Plant-based Diet Index and Risk of Pancreatic Cancer:

Findings from a Prospective Cohort Study

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Abbreviations:

BMI: body mass index

CI: confidence interval

HR: hazard ratio

hPDI: healthy plant-based dietary index

PDI: plant-based dietary index

PLCO: prostate, lung, colorectal and ovarian cancer screening trial.

SCHS: Singapore Chinese Health Study

SD: standard deviation

uPDI: unhealthy plant-based dietary index

ABSTRACT

Background: Data on the association between the plant-based diet and pancreatic cancer is sparse. We, therefore, examined associations for plant-based dietary indices (PDI), healthy PDI (hPDI) and unhealthy PDI (uPDI) with pancreatic cancer risk.

Methods: We used data from the Singapore Chinese Health Study, a prospective cohort study of 63,275 participants aged 45-74 living in Singapore who were recruited during 1993-1998 period. The three plant-based dietary scores were calculated from the semi-quantitative food frequency questionnaire that was collected at the baseline. We identified pancreatic cancer cases using record linkage with the Singapore Cancer Registry. Cox proportional hazard regression method was used to generate hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer in relation with PDI, hPDI and uPDI scores, adjusted for potential confounders.

Results: After 17.6 years of follow-up, we identified 316 pancreatic cancer cases. uPDI was associated with increased risk of pancreatic cancer with a dose-response trend ($HR_{per\text{-}SD\ increment}$=1.20, 95% CI: 1.06-1.37). The adjusted HRs (95% CIs) for quartiles 2, 3, and 4 relatives to quartile 1 of uPDI were 1.32 (0.94-1.86), 1.22 (0.86-1.71), and 1.68 (1.18-2.39), respectively (P_{trend}=0.01). Null association was found for PDI and hPDI with pancreatic cancer risk.

Conclusions: We showed that unhealthy PDI was associated with increased risk of pancreatic cancer.

Impact: Our results have public health implications for primary prevention against pancreatic cancer development, one of the deadliest malignancies worldwide.

INTRODUCTION

Pancreatic cancer is ranked 6th global cancer mortality with more than 510,000 new cases and approximately 470,000 deaths annually.[1] in 2025, there is an approximate 52,000 deaths due to pancreatic cancer, making it the 3rd cause of cancer-related death In the United States.[2] While the incidence trends of most common cancers have been declined during the past decade, pancreatic cancer incidence was seen to be increased by about 1% per year since the late 1990s in both sexes.[3] Pancreatic cancer is considered a fatal disease due to the short survival with post-diagnostic 5-year survival rate at only 13%.[3] In Singapore, the mortality rate of pancreatic cancer has increased during the past two decades in both sexes. Accordingly, it increased from 1.7/100,000 population (ranked 9th) during 1968-1972 period to 5.5/100,000 population (ranked 6th) during 2013-2017 period in male and from out of top 10 most common cancers during 1968-1972 period to 4.1 per 100,000 population (ranked 4th) during 2013-2017 period in female.[4] While type 2 diabetes, obesity, tobacco smoking and chronic pancreatitis are considered established risk factors for pancreatic cancer, they account for less than 50% of pancreatic cancer burden in the U.S[5]. It is, therefore, an urgent unmet need to identify other risk factors for pancreatic cancer, one of the deadliest malignancies.

Great attention has been paid recently to plant-based diets and dietary patterns, focusing on plant food intake with exclusion of some or all animal foods[6] due to their potential benefits to cancers and other chronic diseases.[7–12] Multiple epidemiologic studies showed the benefits of plant-based foods, such as fiber and whole grains, towards digestive system cancers.[13,14] However, several other reports, including data from our group also found some plant-based foods such as refined grains and sugar-sweetened beverages were associated with increased risk of digestive cancers.[15–19] The healthfulness and quality of the plant-based diet are thus critical and need to be taken into consideration when evaluating evaluate the association between plant-based dietary patterns and cancer risk.

Recently, three plant-based diet patterns were developed to better account for the quality of plant foods and were based overall intake and sub-categories of “healthfulness”; including the overall plant-based dietary index (PDI), healthy plant-based dietary index (hPDI) and unhealthy plant-based dietary index (uPDI).[20,21] Data on the association between PDI scores and pancreatic cancer risk are limited. To date, only one study, using data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (or PLCO) that was carried out and showed the inverse association between PDI and hPDI with pancreatic cancer risk as well as a positive association between uPDI with increased risk of pancreatic cancer.[22]

The objective of the current study was, therefore, to determine the associations between PDI, hPDI and uPDI scores with risk of pancreatic cancer in the Chinese Singaporeans using the Singapore Chinese Health Study (SCHS), an on-going prospective cohort study of more than 63,000 study participants.

METHODS

Study Population

The current analysis was performed using data from the Singapore Chinese Health Study (SCHS). Its protocol and enrollment information was described in prior study.[23] Briefly, the SCHS is an on-going prospective cohort study that enrolled 63,257 participants, aged 45-74 years old between April 1993 and December 1998. The SCHS's participants were Chinese Singaporeans belonging to two main dialect groups, the Hokkiens who migrated from Fujian province and the Cantonese who migrated from Guangdong province, both of which in southern China. All participants agreed to provide written informed consents. The SCHS study has been continuously approved by the participating Institutional Review Boards (IRBs) of the National University of Singapore and the University of Pittsburgh. The study was conducted following the Declaration of Helsinki

At baseline, trained interviewers conducted the interviews at home, using the structured questionnaire to collect information from study participants, including demographics, body weight and height, family history of cancer, lifetime use of tobacco, medical history, current physical activity, occupational exposure, and menstrual/reproductive history (women only). We also conducted a follow-up visit between July 1999 and December 2003 in which we asked study participants to provide blood for research purposes. Approximately 57% cohort participants (n=28,346) agreed to provide blood to our cohort study.

Dietary Assessment

The semi-quantitative food frequency questionnaire (FFQ) was used to collect information of dietary from all SCHS participants. The detailed description of the SCHS FFQ which was developed and validated in prior study.[24] Briefly, The FFQ included 165 commonly consumed food items and groups among Chinese Singaporeans. Participants reported their consumption frequency across eight categories, ranging from "*never or rarely*" to "*two or more times daily*." They were then asked to provide portion size, selecting from three options (i.e.,

small, medium, or large) with the aid of food photographs. Using the Singapore Food Composition Database, we estimated each participant's average daily intake of about 100 nutrients and non-nutrient compounds..[24] The validation study of the FFQ was conducted between April 1994 and March 1997 in 810 study participants who were randomly chosen among SCHS study participants. In our validation study, the FFQ was compared against two 24-hour dietary recalls (24-HDRs), one conducted on a weekday and the other on a weekend, approximately two months apart. The correlation coefficients between the FFQ and 24-HDR for most calorie-adjusted nutrients ranged from 0.24 (saturated fat intake among Hokkien women) to 0.73 (saturated fat intake among Cantonese men).[24]

Plant-based Dietary Index Calculation

Three indices, including the plant-based dietary index (PDI), healthy PDI (hPDI) and unhealthy PDI (uDPI) were constructed using the methods developed by Satija et al..[20,21] These indices were calculated based on food quintiles and reverse-code intakes of animal foods, or higher intakes/consumption levels received lower points toward final score or index. Accordingly, the PDI was assigned positive scores toward all plant foods (or from 1 to 5), regardless of healthiness, with the highest consumption at the highest score (or score 5) and lowest consumption at the lowest score (or score 1). For hPDI, we assigned positive scores (or from 1 to 5) to healthy plant foods and inverse scores (from 5 to 1) to all less healthy plant foods and animal foods with increasing intakes or consumption levels. For the uPDI score, higher scores or positive scores (i.e., 1 to 5) were assigned to all less healthy plant foods and animal foods with increasing intakes or consumption levels whereas inverse scores (i.e., 5 to 1) were assigned to healthy plant food groups and animal food groups with increasing intakes or consumption level.

We considered that in our population, such three indices comprised 15 non-overlapping food groups with sufficiently high and meaningful intake levels. Animal fat and potato components, that were included in the method developed by Satija et al.[20,21] were excluded from

the our analysis because of the very low levels of consumption in the our study population. We also excluded the “miscellaneous animal-based foods” component in the Satija et al.[20,21] because it overlapped with some other components, including red and processed meat and vegetables for which the consumption of such component was derived from mixed dishes in the our cohort. As done for Satija et al.,[20,21] we excluded potatoes from the total vegetable calculation. Furthermore, we excluded a few high sugar/preserved items from fruit (i.e., preserved and dried fruit), vegetables (i.e., preserved vegetables), and legumes (i.e., sweetened soy products) to ensure these fully reflect consumption of healthy plant foods. As each food component was scored from 1 to 5 (i.e., based on quintiles of intake), the total score for each index were ranged from 15 to 75 (**Supplementary Table 1**).[25] The correlation coefficients between PDI and hPDI was 0.46, PDI and uPDI was -0.31 and hPDI and uPDI was -0.24 (All *P's*<0.0001) (**Supplementary Table 2**).

Assessment of Other Covariates

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking status was categorized into three groups, including never, current, and former smokers.[26] For ever-smokers (current and former), we collected additional information, including the average number of cigarettes smoked per day and total years of smoking. We classified alcohol consumption as non-drinker, monthly, weekly, or daily drinker. We also classified coffee drinking status into the following categories: non-/monthly/weekly drinker, 1 cup per day, 2–3 cups per day, and ≥4 cups per day. For history of type 2 diabetes, we asked participants if they have ever been diagnosed by a doctor and, if so, the age at first diagnosis. Physical activity was evaluated using an eight-level scale (never; 0.5–1; 2–3; 4–6; 7–10; 11–20; 21–30; and ≥31 hours per week) across three activity domains: (1) strenuous sports (e.g., jogging, hill cycling, swimming laps, squash, aerobics or tennis,); (2) vigorous work (e.g., shoveling, truck loading/unloading, moving heavy furniture, or similar manual labor); and (3) moderate activities (e.g., level-ground cycling, bowling, brisk walking, chi kung or tai chi).[27]

Ascertainment of Pancreatic Cancer Cases

Cancer diagnosis and deaths were ascertained among cohort participants using the linkage analysis with and the Singapore Cancer Registry and the Singapore Registry of Births and Deaths, respectively. Accordingly, information on cancer diagnosis has been continuously and comprehensively collected in the Singapore Cancer Registry since 1968.[28] The International Classification of Diseases-Oncology, 9th Edition (ICD-O-9) code 157 or ICD 10th Edition (ICD-10) revision code C25 were used to identify pancreatic cancer cases from the cancer registry file for the current analysis. As of December 31, 2015, 56 participants (or <0.1%) were lost to follow-up due to their migration out of Singapore. We further excluded 1,936 participants with a history of cancer at recruitment. Finally, 316 incident cases of pancreatic cancer were identified for the current analysis and 61,005 study participants who did not have cancer at baseline. There were no endocrine pancreatic cancers that were identified during the linkage with the Singapore Cancer Registry file.

Statistical Analysis

In this analysis, frequencies were calculated for categorical variables whereas means and standard deviations (SD) were computed for continuous variables. Differences in the distributions of continuous and categorical variables across categories of PDI, hPDI, and uPDI scores, as well as between pancreatic cancer cases and non-cases, were assessed using the *t*-test and the χ^2 test, respectively. We defined the quartiles of PDI, hPDI and uPDI based on their distributions among the entire cohort. Person-years at risk were calculated for each study participant from the date of the baseline until the earliest of the following events: pancreatic cancer, death, migration out of Singapore, or December 31, 2015..

In the main analysis, we employed Cox proportional hazard regression model to examine the associations between PDI, hPDI and uPDI scores with pancreatic cancer risk. We calculated hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer across quartiles and continuous measures of PDI, hPDI and uPDI scores.

We included the following covariates into the multivariable regression models: 1) age at recruitment (years), 2) sex, 3) dialect group (i.e., Hokkien or Cantonese), 4) year of enrollment (i.e., 1993-1995 vs 1996-1998), 5) level of education (i.e., no formal education, primary school, secondary or higher education), 6) BMI (kg/m^2, 18.5, 18.5-<23.0, 23.0-<27.0, ≥27.0), 7) smoking status (i.e., never-smokers, current-smokers and past-smokers), 8) smoking pack-years, 9) alcohol intake (i.e., non/monthly drinkers, weekly, daily drinkers), 10) coffee drinking status (i.e., non-drinker/monthly/weekly drinker, 1 cup/day, 2-3 cups/day and ≥4 cups/day), 11) physical activity (i.e., yes vs. no), 12) history of type 2 diabetes (i.e., yes vs. no), 13) sleep duration, and 14) total energy intake (i.e., KCal/day). Overweight or obese were defined as BMI 23-27.5 kg/m^2 and >27.5 kg/m^2, respectively, according the recommendation by the World Health Organization (WHO) for Asian population.[29,30] Smoking pack-years was calculated as the product of the number of cigarette packs smoked per day and the total number of years of smoking.

Stratified analysis was further performed by 1) sex (i.e., male vs. female), 2) BMI (i.e., <23 kg/m^2 vs. ≥23 mg/m^2), 3) smoking status (i.e., ever vs. never), 4) alcohol drinking status (i.e., non/monthly drinker vs. weekly/daily drinker) and 5) history of type 2 diabetes (i.e., yes vs. no) to explore whether there was a difference in the association between PDI, hPDI and uPDI scores with risk of pancreatic cancer across such strata. We conducted a sensitivity analysis by excluding pancreatic cancer cases and person-years accrued during the first two years of follow up to minimize the potential for reverse causality. We used the Schoenfeld residual test to examine the proportionality assumption for hazards over follow-up time. No violation was found. We also tested the linear trend for pancreatic cancer risk with PDI, hPDI and uPDI scores based upon the ordinal values of their quartiles. We tested the interaction effect on pancreatic cancer incidence between PDI hPDI and uPDI scores and selected factors, including sex, BMI, smoking status, alcohol drinking status, and history of type 2 diabetes by adding a product term to the multivariable regression models.

All statistical analysis was performed using the SAS version 9.4 computer software (SAS Institute Inc., Cary, NC). All *P* values were two-sided, and we used *P*-values of less than 0.05 as a threshold for statistical significance.

Data Availability Statement

The data generated in this study are available upon reasonable request from the corresponding author.

RESULTS

Overall, we identified 316 incident cases of pancreatic cancer among 61,321 study participants who were free of cancer at baseline after a mean (standard deviation) follow-up of 17.7 (5.3) years (or 1,084,239 person-years). The median (SD) age of cancer diagnosis was 72.5.4 (8.4) years of age.

Compared with participants who were free of pancreatic cancer during the study period (or non-cases), individuals who developed incident pancreatic cancer (called cases) were older, more likely to be male, Hokkien, ever smokers (i.e., past-and current-smokers) and drink more coffee (all *P*-values <0.05). There were no differences between pancreatic cancer cases and non-cases in distributions by education level, weekly physical activity, alcohol consumption, history of type 2 diabetes, family history of cancer, BMI, total energy intake and other micronutrient intakes (**Table 1**).

Individuals in the highest quartile of PDI score, compared to those in the lowest quartile of PDI score, were younger, more likely to be male, having higher level of education, more likely to be Cantonese, more likely to be coffee drinkers and have family history of cancer, but less likely to be cigarette smokers (i.e., past-and current-smokers) or alcohol drinkers, less likely to to have history of type 2 diabetes. In addition, they had higher intakes of calories, protein and fat as well as carbohydrate. Also, compared to individuals in the lowest quartile of hPDI score, those in the highest quartile of hPDI score were older, more likely to be female, having lower education level, more likely to be coffee drinkers and to have history of type 2 diabetes, but less likely to be cigarette smokers or alcohol drinkers. They also had lower intakes of calories, protein, fat and carbohydrate (all *P*-values <0.05). Additionally, compared to participants in the lowest quartile of uPDI score, those with the highest quartile of uPDI score were older, more likely to be female, having lower education level, more likely to be Hokkien and cigarette smokers but less likely to be coffee drinkers, weekly physical activity, or to have history of type 2

diabetes and family history of cancer. They also had lower intakes of calories, protein, fat and carbohydrate (all *P*-values <0.05) (**Supplementary Table 3**).

Overall, there was a positive association between uPDI score and risk of pancreatic cancer ($HR_{per\text{-}SD\ increment}$ =1.20, 95% CI: 1.06-1.37; P_{trend}=0.01) after adjustment for multiple risk factors for pancreatic cancer. Compared with the lowest quartile, the HRs (95% CIs) of pancreatic cancer for quartiles 2, 3, and 4 of uPDI score were 1.32 (0.94-1.86), 1.22 (0.86-1.71), and 1.68 (1.18-2.39), respectively. No association was observed between PDI ($HR_{per\text{-}SD\ increment}$=0.99, 95% CI: 0.88-1.12; P_{trend}=0.86) and hPDI ($HR_{per\text{-}SD\ increment}$=0.90, 95% CI: 0.80-1.01; P_{trend}=0.41) with risk of pancreatic cancer (**Table 2**).

In stratified analysis, the positive association between uPDI score and pancreatic cancer risk was more apparent among men ($HR_{per\text{-}SD\ increment}$=1.38, 95% CI: 1.16-1.65; P_{trend}=0.001), individuals with BMI≥23 ($HR_{per\text{-}SD\ increment}$=1.34, 95% CI: 1.12-1.60; P_{trend}=0.008) , ever smokers ($HR_{per\text{-}SD\ increment}$=1.28, 95% CI: 1.04-1.58; P_{trend}=0.05), non-drinkers of alcoholic beverage ($HR_{per\text{-}SD\ increment}$=1.21, 95% CI: 1.06-1.39; P_{trend}=0.01), and those without history of diabetes at baseline ($HR_{per\text{-}SD\ increment}$=1.24, 95% CI: 1.08-1.42; P_{trend}=0.006) (**Table 3**). However, none of these interactions reached the level of statistical significance (All $P's_{interaction}$>0.05) (**Table 3**).

In the sensitivity analysis on the entire cohort after excluding pancreatic cancer cases and person-years within the first two years of observation, the positive association between uPDI score and risk of pancreatic cancer was not materially changed. No change in null association between PDI and hPDI score and risk of pancreatic cancer was found as well. Accordingly, compared to the lowest quartile, the HRs of pancreatic cancer for the highest quartiles of PDI, hPDI and uPDI scores, in comparison to respective lowest quartiles, were 1.00 (95% CI: 0.70-1.44, P_{trend}=0.97), 0.81 (95% CI: 0.57-1.16, P_{trend}=0.39) and 1.68 (95% CI: 1.17-2.41; P_{trend}=0.01) respectively. Before adjustment for multiple risk factors, higher levels of hPDI were significantly associated with lower risk of pancreatic cancer ($HR_{per\text{-}SD\ increment}$=0.89, 95% CI: 0.79-1.00; P_{trend} = 0.04) whereas higher uPDI was associated with higher risk ($HR_{per\text{-}SD}$

$_{increment}$=1.12, 95% CI: 1.00-1.26; P_{trend}=0.04) in the age-and sex-adjusted models. Adjustment for various factors diminished the association for hPDI but enhanced the association for uPDI with risk of pancreatic cancer. HRs (95% CIs) of pancreatic cancer incidence per SD of PDI, hPDI and uPDI scores were 0.99 (0.87-1.12) and 0.89 (0.79-1.01)**.** 1.21 (1.06-1.38) (**Table 4)**.

DISCUSSION

The current study of 61,321 participants from the found that adherence to the less healthy plant-based diet was associated with increased risk of pancreatic cancer. We also observed null association between overall PDI and healthy PDI scores with risk of pancreatic cancer. In the stratified analysis, even though the positive association between less healthy PDI score and pancreatic cancer risk was more apparent among men than in women, among individuals with BMI≥23 more than those with BMI<23, among ever smokers more than never smokers, among non/monthly drinker more than among frequent drinkers, and among those without history of diabetes more than among individuals with history of diabetes, there p-interaction in such strata did not reach the level of statistical significance.

To date, to our knowledge, only one study that has evaluated the association between PDI, hPDI and uPDI scores and pancreatic cancer risk. Accordingly, a recent study by Zhong et al, [22] using data from the PLCO trial which comprised 101,748 US adults and identified 421 pancreatic cancer cases, found that uPDI score was associated with increased risk of pancreatic cancer ($HR_{\text{quartile 4 versus 1}}$=1.38; 95% CI: 1.02-1.85; P_{trend}= 0.01) while there were inverse associations between overall PDI ($HR_{\text{quartile 4 versus 1}}$=0.74; 95% CI: 0.57-0.96; P_{trend}=0.02) and hPDI ($HR_{\text{quartile 4 versus 1}}$=0.56; 95% CI: 0.42-0.75; P_{trend}<0.001) scores with risk of pancreatic cancer. The majority of study participants in the PLCO trial were adult American Caucasians whereas our study participants were Singaporean Chinese with different lifestyle and dietary habits. Although their dietary habits were quite different, the similar results in the two different study populations in the inverse hPDI-pancreatic cancer association and the positive uPDI-pancreatic cancer association strengthened our findings.

While the mechanism of harmful effect by unhealthy PDI score on pancreatic cancer risk is not fully understood, there are several biological plausibility or studies supporting this effect as well. For example, fruit juices are considered a class of high-calorie and high-sugar sources and their consumptions or high intake have been found to be associated with increased risk of

metabolic syndrome, weight gain, and type 2 diabetes, all of which are established risk factors for pancreatic cancer.[31] Fruit juices, on the other hand, also contain artificial sweeteners, which is found to be associated with increased risk of obese-related cancers ($HR_{\text{high consumption vs. noconsumption}}$=1.13, 95% CI: 1.00-1.28, P_{trend}=0.04), including pancreatic cancer, as reported recently in the NutriNet-Santé, a population-based prospective cohort study of 102,865 French adults.[32] In our cohort, we also found that individuals consuming ≥2 soft drinks per week, with individuals who did not consume soft drinks, experienced a statistically significant increased risk of pancreatic cancer (HR=1.87; 95% CI: 1.10-3.15).[19] Findings from our cohort is also consistent with results from a recent study of the MJ Cohort, a prospective cohort study of approximately 500,000 Taiwanese adults in which they reported that compared to individuals who consumed 0 to less than 0.5 serving of sugar-sweetened beverages, those who consumed 2 serving/day had a 50% increased risk of pancreatic cancer mortality (HR=1.55, 95% CI: 1.08-2.24).[33]

The current study has several limitations. First, it is not possible to evaluate the changes of diets, smoking and other covariates over time in relation to pancreatic cancer risk, because we could only be able to obtain such information at baseline from study participants. This might lead to the non-differential misclassification phenomenon and change the overall association toward the null.[33] Second, our results are not generalizable to other populations which have different dietary habits and prevalence of risk factors for pancreatic cancer. Third, residual confounding cannot be ruled out completely, a common limitation seen in observational studies, particularly potential confounding from smoking. Another potential limitation was the measurement error of dietary intake. And finally, results from the stratified (or sub-group) analysis should be interpreted cautiously because of small number and spurious association could occur due to chance and such analysis was hypothesis driven only and we did not control for multiple comparison.

The current study also has several strengths. First, to our knowledge, this might be the first attempt to examine the association between PDI scores and pancreatic cancer risk in a

Chinese population. Second, due to the prospective cohort study design, potential effect of pancreatic cancer symptoms and diagnosis/treatment procedure on diet and lifestyle habits of the pancreatic cancer patients (or reverse causation effect) was minimized. Furthermore, with a long-time follow-up, we would be able to perform the sensitivity analysis by excluding incident cases of pancreatic cancer and respective person-years of follow-up in the first two year after the recruitment; thus, further removing the potential reverse causation effect of subjects with imminent pancreatic cancer diagnosis or death on the observed association between PDI scores and risk of pancreatic cancer. Third, we used a validated FFQ, allowing us to obtain comprehensively information on dietary and other lifestyle factors (i.e., smoking, alcohol intake, physical activity) and history of diseases (i.e., type 2 diabetes), and used them as covariate set in the multivariable regression model, thus minimizing the potential confounding effect in the observed associations.

In summary, in the analysis of data from the Singapore Chinese Health Study, a prospective cohort study of more than 63,000 Chinese Singaporeans, we found an association between unhealthy PDI score and increased risk of pancreatic cancer. We also observed a null association between overall PDI and pancreatic cancer risk and a weak inverse association between healthy PDI scores and risk of pancreatic cancer. Our results suggest that dietary modification with more plant food and less animal food may be a potential strategy for primary prevention against the development of pancreatic cancer.

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Table 1. Distribution of Baseline Characteristics among Study Participants, the Singapore Chinese Health Study, 1993-2015

Characteristics	Total population (N=61,321)	Pancreatic Cancer Cases (n=316)	Non-cases (n=61,005)	*P-value*
Age, (Mean±SD)	56.4±8.0	56.3±7.7	56.4±8.0	<0.0001
Sex				
Male	27,293 (44.5)	164 (52.0)	27,129 (44.5)	0.008
Female	34,028 (55.5)	152 (48.0)	33,876 (55.5)	
Highest level of education				
No formal education	16,661 (27.2)	95 (30.1)	16,566 (27.2)	0.36
Primary school	27,224 (44.4)	141 (44.6)	27,083 (44.4)	
Secondary school or higher	17,436 (28.4)	80 (25.3)	17,356 (28.4)	
Dialect				
Cantonese	28,325 (46.2)	132 (41.8)	28,193 (46.2)	0.11
Hokkien	32,996 (53.8)	184 (58.2)	32,812 (53.8)	
Weekly physical activity[a]				
Yes	20,238 (30.4)	96 (30.4)	20,142 (33.0)	0.32
No	41,083 (67.0)	220 (69.6)	40,863 (67.0)	
Smoking status				
Never smokers	42,583 (69.4)	195 (61.7)	42,388 (69.5)	0.0009
Past smokers	6,681 (10.9)	40 (12.7)	6,641 (10.9)	
Current smokers	12,057 (19.7)	81 (25.6)	1,1976 (19.6)	
Alcohol consumption				
Non-drinker/Monthly drinker	54,144 (88.4)	278 (88.0)	53,866 (88.3)	0.86
Weekly drinker	5,018 (8.2)	28 (8.9)	4,990 (8.2)	
Daily drinker	2,159 (3.5)	10 (3.2)	2,149 (3.5)	
History of diabetes				
Yes	5,469 (8.9)	34 (10.8)	5,435 (8.9)	0.25
No	55,852 (91.1)	282 (89.2)	55,570 (91.1)	
Coffee drinking status				
Non-drinker/monthly/weekly	18,149 (29.7)	91 (28.8)	18,058 (29.6)	0.02
1 cup/day	22,087 (36.0)	103 (32.6)	21,984 (36.0)	
2-3 cups/day	18,663 (30.4)	99 (31.3)	18,564 (30.4)	
≥4 cups/day	2,422 (3.9)	23 (7.3)	2,399 (3.9)	
Family history of cancer				
Yes	1,349 (2.2)	9 (2.8)	1,340 (2.2)	0.43
No	59,972 (97.8)	307 (97.1)	59,665 (97.8)	
BMI, kg/m (Mean±SD)	23.1±3.3	23.0±3.2	23.1±3.3	0.59
Total Energy Intake (kcal/day)	1,556.6±566.2	1,564.7±574.5	1,556.6±566.2	0.80
Carbohydrate 1(gr/day) (Mean±SD)	227.8±81.1	233.4±81.2	227.8±81.0	0.22
Dietary fiber (gr/day) (Mean±SD)	12.7±5.8	12.3±5.6	12.7±5.8	0.27
Total fat (gr/day) (Mean±SD)	44.1±21.1	43.2±22.0	44.1±21.1	0.47
Animal fat (gr/day) (Mean±SD)	15.2±9.8	15.2±10.1	15.2±9.8	0.95
Plant fat (gr/day) (Mean±SD)	28.9±13.6	28.0±13.7	28.9±13.6	0.24
Saturated fat (gr/day) (Mean±SD)	15.6±8.1	15.3±8.2	15.6±8.1	0.58
Monounsaturated fat (gr/day) (Mean±SD)	14.9±7.4	14.7±7.7	14.9±7.4	0.68
Polyunsataturated fat (gr/day) (Mean±SD)	8.9±4.9	8.7±4.8	8.9±4.9	0.31
Total Protein (g/day) (Mean±SD)	59.2±24.2	58.1±25.3	59.2±24.2	0.39
Animal protein	32.0±16.5	30.6±16.5	32.0±16.5	0.15

Plant protein	11.3±6.8	10.9±7.4	11.3±6.8	0.38

[a]Including strenuous physical activity and/or vigorous work

Table 2. Association Between Plant-based Diet Indices and Risk of Pancreatic Cancer: the Singapore Chinese Health Study, 1993-2015

Characteristics	Person-year	# pancreatic cancer cases	Age- and sex-adjusted Model HR[a] (95% CI)	Multivariable Model HR[a] (95% CI)
PDI				
Q1 (lowest)	247,914	68	1.00	1.00
Q2	279,796	85	1.14 (0.83-1.57)	1.14 (0.82-1.57)
Q3	269,538	85	1.20 (0.87-1.65)	1.19 (0.85-1.65)
Q4 (highest)	286,991	78	1.05 (0.76-1.45)	1.02 (0.72-1.46)
P_{trend}			0.75	0.86
Continuous scale (per SD increment)			1.00 (0.90-1.12)	0.99 (0.88-1.12)
Heatthy PDI (hPDI)				
Q1 (lowest)	260,642	80	1.00	1.00
Q2	286,641	80	0.88 (0.64-1.20)	0.89 (0.65-1.22)
Q3	284,744	87	0.92 (0.68-1.25)	0.94 (0.68-1.29)
Q4 (highest)	252,212	69	0.82 (0.59-1.14)	0.84 (0.59-1.18)
P_{trend}			0.32	0.41
Continuous scale (per SD increment)			0.90 (0.80-1.01)	0.90 (0.80-1.01)
Unheatthy PDI (uPDI)				
Q1 (lowest)	306,245	71	1.00	1.00
Q2	238,912	70	1.24 (0.89-1.72)	1.32 (0.94-1.86)
Q3	293,619	70	1.09 (0.79-1.5)	1.22 (0.86-1.72)
Q4 (highest)	245,464	96	**1.44 (1.05-1.96)**	**1.68 (1.18-2.39)**
P_{trend}			**0.05**	**0.01**
Continuous scale (per SD increment)			**1.13 (1.01-1.26)**	**1.20 (1.06-1.37)**

[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status (never smoker, current smoker, past smoker), smoking pack-years, coffee drinking status, alcohol drinking status (non-drinker/monthly drinker, weekly drinker, daily drinker), total energy intake, BMI (<18.5, 18.5-<23.0, 23.0-<27.0, ≥27.0), physical activity, sleep duration and history of diabetes status.

CI: confidence interval; HR: hazard ratio; PDI: plant-based diet index.
Bold numbers: statistically significant (P<0.05)

Table 3. Association Between Plant-based Diet Index and Risk of Pancreatic Cancer, stratified by sex, BMI levels, smoking status, Alcohol Drinking Status, and History of Diabetes: the Singapore Chinese Health Study, 1993-2015[a]

		Q1	Q2	Q3	Q4	P_{Trend}	Continuous scale (per SD increment)	$P_{Interaction}$
PDI								
Men	# Cases	34	42	45	43			
	HR (95% CI)	1.00	1.13 (0.71-1.78)	1.19 (0.75-1.89)	1.01 (0.62-1.65)	0.94	1.02 (0.86-1.21)	0.93
Women	# Cases	34	43	40	35			
	HR (95% CI)	1.00	1.15 (0.73-1.81)	1.19 (0.74-1.90)	1.04 (0.62-1.73)	0.86	0.97 (0.81-1.15)	
BMI<23	# Cases	29	37	41	38			
	HR (95% CI)	1.00	1.14 (0.69-1.86)	1.29 (0.79-2.11)	1.11 (0.66-1.86)	0.63	1.01 (0.84-1.21)	0.38
BMI≥23	# Cases	39	48	44	40			
	HR (95% CI)	1.00	1.13 (0.74-1.74)	1.11 (0.71-1.72)	0.97 (0.60-1.56)	0.88	0.98 (0.83-1.16)	
Never smokers	# Cases	39	54	50	52			
	HR (95% CI)	1.00	1.18 (0.78-1.79)	1.13 (0.73-1.73)	1.08 (0.69-1.68)	0.87	1.00 (0.86-1.17)	0.86
Ever smokers	# Cases	29	31	35	26			
	HR (95% CI)	1.00	1.07 (0.64-1.78)	1.35 (0.81-2.24)	0.97 (0.55-1.71)	0.83	0.99 (0.81-1.21)	
Non/monthly drinker	# Cases	58	72	78	70			
	HR (95% CI)	1.00	1.12 (0.79-1.59)	1.26 (0.89-1.79)	1.09 (0.75-1.59)	0.54	1.01 (0.89-1.15)	0.29
Weekly/daily drinker	# Cases	10	13	7	8			
	HR (95% CI)	1.00	1.28 (0.56-2.96)	0.76 (0.28-2.06)	0.63 (0.22-1.76)	0.25	0.86 (0.60-1.24)	
No diabetics history	# Cases	61	76	77	68			
	HR (95% CI)	1.00	1.12 (0.80-1.57)	1.18 (0.83-1.67)	0.96 (0.66-1.39)	0.89	0.97 (0.85-1.10)	0.49
Diabetes history	# Cases	7	9	8	10			
	HR (95% CI)	1.00	1.33 (0.49-3.63)	1.30 (0.46-3.71)	1.83 (0.65-5.19)	0.29	1.23 (0.86-1.77)	
Follow-up <10 years	# Cases	27	30	38	23			
	HR (95% CI)	1.00	1.15 (0.68-1.95)	1.64 (0.98-2.73)	0.97 (0.53-1.78)	0.63	0.97 (0.80-1.19)	0.37
Follow-up ≥10 years	# Cases	41	55	47	55			
	HR (95% CI)	1.00	1.19 (0.79-1.79)	1.05 (0.68-1.61)	1.13 (0.73-1.76)	0.76	1.00 (0.86-1.17)	
Healthy PDI								
Men	# Cases	55	40	43	26			
	HR (95% CI)	1.00	0.78 (0.52-1.18)	0.92 (0.61-1.40)	0.69 (0.42-1.12)	0.24	0.85 (0.72-1.01)	0.32
Women	# Cases	25	40	44	43			
	HR (95% CI)	1.00	1.12 (0.67-1.85)	1.06 (0.64-1.77)	1.07 (0.64-1.81)	0.90	0.96 (0.81-1.14)	

BMI<23	# Cases	33	39	44	29			
	HR (95% CI)	1.00	1.09 (0.68-1.74)	1.28 (0.80-2.05)	0.95 (0.56-1.62)	0.93	0.93 (0.78-1.11)	0.43
BMI≥23	# Cases	47	41	43	40			
	HR (95% CI)	1.00	0.75 (0.49-1.16)	0.73 (0.47-1.13)	0.76 (0.48-1.19)	0.24	0.88 (0.74-1.04)	
Never smokers	# Cases	38	47	58	52			
	HR (95% CI)	1.00	1.00 (0.65-1.54)	1.12 (0.73-1.72)	1.08 (0.69-1.68)	0.64	1.00 (0.85-1.16)	0.09
Ever smokers	# Cases	42	33	29	17			
	HR (95% CI)	1.00	0.81 (0.51-1.28)	0.79 (0.48-1.29)	0.57 (0.32-1.04)	0.08	0.77 (0.63-0.94)	
Non/monthly drinker	# Cases	64	78	77	67			
	HR (95% CI)	1.00	0.94 (0.67-1.33)	0.98 (0.69-1.38)	0.93 (0.65-1.35)	0.80	0.92 (0.81-1.05)	0.08
Weekly/daily drinker	# Cases	16	10	10	2			
	HR (95% CI)	1.00	0.66 (0.29-1.47)	0.76 (0.33-1.75)	**0.22 (0.05-0.98)**	0.07	0.72 (0.50-1.04)	
No diabetics history	# Cases	75	72	77	58			
	HR (95% CI)	1.00	0.85 (0.61-1.18)	0.90 (0.64-1.26)	0.77 (0.54-1.11)	0.23	0.88 (0.77-1.00)	0.36
Diabetes history	# Cases	5	8	10	11			
	HR (95% CI)	1.00	1.54 (0.49-4.84)	1.60 (0.52-4.90)	1.87 (0.60-5.77)	0.31	1.12 (0.78-1.60)	
Follow-up <10 years	# Cases	30	33	27	28			
	HR (95% CI)	1.00	0.84 (0.50-1.39)	0.77 (0.45-1.31)	1.02 (0.59-1.74)	0.94	0.91 (0.74-1.11)	0.88
Follow-up ≥10 years	# Cases	47	50	60	41			
	HR (95% CI)	1.00	0.96 (0.64-1.44)	1.12 (0.75-1.67)	0.85 (0.55-1.34)	0.69	0.89 (0.77-1.04)	
Unhealthy PDI								
Men	# Cases	39	37	27	61			
	HR (95% CI)	1.00	1.38 (0.87-2.18)	0.88 (0.52-1.47)	**2.43 (1.53-3.86)**	**0.001**	**1.38 (1.16-1.65)**	0.06
Women	# Cases	32	33	52	35			
	HR (95% CI)	1.00	1.25 (0.75-2.05)	1.47 (0.91-2.37)	1.03 (0.59-1.79)	0.77	1.02 (0.84-1.23)	
BMI<23	# Cases	36	36	34	39			
	HR (95% CI)	1.00	1.34 (0.84-2.16)	1.04 (0.63-1.72)	1.39 (0.83-2.33)	0.38	1.05 (0.87-1.27)	0.16
BMI≥23	# Cases	35	34	45	57			
	HR (95% CI)	1.00	1.29 (0.80-2.10)	1.39 (0.87-2.23)	**1.95 (1.20-3.18)**	**0.008**	**1.34 (1.12-1.60)**	
Never smokers	# Cases	47	42	52	54			
	HR (95% CI)	1.00	1.23 (0.80-1.89)	1.26 (0.82-1.92)	1.49 (0.95-2.34)	0.10	1.15 (0.98-1.36)	0.40
Ever smokers	# Cases	24	28	27	42			
	HR (95% CI)	1.00	1.51 (0.86-2.64)	1.16 (0.64-2.07)	**1.97 (1.11-3.49)**	**0.05**	**1.28 (1.04-1.58)**	
Non/monthly drinker	# Cases	60	59	72	87			

	HR (95% CI)	1.00	1.29 (0.89-1.87)	1.27 (0.88-1.83)	**1.69 (1.16-2.47)**	**0.01**	**1.21 (1.06-1.39)**	0.76
Weekly/daily drinker	# Cases	11	11	7	9			
	HR (95% CI)	1.00	1.51 (0.63-3.59)	0.88 (0.32-2.42)	1.57 (0.58-4.28)	0.62	1.15 (0.80-1.66)	
No diabetics history	# Cases	60	62	73	87			
	HR (95% CI)	1.00	1.38 (0.96-1.98)	1.31 (0.91-1.89)	**1.78 (1.22-2.61)**	**0.006**	**1.24 (1.08-1.42)**	0.35
Diabetes history	# Cases	11	8	6	9			
	HR (95% CI)	1.00	0.97 (0.38-2.49)	0.64 (0.22-1.87)	0.98 (0.35-2.74)	0.79	0.91 (0.62-1.36)	
Follow-up <10 years	# Cases	21	27	26	44			
	HR (95% CI)	1.00	1.75 (0.97-3.15)	1.25 (0.67-2.33)	**2.10 (1.15-3.84)**	**0.04**	**1.37 (1.11-1.69)**	0.94
Follow-up ≥10 years	# Cases	50	43	53	52			
	HR (95% CI)	1.00	1.15 (0.75-1.74)	1.16 (0.77-1.76)	1.30 (0.84-2.04)	0.26	1.11 (0.94-1.30)	

[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status (never smoker, current smoker, past smoker), smoking pack-years, coffee drinking status, alcohol drinking status (non-drinker/monthly drinker, weekly drinker, daily drinker), total energy intake, BMI (<18.5, 18.5-<23.0, 23.0-<27.0, ≥27.0), physical activity, sleep duration and history of diabetes status (if possible)
CI: confidence interval; HR: hazard ratio; PDI: plant-based diet index.;

Bold **number**: statistically significant (P<0.05)

Table 4. Association Between Plant-based Diet Indices and Risk of Pancreatic Cancer: the Singapore Chinese Health Study, 1993-2015, after excluding observation and follow-up during the first 2 years

Characteristics	Person-year	# pancreatic cancer cases	Age- and sex-adjusted Model HR[a] (95% CI)	Multivariable Model HR[a] (95% CI)
PDI				
Q1 (lowest)	219,086	64	1.00	1.00
Q2	248,268	79	1.12 (0.81-1.56)	1.11 (0.80-1.55)
Q3	239,544	79	1.18 (0.85-1.64)	1.15 (0.82-1.62)
Q4 (highest)	255,629	74	1.04 (0.74-1.46)	1.00 (0.70-1.44)
P_{trend}			0.78	0.97
Continuous scale (per SD increment)			1.00 (0.90-1.12)	0.99 (0.87-1.12)
Heatthy PDI (hPDI)				
Q1 (lowest)	230,906	76	1.00	1.00
Q2	254,251	74	0.86 (0.62-1.18)	0.88 (0.64-1.22)
Q3	252,947	84	0.94 (0.69-1.29)	0.98 (0.71-1.35)
Q4 (highest)	224,423	62	0.79 (0.56-1.10)	0.81 (0.57-1.16)
P_{trend}			**0.04**	0.39
Continuous scale (per SD increment)			**0.89 (0.79-1.00)**	0.89 (0.79-1.01)
Unheatthy PDI (uPDI)				
Q1 (lowest)	272,891	68	1.00	1.00
Q2	212,462	65	1.20 (0.86-1.69)	1.30 (0.92-1.84)
Q3	260,446	74	1.07 (0.77-1.49)	1.22 (0.86-1.74)
Q4 (highest)	216,729	89	**1.41 (1.02-1.94)**	**1.68 (1.17-2.41)**
P_{trend}			**0.04**	**0.01**
Continuous scale (per SD increment)			**1.12 (1.00-1.26)**	**1.21 (1.06-1.38)**

[a]Models adjusted for age, sex, dialect, year of enrollment, education level, smoking status (never smoker, current smoker, past smoker), smoking pack-years, coffee drinking status, alcohol drinking status (non-drinker/monthly drinker, weekly drinker, daily drinker), total energy intake, BMI (<18.5, 18.5-<23.0, 23.0-<27.0, ≥27.0), physical activity, sleep duration and history of diabetes status.

CI: confidence interval; HR: hazard ratio; PDI: plant-based diet index.
Bold numbers: statistically significant (P<0.05).