HHS Public Access

Author manuscript

Cancer Prev Res (Phila). Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Cancer Prev Res (Phila). 2022 January ; 15(1): 29–36. doi:10.1158/1940-6207.CAPR-21-0205.

Composite Score of Healthy Lifestyle Factors and the Risk of Pancreatic Cancer in a Prospective Cohort Study

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Abstract

While the associations between individual lifestyle factors and risk of pancreatic cancer were studied extensively, their combined impact has not been examined. We evaluated the association of a composite score of healthy lifestyle factors, including body mass index, cigarette smoking, the Alternative Healthy Eating Index-2010 (AHEI-2010), sleep duration, and physical activity with pancreatic cancer risk in the Singapore Chinese Health Study, an on-going prospective cohort study of 63,257 Chinese aged 45–74 at enrollment in 1993–1998 with up to 25 years of follow-up. Cox proportional hazard regression method was used to estimate hazard ratio (HR) and its 95% confidence interval (CI) with adjustment for multiple potential confounders. We identified 316 incident pancreatic cancer cases among the cohort participants after a mean 17 years of follow-up. Individuals with higher composite scores representing healthier lifestyle were at significantly lower risk of pancreatic cancer. The multivariate-adjusted HRs (95% CIs) of pancreatic cancer incidence for the composite scores 2, 3, 4, 5, 6–7 were 0.60 (0.50–0.91), 0.48 (0.32–0.71), 0.45 (0.31–0.67), 0.41 (0.27–0.62) and 0.38 (0.24–0.62), respectively, compared with the scores 0–1 (P_{trend}<0.0001). The inverse association was more apparent among participants without diabetes history and was robust in men and women as well as in alcohol drinkers and non-drinkers. In summary, the association for pancreatic cancer risk was stronger for the aggregated than individual healthy lifestyle factors. These findings suggest that a more comprehensive lifestyle modification strategy would be more effective for prevention of pancreatic cancer than the change of a single lifestyle factor.

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Conflict of Interest Statement

The authors declare no potential conflicts of interest

Keywords

Composite score; lifestyle factors; pancreatic cancer risk

INTRODUCTION

Pancreatic cancer is ranked 7th global cancer mortality with more than 459,000 new cases and more than 432,000 deaths annually[1]. With an approximate 47,050 deaths in 2020, pancreatic cancer is the 3rd cause of cancer-related death In the United States[2]. Despite the fact that the trends in incidence and mortality rates of most of common cancer types have been declined over the past two decades, it is not the case for pancreatic cancer as its incidence rate has been up-trending by 1.5% per year[3,4]. Pancreatic cancer has relatively short survival[4], with post-diagnostic 5-year survival rate at only 8%[5]. In Singapore, the mortality rate of pancreatic cancer in male has increased from 1.7 per 100,000 population during 1968–1972 period (ranked 9th) to 5.5 per 100,000 population during 2013–2017 period (ranked 6th)[6]. Similarly, the mortality rate of pancreatic cancer among Singaporean females was 4.1 per 100,000 population during 2013–2017 period, a dramatic increase during the past four decades from out of top 10 most common cancers in Singapore to the 4th in 2017[6]. The established risk factors for pancreatic cancer are type 2 diabetes, obesity, tobacco smoking and chronic pancreatitis, which are reported in less than half of pancreatic cancer burden in the U.S[7]. To better understand the carcinogenesis for proper prevention and cancer of pancreatic cancer, there is an urgent need to identify the other risk factors for this deadly disease.

Prior epidemiologic studies have shown that higher body mass index (BMI) and unhealthy lifestyle factors including physical inactivity, cigarette smoking and a diet with high red/processed meat and low fiber are individually associated with higher risk of pancreatic cancer[7]. A recent study[8] in the UK Biobank participants showed a suggestive genetic liability for the short-sleep duration with elevated risk of pancreatic cancer whereas in another meta-analysis of 32 studies, Stone et al.[9] reported that both short (5 or 6 hours per night) and long (9 or 10 hours per night) sleep duration were associated with elevated risk of all-cancer-specific mortality, including pancreatic cancer, with a pooled hazard ratio-HR of 1.03 (95% confidence interval-CI: 1.00–1.06) and 1.09 (95% CI: 1.04–1.13), respectively.

Limited evidence has reported an inverse association between healthy lifestyle composite score and the risk of pancreatic cancer among Western populations[10,11]. Yet no such effort has been made in Asian population. To address this gap of knowledge, we assessed the association between a composite score of healthy lifestyle factors and pancreatic cancer risk in a population-based prospective cohort study that comprises more than 60,000 study participants in Singapore and up to 25 years of follow-up.

METHODS

Study Population

Data for the current analysis was derived from the Singapore Chinese Health Study (SCHS), which was described in details previously[12]. Briefly, the Singapore Chinese Health Study is a large on-going population-based prospective cohort study that recruited 63,257 Chinese men and women of two main Chinese dialects, Hokkiens and Cantonese, in Singapore. The study participants resided in the government-built housing estates and were 45–74 years between April 1993 and December 1998. The origin of Hokkiens was those from Fujian province while the Cantonese was those from Guangdong province; both of which are Southern provinces of China. Prior enrollment, all study participants provided written informed consent. The SCHS has been approved by the Institutional Review Boards (IRB) of the participating institutions (i.e., the University of Pittsburgh and the National University of Singapore).

Assessment of Lifestyle Risk Factors

At baseline, trained interviewers used study a structured questionnaire to ask study participants for information on demographics, body weight and height, current physical activity status, lifetime use of tobacco (i.e., cigarettes and water-pipe), occupational exposure, family history of cancer, medical history, the past 12 months dietary habits and menstrual and reproductive history (for women only). BMI was calculated by dividing weight in kg to height in meters squared. For cigarette smoking, we first asked study participants their smoking status (i.e., never, current, and former smokers). Those who were former and current smokers were subsequently asked for further information on: 1) number of years of smoking, 2) age of starting and age of quitting smoking, and 3) number of cigarette per day[13]. For physical activity, the questionnaire listed the following categories: 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: 1) strenuous sports (i.e., swimming laps, tennis, jogging, aerobics, bicycling on hills, or squash); 2) vigorous work (i.e., moving heavy furniture, loading or unloading trucks, shoveling, or equivalent manual labor), and 3) moderate activities (i.e., bowling, brisk walking, chi kung, bicycling on level ground, or tai chi)[14]. Sleep duration was evaluated using the following question: *"On average, during the last year, how many hours in a day did you sleep?"* with a response choice of 6 pre-defined categories: ≤5, 6, 7, 8, 9 and ≥10 hours/day.

Dietary intake was assessed using semi-quantitative food frequency questionnaire (FFQ), which was developed for and validated in the SCHS using a series of 24-hour dietary recall interviews[15] and selected biomarkers studies[16,17]. The dietary questionnaire included 165 food and beverage items that were commonly consumed by Chinese Singaporeans. We asked how frequently the study participants consumed the food or food groups in eight pre-defined categories, from "*never or hardly ever*" to "*two or more times a day*", followed by predetermined portion sizes assisted with the illustration of food photos in an album. For alcohol consumption, each study participant was asked about his/her drinking frequency during the past 12 months of four types of alcoholic beverages, including Chinese hard liquor, beer, Western hard liquor, and wine; with a response choice of eight pre-defined

categories for each beverage: 1) never or hardly, 2) once a month, 3) 2–3 times a month, 4) once a week, 5) 2–3 times a week, 6) 4–6 times a week, 7) once a day, and 8) ≥2 times a day. The portion size for each alcoholic beverage was categorized to the following groups: 1) Western or Chinese hard liquor: ≤1 shot (30 mL), 2, 3, and ≥4 shots; 2) Beer: ≤1 small bottle (375 mL), 2 small bottles or 1 large bottle (750 mL), and ≥3 large bottles; and 3) Wine: ≤1 glass (118 mL), 2, 3 and ≥4 glasses. During the period of April 1994 and March 1997, we used two 24-hour dietary recalls, one on a weekday and the other on a weekend that was approximately two months apart to validate the FFQ among a random sample of 810 participants of the SCHS. The correlation coefficients between the FFQ and 24-hour recall surveys for the majority of calorie-adjusted nutrients ranged from 0.24 to 0.79[15].

Classification of the Composite Score of Healthy Lifestyle Factors

The classification of the composite score of healthy lifestyle factors was in accordance with their independent association with pancreatic cancer[18,19]. The lifestyle factors are BMI (kg/m^2) cigarette smoking, sleep duration, physical activity, and Alternative Healthy Eating Index-2010 score.

Alternative Healthy Eating Index-2010 (AHEI-2010) score.—The AHEI-2010 was chosen because it included sugar-sweeten beverage, which was a pancreatic cancer risk factor in this cohort study[18]. The AHEI-2010 was originally developed to examine the impact of foods and nutrients on chronic disease risk[20] and consist of 11 components[21]. In our analysis, we included all components[21] with the exception of *trans* fat due to the unavailability of this variable. Components included in our AHEI-2010 score were: 1) fruit 2) vegetables, 3) legumes, 4) whole grains, 5) alcohol, 6) long chain (n-3) fat, 7) polyunsaturated fatty acids (PUFAs), 8) red or processed meat, 9) sugar-sweetened beverage and fruit juice, and 10) sodium. We assigned each component a score of 0 to 10, based on the level of consumption and healthy/unhealthy status of that component. The total AHEI-2010 score ranged from 0 to 100 per study participant.

The normal BMI range was defined as 20 to <23 kg/m^2 based on the World Health Organization's recommendations for the Asia-Pacific populations[22,23] as well as a large pooled analysis revealing that Asians with BMI <20 kg/m^2 were at higher risk of death from all causes and cancer[24]. Furthermore, cigarette smokers usually have lower BMI, but have higher risk for pancreatic cancer, as shown in our prior analysis[19]. We, therefore created a combined healthy lifestyle score that included BMI and smoking: 0 for ever smokers (former or current) with BMI <20 or >23 kg/m^2, 1 for ever smokers with BMI 20-<23 kg/m^2, 2 for never smokers with BMI <20 or >23 kg/m^2, and 3 for never smokers with BMI 20-<23 kg/m^2. For AHEI-2010, which included alcohol consumption, we divided all study participants into 3 groups by their AHEI-2010 scores: zero was assigned to the lowest quartile of AHEI-2010 score, one to quartiles 2 and 3, and two to quartile 4. For sleep duration, one was assigned to those with 6–8 hours of sleep per day as normal and healthy lifestyle according to recent findings[9] and zero otherwise. The sum of the five individual scores represented the overall combined lifestyle index score, ranging from 0 to 7, where the higher scores the healthier lifestyle.

Ascertainment of Incident Cases of Pancreatic Cancer

Incident cases of pancreatic cancer and deaths were identified by 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. We used the International Classification of Diseases-Oncology 2nd Edition (ICD-O2), Codes C25 to ascertain pancreatic cancer cases[25]. To date, we found that only 56 study participants of the SCSH were lost to follow-up due to migration out of Singapore or less than 0.1% of the entire cohort. For these reasons, we considered that the ascertainment of incident cancer cases and deaths among the SCHS participants are virtually complete. After excluding 1,936 with a history of cancer diagnosis at baseline, the final sample size of the SCHS for the current analysis was 61,321 participants..

Statistical Analysis

We computed means and standard deviation (SD) for continuous variables and counts and proportions for categorical variables. To compare the distributions of continuous variables between cases and non-cases, we used χ^2 test whereas *t*-test were applied for categorical variables. Analysis of variance (ANOVA) was used for the comparisons across different levels of the healthy lifestyle composite score. Person-years at risk for each participant was computed from the date of interview at enrollment until the date of diagnostic of pancreatic cancer, date of death, or date of migration out of Singapore, or December 31, 2015, whichever happened first.

We used Cox proportional hazard regression method to evaluate the association between the individual and composite scores of healthy lifestyle factors with the risk of developing pancreatic cancer. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) of pancreatic cancer associated with higher individual and composite score of healthy lifestyle factors were derived from the Cox proportional hazard regression models. Schoenfeld residuals test was used to test the proportional hazard assumption and we did not find any violation. An ordinal variable was used for the linear trend test for the composite score of healthy lifestyle factors and risk of pancreatic cancer. Potential confounders that were adjusted for in the multivariable Cox proportional hazards models included age, gender, dialect group (Hokkien or Cantonese), year of enrollment (1993–1995 and 1996–1998), level of education (no formal education, primary school, secondary or higher education), pre-existing of type 2 diabetes (no, yes) and total energy intake (Kcal/d). We also performed stratified analysis by gender, diabetes status (no, yes), BMI (normal/underweight, overweight/obese), and alcohol drinking status (ever, never). Sensitivity analysis was also performed by removing all pancreatic cancer cases and person-years detected within the first 2 years after the baseline interview.

We used SAS version 9.4 (SAS Institute Inc., Cary, NC) for all statistical analyses. All *P* values were two-sided and we used 0.05 as a level for statistical significance.

RESULTS

We identified 316 incident cases of pancreatic cancer among 61,321 participants after a mean (standard deviation-SD) follow-up of 17.7 (5.3) years. All subjects were free of cancer at baseline. The mean (SD) age of cancer cases was 72.5 (8.4) years at the time of cancer diagnosis.

Patients who developed pancreatic cancer during the follow-up were more likely to be male, ever smoking, with lower score of AHEI-2010 or sleeping <6 or ≥9 hours/day compared with non-pancreatic cancer group (all P<0.05) (Table 1). We found no statistically significant difference between the case and non-case groups regarding the dialect group, level of education, BMI, alcohol drinking, weekly physical activity or diabetes history (Table 1).

Compared to those in the lowest composite score (i.e., score 0 to 1), those in the highest score (i.e., score 6 to 7) were younger, more likely to be women, speaking Cantonese dialect and attained higher level of education while were less likely to consume alcohol or having a history of diabetes (all P<0.0001). Overall, only 3.5% of the study participants were daily drinkers (Supplementary Table S1).

Compared with BMI 20-<23 kg/m^2, HRs (95% CIs) of pancreatic cancer for BMI <20, 23-<27.5, and ≥27.5 were 1.34 (0.96–1.88), 1.25 (0.96–1.62) and 0.99 (0.62–1.57), respectively (P_{trend}=0.34). We therefore chose BMI 20-<23 kg/m^2 as healthy range, otherwise as unhealthy. Given that smokers were at increased risk of pancreatic cancer (HR=1.68, 95% CI: 1.34–2.11), but had lower BMI (Mean±SD: 22.8±3.3 vs 23.7±3.2 kg/m^2, P<0.0001), we therefore constructed a combined healthy lifestyle score for smoking and BMI. As shown in Table 2, HR of pancreatic cancer was 0.68 (95% CI: 0.47–1.00) for never smokers with BMI in the range of 20-<23 kg/m^2 compared with ever smokers with BMI of <20 or ≥23 kg/m^2, after adjustment for multiple covariates. Subjects in the highest 25th percentile of the AHEI-2010 index were at significantly lower risk of pancreatic cancer (HR=0.61, 95% CI: 0.44–0.85) in a dose-dependent manner whereas 6–8 hours of sleep a day was associated with a statistically borderline significant 20% lower risk of pancreatic cancer (HR=0.79, 95% CI: 0.60–1.03). Weekly physical activity was associated with statistically non-significant reduction of pancreatic cancer risk (adjusted HR=0.85, 95% CI: 0.66–1.09) (Table 2).

Higher composite scores of healthy lifestyle factors were significantly associated with lower risk of pancreatic cancer in a dose-dependent manner (P_{trend}<0.0001) (Table 3). Compared with the most unhealthy lifestyle score (0–1), HRs (95% CIs) of pancreatic cancer for those with the scores 2, 3, 4, 5, and 6 to 7 (healthiest lifestyle) were 0.60 (0.50–0.91), 0.48 (0.32–0.71), 0.45 (0.31–0.67), 0.41 (0.27–0.62) and 0.38 (0.24–0.62), respectively, after adjustment for age, gender, level of education, year of enrollment, dialect group, history of diabetes, and total energy intake.

In the stratified analysis, the inverse association between the healthy lifestyle composite score and pancreatic cancer risk was robust in both men and women as well as in alcohol drinkers and non-drinkers (Table 4). The inverse composite score-pancreatic cancer risk

association was more apparent in non-diabetic subjects than those with diabetes, most likely that latter had much smaller sample size and fewer number of pancreatic cancer cases. However, none of these differences was statistically significant (all $P_{heterogeneity}$>0.05) (Table 4).

In the sensitivity analysis, after removing all pancreatic cancer cases and person-years occurred within the first 2 years post-enrollment we found that the results remained almost the same as those based on the entire cohort. Accordingly, compared with the composite score of 0–1, the multivariable-adjusted HRs (95% CIs) of pancreatic cancer for the composite scores of 2, 3, 4, 5 and 6 to 7 were 0.57 (0.38–0.88), 0.46 (0.30–0.69), 0.43 (0.29–0.64), 0.38 (0.25–0.59) and 0.38 (0.23–0.61), respectively (P_{trend}< 0.0001) (Supplementary Table S2).

DISCUSSION

In an on-going prospective cohort study of 61,321 study participants with an average follow-up of 17.7 years, we found that increasing composite score of healthy lifestyle factors was strongly associated with decreased risk of pancreatic cancer in a dose-dependent fashion. This inverse relationship was robust across subgroups with different levels of risk factors, including gender, history of type 2 diabetes, and alcohol drinking status.

The current study showed a strong support for lowering the risk of pancreatic cancer for individuals who adhered to a heathier diet, as defined per the Alternative Healthy Eating Index, which includes more vegetables, fruit and nuts/legumes and fish, never smoked cigarettes, and maintained a normal range of BMI, weekly physical activity status, and a sleep duration of 6–8 hours a day. Individuals with the highest composite score (or score 6 to 7) of healthy lifestyle factors had a −62% (95% CI: −38% to −74%) reduction in the risk of pancreatic cancer development compared with those with the lowest composite score (or score 0 to 1).

To the best of our knowledge, the current study is the first that prospectively investigated the effect of an aggregated lifestyle factors on the risk of pancreatic cancer in an Asian population. Previously, we reported a consistently inverse association between a similarly constructed composite score of healthy lifestyle factors and risk of colon, gastric cancers, and hepatocellular carcinoma[,26–28]. Accordingly, Odegaard et al.[26] found that a combined lifestyle factors, including BMI, cigarette smoking, alcohol drinking, and dietary pattern score (i.e., vegetable-fruit-soy pattern versus meat-dim sum pattern) was significantly associated with lower risk of colon cancer, but was not associated with the risk of rectal cancer. A similar inverse association between a similarly derived composite score of healthy lifestyle factors and the risk of gastric cancer was also observed in our study population[27]. Recently, we also reported an inverse association for a composite score of healthy lifestyle factors including BMI, cigarette smoking, alcohol consumption, alternative Mediterranean diet and sleep duration with the risk of hepatocellular carcinoma in the same study population, the Singapore Chinese Health Study[28]. There results further support a robust effect of aggregated healthy lifestyle factors on reducing the risk of multiple cancers. Thus,

it is important to emphasize the protective effect of these lifestyle factors on many different types of cancer as an effective means for primary prevention of cancer.

Findings from our study is in line with previous studies among Western populations. The National Institutes of Health-AARP Diet and Health Study involving 450,416 adult Americans with 1,057 incident cases of pancreatic cancer cases found that the highest score of healthy lifestyle factors consisting of alcohol use, BMI, cigarette smoking, dietary habits and physical activity was associated with a statistically significant −58% (95% CI: −34% to −78%) reduction in risk of pancreatic cancer[10]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study involving 400,577 participants with 1,113 incident cases of pancreatic cancer from 10 European countries demonstrated that a higher composite score of healthy lifestyle factors including alcohol use, cigarette smoking, BMI, dietary habits, measurement of overall and central adiposity and physical activity status was significantly associated with reduced risk of pancreatic cancer; each standard deviation increment of the score was associated with a −16% (95% CI: −11% to −21%) reduction in the risk of pancreatic cancer[11]. These results suggest a robust protective effect of the composite score of healthy lifestyle factors against the development of pancreatic cancer across different populations with distinct cultural and social environments, different diet as well as different genetic background.

In the analysis of individual factors, the AHEI-2010 index was significantly associated with diminished risk of pancreatic cancer, suggesting that diet may play a more prominent role in the development of pancreatic cancer. This finding is consistent with the result of a pooled analysis of two case-control studies in Italy, including 362 and 326 pancreatic cancer cases and 1,552 and 652 hospital-controls, respectively, in which the risk of pancreatic cancer was approximately −50% (95% CI: −33% to −65%) lower for a score ≥6 than <3 of the Mediterranean diet[29]. We also observed a non-significant inverse association between weekly physical activity and the risk of pancreatic cancer. A recent meta-analysis of 30 studies involving 10,501 pancreatic cancer cases, Behrens et al.[30] reported that the case-control studies produced a statistically significant lower risk of pancreatic cancer for regular physical activity (reduced by −7%, 95% CI: −2% to −12%) whereas the cohort studies did not show that physical activity was associated with a statistically non-significant −5% reduction of pancreatic cancer risk. Our findings are in line with the result of the cohort studies within this meta-analysis. Furthermore, our findings for the associations for BMI, cigarette smoking and sleep duration with the risk of pancreatic cancer were also in line with prior surveys in various populations[7,8]. It should be noted that even though several individual lifestyle factors did not reach statistical significance level, their aggregated composite score showed a much stronger effect on reducing the risk of pancreatic cancer in our study. Collectively, these findings suggest that the composite lifestyle score more precisely characterized a risk profile with less likelihood in misclassification of study subjects for the assessment of pancreatic cancer risk. The findings of the current study encourage the simultaneous change of multiple lifestyle factors as oppose to a single factor for primary prevention of pancreatic cancer.

Our study had a number of strengths including the prospective study design that enabled the researchers to assess all the lifestyle factors at baseline before the occurrence of

pancreatic cancer with long-term follow-up minimized potential impact of the underlying disease progression on the modifiable lifestyle factors. The comprehensive assessment of lifestyle factors in a population with homogeneous cultural and social environment, similar dietary habits, and identical genetic background minimized potential founding effect on the observed lifestyle composite score-pancreatic cancer risk association. A relatively large sample size with prolonged follow-up produced robust estimates for the composite lifestyle score with the pancreatic cancer risk. Also, potential bias due to loss to follow-up was minimized owing to the fact that virtual completeness in following-up of SCHS participants was done.

One possible limitation in our study was the single point of time for the assessment of lifestyle factors at baseline, which might change over time during the follow-up period, resulting in potential misclassification of their true level of exposure to various lifestyle factors included in the analysis. Although it is typical in any long-term prospective studies, such a misclassification is non-differential to those who developed pancreatic cancer and those without pancreatic cancer. Non-differential misclassification usually results in the under-estimation of a hazard ratio toward null. Thus, the significant association between composite score of healthy lifestyle factors and risk of pancreatic cancer observed in the present study may be underestimated, but valid.

In summary, the current study underlines a strong, dose-dependent association between the composite score of healthy lifestyle factors and lower risk of pancreatic cancer development in an Asian population. The overall robust results support that the simultaneous change of multiple lifestyle factors rather than single factor would have significantly greater impact on reducing incidence of pancreatic cancer. Given a robust effect on lowering the risk of many different types of cancer in populations from distinct cultural and social environment and genetic backgrounds, it should be more emphasized that a comprehensive modification of lifestyle factors is a universal cost-effective means for primary prevention of many types of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study. We also thank the Singapore Cancer Registry for the identification of incident cancer cases among participants of the Singapore Chinese Health Study.

Funding:

The Singapore Chinese Health Study was supported by the National Institutes of Health (NIH) of the United States (grants # R01 CA144034 and UM1 CA182876; PI: J-M Yuan). P Paragomi was supported by the NIH T32CA186873 training grant in cancer epidemiology and prevention (PI: J-M Yuan). HN Luu is partially supported by the University of Pittsburgh Medical Center Hillman Cancer Center start-up grant.

Data Availability

De-identified data relevant to the report can be shared and is available upon request through the University of Pittsburgh for researchers who meet the criteria for access to confidential data. Data is accessible to the corresponding author and also is available from the University of Pittsburgh Institutional Data Access/Ethics Committee with the following contact information: 3500 Fifth Avenue, Hieber Building Main Office, Suite 106 Pittsburgh, PA 15213. Main Phone: (412) 383-1480. Main Fax: (412) 383-1508. Email: askirb@pitt.edu.

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PREVENTION RELEVANCE

In this large prospective Asian study, we calculated a composite score of healthy lifestyle factors, including body mass index, cigarette smoking, the Alternative Healthy Eating Index-2010 (AHEI-2010), sleep duration, and physical activity and found this composite score was associated with a significant reduction in pancreatic cancer risk, by as much as 62%. This finding suggests that public health programs emphasizing comprehensive lifestyle modification strategy would be more effective for prevention of pancreatic cancer than the change of a single lifestyle factor.

Table 1.

Distributions of Baseline Characteristics among Study Participants, The Singapore Chinese Healthy Study, 1993–2015

Characteristics	Non-cases (n=61,005)	Cases (n=316)	*P-value*
Mean age (±SD)	56.4 (8.0)	60.3 (7.6)	**<0.001**
Gender (%)			
Male	27,129 (44.5)	164 (51.9)	**0.008**
Female	33,876 (55.5)	152 (48.1)	
Dialect (%)			
Cantonese	28,193 (46.2)	132 (41.8)	0.11
Hokkien	32,812 (53.8)	184 (58.2)	
Highest level of education (%)			
No formal education	16,566 (27.2)	95 (30.1)	0.36
Primary school	27,083 (44.4)	141(44.6)	
Secondary school or higher	17,356 (28,4)	80 (25.3)	
Mean body mass index-BMI (±SD), Kg/m^2	23.13±3.26	23.03±3.22	0.59
Smoking status (%)			
Never smoker	42,388 (69.5)	195 (61.7)	**0.003**
Ever smoker	18,617 (30.5)	121 (38.3)	
AHEI-2010[a]			
Lowest 25th percentile	15,272 (25.0)	94 (29.7)	**0.01**
Middle 50th percentile	30,506 (50.0)	164 (51.9)	
Highest 25th percentile	15,227 (25.0)	58 (18.3)	
Alcohol drinking			
Never drinkers	49,395 (81.0)	255 (80.7)	0.30
Ever drinkers			
Monthly drinkers	4,471 (7.3)	23 (7.3)	
Weekly drinkers	4,990 (8.2)	28 (8.9)	
Daily drinkers	2,149 (3.5)	10 (3.2)	
Sleep (%), hours/day			
<6 or ≥9	10,063 (16.5)	69 (21.8)	**0.01**
6–8	50,942 (83.5)	247 (78.2)	
Weekly physical activity			
No	40,863 (67.0)	220 (69.6)	0.32
Yes	20,142 (33.0)	96 (30.4)	
Diabetes (%)			
No	55,570 (91.1)	282 (89.2)	0.25
Yes	5,435 (8.9)	34 (10.8)	
Total energy intake (±SD), Kcal/d	1,556.6±566.2	1564.7±574.5	0.80

[a]AHEI-2010: Alternative Healthy Eating Index without alcohol drinking component.

Table 2.

Association Between Individual Lifestyle Factors and Risk of Pancreatic Cancer in the Singapore Chinese Health Study, 1993–2015

Lifestyle Factor (index score)	%	Rate*	HR[a] (95% CI)	HR[b] (95% CI)
Smoking status and BMI (Kg/m^2)				
Ever smoking and BMI <20.0 or >23.0 (0)	19.6	38.9	1.00	1.00
Ever smoking and BMI=20-<23 (1)	11.0	32.8	0.89 (0,61–1.30)	0.90 (0.61–1.30)
Never smoking and BMI <20.0 or >23.0 (2)	47.7	30.2	0.86 (0.63–1.17)	0.91 (0.67–1.24)
Never smoking and BMI=20.0–23.0 (3)	21.7	22.2	**0.64 (0.44–0.93)**	**0.68 (0.47–1.00)**
AHEI-2010±				
Lowest 25th percentile (0)	25.1	34.9	1.00	1.00
Middle 50th percentile (1)	50.0	29.9	0.84 (0.65–1.09)	0.86 (0.67–1.11)
Highest 25th percentile (2)	24.9	20.8	**0.60 (0.43–0.83)**	**0.61 (0.44–0.85)**
Sleep (%), hours/day				
<6 or ≥9 (0)	16.5	37.6	1.00	1.00
6–8 (1)	83.5	27.5	**0.75 (0.58–0.98)**	0.79 (0.60–1.03)
Weekly physical activity				
No (0)	67.0	31.3	1.00	1.00
Yes (1)	33.0	27.4	0.82 (0.64–1.05)	0.85 (0.66–1.09)

*Rate: age- and sex-standardized incident rate of pancreatic cancer per 100,000 person-years.

[a]Model adjusted for age and gender

[b]Model adjusted for age, sex, dialect, year of enrollment, education level, diabetes history, and total energy intake, as well as all variables in the table, when applicable.

±AHEI-2010: Alternative Healthy Eating Index without alcohol drinking component.

Table 3.

Association Between Composite Score of Healthy Lifestyle Factors and Risk of Pancreatic Cancer in the Singapore Chinese Health Study, 1993–2015

Composite Score	Persons	Person-year	Cases	HR[a] (95% CI)	HR (95% CI)
Total subjects[b]					
0 to 1	3,953	59,610	42	1.00	1.00
2	7,475	119,596	48	**0.60 (0.40–0.91)**	**0.60 (0.40–0.91)**
3	11,432	195,323	59	**0.48 (0.32–0.72)**	**0.48 (0.32–0.71)**
4	16,473	298,298	77	**0.46 (0.31–0.67)**	**0.45 (0.31–0.67)**
5	13,923	258,467	58	**0.41 (0.27–0.62)**	**0.41 (0.27–0.62)**
6 to 7	8,065	152,945	32	**0.39 (0.24–0.63)**	**0.38 (0.24–0.62)**
P_{trend}				**<0.0001**	**<0.0001**

[a]Model adjusted for age and gender

[b]Model adjusted for year of enrollment, age, gender, dialect group, level of education, history of type 2 diabetes, and total energy intake.

Table 4.

Association Between Composite Score of Healthy Lifestyle Factors and Risk of Pancreatic Cancer among Participants Stratified by Selected Characteristics in the Singapore Chinese Health Study, 1993–2015

Composite Score	Person-years	Number of cases	HR (95% CI)
By Gender [a]			
Men			
0 to 1	47,349	35	1.00
2	88,612	34	**0.54 (0.34–0.87)**
3	100,299	34	**0.47 (0.29–0.75)**
4	94,341	26	**0.39 (0.23–0.66)**
5	75,888	19	**0.37 (0.21–0.65)**
6 to 7	53,095	16	**0.42 (0.23–0.77)**
P_{trend}			**0.0008**
Women			
0 to 1	12,261	7	1.00
2	30,984	14	0.86 (0.35–2.14)
3	95,025	25	0.57 (0.25–1.32)
4	203,957	51	0.58 (0.26–1.29)
5	182,579	39	0.51 (0.23–1.15)
6 to 7	99,850	16	0.41 (0.17–1.01)
P_{trend}			0.02
$P_{heterogeneity}$			0.07
By Diabetes History [b]			
No Diabetes History			
0 to 1	55,144	39	1.00
2	110,300	45	**0.61 (0.40–0.94)**
3	181,287	53	**0.46 (0.30–0.70)**
4	276,759	69	**0.44 (0.29–0.66)**
5	239,739	48	**0.37 (0.23–0.57)**
6 to 7	142,807	28	**0.36 (0.22–0.60)**
P_{trend}			**<0.0001**
Diabetes History			
0 to 1	4,466	3	1.00
2	9,296	3	0.49 (0.10–2.41)
3	14,037	6	0.68 (0.17–2.75)
4	21,539	8	0.63 (0.16–2.48)
5	18,728	10	0.94 (0.24–3.62)
6 to 7	10,138	4	0.68 (0.15–3.22)
P_{trend}			0.77
$P_{hererogeneity}$			0.10

Composite Score	Person-years	Number of cases	HR (95% CI)
By Alcohol Drinking Status [c]			
Non-drinker			
0 to 1	40,921	28	1.00
2	83,447	36	0.67 (0.41–1.10)
3	151,763	49	**0.56 (0.35–0.88)**
4	251,496	66	**0.52 (0.33–0.82)**
5	221,261	47	**0.43 (0.26–0.70)**
6 to 7	128,983	29	**0.45 (0.26–0.78)**
P_{trend}			**0.001**
Ever-drinkers			
0 to 1	18,689	14	1.00
2	36,149	12	0.48 (0.22–1.03)
3	43,560	10	**0.31 (0.14–0.70)**
4	46,802	11	**0.32 (0.14–0.72)**
5	37,206	11	**0.41 (0.18–0.95)**
6 to 7	23,962	3	**0.18 (0.05–0.65)**
P_{trend}			**0.008**
$P_{hererogeneity}$			0.61

[a] Model adjusted for age, dialect group, level of education, diabetes history, year of enrollment, and total energy intake.

[b] Adjusted for age, gender, dialect group, level of education, year of enrollment, and total energy intake.

[c] Adjusted for age, gender, dialect group, level of education, year of enrollment, diabetes history, and total energy intake.