and risk of pancreatic cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Int J Cancer 2018;142(12):2461–70 doi 10.1002/ijc.31271. [PubMed: 29355939]
13. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9(3):178–87 doi 10.1016/s1047-2797(98)00055-6. [PubMed: 10192650]
14. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc 1988;88(10):1268–71. [PubMed: 3171020]
15. Meinhold CL, Dodd KW, Jiao L, Flood A, Shikany JM, Genkinger JM, et al. Available carbohydrates, glycemic load, and pancreatic cancer: is there a link? Am J Epidemiol 2010;171(11):1174–82 doi 10.1093/aje/kwq061. [PubMed: 20452999]
16. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71(6):1455–61 doi 10.1093/ajcn/71.6.1455. [PubMed: 10837285]
17. Wang W, Fung TT, Wang M, Smith-Warner SA, Giovannucci EL, Tabung FK. Association of the Insulinemic Potential of Diet and Lifestyle With Risk of Digestive System Cancers in Men and Women. JNCI Cancer Spectr 2018;2(4):pky080 doi 10.1093/jncics/pky080. [PubMed: 30740588]
18. Patterson RE, Levy L, Tinker LF, Kristal AR. Evaluation of a simplified vitamin supplement inventory developed for the Women's Health Initiative. Public Health Nutr 1999;2(3):273–6 doi 10.1017/s1368980099000361. [PubMed: 10512561]
19. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials 2008;5(3):240–7 doi 10.1177/1740774508091749. [PubMed: 18559413]
20. Liu S, Tinker L, Song Y, Rifai N, Bonds DE, Cook NR, et al. A prospective study of inflammatory cytokines and diabetes mellitus in a multiethnic cohort of postmenopausal women. Arch Intern Med 2007;167(15):1676–85 doi 10.1001/archinte.167.15.1676. [PubMed: 17698692]
21. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4 Suppl):1220S–8S; discussion 9S-31S doi 10.1093/ajcn/65.4.1220S. [PubMed: 9094926]

22. Schernhammer ES, Michaud DS, Leitzmann MF, Giovannucci E, Colditz GA, Fuchs CS. Gallstones, cholecystectomy, and the risk for developing pancreatic cancer. Br J Cancer 2002;86(7):1081–4 doi 10.1038/sj.bjc.6600193. [PubMed: 11953853]

23. Jiao L, Chen L, White DL, Tinker L, Chlebowski RT, Van Horn LV, et al. Low-fat Dietary Pattern and Pancreatic Cancer Risk in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2018;110(1) doi 10.1093/jnci/djx117.

24. Aitchison J, Silvey SD. Maximum-Likelihood Estimation of Parameters Subject to Restraints. The Annals of Mathematical Statistics 1958;29(3):813–28.

25. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. Br J Nutr 2015;113(2):292–8 doi 10.1017/s0007114514003626. [PubMed: 25515552]

26. Antwi SO, Bamlet WR, Pedersen KS, Chaffee KG, Risch HA, Shivappa N, et al. Pancreatic cancer risk is modulated by inflammatory potential of diet and ABO genotype: a consortia-based evaluation and replication study. Carcinogenesis 2018;39(8):1056–67 doi 10.1093/carcin/bgy072. [PubMed: 29800239]

27. Bao Y, Nimptsch K, Wolpin BM, Michaud DS, Brand-Miller JC, Willett WC, et al. Dietary insulin load, dietary insulin index, and risk of pancreatic cancer. Am J Clin Nutr 2011;94(3):862–8 doi 10.3945/ajcn.110.011205. [PubMed: 21775564]

28. Turati F, Galeone C, Augustin LSA, La Vecchia C. Glycemic Index, Glycemic Load and Cancer Risk: An Updated Meta-Analysis. Nutrients 2019;11(10) doi 10.3390/nu11102342.

29. Aune D, Chan DS, Vieira AR, Navarro Rosenblatt DA, Vieira R, Greenwood DC, et al. Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23(10):2536–46 doi 10.1093/annonc/mds076. [PubMed: 22539563]

30. Simon MS, Shikany JM, Neuhouser ML, Rohan T, Nirmal K, Cui Y, et al. Glycemic index, glycemic load, and the risk of pancreatic cancer among postmenopausal women in the women's health initiative observational study and clinical trial. Cancer Causes Control 2010;21(12):2129–36 doi 10.1007/s10552-010-9632-4. [PubMed: 20711806]

31. Quoc Lam B, Shrivastava SK, Shrivastava A, Shankar S, Srivastava RK. The Impact of obesity and diabetes mellitus on pancreatic cancer: Molecular mechanisms and clinical perspectives. J Cell Mol Med 2020 doi 10.1111/jcmm.15413.

32. Abbruzzese JL, Andersen DK, Borrebaeck CAK, Chari ST, Costello E, Cruz-Monserrate Z, et al. The Interface of Pancreatic Cancer With Diabetes, Obesity, and Inflammation: Research Gaps and Opportunities: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Pancreas 2018;47(5):516–25 doi 10.1097/MPA.0000000000001037. [PubMed: 29702529]

33. Hu Y, Zhang X, Ma Y, Yuan C, Wang M, Wu K, et al. Incident type 2 diabetes duration and cancer risk: a prospective study in two US cohorts. JNCI: Journal of the National Cancer Institute 2020 doi 10.1093/jnci/djaa141.

34. Eibl G, Cruz-Monserrate Z, Korc M, Petrov MS, Goodarzi MO, Fisher WE, et al. Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer. J Acad Nutr Diet 2018;118(4):555–67 doi 10.1016/j.jand.2017.07.005. [PubMed: 28919082]

35. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer 2011;47(13):1928–37 doi 10.1016/j.ejca.2011.03.003. [PubMed: 21458985]

36. Song S, Wang B, Zhang X, Hao L, Hu X, Li Z, et al. Long-Term Diabetes Mellitus Is Associated with an Increased Risk of Pancreatic Cancer: A Meta-Analysis. PLoS One 2015;10(7):e0134321 doi 10.1371/journal.pone.0134321. [PubMed: 26222906]

37. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol 2014;21(7):2453–62 doi 10.1245/s10434-014-3625-6. [PubMed: 24609291]

38. Molina-Montes E, Coscia C, Gomez-Rubio P, Fernandez A, Boenink R, Rava M, et al. Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes and obesity/BMI through causal inference and mediation analyses. Gut 2020 doi 10.1136/gutjnl-2019-319990.

39. Yuan C, Babic A, Khalaf N, Nowak JA, Brais LK, Rubinson DA, et al. Diabetes, Weight Change, and Pancreatic Cancer Risk. JAMA Oncol 2020 doi 10.1001/jamaoncol.2020.2948.
40. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. The Lancet Gastroenterology & Hepatology 2016;1(3):226–37 doi 10.1016/s2468-1253(16)30106-6. [PubMed: 28404095]
41. Mizuno S, Nakai Y, Isayama H, Yanai A, Takahara N, Miyabayashi K, et al. Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age. J Gastroenterol 2013;48(2):238–46 doi 10.1007/s00535-012-0622-z. [PubMed: 22735942]
42. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134(4):981–7 doi 10.1053/j.gastro.2008.01.039. [PubMed: 18395079]
43. Gardner TB, Hessami N, Smith KD, Ripple GH, Barth RJ, Klibansky DA, et al. The effect of neoadjuvant chemoradiation on pancreatic cancer-associated diabetes mellitus. Pancreas 2014;43(7):1018–21 doi 10.1097/MPA.0000000000000162. [PubMed: 25000339]
44. Tuomisto AE, Makinen MJ, Vayrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. World J Gastroenterol 2019;25(31):4383–404 doi 10.3748/wjg.v25.i31.4383. [PubMed: 31496619]
45. Rahn S, Zimmermann V, Viol F, Knaack H, Stemmer K, Peters L, et al. Diabetes as risk factor for pancreatic cancer: Hyperglycemia promotes epithelial-mesenchymal-transition and stem cell properties in pancreatic ductal epithelial cells. Cancer Lett 2018;415:129–50 doi 10.1016/j.canlet.2017.12.004. [PubMed: 29222037]
46. Sanchez GV, Weinstein SJ, Stolzenberg-Solomon RZ. Is dietary fat, vitamin D, or folate associated with pancreatic cancer? Mol Carcinog 2012;51(1):119–27 doi 10.1002/mc.20833. [PubMed: 22162236]
47. Nadella S, Burks J, Al-Sabban A, Inyang G, Wang J, Tucker RD, et al. Dietary fat stimulates pancreatic cancer growth and promotes fibrosis of the tumor microenvironment through the cholecystokinin receptor. Am J Physiol Gastrointest Liver Physiol 2018;315(5):G699–G712 doi 10.1152/ajpgi.00123.2018. [PubMed: 29927319]
48. Shen QW, Yao QY. Total fat consumption and pancreatic cancer risk: a meta-analysis of epidemiologic studies. Eur J Cancer Prev 2015;24(4):278–85 doi 10.1097/CEJ.0000000000000073. [PubMed: 25089377]
49. Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. Am J Epidemiol 2008;167(10):1247–59 doi 10.1093/aje/kwn026. [PubMed: 18344516]
50. Prentice RL, Mossavar-Rahmani Y, Huang Y, Van Horn L, Beresford SA, Caan B, et al. Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. Am J Epidemiol 2011;174(5):591–603 doi 10.1093/aje/kwr140. [PubMed: 21765003]
51. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Tylavsky FA, et al. Longitudinal changes in the dietary inflammatory index: an assessment of the inflammatory potential of diet over time in postmenopausal women. Eur J Clin Nutr 2016;70(12):1374–80 doi 10.1038/ejcn.2016.116. [PubMed: 27380883]

Table 1.

Baseline characteristics of study participants in dietary patterns quintiles, Women's Health Initiative, n=129,241

	Empirical Dietary Index for Hyperinsulinemic (EDIH) score[a,b]			Empirical Dietary Inflammatory Pattern (EDIP) score[a,c]			Dietary Glycemic Index (GI)[a]			Dietary Glycemic Load (GL)[a]		
Characteristic	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Quintile 1**	**Quintile 3**	**Quintile 5**	**Quintile 1**	**Quintile 3**	**Quintile 5**
Range of Dietary Indices	(−10.52, −0.79)	(−0.26,0.16)	(0.67,8.51)	(−13.42, −0.82)	(−0.21, 0.24)	(0.73,6.90)	(−13.57, −0.76)	(−0.22, 0.25)	(0.80,4.00)	(−8.58, −0.70)	(−0.21, 0.20)	(0.74, 8.07)
Sample Size	25848	25849	25848	25848	25849	25848	25848	25849	25848	25848	25849	25848
Race/ethnicity, %												
Black/African American	3.8	6.5	12.3	2.9	5.7	14.8	4.3	5.8	13.3	6.1	7.3	8.6
American Indian or Alaskan Native	0.3	0.5	0.5	0.3	0.4	0.5	0.5	0.3	0.5	0.4	0.4	0.4
Hispanic/Latino	2.4	3.2	4.6	1.4	2.4	7.6	3.9	3.2	3.1	3.6	3.3	3.2
Asian or Pacific Islander	2.0	2.9	2.5	1.2	2.1	4.9	2.5	3.0	1.8	1.6	2.9	3.0
White (not of Hispanic origin)	90.1	85.6	78.6	92.9	88.0	70.5	87.5	86.3	80.1	86.9	84.6	83.5
Other race groups	1.4	1.3	1.5	1.3	1.4	1.7	1.5	1.4	1.4	1.4	1.5	1.4
Age, years, mean ± SD	63.1±7.2	63.7±7.2	61.9±7.1	62.7±7.0	63.5±7.2	62.4±7.3	63.6±7.2	63.1±7.2	62.3±7.1	62.7±7.0	63.4±7.2	62.8±7.4
BMI, kg/m^2, mean ± SD	26.0± 4.9	27.0± 5.3	29.4± 6.2	26.5± 5.0	27.1± 5.3	28.8± 6.2	26.7± 5.3	27.3± 5.5	28.1± 5.9	28.2± 5.8	27.3± 5.4	26.9± 5.5
Underweight (15≤BMI < 18.5), %	2.2	2.2	1.9	2.0	2.0	2.2	2.2	2.0	2.2	1.9	2.0	2.5
Normal weight (18.5≤BMI < 25), %	46.4	37.3	23.2	41.6	37.1	27.1	40.6	36.2	31.2	31.0	36.5	40.0
Overweight (25≤BMI < 30), %	33.3	35.9	32.9	35.1	35.4	33.0	34.5	35.1	33.9	34.4	35.3	33.2
Obese (BMI ≥30), %	18.0	24.7	42.0	21.3	25.5	37.7	22.7	26.7	32.8	32.8	26.2	24.3
Physical activity, MET-hours/week, mean ± SD	16.7± 15.6	12.8± 13.1	9.1± 11.3	15.3 ±14.7	12.9± 13.1	9.9 ±12.2	16.1± 15.2	12.8± 13.3	9.5± 11.7	11.3± 12.6	12.4± 13.0	14.9± 15.1
Pack Years of Smoking, mean ± SD	10.8± 18.2	9.2 ±17.3	10.6± 19.3	13.1± 20.1	9.2 ±17.1	8.1± 16.8	10.1 ±18.0	9.5± 17.5	10.9± 19.2	13.6 ±21.0	9.0 ±16.9	8.5 ±16.7
Current Smoking, %	6.1	6.1	9.5	8.9	6.1	6.8	5.6	6.0	9.8	11.3	5.9	4.6
Aspirin/NSAIDs use, %	13.9	13.5	13.1	14.4	13.8	12.4	13.8	13.5	13.6	13.9	13.6	13.1
Statin Use, %	2.0	2.4	2.1	1.9	2.3	2.3	2.1	2.2	2.3	1.6	2.5	2.7
Hypercholestrolemia, %	12.0	13.9	13.5	11.6	13.9	14.6	12.4	13.7	14.2	10.9	13.5	15.9

Characteristic	Empirical Dietary Index for Hyperinsulinemic (EDIH) score[a,b]			Empirical Dietary Inflammatory Pattern (EDIP) score[a,c]			Dietary Glycemic Index (GI)[a]			Dietary Glycemic Load (GL)[a]		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Educational level, %												
Less than high school	3.0	4.4	7.1	2.7	3.8	8.7	3.3	4.1	7.6	4.6	4.8	4.8
High school/GED/Some college	45.1	54.8	61.7	50.0	54.2	57.9	47.5	53.3	61.9	55.7	54.7	50.9
≥4 years of college	51.0	40.1	30.0	46.6	41.4	32.6	48.4	41.9	29.7	39.0	39.7	43.5
Total Alcohol Intake, alcohol Servings/week[4]	4.8± 7.5	1.9 ±3.7	1.6± 3.7	5.3 ±7.8	2.0 ±3.6	0.9 ±2.6	3.6 ±6.5	2.4 ±4.4	1.7± 4.1	5.5 ±8.1	1.8± 3.3	1.1 ±2.6
Gallbladder removed, %	9.1	11.6	15.2	9.7	11.4	14.4	9.7	11.7	14.4	11.3	11.8	12.5
Total energy, kcal/day	1832±626	1482±556	1829±744	1731±620	1548±578	1789±761	1591±625	1680±642	1605±631	1826±713	1489±573	1831±646

[a] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake using the residual method. Lower EDIP indicates anti-inflammatory diets while higher EDIP scores indicate pro-inflammatory diets. Lower EDIH indicates low insulinemic dietary patterns while a higher score indicates hyperinsulinemic diet. We used pre-computed GI and GL (total carbohydrate) from WHI FFQ.

[b] The EDIH component foods (servings/d) in the WHI were listed in TableS3.

[c] The EDIP component foods (servings/d) in the WHI were listed in TableS3.

Table 2

· Distribution of dietary intakes across quintiles of the dietary indices

	Empirical Dietary Index for Hyperinsulinemic (EDIH) score[a,b]			Empirical Dietary Inflammatory Pattern (EDIP) score[a,c]			Dietary Glycemic Index (GI)[a]			Dietary Glycemic Load (GL)[a]		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Food/food groups, med servings/week (means ± standard deviations)												
Red meat	2.3±2.2	3.0±2.4	6.2±4.3	3.2±2.9	3.3±2.8	4.7±4.1	3.1±3.1	3.7±3.2	3.7±3.2	5.6±4.2	3.2±2.6	2.5±2.5
Processed meat	1.2±1.5	1.5±1.7	3.2±3.0	1.5±1.8	1.6±1.8	2.6±2.9	1.5±2.0	1.9±2.1	2.1±2.3	2.7±2.8	1.6±1.8	1.4±1.9
Sugar-sweetened beverages	0.4±1.4	0.7±1.7	3.2±6.5	0.4±1.4	0.7±1.8	3.1±6.4	0.3±1.0	0.8±2.2	2.8±6.1	0.6±1.6	0.8±1.9	2.7±6.5
Tomatoes	4.1±3.5	3.4±3.1	4.1±4.2	4.0±3.4	3.5±3.1	4.1±4.4	4.3±3.8	3.9±3.5	2.9±3.1	4±3.6	3.4±3.2	4.2±4.0
Refined grains	15.3±9.3	12.3±7.2	13.1±8.1	12.0±7.1	12.4±7.2	16.5±10.0	9.4±6.1	13.6±7.6	16.3±9.3	11.1±7.2	12.2±6.9	17.8±9.8
Whole grains[e]	10.6±6.3	9.1±5.1	9.3±5.1	10.1±5.7	9.4±5.2	9.4±5.6	8.7±5.1	9.9±5.5	9.4±5.6	8.6±4.8	9.1±4.9	11.7±6.6
Wine	3.6±6.0	0.9±1.9	0.5±1.2	3.7±6.1	0.9±1.7	0.3±0.9	2.4±5.0	1.4±2.9	0.7±1.8	3±5.7	1.1±2.3	0.7±1.7
Fruit juice	5.0±5.2	4.1±4.1	3.7±4.0	4.5±4.9	4.3±4.3	3.6±4.0	4.3±4.8	4.5±4.5	3.3±3.7	3.3±3.6	3.9±3.9	5.6±5.7
Yellow vegetables	6.7±5.2	5.0±3.7	4.8±4.0	7.4±5.7	5.1±3.6	3.8±3.1	5.8±4.6	5.5±4.2	4.4±3.7	4.8±3.9	4.9±3.8	6.7±5.2
Green-leafy vegetables	8.3±6.4	5.6±4.3	4.9±4.1	9.2±6.8	5.6±3.9	3.9±3.3	8.1±6.1	6±4.5	4.1±3.7	6.5±5.2	5.7±4.5	6.4±5.5
Coffee or tea	22.6±14.9	13.8±10.6	11.1±10.6	28.4±15.5	13.6±7.8	6.5±6.6	15.8±13.1	15.3±12.2	14.8±12.5	17.3±13.6	14.5±11.9	14.8±12.6
Pizza	0.4±0.6	0.3±0.5	0.4±0.6	0.5±0.8	0.3±0.4	0.3±0.4	0.3±0.4	0.4±0.5	0.4±0.6	0.4±0.6	0.4±0.5	0.4±0.6
Nutrient Intakes (means ± standard deviations)												
Total fiber, g/d	20.1±7.7	15.2±5.8	14.2±6.2	17.9±7.3	15.7±6.4	15.2±6.8	17±7.2	16.7±6.8	13.6±5.9	13.7±5.9	14.9±5.8	21.2±7.6
Total carbohydrate, g/d	243.1±84.2	187.0±66.8	202.4±87.0	213.1±79.4	194.2±72.6	217.7±91.7	196.8±78.7	207.9±78.8	199.8±80.1	176.2±73.5	186±64.3	272.6±81.8
Total protein, g/d	72.5±27.7	62.1±25.2	78±33.3	71.7±28.1	64.9±26.0	72.9±33.3	72.5±30.9	69.6±27.8	60.4±25.2	79.6±33.0	62.5±25.8	70.5±27.3
BCAA[d], g/d	12.9±5.2	11.0±4.6	13.8±6.0	12.7±5.2	11.6±4.8	13±6.0	13.2±5.8	12.3±5.0	10.6±4.5	14.3±6.0	11.1±4.7	12.4±5.0
Total fat, g/d	59.5±31.7	53.9±27.7	78.5±38.1	60.5±31.7	56.8±29.0	71.1±38.8	54.8±31.2	62.7±33.0	62.6±31.7	82.4±38.5	55±27.0	53.9±30.0

	Empirical Dietary Index for Hyperinsulinemic (EDIH) score[a,b]			Empirical Dietary Inflammatory Pattern (EDIP) score[a,c]			Dietary Glycemic Index (GI)[a]			Dietary Glycemic Load (GL)[a]		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Saturated fat, g/d	20.2±11.9	18.0±9.9	26.5±13.7	20.4±11.7	19.1±10.6	23.9±13.8	18.5±11.4	21.1±12.0	20.9±11.4	28±14.1	18.5±9.8	17.8±10.9
Total cholesterol, g/d	196.8±113.6	193.4±107.0	295.7±160.8	216.4±126.4	203.6±116.0	254.8±153.9	212.9±139.1	222.6±126.3	212.6±124.1	304.3±163.9	196.7±102.6	183±108.9
Dietary calcium, mg/d	1045.3±526.6	768.2±395.0	746.9±413.1	911.1±486.0	802.9±421.9	810±467.6	1013.1±563.4	826.4±405.9	641.6±321.8	836.5±475.0	769.1±412.9	964±487.1
Lycopene, mcg/d	5862.8±3685.0	4679.5±2954.0	4673.7±3080.2	5554.6±3412.7	4811.8±3006.8	4677.7±3384.6	5778.9±3629.0	5152.7±3138.8	3693.2±2471.8	4750.6±2920.3	4622±2924.0	5898.6±3924.4
Dietary Magnesium (mg/day)	317.5±98.5	237.1±81.2	237.6±94.7	295.5±97.0	245.7±87.7	241.4±99.6	277.0±102.8	263.2±92.1	217.5±81.6	252.3±96.2	236.0±86.1	306.2±100.2
Dietary Manganese (mg/day)	4.4±1.5	3.0±1.1	2.7±1.2	4.2±1.4	3.0±1.2	2.7±1.3	3.3±1.4	3.4±1.4	2.9±1.3	3.1±1.4	3.0±1.2	4.0±1.5
Dietary Vitamin D (mcg/day)	5.1±3.7	4.1±2.7	4.3±2.8	4.4±3.3	4.2±2.8	4.6±3.2	5.4±4.2	4.4±2.7	3.4±2.0	4.8±3.4	4.1±2.8	4.6±3.1

[a] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake using the residual method. Lower EDIP indicates anti-inflammatory dietary patterns while higher EDIP scores indicate pro-inflammatory diets. Lower EDIH indicates low insulinemic dietary patterns while a higher score indicates hyperinsulinemic dietary patterns. We used pre-computed GI and GL (from total carbohydrates).

[b] The EDIH component foods (servings/d) in the WHI were listed in TableS3·

[c] The EDIP component foods (servings/d) in the WHI were listed in TableS3·

[d] BCAA, branched chain amino acids

[e] Whole grain was calculated by taking the sum of dark bread, corn tortilla, popcorn, cooked cereal, corn/ hominy.

Table 3.

Hazard ratios (95% CI) for the associations of dietary patterns with risk of developing pancreatic cancer[a]

	Hazard ratios for pancreatic cancer risk					P value for linear trend[d]	Per 1-SD increment in dietary score	P-value for continuous dietary score
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5			
Empirical dietary index for hyperinsulinemic (EDIH) score[b]								
Cases/Noncases	170/25678	174/25674	183/25666	174/25674	149/25699			
Age-Adjusted	1(Ref)	1.02 (0.83, 1.26)	1.09 (0.88, 1.34)	1.08 (0.87, 1.33)	1.01 (0.81, 1.25)	0.79	1.04 (0.97, 1.11)	0.24
Multivariable Adjusted	1(Ref)	1.02 (0.83, 1.27)	1.09 (0.88, 1.34)	1.06 (0.85, 1.31)	0.96 (0.76, 1.20)	0.88	1.03 (0.96, 1.10)	0.43
Multivariable+ BMI Adjusted	1(Ref)	1.01 (0.82, 1.25)	1.09 (0.88, 1.34)	1.06 (0.85, 1.31)	0.95 (0.75, 1.19)	0.83	1.03 (0.96, 1.10)	0.47
Empirical dietary inflammatory pattern (EDIP) score[b]								
Cases/Noncases	200/25648	183/25665	152/25697	158/25690	157/25691			
Age-Adjusted	1(Ref)	0.91 (0.75, 1.11)	0.75 (0.61, 0.93)	0.81 (0.66, 1.00)	0.88 (0.71, 1.08)	0.071	0.96 (0.90, 1.02)	0.16
Multivariable Adjusted	1(Ref)	0.92 (0.75, 1.12)	0.77 (0.62, 0.95)	0.82 (0.66, 1.01)	0.88 (0.71, 1.09)	0.069	0.95 (0.89, 1.02)	0.16
Multivariable+ BMI Adjusted	1(Ref)	0.91 (0.74, 1.11)	0.76 (0.61, 0.94)	0.82 (0.66, 1.01)	0.87 (0.70, 1.09)	0.066	0.95 (0.89, 1.02)	0.15
Dietary glycemic index (GI)[c]								
Cases/Noncases	186/25662	169/25679	175/25674	164/25684	156/25692			
Age-Adjusted	1(Ref)	0.91 (0.74, 1.12)	0.95 (0.77, 1.17)	0.91 (0.74, 1.12)	0.92 (0.74, 1.13)	0.45	0.97 (0.90, 1.04)	0.37
Multivariable Adjusted	1(Ref)	0.90 (0.73, 1.11)	0.94 (0.76, 1.15)	0.89 (0.72, 1.10)	0.88 (0.71, 1.10)	0.28	0.96 (0.89, 1.03)	0.23
Multivariable+ BMI Adjusted	1(Ref)	0.90 (0.73, 1.11)	0.93 (0.76, 1.15)	0.89 (0.72, 1.10)	0.88 (0.71, 1.10)	0.28	0.96 (0.89, 1.03)	0.23
Dietary glycemic load (GL)[c]								
Cases/Noncases	162/25686	200/25648	190/25659	145/25703	153/25695			
Age-Adjusted	1(Ref)	1.20 (0.97, 1.47)	1.12 (0.91, 1.39)	0.85 (0.68, 1.07)	0.92 (0.74, 1.15)	0.064	0.94 (0.88, 1.01)	0.10
Multivariable Adjusted	1(Ref)	1.23 (1.00, 1.51)	1.16 (0.94, 1.43)	0.89 (0.71, 1.12)	0.95 (0.76, 1.20)	0.16	0.96 (0.89, 1.03)	0.25
Multivariable+ BMI Adjusted	1(Ref)	1.23 (1.00, 1.51)	1.17 (0.95, 1.45)	0.89 (0.71, 1.12)	0.95 (0.76, 1.20)	0.19	0.96 (0.90, 1.03)	0.28

[a] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake using the residual method. The multivariable adjusted models were stratified by hormone use, education, and age, and further adjusted for family history of T2D, physical activity, race/ethnicity, pack-years of smoking, hormone therapy trial arms, NSAID use, supplement use, dietary modification trial arms, cholecystectomy status, and comorbidity score. The multivariable + BMI adjusted models were further stratified by BMI.

[b] Lower EDIP scores indicate anti-inflammatory dietary patterns while higher EDIP scores indicate pro-inflammatory patterns. Lower EDIH indicates low insulinemic dietary patterns while higher scores indicate more hyperinsulinemic dietary patterns.

[c] GI and GL scores were calculated using total carbohydrates. Lower GI/GL scores indicate low glycemic diets while higher scores indicate hyperglycemic dietary patterns.

[d] P values for linear trend across dietary index quartiles were estimated by assigning the median dietary index value for each quintile to all participants in the corresponding quartile, as an ordinal variable. Models for linear trend were adjusted for all covariates listed in the corresponding models in footnote a.

Table 4.

Hazard ratios (95% CI) for the associations of dietary patterns with risk of developing pancreatic cancer in subgroups defined by diabetes status and duration[a,e]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value for linear trend[d]	Per 1-SD increment in dietary score	P-value for continuous dietary score
No T2D							
Cases/Noncases	171/27755	177/27406	173/26796	148/25659			
Empirical dietary index for hyperinsulinemic (EDIH) score[b]	1(ref)	1.06 (0.85, 1.30)	1.09 (0.88, 1.35)	1.04 (0.83, 1.32)	0.67	1.02 (0.94, 1.10)	0.68
Cases/Noncases	203/27518	178/27317	152/26901	136/25880			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(ref)	0.88 (0.72, 1.08)	0.79 (0.64, 0.97)	0.81 (0.65, 1.02)	0.02	0.93 (0.86, 1.00)	0.051
Cases/Noncases	184/27248	170/26822	167/26819	148/26727			
Dietary glycemic index (GI)[c]	1(ref)	0.94 (0.76, 1.15)	0.93 (0.75, 1.15)	0.87 (0.70, 1.09)	0.23	0.94 (0.87, 1.02)	0.14
Cases/Noncases	164/26671	199/26807	167/27030	139/27108			
Dietary glycemic load (GL)[c]	1(ref)	1.19 (0.96, 1.46)	0.99 (0.79, 1.23)	0.83 (0.66, 1.05)	0.07	0.93 (0.86, 1.01)	0.09
Recent Onset T2D (T2D diagnosed ≤3 years before pancreatic cancer diagnosis)							
Cases/Noncases	30/1473	35/1548	24/1587	29/1781			
Empirical dietary index for hyperinsulinemic (EDIH) score[b]	1(ref)	1.14 (0.69, 1.90)	0.75 (0.43, 1.31)	0.83 (0.47, 1.44)	0.47	0.96 (0.80, 1.14)	0.63
Cases/Noncases	32/1525	27/1551	25/1612	34/1701			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(ref)	0.86 (0.51, 1.46)	0.69 (0.40, 1.19)	0.88 (0.53, 1.48)	0.57	0.95 (0.80, 1.13)	0.58
Cases/Noncases	31/1547	35/1605	25/1626	27/1611			
Dietary glycemic index (GI)[c]	1(ref)	1.10 (0.67, 1.80)	0.72 (0.42, 1.25)	0.79 (0.46, 1.37)	0.30	0.90 (0.74, 1.10)	0.30
Cases/Noncases	28/1537	39/1607	26/1602	25/1643			
Dietary glycemic load (GL)[c]	1(ref)	1.40 (0.85, 2.31)	0.78 (0.45, 1.37)	0.73 (0.41, 1.30)	0.10	0.93 (0.77, 1.12)	0.46
Longstanding T2D (T2D diagnosed > 3 years before pancreatic cancer diagnosis)							
Cases/Noncases	11/2853	11/3116	12/3705	28/4645			

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value for linear trend[d]	Per 1-SD increment in dietary score	P-value for continuous dietary score
Empirical dietary index for hyperinsulinemic (EDIH) score[b]	1(ref)	0.87 (0.37, 2.03)	0.75 (0.32, 1.75)	1.47 (0.70, 3.08)	0.21	1.33 (1.06, 1.66)	0.01
Cases/Noncases	10/3004	18/3205	15/3590	19/4520			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(ref)	1.74 (0.79, 3.81)	1.31 (0.58, 2.95)	1.33 (0.60, 2.93)	0.71	1.26 (0.98, 1.63)	0.07
Cases/Noncases	12/3262	15/3650	15/3645	20/3762			
Dietary glycemic index (GI)[c]	1(ref)	1.04 (0.48, 2.2)	1.06 (0.49, 2.31)	1.61 (0.76, 3.37)	0.25	1.26 (0.96, 1.67)	0.10
Cases/Noncases	20/3877	11/3627	17/3446	14/3369			
Dietary glycemic load (GL)[c]	1(ref)	0.62 (0.29, 1.30)	1.10 (0.57, 2.15)	1.18 (0.57, 2.42)	0.62	1.23 (0.96, 1.57)	0.10

[a] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake using the residual method. The multivariable adjusted +BMI models were stratified by hormone use, education, BMI, and age, and further adjusted for family history of T2D, physical activity, race/ethnicity, pack-years of smoking, hormone therapy trial arms, NSAID use, supplement use, dietary modification trial arms, cholecystectomy status, and comorbidity score.

[b] Lower EDIP scores indicate anti-inflammatory dietary patterns while higher EDIP scores indicate pro-inflammatory patterns. Lower EDIH indicates low insulinemic dietary patterns while a higher score indicates hyperinsulinemic patterns.

[c] GI and GL were computed using total carbohydrates. Lower GI/GL scores indicate low glycemic diets while higher scores indicate hyperglycemic diets.

[d] P values for linear trend across dietary index quartiles were estimated by assigning the median dietary index value for each quartile to all participants in the corresponding quartile, as an ordinal variable. Models for linear trend were adjusted for all covariates listed in the corresponding models in footnote a.

[e] We tested for interaction using the likelihood ratio test, comparing the full model (with dietary score × diabetes terms) and reduced model (without the interaction terms). P values for interaction with each dietary index were as follows: EDIH: 0.96, EDIP: 0.41, GI: 0.94, GL: 0.28. There were 62 cases of pancreatic cancer in the longstanding T2D category and 118 in the recent onset T2D category.

Table 5.

Hazard ratios (95% CI) for the associations of dietary patterns with risk of developing pancreatic cancer in subgroups defined by body weight categories.[a,e]

	Hazard ratios for pancreatic cancer risk						
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P value for linear trend[d]**	**Per 1-SD increment in dietary score**	**P-value for continuous dietary score**
Normal weight women (BMI: 18.5 −24.9 kg/m^2)							
Cases/Noncases	89/14696	93/12945	72/10817	50/7954			
Empirical dietary index for hyperinsulinemic (EDIH)[b] score	1(Ref)	1.20 (0.90, 1.61)	1.16 (0.84, 1.59)	1.16 (0.81, 1.65)	0.37	1.04 (0.92, 1.17)	0.57
Cases/Noncases	104/13273	81/12513	67/11469	52/9157			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(Ref)	0.83 (0.62, 1.12)	0.78 (0.57, 1.07)	0.81 (0.57, 1.14)	0.13	0.94 (0.84, 1.05)	0.27
Cases/Noncases	104/12986	78/12146	68/11141	54/10139			
Dietary glycemic index (GI)[c]	1(Ref)	0.80 (0.60, 1.08)	0.77 (0.56, 1.05)	0.69 (0.49, 0.97)	0.025	0.86 (0.76, 0.96)	0.009
Cases/Noncases	74/10075	89/11315	88/12139	53/12883			
Dietary glycemic load (GL)[c]	1(Ref)	1.07 (0.78, 1.46)	0.97 (0.71, 1.33)	0.54 (0.38, 0.78)	0.0008	0.83 (0.73, 0.93)	0.002
Overweight women (BMI: 25 −29.9 kg/m^2)							
Cases/Noncases	74/10775	79/11404	84/11566	67/10701			
Empirical dietary index for hyperinsulinemic (EDIH) score[b]	1(Ref)	1.00 (0.72, 1.37)	1.06 (0.78, 1.46)	1.00 (0.71, 1.40)	0.92	1.00 (0.89, 1.13)	0.93
Cases/Noncases	86/11231	87/11343	64/11222	67/10650			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(Ref)	0.98 (0.72, 1.32)	0.73 (0.52, 1.01)	0.92 (0.66, 1.27)	0.26	0.95 (0.85, 1.06)	0.34
Cases/Noncases	73/11027	88/11221	79/11294	64/10904			
Dietary glycemic index (GI)[c]	1(Ref)	1.18 (0.86, 1.61)	1.05 (0.76, 1.45)	0.93 (0.66, 1.32)	0.5903	0.96 (0.85, 1.08)	0.50
Cases/Noncases	69/11082	98/11367	63/11265	74/10732			
Dietary glycemic load (GL)[c]	1(Ref)	1.33 (0.98, 1.81)	0.87 (0.61, 1.22)	1.10 (0.78, 1.54)	0.87	1.00 (0.88, 1.13)	0.95
Obese women (BMI: ≥30 kg/m^2)							
Cases/Noncases	44/5917	47/7053	53/9073	82/12831			

	Hazard ratios for pancreatic cancer risk						
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P value for linear trend[d]**	**Per 1-SD increment in dietary score**	**P-value for continuous dietary score**
Empirical dietary index for hyperinsulinemic (EDIH)[b] score	1(Ref)	0.92 (0.61, 1.38)	0.82 (0.55, 1.23)	0.91 (0.63, 1.33)	0.64	1.05 (0.93, 1.19)	0.42
Cases/Noncases	51/6910	51/7597	58/8732	66/11635			
Empirical dietary inflammatory pattern (EDIP) score[b]	1(Ref)	0.92 (0.63, 1.36)	0.95 (0.65, 1.39)	0.85 (0.59, 1.24)	0.44	0.99 (0.87, 1.12)	0.85
Cases/Noncases	42/7370	54/8090	58/9034	72/10380			
Dietary glycemic index (GI)[c]	1(Ref)	1.18 (0.79, 1.77)	1.16 (0.78, 1.73)	1.33 (0.90, 1.97)	0.17	1.11 (0.96, 1.27)	0.15
Cases/Noncases	67/10320	59/8760	52/8054	48/7740			
Dietary glycemic load (GL)[c]	1(Ref)	1.08 (0.76, 1.53)	1.04 (0.72, 1.51)	1.05 (0.71, 1.54)	0.83	1.08 (0.95, 1.23)	0.22

[a.] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake using the residual method. The multivariable adjusted models were stratified by hormone use, education, and age, and further adjusted for family history of T2D, physical activity, race/ethnicity, pack-years of smoking, hormone therapy trial arms, NSAID use, supplement use, dietary modification trial arms, cholecystectomy status, and comorbidity score.

[b] Lower EDIP scores indicate low inflammatory dietary patterns whereas higher EDIP scores indicate pro-inflammatory patterns. Lower EDIH indicates low insulinemic dietary pattern whereas higher scores indicate hyperinsulinemic dietary patterns

[c] GI and GL were calculated using total carbohydrates. Lower GI/GL scores indicate low glycemic diets while higher scores indicate hyperglycemic dietary patterns

[d] P values for linear trend across dietary index quartiles were estimated by assigning the median dietary index value for each quartile to all participants in the corresponding quartile, as an ordinal variable. Models for linear trend were adjusted for all covariates listed in the corresponding models in footnote a.

[e] We tested for interaction using the likelihood ratio test, comparing the full (with dietary score × BMI terms) and reduced models (without interaction terms).

P values for interaction for each dietary index were as follows: EDIH = 0.80; EDIP = 0.43; GI = 0.0068; GL = 0.0075

Table 6.

Incidence rate of pancreatic cancer in dietary index quintiles overall, by diabetes status, and by body mass index category.[a]

Overall incidence rate of pancreatic cancer per 100,000 person-years						
Overall study sample	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**Difference (Q5–Q1)[b]**
Empirical dietary index for hyperinsulinemic (EDIH) score	36	35	41	38	35	−1
Empirical dietary inflammatory pattern (EDIP) score	42	38	36	32	35	−7
Dietary glycemic index (GI)[c]	39	36	38	37	34	−5
Dietary glycemic load (GL)[c]	37	42	40	33	33	−4
Incident pancreatic cancer cases per 100,000 person-years by diabetes status and duration						
NoT2D	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**Difference (Q5–Q1)[b]**
Empirical dietary index for hyperinsulinemic (EDIH) score	34	33	40	36	33	−2
Empirical dietary inflammatory pattern (EDIP) score	43	36	33	31	34	−9
Dietary glycemic index (GI)[c]	40	31	36	37	31	−9
Dietary glycemic load (GL)[c]	36	40	38	33	30	−7
Recent onset T2D						
Empirical dietary index for hyperinsulinemic (EDIH) score	103	96	96	97	67	−36
Empirical dietary inflammatory pattern (EDIP) score	102	100	99	71	86	−17
Dietary glycemic index (GI)[c]	69	144	93	67	84	15
Dietary glycemic load (GL)[c]	94	125	94	63	82	−12
Longstanding T2D						
Empirical dietary index for hyperinsulinemic (EDIH) score	17	20	22	20	30	13
Empirical dietary inflammatory pattern (EDIP) score	11	30	31	16	23	11
Dietary glycemic index (GI)[c]	20	18	23	18	32	12
Dietary glycemic load (GL)[c]	20	18	23	18	32	12
Incident pancreatic cancer cases per 100,000 person-years by BMI categories						
Normal weight women (BMI: 18.5 −24.9 kg/m2)	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**Difference (Q5–Q1)[b]**
Empirical dietary index for hyperinsulinemic (EDIH) score	33	32	42	37	35	2
Empirical dietary inflammatory pattern (EDIP) score	42	34	35	32	36	−6

Dietary glycemic index (GI)[c]	47	29	42	32	28	−19
Dietary glycemic load (GL)[c]	44	41	44	26	24	−20
Overweight women (BMI: 25 −29.9 kg/m^2)						
Empirical dietary index for hyperinsulinemic (EDIH) score	36	38	41	40	35	−1
Empirical dietary inflammatory pattern (EDIP) score	47	40	35	33	35	−11
Dietary glycemic index (GI)[c]	36	45	33	42	34	−2
Dietary glycemic load (GL)[c]	31	51	33	39	35	4
Obese women (BMI: ≥30 kg/m^2)						
Empirical dietary index for hyperinsulinemic (EDIH) score	40	37	39	34	36	−4
Empirical dietary inflammatory pattern (EDIP) score	37	43	42	32	33	−4
Dietary glycemic index (GI)[c]	32	34	40	37	42	9
Dietary glycemic load (GL)[c]	37	34	40	33	42	5

[a.] EDIP, EDIH, GI, and GL scores were adjusted for total energy intake, family history of T2D, physical activity, race/ethnicity, pack-years of smoking, hormone replacement therapy arms, NSAID, supplement, dietary modification trial arms cholecystectomy status, comorbidity score, hormone use, education, BMI, age.

[b] Q5–Q1: The excess incidence due to consuming a hyperinsulinemic, pro-inflammatory or hyperglycemic dietary.

[c] GI and GL were calculated using total carbohydrates.