Quality Diet Index and Risk of Pancreatic Cancer: Findings from the Singapore Chinese Health Study

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ABSTRACT

Background: Limited research has been conducted on the effect of quality diet index (QDI), which represents a comprehensive assessment of healthy diet quality and quantity, on pancreatic cancer risk in Asian populations.

Methods: Using data from the Singapore Chinese Health Study, a prospective cohort of 63,257 middle-aged or older Chinese men and women, four QDI scores: the Alternative Health Eating Index-2010 (AHEI-2010), the alternate Mediterranean Diet (aMED), the Dietary Approaches to Stop Hypertension (DASH), and the Heathy Diet Indicator (HDI), at baseline were calculated. After 25 years of follow-up, 311 cohort participants developed pancreatic cancer. Cox proportional hazard regression method was used to estimate HR and 95% confidence interval (CI) for pancreatic cancer associated with higher QDI scores.

Results: Higher scores of AHEI-2010, aMED, and DASH were significantly associated with lower pancreatic cancer risk (all $P_{\text{trend}} < 0.05$). Compared with the lowest quartile, HRs (95% CIs) of pancreatic cancer for the highest quartiles of AHEI-2010, aMED, and DASH scores were 0.65 (0.46–0.90), 0.57 (0.38–0.85), and 0.66 (0.46–0.95), respectively. These associations were more apparent among men. Overall, there was no statistically significant difference in the QDI–pancreatic cancer risk association between subgroups stratified by levels of body mass index, history of diabetes, and smoking status.

Conclusions: Higher QDI scores were significantly associated with reduced risk of pancreatic cancer.

Impact: The consistent results across multiple QDIs shows that adherence to a healthy diet may lower pancreatic cancer risk, suggesting that dietary modification may be a promising approach for primary prevention of pancreatic cancer.

Introduction

There are about 459,000 newly diagnosed cases of pancreatic cancer and more than 432,000 related deaths worldwide each year, making it the seventh most common cancer-related cause of death (1). In the United States, pancreatic cancer is the third leading cause of cancer-related death with an estimated 47,050 deaths in 2020 (2). The incidence rate of pancreatic cancer has shown a steady increase by 1.5% per year (3, 4), which was in the opposite trend with other common cancer types. Because most of pancreatic cancers are detected at an advanced stage, the prognosis is dismal with a 5-year survival rate at only 8% after diagnosis (4, 5). In Singapore, the mortality rates of pancreatic cancer have also been increased from 1.7 (per 100,000) in men and 1.5 (per 100,000) in women in 1968–1972 period to 5.5 in men and 4.1 in women in the 2013-to-2017 period (6). Chronic pancreatitis, obesity, type 2 diabetes, and tobacco smoking are the established risk factors for pancreatic cancer. However, these risk factors collectively account for less than half of pancreatic cancer cases in the United States. (7). There is an urgent need to identify other potential risk factors for pancreatic cancer to understand the etiology, which may facilitate the development of effective prevention and control strategy against pancreatic carcinogenesis.

Diet plays an important role in the development of certain chronic diseases including cancer. Diet itself is complex with many different constituents. In addition, dietary habits are greatly influenced by the culture, tradition, and economic status for a given population. Therefore, it is very challenging to assess the role of individual dietary component on the risk of cancer including pancreatic cancer and other chronic diseases given their shared common sources and potential synergistic or counteractive effect on the health outcomes (8). Quality diet index (QDI) may represent the common dietary habit for a given individual. There are four QDIs, including the Healthy Eating Index-2010 (HEI-2010) (9), the Alternative Health Eating Index-2010 (AHEI-2010) (10), the alternate Mediterranean Diet (aMED) (11, 12), the Dietary Approaches to Stop Hypertension (DASH) (13), that have been constructed according to the adherence to dietary guidelines promoted by the NIH and other health professional organizations. In addition, the Heathy Diet Indicator (HDI) has been developed per World Health Organization (WHO) nutrition guideline (14). Several cancer epidemiology cohort studies have examined the association between some of these QDIs and risk of pancreatic cancer in the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study (15), the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (16) and two Dutch cohorts [ref. 17; i.e., the Netherlands Cohort Study (NLCS) and the Dutch EPIC-EPIC-NL cohort], which reported inconsistent results. None of the studies examined the association between multiple QDIs and the risk of pancreatic cancer.

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Dietary components and dietary habits in Asia differ from those in the United States and Europe. Asian diet typically includes higher levels of soy food and rice, and lower levels of dairy products and red meat (18, 19). To our knowledge, no prospective study has simultaneously examined the associations between multiple QDIs and pancreatic cancer risk in any population. We, therefore, evaluated such associations utilizing the large prospectively-ascertained data from the Singapore Chinese Health Study (SCHS), a population-based cohort with more than 60,000 individuals with an extensive follow up of up to 25 years.

Materials and Methods

Study population

The detailed methodology of the SCHS was previously described elsewhere (20). Briefly, the SCHS is an ongoing population-based prospective cohort study, which recruited 63,257 Chinese subjects from both genders, aged 45 to 74 years from two main dialect groups of Chinese in Singapore (i.e., Hokkien and Cantonese). All participants resided in the government-built housing estates between April 1993 and December 1998. The Hokkiens were originally from the Fujian Province whereas the Cantonese were from Guangdong Province, both located in southern China. All the study participants were asked to sign written informed consents. The Institutional Review Boards of the National University of Singapore and the University of Pittsburgh approved the SCHS protocol.

Dietary assessment

Dietary assessment in SCHS cohort was performed via a validated semiquantitative food frequency questionnaire (FFQ). This FFQ contained 165 food items and food groups commonly consumed by Chinese population in Singapore. Study participants were asked about frequency of consumption (in 8 categories: ranging from "*never or hardly ever*" to "*two or more times a day*") for each food or food group. Subsequently, a question on a portion size, assisted with photographs showing 3 portion sizes (i.e., small, medium, and large) was completed. Average daily intake of approximately 100 nutrients and nonnutrient compounds was calculated for each subject using the Singapore Food Composition Database (21). The validation of the FFQ was conducted through two 24-hour dietary recalls, one on a weekday and the other on a weekend, in a random sample of 810 participants from the SCHS. The two 24-hour dietary recall surveys were approximately 2 months apart. The correlation coefficients among most of calorie-adjusted nutrients based on the 24-hour dietary recalls and the FFQ ranged from 0.24 to 0.79 (21).

QDI scores

Four QDI scores were calculated using the information from the FFQ. These QDIs were AHEI-2010, aMED, DASH, and HDI. Previously, we reported two distinct Chinese dietary patterns in the SCHS: (i) the vegetable-fruit-soy (VFS) pattern, characterized by vegetables, fruit, and soy food and (ii) the meat-dim-sum (MDS) pattern, characterized by high consumption meat and refined starchy foods (22). For the purpose of the current analysis, the AHEI-2010 was selected over the VFS because the former is more representative for a wide range of populations while the latter is more confined to Chinese in Singapore and southern China. aMED is based on Mediterranean diet, which has shown health benefit in prior studies (11, 12), whereas DASH, high in fruits and vegetables, high in plant protein but lower in animal protein and moderate in low-fat dairy products, has shown to lower blood pressure (23). HDI is representative of the WHO dietary guidelines. Higher QDI scores mean greater adherences to the dietary guidelines.

The dietary components and standards for scoring in the calculation of each of the four QDIs are summarized in Supplementary Table S1. Daily food consumption in grams was converted to standard serving equivalents. Accordingly, the defined serving-size categories were follows: 67 grams (0.5 cup) of local vegetables (10, 24), 16 grams of whole grains (i.e., 1 slice of whole-wheat bread, 0.5 cup of oatmeal; ref. 25), 28 grams of nuts or 16 grams (1 tablespoon) of peanut butter (10), and 90 grams of fish (24). For the representation of healthy dietary components, potatoes and preserved vegetables were excluded from the total vegetables. Similarly, preserved or dried fruit were excluded from total fruit, and sweetened soy products and sweetened bean soup were excluded from legumes. One drink of alcoholic beverage was defined as 10 g of ethanol (24). Heavy drinking was defined as ≥15 drinks per week for men or ≥8 drinks per week for women, following the recommendation of the US Center for Disease Control and Prevention (CDC; ref. 26).

AHEI-2010 score

The AHEI-2010 was originally developed to assess the role of food and nutrients on the risk of chronic disease (26). In our analysis with AHEI-2010 score, we included all components (10) except *trans*-fat due to unavailability. Included components were (i) vegetables, (ii) fruit, (iii) whole grains, (iv) legumes, (v) alcohol, (vi) long-chain n-3 fat acids, (vii) polyunsaturated fatty acids (PUFA), (viii) red/processed meat, (ix) sugar-sweetened beverage and fruit juice, and (x) sodium. Each component was assigned a score of 0 to 10 according to the consumption level in conjunction with its healthy (higher score) or unhealthy (lower score) status. The sum of the AHEI-2010 scores ranged from 0 to 100 per subject (Supplementary Table S1).

aMED score

The aMED was originally developed to study the association between Mediterranean dietary habits and the risk of chronic diseases (11, 12). It included 9 items: (i) vegetables, (ii) fruit and nuts, (iii) cereals, (iv) dairy, (v) legumes, (vi) fish, (vii) alcohol, (viii) the ratio of monounsaturated fatty acids (MUFA) over saturated fatty acids (SFA), and (ix) meat and meat products (27). A score of 0 or 1 was assigned for each component according to the consumption level (0: below or 1: above the study population–specific median) in conjunction with its healthy/unhealthy status. The sum of the aMED scores ranged from 0 to 9 per subject (Supplementary Table S1).

DASH score

The DASH was originally developed to study dietary patterns in hypertension management. It contained 8 components: (i) fruit, (ii) whole grains, (iii) nuts and legumes, (iv) vegetables, (v) low-fat dairy, (vi) red and processed meat, (vii) sweetened beverages, and (viii) sodium (13). Each component was assigned a score of 1 to 5 according to the quintiles of consumption in conjunction with healthy/unhealthy status. The sum of the DASH scores ranged from 5 to 40 per subject (Supplementary Table S1).

HDI score

The HDI score was originally developed in accordance with 1990 WHO Dietary Guidelines to reflect an optimal diet to reduce the risk of chronic disease (14, 28). In the current analysis an updated version of the HDI was used, per the 2003 WHO Dietary Guidelines (29), which included 7 components: (i) percentage of energy intake from PUFAs, (ii) percentage of energy intake from SFAs, (iii) percentage of energy

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intake from mono- and disaccharides, (iv) fruit and vegetables combined (g/d), (v) cholesterol (mg/d), (vi) total dietary fiber (g/d), and (vii) percentage of energy intake from protein. Each component was assigned a score of 0 to 10 according to the decile of consumption in conjunction with its healthy/unhealthy status. The sum of the HDI scores ranged from 0 to 70 per subject (Supplementary Table S1).

Assessment of other covariates

At baseline, trained interviewers asked questions from participants at their homes. The structured questionnaire collected information on demographics, body weight and height, tobacco use during lifetime, current physical activity status, occupational exposures, medical history menstrual/reproductive history (women only), and family history of cancer. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared (kg/m^2). With regard to cigarette smoking, current and former smokers were further asked for age at starting to smoke, number of cigarette per day, and duration of smoking in years (30). For physical activity, we used a continuous scale of eight, that is, never, 0.5–1, 2–3, 4–6, 7–10, 11–20, 21–30, and 31 hours or more per week, for each of three physical activity categories: (i) moderate activities (i.e., brisk walking, bowling, bicycling on level ground, tai chi, and chi kung); (ii) vigorous work (i.e., moving heavy furniture, loading or unloading trucks, shoveling, or equivalent manual labor), and (iii) strenuous sports (i.e., jogging, bicycling on hills, tennis, squash, swimming laps, or aerobics; ref. 31). For occupational exposures, study participants were asked for their current and/or previous occupations, specific job titles, and potential exposures on the job with 1 year or longer. For medical history, besides type-2 diabetes mellitus, we asked if study participants reported the following diseases/conditions and age at first diagnosis: high blood pressure, heart attack or angina, stroke, tuberculosis, malaria, stomach or duodenal ulcer, partial removal of stomach, intestinal polyps, blood transfusions, rhinitis, allergic rhinitis, nasal polyps, sinusitis, repeated middle ear infection, other ear or nose diseases, asthma, hay fever, skin allergy, food allergy or any other allergy, or vasectomy (male only).

Ascertainment of pancreatic cancer case

Incident cases of pancreatic cancer and deaths were identified via annual linkage analysis of all surviving cohort participants with the national databases of the Singapore Cancer Registry and the Singapore Birth and Death Registry, respectively. To date, ascertainment of incident cancer cases and deaths among the cohort participants had been virtually complete; only 56 (<0.1%) of the entire cohort were known to be lost to follow up due to migration out of Singapore. After excluding 1,936 with a history of cancer at baseline, the study included 61,321 participants.

Among the eligible participants, 316 developed pancreatic cancer, determined by the International Classification of Diseases-Oncology 2nd Edition Codes C25 (32), during the follow up from the date of completion of the baseline questionnaire up to December 31, 2016 (the cut-off date of the present analysis). Of the 316 incident cases, 184 were pancreatic ductal adenocarcinoma confirmed histologically, 5 were neuroendocrine carcinoma, and the remaining 127 were unknown histology and their diagnoses were based on clinical symptoms and imaging. To maximize the sample size, we included all cases except for 5 cases of neuroendocrine carcinoma; the final number of cases included in the present analysis was 311.

Statistical analysis

Means and SD were calculated for continuous variables while counts and proportions were presented as frequencies among the study subjects. To compare the distributions of continuous and categorical variables between cases and noncases or across quartiles of each QDI score, the *t* test, ANOVA, and χ^2 statistics were used, respectively. Person-years at risk for each participant was calculated from the date of baseline interview to the date of pancreatic cancer diagnosis, death, migration out of Singapore, or December 31, 2015, whichever occurred first.

To calculate HRs and their corresponding 95% confidence intervals (CI) of pancreatic cancer for higher quartiles relative to the lowest quartile and per SD increment of the QDI, the Cox proportional hazard regression method was used. The Cox regression models also included potential confounders – age (years), gender (male vs. female), dialect group (Hokkien vs. Cantonese), level of education (no formal education, primary school, secondary or higher education), year of enrollment (1993–1995 vs. 1996–1998), smoking status (ever vs. never), number of pack-years of smoking, BMI (<20, 20–23.9, 24–27.9, or ≥28 kg/m^2), history of type-2 diabetes (yes vs. no) and total energy intake (Kcal/d). An ordinal variable for quartiles of a given QDI was used for the linear trend test for its association with pancreatic cancer risk. Proportional hazard assumption was tested using Schoenfeld residuals test, and no violation was found.

Using the same Cox proportional hazard regression models, we repeated the analyses on subsets of subjects stratified by BMI ≥ 23 kg/m^2, the cutoff for overweight or obesity for Asian populations recommended by WHO (33, 34), preexisting type 2 diabetes (no or yes) and smoking status (never or ever smokers). Furthermore, a sensitivity analysis was similarly performed by excluding pancreatic cancer cases and person-years observed within the first 2 years of follow-up after enrollment. In addition, we performed analyses for the associations of individual food items and nutrients with risk of pancreatic cancer.

All statistical analyses were performed using the computing software SAS version 9.4 (SAS Institute Inc). All *P* values were two-sided. A two-sided $P < 0.05$ was considered to be statistically significant.

Results

After a mean follow-up of 17.7 (SD 5.3) years, we identified 311 incident cases of pancreatic cancer among 61,321 participants who were free of cancer at baseline. The mean age at diagnosis was 72.5.4 (SD 8.4) years.

The various QDI scores were correlated with each other. The correlation coefficients were 0.65 between AHEI-2010 and aMED, 0.76 between AHEI-2010 and DASH, 0.59 between aMED and DASH whereas the corresponding figures for these 3 QDIs with HDI was 0.31 to 0.33 (all *P's* < 0.0001). Across the 4 QDI scores, there were higher proportions of Cantonese, higher level of education (i.e., secondary school or higher), never smokers, moderate drinkers, or diabetics in the highest quartile of the DASH and HDI scores; higher frequency of diabetics in the highest quartile of the AHEI-2010 score; higher proportions of participants with weekly physical activity in the highest quartile of aMED and HDI scores, compared with the lowest quartile of their respective QDI scores. Overall, participants with the highest quartile of a given QDI had a lower consumption of red meat, higher intake of fruits, vegetables, and fish, as well as dietary fiber (**Table 1**).

Pancreatic cancer cases were older, more likely to be male, ever smokers, or those with higher consumption of vegetables than those without pancreatic cancer. The distributions of other demographics, lifestyle factors, history of type-2 diabetes and intake of fruits and fish

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Table 1. Distributions of baseline characteristics among study participants by highest versus lowest quartile of the high QDIs in the SCHS, 1993–2015.

	AHEI-2010 (*n*, %)		aMED (*n*, %)		DASH (*n*, %)		HDI (*n*, %)	
	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Gender (%)								
Male	8,498 (55.4)	5,681 (37.1)	6,073 (47.0)	5,116 (42.8)	9,489 (55.4)	4,443 (33.6)	6,626 (43.2)	7,644 (49.9)
Female	6,832 (44.6)	9,649 (62.9)	6,842 (53.0)	6,844 (57.2)	7,623 (44.6)	8,788 (66.4)	8,704 (56.8)	7,686 (50.1)
Dialect								
Cantonese	6,526 (42.6)	7,778 (50.7)	4,977 (38.5)	6,525 (54.6)	7,105 (41.5)	6,894 (52.1)	6,097 (39.8)	8,129 (53.0)
Hokkien	8,804 (57.4)	7,552 (49.3)	7,938 (61.5)	5,435 (45.4)	10,007 (58.5)	6,337 (47.9)	9,233 (60.2)	7,201 (47.0)
Highest level of education (%)								
No formal education	4,548 (29.6)	3,439 (22.4)	4,708 (36.5)	2,097 (17.5)	4,889 (28.6)	3,159 (23.9)	4,951 (31.6)	3,221 (21.0)
Primary school	7,123 (46.5)	6,430 (41.9)	5,829 (45.1)	5,004 (41.8)	8,044 (47.0)	5,513 (41.7)	6,709 (43.8)	6,830 (44.5)
Secondary school or higher	3,849 (25.1)	5,461 (35.6)	2,378 (18.4)	4,859 (40.6)	4,179 (24.4)	4,559 (34.5)	3,770 (24.6)	5,279 (34.4)
Mean body mass index (±SD), kg/m^2	23.0 ± 3.3	23.2 ± 3.2	23.0 ± 3.3	23.1 ± 3.3	23.2 ± 3.3	23.0 ± 3.2	23.2 ± 3.4	23.1 ± 3.2
Smoking status[a] (%)								
Never smoker	8,936 (58.3)	12,109 (79.0)	7,952 (61.6)	9,187 (76.8)	9,848 (57.5)	10,713 (81.0)	9,754 (63.6)	11,095 (72.4)
Former smoker	1,873 (12.2)	1,540 (10.0)	1,372 (10.6)	1,325 (11.1)	2,036 (11.9)	1,280 (9.7)	1,539 (10.0)	1,971 (12.9)
Current smoker	4,521 (29.5)	1,681 (11.0)	3,591 (27.8)	1,448 (12.1)	5,228 (30.5)	1,238 (9.4)	4,037 (26.3)	2,264 (14.8)
Alcohol consumption[b] (%)								
Nondrinkers	12,939 (84.4)	11,360 (74.1)	10,521 (83.3)	9,514 (77.4)	12,779 (74.7)	11,528 (87.1)	11,906 (77.7)	12,567 (82.0)
Moderate drinkers	1,526 (9.9)	3,380 (22.0)	1,601 (12.7)	2,239 (18.2)	3,127 (18.3)	1,517 (11.5)	2,332 (15.2)	2,458 (16.0)
Heavy drinkers	865 (5.6)	530 (3.8)	515 (4.1)	52 (4.3)	1,206 (7.0)	186 (1.4)	1,092 (7.1)	305 (2.0)
Diabetes (%)								
No	14,196 (92.6)	13,767 (89.8)	11,834 (91.6)	10,865 (90.8)	15,870 (92.7)	11,818 (89.3)	13,889 (90.6)	14,105 (92.0)
Yes	1,134 (7.4)	1,563 (10.2)	1,081 (8.4)	1,095 (9.2)	1,242 (7.3)	1,413 (10.7)	1,441 (9.4)	1,225 (8.0)
Any weekly physical activity[b] (%)								
No	13,507 (88.1)	14,089 (91.9)	11,800 (91.4)	10,673 (89.2)	15,191 (88.8)	12,217 (92.3)	14,094 (91.9)	13,748 (89.7)
Yes	1,623 (11.9)	1,241 (8.1)	1,115 (8.6)	1,287 (10.8)	1,921 (11.2)	1,014 (7.7)	1,236 (8.1)	1,582 (10.3)
Mean total energy intake (±SD), Kcal	1,563.5 ± 604.2	1,632.0 ± 543.3	1,284.3 ± 441.8	1,860.7 ± 613.9	1,545.3 ± 565.6	1,580.2 ± 513.0	1,474 ± 665.2	1,739.5 ± 507.3
Red meat (g/d; ±SD)	22.0 ± 12.8	15.2 ± 9.1	20.5 ± 11.7	17.3 ± 10.8	24.8 ± 11.7	12.3 ± 19.4	23.9 ± 13.3	14.5 ± 8.2
Vegetables (g/d; ±SD)	81.7 ± 44.7	150.6 ± 78.2	67.6 ± 31.4	161.1 ± 71.5	85.0 ± 46.2	142.0 ± 72.4	100.1 ± 63.4	129.4 ± 63.6
Fruits (g/d; ±SD)	137.6 ± 131.6	301.2 ± 196.6	98.8 ± 92.9	321.3 ± 189.9	130.5 ± 124.7	290.1 ± 182.9	133.9 ± 145.3	290.6 ± 179.1
Fiber (g/d; ±SD)	9.9 ± 4.5	16.8 ± 6.4	8.0 ± 3.2	18.1 ± 6.2	9.7 ± 4.2	16.6 ± 6.0	10.2 ± 5.6	16.0 ± 5.4
Fish (g/d; ±)	28.0 ± 15.6	41.1 ± 17.9	30.9 ± 16.5	40.5 ± 16.9	36.0 ± 17.5	35.0 ± 18.2	43.4 ± 20.1	28.0 ± 12.3

Abbreviations: Q1, lowest quartile or first quartile; Q4, highest quartile or fourth quartile; SSB, sugar sweetened beverages. Values are means ± SDs for continuous variables unless otherwise specified; percentages are based on nonmissing data.

[a]Cigarette smoking: The "heavy" smokers were those who started to smoke before 15 years of age and smoked 13 or more cigarettes/d; all remaining ever smokers were defined as light smokers.

[b]Physical activity represents amount of strenuous physical activity and/or vigorous work.

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Table 2. Associations between the high QDIs and the risk of pancreatic cancer in the SCHS, 1993–2015.

	Overall			Male			Female		
	Person-years	Cases	HR (95% CI)[a]	Person-years	Cases	HR (95% CI)[b]	Person-years	Cases	HR (95% CI)[b]
AHEI-2010									
Q1 (lowest)	260,664	93	1.00	130,425	57	1.00	130,240	36	1.00
Q2	269,889	80	0.85 (0.63–1.15)	110,472	40	0.80 (0.53–1.20)	159,417	40	0.92 (0.59–1.45)
Q3	273,629	77	0.85 (0.61–1.13)	106,772	39	0.80 (0.53–1.21)	166,857	38	0.89 (0.56–1.40)
Q4 (highest)	280,066	61	**0.65 (0.46–0.90)**	111,916	26	**0.50 (0.31–0.81)**	168,149	35	0.84 (0.52–1.35)
P_{trend}			**0.01**			**0.008**			0.46
Continuous scale (per SD increase)			**0.87 (0.78–0.98)**			**0.80 (0.68–0.94)**			0.97 (0.82–1.15)
$P_{heterogeneity}$							0.24		
aMED									
Q1 (lowest)	213,406	83	1.00	92,728	47	1.00	120,678	36	1.00
Q2	207,917	51	**0.65 (0.46–0.92)**	86,602	24	**0.55 (0.34–0.90)**	121,316	27	0.79 (0.47–1.30)
Q3	436,224	131	0.82 (0.62–1.10)	185,587	70	0.76 (0.51–1.12)	250,637	61	0.93 (0.60–1.43)
Q4 (highest)	226,700	46	**0.57 (0.38–0.85)**	94,668	21	**0.43 (0.24–0.75)**	132,032	25	0.79 (0.45–1.39)
P_{trend}			**0.03**			**0.02**			0.57
Continuous scale (per SD increase)			**0.87 (0.77–0.99)**			**0.81 (0.69–0.96)**			0.95 (0.79–1.14)
$P_{heterogeneity}$							0.30		
DASH									
Q1 (lowest)	296,472	90	1.00	158,079	61	1.00	138,394	29	1.00
Q2	192,732	66	1.10 (0.80–1.51)	85,454	38	1.05 (0.70–1.58)	107,278	28	1.24 (0.73–2.08)
Q3	356,238	106	0.96 (0.72–1.28)	140,471	50	0.80 (0.55–1.18)	215,767	56	1.24 (0.79–1.95)
Q4 (highest)	238,805	49	**0.66 (0.46–0.95)**	75,581	13	**0.36 (0.19–0.66)**	163,224	36	1.09 (0.66–1.80)
P_{trend}			**0.04**			**0.002**			0.73
Continuous scale (per SD increase)			**0.86 (0.76–0.97)**			**0.77 (0.66–0.91)**			0.97 (0.82–1.15)
$P_{heterogeneity}$							**0.04**		
HDI									
Q1 (lowest)	263,364	67	1.00	106,666	32	1.00	156,698	35	1.00
Q2	270,646	69	1.04 (0.74–1.46)	105,265	30	0.96 (0.58–1.58)	165,380	39	1.13 (0.71–1.79)
Q3	272,256	86	1.27 (0.92–1.75)	114,148	43	1.26 (0.79–2.00)	158,108	43	1.30 (0.82–2.04)
Q4 (highest)	277,982	89	1.35 (0.97–1.87)	133,505	57	1.54 (0.98–2.42)	144,477	32	1.12 (0.68–1.84)
P_{trend}			**0.04**			**0.03**			0.51
Continuous scale (per SD increase)			1.08 (0.96–1.21)			1.12 (0.95–1.32)			1.04 (0.88–1.23)
$P_{heterogeneity}$							0.20		

Note: Figures in bold are statistically significant ($P < 0.05$).
Abbreviations: Q2, second quartile; Q3, third quartile.
[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee drinking status, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.
[b]Models adjusted for age, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee drinking status, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.

as well as dietary fiber and total calories were comparable between the case and noncase groups (Supplementary Table S2).

The associations between individual QDIs and risk of pancreatic cancer are shown in **Table 2**. Overall, higher levels of 3 food-based QDIs (i.e., AHEI-2020, aMED, and DASH) were inversely associated with the risk of pancreatic cancer (all $P_{trend} < 0.05$) whereas the nutrient-based QDI (i.e., HDI) was associated with higher risk of pancreatic cancer ($P_{trend} = 0.04$). Compared with the lowest quartile, HRs (95% CIs) of pancreatic cancer for the highest quartile of AHEI-2010, aMED, DASH, and HDI were 0.65 (0.46–0.90), 0.57 (0.38–0.85), 0.66 (0.46–0.95), and 1.35 (0.97–1.87), respectively. The associations between all four QDIs and risk of pancreatic cancer were more apparent in men compared with women. The heterogeneity between men and women was statistically significant for DASH ($P_{heterogeneity} = 0.04$) but was not for other three QDIs, with pancreatic cancer risk (**Table 2**).

In stratified analysis, in general a stronger inverse association for each of three food-based QDIs with pancreatic cancer risk were seen in overweight/obese individuals (BMI ≥ 23 kg/m^2), those without a history of diabetes, or current/former smokers (**Table 3**). However, the heterogeneity between these subgroups was not statistically significant except for DASH between ever and never smokers ($P_{heterogeneity} = 0.02$), although it was based on a very small sample size, with only 3 cases of pancreatic cancer in the highest quartile of DASH (**Table 3**).

We also conducted sensitivity analysis by excluding the pancreatic cancer subjects and person-years within the first 2 years of follow-up postenrollment. This sensitivity analysis yielded similar result as shown in **Table 4**. We also evaluated the associations for individual components of the four QDIs including food groups and macronutrients, especially dietary SFAs, MUFAs, and PUFAs, with pancreatic risk. None of these individual components of the four QDIs studied showed a significant association with the risk of pancreatic cancer (**Figs. 1** and **2**).

Discussion

The present analysis showed that higher scores of AHEI-2010, aMED, and DASH, representing better adherence to a healthy diet,

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Table 3. Associations between the high QDIs and the risk of pancreatic cancer stratified by BMI, history of diabetes, and smoking status in the SCHS, 1993–2015.

	By BMI status				By history of diabetes				By smoking status			
	BMI < 23		BMI ≥ 23		No Diabetes		Diabetes		Never-smokers		Smokers	
	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[b]	Cases	HR (95% CI)[b]	Cases	HR (95% CI)[c]	Cases	HR (95% CI)[c]
AHEI-2010												
Q1 (lowest)	40	1.00	53	1.00	86	1.00	7	1.00	47	1.00	46	1.00
Q2	43	1.13 (0.73–1.74)	37	**0.66 (0.43–1.00)**	70	0.81 (0.59–1.12)	10	1.31 (0.49–3.44)	47	0.86 (0.57–1.29)	33	0.86 (0.55–1.35)
Q3	35	0.96 (0.60–1.51)	42	0.74 (0.49–1.11)	75	0.89 (0.65–1.22)	2	0.23 (0.05–1.10)	48	0.85 (0.56–1.27)	29	0.85 (0.53–1.35)
Q4 (highest)	24	0.63 (0.38–1.07)	37	0.65 **(0.42–1.00)**	46	**0.54 (0.38–0.78)**	15	1.67 (0.67–4.20)	49	0.82 (0.54–1.23)	12	**0.37 (0.19–0.70)**
P_{trend}		0.08		0.08		**0.005**		0.53		0.35		**0.006**
$P_{heterogeneity}$			0.79				0.13				0.09	
Continuous scale (per SD increase)		0.89 (0.75–1.06)		**0.85 (0.73–1.00)**		**0.85 (0.75–0.96)**		1.05 (0.75–1.47)		0.94 (0.81–1.08)		**0.78 (0.65–0.94)**
aMED						0.260						
Q1 (lowest)	33	1.00	50	1.00	75	1.00	8	1.00	49	1.00	34	1.00
Q2	23	0.76 (0.44–1.29)	28	**0.58 (0.37–0.93)**	47	**0.66 (0.46–0.96)**	4	0.52 (0.16–1.72)	30	0.60 (0.38–0.95)	21	0.72 (0.42–1.25)
Q3	65	1.12 (0.72–1.73)	66	**0.65 (0.44–0.95)**	120	0.84 (0.62–1.14)	11	0.66 (0.26–1.69)	74	0.70 (0.48–1.02)	57	1.06 (0.67–1.66)
Q4 (highest)	21	0.72 (0.40–1.31)	25	**0.48 (0.28–0.82)**	35	**0.49 (0.32–0.76)**	11	1.20 (0.44–3.27)	38	0.66 (0.41–1.06)	8	**0.33 (0.15–0.75)**
P_{trend}		0.74		**0.009**		**0.01**		0.70		0.11		0.14
$P_{heterogeneity}$			0.20				0.22				0.76	
Continuous scale (per SD increase)		0.99 (0.80–1.17)		**0.79 (0.66–0.93)**		**0.84 (0.73–0.96)**		1.09 (0.75–1.57)		0.89 (0.76–1.05)		**0.82 (0.67–1.00)**
DASH												
Q1 (lowest)	41	1.00	49	1.00	82	1.00	8	1.00	38	1.00	52	1.00
Q2	32	1.27 (0.80–2.02)	34	0.98 (0.63–1.52)	63	1.19 (0.85–1.65)	3	0.42 (0.11–1.61)	41	1.36 (0.87–2.12)	25	0.91 (0.56–1.46)
Q3	50	1.08 (0.70–1.65)	56	0.87 (0.59–1.29)	92	0.96 (0.70–1.28)	14	1.02 (0.42–2.47)	66	1.10 (0.73–1.64)	40	0.89 (0.59–1.36)
Q4 (highest)	19	0.62 (0.35–1.10)	30	0.71 (0.44–1.13)	40	**0.64 (0.43–0.94)**	9	0.82 (0.30–2.21)	46	1.03 (0.66–1.61)	3	**0.13 (0.04–0.42)**
P_{trend}		0.19		0.14		**0.03**		0.95		0.85		**0.003**
$P_{heterogeneity}$			0.71				0.39				**0.02**	
Continuous scale (per SD increase)		0.86 (0.72–1.03)		0.86 (0.73–1.01)		**0.84 (0.74–0.96)**		1.00 (0.70–1.42)		0.94 (0.81–1.09)		**0.75 (0.62–0.91)**
HDI												
Q1 (lowest)	33	1.00	34	1.00	59	1.00	8	1.00	36	1.00	31	1.00
Q2	31	1.00 (0.61–1.64)	38	1.08 (0.68–1.72)	66	1.12 (0.79–1.59)	4	0.47 (0.14–1.58)	39	0.97 (0.61–1.52)	30	1.17 (0.70–1.94)
Q3	39	1.18 (0.74–1.89)	47	1.36 (0.87–2.13)	77	1.30 (0.92–1.83)	9	1.06 (0.40–2.77)	59	1.42 (0.93–2.15)	27	1.06 (0.63–1.79)
Q4 (highest)	39	1.23 (0.76–2.00)	50	1.47 (0.94–2.31)	76	1.29 (0.91–1.84)	13	1.73 (0.69–4.35)	57	1.38 (0.89–2.12)	32	1.31 (0.78–2.18)
P_{trend}		0.31		0.054		0.11		0.11		**0.05**		0.39
$P_{heterogeneity}$			0.51				0.31				0.50	
Continuous scale (per SD increase)		1.02 (0.86–1.21)		1.14 (0.97–1.34)		1.06 (0.93–1.20)		1.29 (0.90–1.86)		1.12 (0.96–1.30)		1.03 (0.85–1.24)

Note: Figures in bold are statistically significant ($P < 0.05$).
[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee drinking status, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.
[b]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee drinking status, total energy intake, and BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2).
[c]Models adjusted for age, sex, dialect, year of enrollment, education level, coffee drinking status, smoking pack-years, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.

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Table 4. Associations between the high QDIs and the risk of pancreatic cancer among participants with 2 or more years of follow-up in the Singapore Chinese Health Study, 1995–2015.

	Overall			Male			Female		
QDI	Person-years	Cases	HR (95% CI)[a]	Person-years	Cases	HR (95% CI)[b]	Person-years	Cases	HR (95% CI)[b]
AHEI-2010									
Q1 (lowest)	230,304	87	1.00	114,651	55	1.00	115,653	32	1.00
Q2	239,471	75	0.86 (0.63–1.17)	97,386	36	0.75 (0.49–1.14)	142,084	40	1.01 (0.63–1.61)
Q3	243,178	74	0.85 (0.62–1.17)	94,323	39	0.83 (0.55–1.26)	148,849	36	0.91 (0.56–1.47)
Q4 (highest)	249,583	55	**0.62 (0.44–0.88)**	99,210	25	**0.50 (0.31–0.81)**	150,374	31	0.79 (0.48–1.32)
P_{trend}			**0.01**			**0.01**			0.32
Continuous scale (per SD increase)			**0.86 (0.77–0.97)**			**0.80 (0.68–0.94)**			0.96 (0.80–1.13)
$P_{heterogeneity}$							0.38		
aMED									
Q1 (lowest)	188,398	78	1.00	81,184	45	1.00	107,214	33	1.00
Q2	184,238	48	**0.65 (0.45–0.93)**	76,297	23	**0.55 (0.33–0.91)**	107,941	**25**	0.78 (0.46–1.32)
Q3	387,647	122	0.80 (0.59–1.08)	164,023	66	0.73 (0.49–1.10)	223,624	57	0.90 (0.57–1.41)
Q4 (highest)	202,253	43	**0.55 (0.36–0.83)**	84,071	21	**0.44 (0.25–0.77)**	118,182	**24**	0.71 (0.39–1.30)
P_{trend}			**0.02**			**0.02**			0.40
Continuous scale (per SD increase)			**0.88 (0.76–0.98)**			**0.81 (0.68–0.96)**			0.92 (0.80–1.11)
$P_{heterogeneity}$							0.38		
DASH									
Q1 (lowest)	262,526	84	1.00	139,300	57	1.00	123,226	27	1.00
Q2	171,039	62	1.11 (0.80–1.55)	75,405	39	1.15 (0.76–1.74)	95,633	25	1.19 (0.69–2.05)
Q3	316,441	99	0.96 (0.72–1.30)	124,080	49	0.84 (0.57–1.25)	192,359	51	1.19 (0.74–1.90)
Q4 (highest)	212,531	46	**0.68 (0.46–0.98)**	66,791	12	**0.35 (0.19–0.67)**	145,735	36	1.10 (0.65–1.85)
P_{trend}			**0.05**			**0.003**			0.73
Continuous scale (per SD increase)			**0.86 (0.76–0.98)**			**0.77 (0.65–0.91)**			0.99 (0.83–1.18)
$P_{heterogeneity}$							0.053		
HDI									
Q1 (lowest)	232,983	61	1.00	93,585	32	1.00	139,397	29	1.00
Q2	240,212	64	1.06 (0.74–1.51)	92,833	28	0.89 (0.54–1.49)	147,379	37	1.27 (0.77–2.07)
Q3	241,840	81	1.31 (0.93–1.83)	100,832	41	1.19 (0.75–1.91)	141,009	40	1.46 (0.90–2.37)
Q4 (highest)	247,501	85	1.40 (0.99–1.96)	118,326	55	1.47 (0.91–2.27)	129,165	33	1.31 (0.77–2.21)
P_{trend}			0.03			0.054			0.24
Continuous scale (per SD increase)			1.10 (0.97–1.24)			1.10 (0.93–1.30)			1.10 (0.92–1.31)
$P_{heterogeneity}$							0.49		

Note: Figures in bold are statistically significant ($P < 0.05$).

[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee-drinking status, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.

[b]Models adjusted for age, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee-drinking status, total energy intake, BMI (<20, 20–23.9, 24–27.9, and ≥28 kg/m^2), and diabetes status.

were reducing the risk of developing pancreatic cancer whereas higher score of HDI, which was primarily derived from nutrients, increased the risk of pancreatic cancer. Further, the inverse associations of these three food-based QDIs with pancreatic cancer risk were mainly observed in men, overweight/obese individuals, ever smokers, or those without preexisting type-2 diabetes.

To the best of our knowledge, this is the first prospective cohort study that simultaneously evaluated the associations of four recommended QDIs with pancreatic cancer risk. Our study demonstrated different associations for the food-based versus the nutrient-based QDIs with the risk of pancreatic cancer. Several prior studies investigated the association between some of the QDIs and pancreatic cancer risk. For example, the NIH-AARP cohort showed a 15% reduction in pancreatic cancer risk among individuals in the highest quintile of HEI-2005 score compared with the lowest quintile after adjustment for multiple confounders, and the inverse association was primarily present in men or overweight/obese individuals (15). Our results on AHEI-2010, an updated version of HEI-2005, with pancreatic cancer risk were compatible with those of the NIH-AAPR cohort.

There have been 3 reports on the association between aMED score and pancreatic cancer risk, all conducted in European populations. The earliest report, based on two hospital-based case–control studies including a total of 688 cases of pancreatic cancer and 2,204 control subjects in Italy, reported a statistically significant 52% lower risk of pancreatic cancer for the highest score (≥6) relative to the lowest score of Mediterranean Diet (MED, <3; ref. 35). The EPIC study, a prospective cohort including more than 477,000 participants from 10 European countries with 865 incident pancreatic cancer cases with a follow-up period of 11 years, reported no overall statistically significant association between aMED and the risk of pancreatic cancer after adjustment for multiple covariates (16). In the subgroup analysis, the highest aMED score (≥10) was associated with a 20%, 33%, and 44% decrease in risk of pancreatic cancer among young individuals (<60 years), current smokers, and obese individuals (BMI ≥ 30 kg/m^2), respectively, compared with the lowest aMED score (≤5), although the reduced risk estimates were not statistically significant. In a similar study for 2 Dutch cohorts combined (1 was part of the EPIC study described above), the highest aMED scores (≥6) had 26% lower risk of pancreatic cancer in men, but

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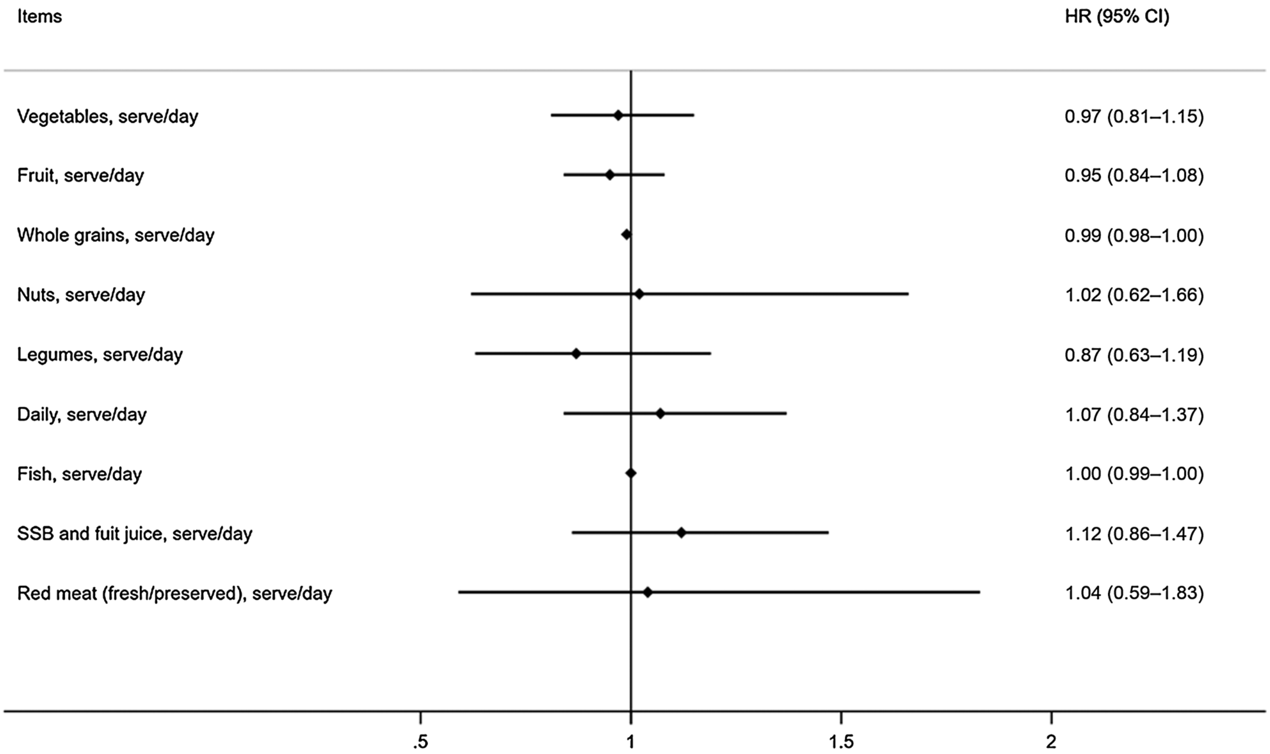

Figure 1.
Association between food groups of high QDIs and pancreatic cancer in the SCHS. Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee drinking status, total energy intake, BMI, and diabetes status. Vegetables, fruits, whole grains, nuts, legumes, dairy, SSB, red meat, and fish. Fish was removed from the Figure as the HR and 95% CI = 1.00 (1.00–1.00).

not in women, compared with the lowest aMED scores (≤3), however this association was not statistically significant (17). These results were somewhat consistent with our findings.

All QDI scores were moderately correlated with each other but HDI showed lowest correlation coefficient with other three QDIs. This might be due to different components of QDIs. The AHEI-2010, aMED, and DASH were primarily based on food items including vegetables, fruits, legumes, nuts, and whole grains, red meat, and sugar-sweetened beverages, and fruit juices while HDI was primarily based on dietary nutrients including cholesterol, fatty acids, protein, mono, and disaccharide (Supplementary Table S1). The different compositions of nutrient-based and food-based QDIs produced opposite results with pancreatic cancer risk. Our findings suggest that food-based QDIs (i.e., AHEI-2010, aMED, and DASH) may reflect a dietary habit that is beneficial for protection against the development of pancreatic cancer whereas the nutrient-based HDI does not. Further, the consistent inverse association for all three food-based QDIs, although developed based on Western populations, with the risk of pancreatic cancer in our study population of Asians suggest that these QDIs may be applicable to non-Western populations.

In the past 40 years, Singapore has experienced drastic economic development along with increased westernization of lifestyle and diet. The westernized lifestyle and diet might have contributed to the increasing trend of metabolic-related disorders such as being overweight (i.e., from 22.1% in 1990 to approximately 32% in 2016; ref. 36). The dietary pattern has been changed rapidly in Singapore, particularly among young people from vegetable-based diet to meat-based diet; resulting in increased percentage of energy derived from fat. It is well recognized that higher fat consumption is associated with insulin resistance and dysregulation of the postprandial lipid metabolism (37, 38), both of which are metabolic disorders related to pancreatic cancer. In addition, dietary fructose consumption in soft drinks has been increased, together with the increase in overweight and/or obesity in Singapore and other Asian countries (39, 40). These changes are believed to contribute to the recent rise in obesity-related cancers including pancreatic cancer.

Previous studies also demonstrated that quality of diet contributes to the development of insulin resistance, diabetes, and obesity (41–43) all of which are underlying mechanisms for the pathogenesis of pancreatic cancer. Red meat consumption was a component of the three food-based QDIs (i.e., AHEI-2010, aMED, and DASH). When red meat is cooked in high temperature, polycyclic aromatic hydrocarbons (PAH) such as beno[a]pyrene (BaP), and heterocyclic amines (HCA) such as 2-amino-3,8-dimethylimidazo [4,5-f]quinoxaline (MeIQx; refs. 44–46) both of which have been implicated in carcinogenesis of pancreatic cancer in experimental studies (47, 48), and to be associated with increased pancreatic cancer risk in humans (44, 49). These QDIs also included higher consumption of fresh fruits and vegetables, rich sources of antioxidant vitamins. In a case–control study of 1,321 patients with pancreatic cancer and 1,061 controls in Texas, Li and colleagues showed that antioxidants, particularly vitamins C and E, were associated with reduced risk of pancreatic cancer (50). While most of cohort studies showed no association between antioxidants and pancreatic cancer, the EPIC-Norfolk cohort showed that individuals in the highest quartiles of all 3 antioxidants (i.e., vitamins C and E and selenium) had a third the risk of pancreatic

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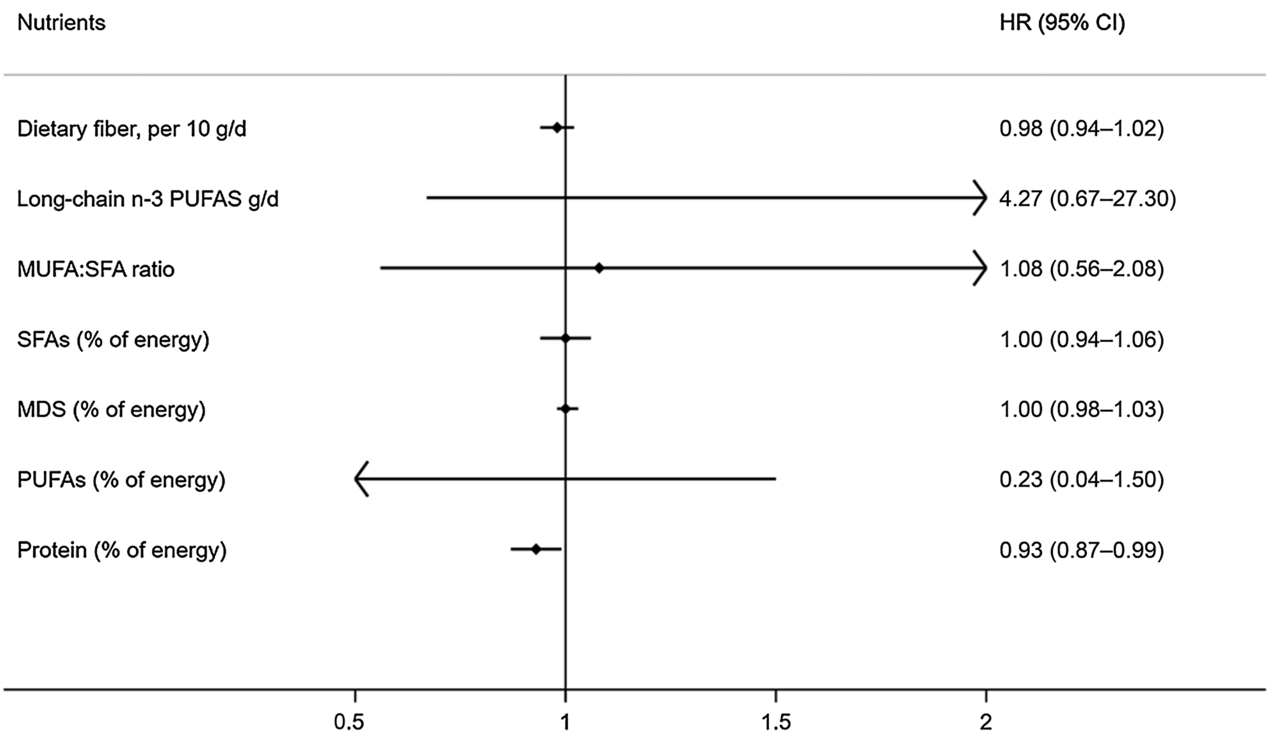

Figure 2.

Association between nutrient components of high QDIs and pancreatic cancer in the SCHS. Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status, smoking pack-years, coffee-drinking status, total energy intake, BMI, diabetes status, fiber, long-chain n-3 PUFAs, MUFA–SFA ratio, SFA, MDS, PUFAs, protein, sodium, and cholesterol. Sodium and cholesterol were removed from the Figure as the HRs and 95% CIs = 1.00 (1.00–1.00). MDS, mono- and disaccharide; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, short-chain fatty acid.

cancer compared with those in the lowest quartiles of the 3 antioxidants (51). The observed lower risk of pancreatic cancer in relation to high scores of these QDIs may be, at least partially, due to lower intake of red meats and higher consumption of fresh vegetables and fruit as well as dietary antioxidants.

The putative mechanism explaining the sex differences in the QDI–pancreatic cancer risk associations is not completely understood. It is conceivable that protection of high-quality diet against the development of pancreatic cancer would be stronger for persons at higher risk than those at lower risk for pancreatic cancer. Men are at higher risk for pancreatic cancer than women, so are smokers and obese individuals. In the current study, we found a stronger protection of three high-quality food-based QDIs, in particular DASH, against the development of pancreatic cancer in men, smokers or overweight/obese individuals. Similar results were reported in several previous studies (15–17). It is warranted that future studies confirm the sex difference in these QDI-pancreatic cancer risk association and elucidate possible mechanisms.

The present study had a number of strengths. The prospective study design allowed the collection of information on dietary and other lifestyle factors prior to the presence of pancreatic cancer, minimizing the potential effect of the disease progression on exposure (i.e., dietary habits). A simultaneous evaluation of four well-established QDIs provided direct comparison for the magnitude and direction of their associations with pancreatic cancer risk, and revealed a statistically significant inverse association for the food-based QDIs (i.e., AHEI-2010, aMED, and DASH) but a positive association for the nutrient-based QDI (i.e., HDI). A comprehensive analysis for the QDIs with other modifiable factors and medical history would minimize the potential confounding effect on the study findings, A large sample size with long-term follow-up provided sufficient statistical power.

The present study also had several limitations. The one-time assessment of dietary intake using FFQ at baseline might not capture the change in diet over time. Due to the prospective study design, the changes in the dietary habits after baseline administration of FFQ would lead to nondifferential misclassification, which might result in the underestimation of the true association towards the null result (52). Furthermore, our calculation of AHEI-2010 did not include *trans*-fat, which may lead to misclassification and difficulty in direct comparison of our results with those of previous studies in the United States. However, our prior study (53) underlined a very low plasma *trans*-fat concentration in our cohort participants, suggesting that removing this component would have limited impact on the AHEI-2010. In addition, because the low intake of dairy products in our studied participants, we used total dairy products instead of the low-fat dairy products in order to calculate the DASH score. A relatively large number ($n = 127$) of pancreatic cancer was not histologically confirmed. However, neuroendocrine carcinoma was very rare in the study population, only 5 (2.6%) out of 189 histologically confirmed cases was neuroendocrine carcinoma. Thus, small number of neuroendocrine carcinoma cases would be projected among histologically nonconfirmed cases of pancreatic cancer. The other limitation is that the four QDIs in the current analysis were derived from the dietary recommendations for North American or European populations, which may not reflect the dietary patterns of Singaporean Chinese. However, the comparable results in our study with those of American and European studies

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suggest that these QDIs may be applicable for Asian populations in the assessment of pancreatic cancer risk.

In summary, our study revealed a consistent inverse association for three food-based QDIs, representing for high adherence to dietary guidelines recommended by the NIH, with risk of pancreatic cancer. Our findings support that dietary modifications according to those well-established dietary guidelines may be beneficial for reducing the risk of pancreatic cancer, especially for those at high risk for pancreatic cancer.

Authors' Disclosures

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Authors' Contributions

H.N. Luu: Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **P. Paragomi:** Formal analysis, investigation, writing–review and editing. **A. Jin:** Data curation, formal analysis, investigation, writing–review and editing. **R. Wang:** Data curation, software, formal analysis, methodology, writing–review and editing. **N. Neelakantan:** Formal analysis, investigation, writing–review and editing. **R.M. van Dam:** Conceptualization, formal analysis, investigation, writing–review and editing. **R.E. Brand:** Formal analysis, investigation, writing–review and editing. **W.-P. Koh:** Conceptualization, resources, formal analysis, funding acquisition, investigation, writing–original draft, writing–review and editing. **J.-M. Yuan:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, writing–review and editing.

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