ORIGINAL INVESTIGATION

A Combined Healthy Lifestyle Score and Risk of Pancreatic Cancer in a Large Cohort Study

Li Jiao, MD; Panagiota N. Mitrou, PhD; Jill Reedy, PhD; Barry I. Graubard, PhD; Albert R. Hollenbeck, PhD; Arthur Schatzkin, MD; Rachael Stolzenberg-Solomon, PhD

Background: Smoking, alcohol use, diet, body mass index (calculated as weight in kilograms divided by height in meters squared), and physical activity have been studied independently in relation to pancreatic cancer. We generated a healthy lifestyle score to investigate their joint effect on risk of pancreatic cancer.

Methods: In the prospective National Institutes of Health–AARP Diet and Health Study, a total of 450 416 participants aged 50 to 71 years completed the baseline food frequency questionnaire (1995-1996) eliciting diet and lifestyle information and were followed up through December 31, 2003. We identified 1057 eligible incident pancreatic cancer cases. Participants were scored on 5 modifiable lifestyle factors as unhealthy (0 points) or healthy (1 point) on the basis of current epidemiologic evidence. Participants received 1 point for each respective lifestyle factor: nonsmoking, limited alcohol use, adherence to the Mediterranean dietary pattern, body mass index (≥18 and <25), or regular physical activity. A combined score (0-5 points) was calculated by summing the scores of the 5 factors. Cox proportional hazards regression models were used to estimate relative risk (95% confidence interval) for pancreatic cancer.

Results: Compared with the lowest combined score (0 points), the highest score (5 points) was associated with a 58% reduction in risk of developing pancreatic cancer in all participants (relative risk, 0.42; 95% confidence interval, 0.26-0.66; P_{trend} <.001). Scores of less than 5 points were associated with 27% of pancreatic cancer cases in our population.

Conclusion: Findings from this large study suggest that having a high score, as opposed to a low score, on an index combining 5 modifiable lifestyle factors substantially reduces the risk of developing pancreatic cancer.

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Author Affiliations: Nutritional Epidemiology Branch (Drs Jiao, Schatzkin, and Stolzenberg-Solomon), Biostatistics Branch (Dr Graubard), Division of Cancer Epidemiology and Genetics, and Applied Research Program, Division of Cancer Control and Population Sciences (Dr Reedy), National Cancer Institute, National Institutes of Health, Bethesda, Maryland; World Cancer Research Fund International, London, and Department of Public Health and Primary Care, University of Cambridge, Cambridge (Dr Mitrou), England; and AARP, Washington, DC (Dr Hollenbeck).

According to Surveillance Epidemiology and End Results (SEER) 2000-2003 statistics, the incidence of pancreatic cancer in the United States ranks 10th in men and 9th in women; however, mortality ranks 4th in both men and women. Because pancreatic cancer is difficult to detect at a potentially resectable stage and remains therapeutically intractable, prevention is the primary hope for reducing the burden of this disease. Cigarette smoking and obesity have been consistently associated with increased risk of pancreatic cancer. Findings on dietary intake and physical activity have been inconsistent.[1,2]

Typically, in epidemiologic studies of individual health behaviors or exposures, other factors are treated as covariates in statistical models. Several studies have identified patterns of health behavior in adults in the United States and suggested that a multidimensional lifestyle approach would be informative in exploring the cause of disease.[3,4] Thus, we scored study participants according to their conformity to a healthy lifestyle using 5 potentially modifiable factors including cigarette smoking, alcohol use, dietary quality, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and physical activity. We examined how the combined lifestyle score was associated with risk of pancreatic cancer in the National Institutes of Health–AARP (NIH-AARP) Diet and Health Study. We hypothesized that a higher healthy lifestyle score would be associated with a lower risk for pancreatic cancer.

METHODS

STUDY POPULATION

The NIH-AARP Diet and Health Study is a large prospective cohort study of AARP members established in 1995-1996. Details of the study design and questionnaire have been described previously.[5] In brief, a self-administered baseline Food Frequency Questionnaire (FFQ) was mailed to 3.5 million AARP members aged 50 to 71 years residing in 6 states (California,

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Table 1. Five Factors of Combined Healthy Lifestyle Score in the National Institutes of Health–AARP Diet and Health Study

Healthy Lifestyle Factor	Score	Interpretation of Score	Percentage
Smoking	0	Smoking: current smokers or quit for <10 y	
	1	Nonsmoking: never smoked or quit for ≥10 y	74.6
Alcohol use[a]	0	Heavy alcohol use; not adherent to alcohol use recommendation in the United States (ie, daily consumption of >2 drinks for men or >1 drink for women)	
	1	Limited alcohol use; adherent to alcohol use recommendation in the US (ie, daily consumption ≤2 drinks for men or ≤1 drink for women)	84.5
Dietary quality[b]	0	Unhealthy diet quality: 0-4 points for alternate Mediterranean diet score, excluding alcohol	
	1	Healthy diet quality: 5-8 points for alternate Mediterranean diet score, excluding alcohol	38.8
BMI[c]	0	Overweight or obese: BMI ≥25	
	1	Normal weight: BMI 18-24.99	36.9
Physical activity[d]	0	Sedentary: never, rarely, or <3-4 times per wk	
	1	Regular: ≥3-4 times per wk	47.5

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Recommendation on daily alcohol consumption in the United States.[10]
[b] Adherence to the no-alcohol alternate Mediterranean diet pattern.[12-15]
[c] According to World Health Organization standard.[11]
[d] At least 20 minutes that causes increased breathing or heart rate or produces perspiration.

Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). The questionnaire was returned by 617 119 members, and 567 169 completed the questionnaire satisfactorily.[5] The study was approved by the National Cancer Institute Special Studies Institutional Review Board. Informed consent was obtained from all participants by virtue of completing the questionnaire.

We excluded 179 participants with duplicate responses, 321 who moved from the study areas before returning the baseline questionnaire, 261 who died before study enrollment, and 6 who withdrew. In the remaining 566 402 participants, we further excluded 15 760 whose questionnaires were completed by proxy respondents, 8583 who had prevalent cancer at baseline as identified by cancer registry matching, 4792 with extreme energy intake (ie, more than 2 interquartile ranges above the 75th or below the 25th percentile of Box-Cox log-transformed intake), 20 169 with missing information on smoking status, 6417 with less than 1 year of follow-up, 11 770 with missing weight and height data, and 3609 with BMI less than 18. We further excluded 44 886 participants with self-reported diabetes mellitus because they might modify their diets and health behaviors and because diabetes is associated with greater risk of pancreatic cancer. Our final analytic cohort consisted of 450 416 members including 263 398 men and 187 018 women.

COHORT FOLLOW-UP AND CASE ASCERTAINMENT

Person-year of follow-up was calculated from 1 year after the response to the FFQ to the date of pancreatic cancer diagnosis, death, moving out of the study areas, or December 31, 2003. Participants who moved to Texas, Nevada, and Arizona were followed up. Vital status was ascertained by linkage to the Social Security Administration Death Master File. Pancreatic cancer cases were identified by linkage between the NIH-AARP cohort membership to 11 state cancer registries and the National Death Index. We included adenocarcinoma of the exocrine pancreas (*ICD–O-3* [*International Classification of Diseases for Oncology*, Third Edition] codes C25.0-C25.3 and C25.7-C25.9) and excluded histology codes 8150-8155, 8240, 8246, and 8502. In addition to 922 cases identified from cancer registries, we included 135 cases identified from the National Death Index. We estimated a minimum sensitivity of 89.2% for case ascertainment from the cancer registries.[6]

EXPOSURE ASSESSMENT

A self-administered FFQ was used to elicit information on smoking, dietary intake, anthropometry, and physical activity, as well as demographic factors and medical history.[5] The FFQ was a grid-based version of the National Cancer Institute Diet History Questionnaire that assessed the frequency of consumption and usual portion size of 124 food items and alcohol use during the last year.[7] The Diet History Questionnaire was validated using two 24-hour dietary recalls that were administered to 2053 randomly chosen NIH-AARP participants.[5] MyPyramid equivalents of all food items were generated by linking the FFQ data with the MyPyramid Equivalents Database (version 1.0; US Department of Agriculture, Washington, DC), which disaggregates all food mixtures into the appropriate food groups using standardized servings.[8,9]

Participants reported whether they smoked 100 cigarettes or more during their entire lifetime to define ever smokers and never smokers. Ever smokers were asked to report whether they currently smoked or whether they had stopped smoking within the last year or 1 to 4, 5 to 9, or 10 years or more previously. Body mass index was calculated from self-reported weight and height information. Participants reported how often (never, rarely, 1-3 times per month, 1-2 times per week, 3-4 times per week, or ≥5 times per week) they had engaged in physical activity at home or at work that lasted at least 20 minutes and caused increased breathing or heart rate or produced perspiration.

SCORES FOR SMOKING, ALCOHOL USE, BMI, AND PHYSICAL ACTIVITY

We generated a healthy lifestyle score based on a priori knowledge of risk factors for pancreatic cancer and current public health recommendations.[1,10,11] We used a binary score for each factor to produce an adequate sample size for the pattern analysis. The participants received 1 point for each factor if they were nonsmokers (never smoked or quit smoking ≥10 years ago), had limited daily alcohol use (≤1 drink for women or ≤2 drinks for men),[10] were of normal weight (BMI ≥18 and <25),[11] or performed regular physical activity; otherwise they received 0 points for each corresponding factor (**Table 1**). We combined ever smokers who quit smoking 10 years or more previously with never smokers into a nonsmoking group because their risk of developing pancreatic cancer was similar to that in never smokers as observed

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in the present study and in previous studies.[12] We generated a score for alcohol use based on the Dietary Guidelines for Americans 2005.[10] We considered maintaining a BMI of 18 or more and less than 25 as a healthy behavior.[11] Regular physical activity was defined as activity performed at least 3 or 4 times per week for at least 20 minutes and that caused increased breathing or heart rate or produced perspiration.

SCORE FOR DIETARY QUALITY

Dietary quality was evaluated on the basis of an alternate Mediterranean diet score (aMDS). The aMDS was derived from the traditional MDS and evaluated adherence to the Mediterranean dietary pattern in the US population.[13-15] We further modified the aMDS by removing the alcohol component[16]; we evaluated alcohol use as a separate factor. This modified score (no-alcohol aMDS) included 8 components (vegetables not including white potato, legumes, fruits, nuts, whole grains, red and processed meat, fish, and the ratio of monounsaturated to saturated fat) and assigned values from 0 to 8 points (minimum to maximum adherence; median, 4 points). Study participants who scored 5 to 8 points were categorized as having a healthy dietary quality and received 1 point for the dietary intake component on the combined healthy lifestyle score; those who scored 0 to 4 points received 0 points (Table 1).

SCORE FOR COMBINED HEALTHY LIFESTYLE

We assigned the healthy lifestyle score to each participant by summing the binary score for each of the 5 lifestyle factors described including smoking, alcohol use, dietary quality, BMI, and physical activity. The healthy lifestyle score ranges from 0 (least healthy) to 5 points (healthiest). Alternatively, we generated a weighted lifestyle score by using the percentage of the β coefficient of each factor to the sum of the β coefficients of each factor in the Cox proportional hazards regression model with all 5 factors included. This score ranges from 0 to 100 points and considers magnitudes of the adjusted relative risk (RR) for each factor in each lifestyle pattern as a combination of 5 factors. We categorized the weighted lifestyle score to 6 levels, where the distribution of the categories is similar with that of the 6 categories of the combined healthy lifestyle score.

STATISTICAL ANALYSES

Cox proportional hazards regression models using age as the underlying time metric were used to calculate (sex-specific or sex-combined) RRs and 95% confidence intervals (CIs) for pancreatic cancer. Age (continuous), sex (in the sex-combined model), race/ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, and other), educational achievement (less than high school or unknown, high school, some college, and college graduate), marital status (married or living as married vs other), and total energy intake (log-transformed) were the variables included in the multivariate models. First, we evaluated the association of each binary lifestyle factor with pancreatic cancer risk, adjusting for the other factors including smoking, alcohol use, dietary quality, BMI, and physical activity. Participants with 0 points were the reference group. Second, we examined the agreement of the combined score and the weighted score in categorizing participants according to their health lifestyles. We evaluated the associations of 2 scores with pancreatic cancer risk separately. We calculated the *P* value for the linear trend using the Wald test, treating the lifestyle score as a continuous variable. Third, we investigated how risk differs by adding each factor to the combined score. We presented the risk estimate for the most common lifestyle pattern in each score category. In this case, the factors excluded from the pattern were adjusted in the models. Fourth, we evaluated whether the associations between the score and the risk varied significantly by age at enrollment (<62 vs ≥62 years) and sex by generating a cross-product term in the multivariate model and using the likelihood ratio test. Fifth, we performed a lag analysis excluding those who died or were censored within the second year of follow-up to reduce the influence of subclinical disease on the lifestyle score. We performed sensitivity analyses by excluding participants with self-reported history of cancer or including only individuals with pancreatic cancer identified from cancer registries.

We calculated the age- and energy-adjusted population-attributable risk (PAR) to estimate the percentage of cases that would have been eliminated had all participants adopted the healthiest lifestyle (5 points) or a healthier lifestyle (4-5 points), assuming a causal relationship between the score and risk of pancreatic cancer. The PAR of pancreatic cancer according to each of 5 factors was also calculated.

Statistical analyses were carried out using commercially available software (SAS version 9.0; SAS Institute, Inc, Cary, North Carolina). All *P* values were based on 2-sided tests, and $P < .05$ was considered statistically significant.

RESULTS

During a mean (range) of 7.2 (1.0-8.2) years of follow-up, 1057 individuals with pancreatic cancer (675 men and 382 women) were identified. We found no deviations from the proportional hazards assumption for our main exposures and covariates using the Grambsch-Therneau test.

In the analyses using the combined lifestyle score and the weighted lifestyle score, we found that the 2 scoring algorithms had high agreement (88% overall) in categorizing participants into the respective score category. The distribution of participants by the combined lifestyle score (0-5 points) was 1.5%, 10.7%, 27.8%, 31.3%, 21.1%, and 7.6%, respectively, and the corresponding distribution for the weighted lifestyle score was 1.5%, 9.3%, 36.3%, 26.4%, 19.0%, and 7.6%. Because the risk estimates based on both algorithms were essentially the same (data not shown), we present the results based on the combined healthy lifestyle score only.

In our study population, 74.6% of participants were nonsmokers, 84.5% had limited alcohol use, 38.8% had healthy dietary quality, 36.9% had normal weight, and 47.5% engaged in regular physical activity (Table 1). **Table 2** gives the baseline characteristics of the study participants according to the combined healthy lifestyle score in men and women. Women had a statistically significant higher mean score compared with men (2.86 vs 2.81 points; $P < .001$). Participants who received a higher score were older, less likely to be African American, and had achieved a higher educational level. A higher combined lifestyle score was related to a lower age-adjusted incident rate, less total energy intake, less total fat and red meat intake, more fruit and vegetable intake, and more folate intake. Family history of any cancer was unrelated to the score.

Table 3 gives the main effect of each factor on pancreatic cancer risk. In all participants, after adjusting for the other risk factors, nonsmoking and normal BMI were associated with statistically significant reduced risk of pancreatic cancer, whereas healthy dietary quality, limited alcohol use, and regular physical activity were related to a nonsignificant re-

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Table 2. Mean and Percentage of Baseline Characteristics of Participants According to the Combined Healthy Lifestyle Score[a]

	Healthy Lifestyle Score												
	Men						Women						
Characteristics	All	0	1	2	3	4	All	0	1	2	3	4	5
No. of participants	**263 398**	4767	29 157	72 228	82 591	55 640	**187 018**	2195	18 776	52 801	58 525	39 580	15 141
Age-adjusted incidence rate	41.8	294.3	59.8	53.1	40.8	25.9	32.8	68.8	43.3	37.8	33.2	29.0	19.1
Age at enrollment, mean, y	62.2	61.0	61.2	61.7	62.3	62.8	61.8	60.9	61.0	61.6	62.0	62.2	62.3
Race/ethnicity, %													
White	93.4	95.0	94.4	93.7	93.1	92.9	90.9	93.0	91.8	91.1	90.5	90.4	91.9
African American	2.3	2.7	2.5	2.5	2.4	2.3	4.7	5.4	5.2	5.1	4.9	4.2	2.5
Never smoker, %	30.8	0	7.1	25.8	34.4	41.2	45.2	0	7.20	39.3	51.4	57.5	62.3
Educational achievement level, college or postcollege, %	46.1	35.2	34.6	39.9	46.3	54.4	31.0	26.7	22.9	25.8	30.8	37.2	44.3
Married, %	85.4	78.7	81.6	85.2	86.3	86.9	44.9	37.6	39.1	42.4	45.7	47.7	50.8
Family history of any cancer, %	48.4	47.8	48.0	48.1	48.6	48.7	52.8	51.0	52.2	53.0	52.9	52.7	52.5
Dietary intake per day													
Alcohol, g	17.4	94.5	44.2	19.2	11.0	7.8	6.2	41.8	16.1	6.4	4.4	3.3	2.4
Total energy intake, kcal	2020	2690	2307	2073	1967	1885	1567	1797	1664	1607	1551	1511	1481
Total fruits, cup/1000 kcal	1.1	0.5	0.7	0.9	1.1	1.4	1.3	0.7	0.9	1.1	1.4	1.6	1.8
Total vegetables, cup/1000 kcal	1.0	0.7	0.8	0.9	1.1	1.2	1.3	1.0	1.1	1.1	1.3	1.4	1.6
Total fat, g/1000 kcal	33.5	30.1	34.3	35.4	34.0	31.7	33.1	33.0	35.6	35.3	33.2	30.8	28.5
Saturated fat, g/1000 kcal	10.5	9.9	11.3	11.4	10.6	9.4	10.3	10.6	11.5	11.3	10.2	9.2	8.1
Red meat, g/1000 kcal	37.2	42.5	45.3	43.7	37.4	29.4	29.1	37.7	37.5	34.5	28.6	22.6	17.2
Total folate, µg/1000 kcal	288	197	226	258	294	333	364	275	299	328	371	408	440
Fiber, g/1000 kcal	10.3	6.42	7.63	8.87	10.4	12.3	11.5	7.74	8.87	10.0	11.6	13.3	15.2

[a] Healthy lifestyle score (range, 0-5 points) was calculated by summing the binary exposure factors (0, 1) including smoking, alcohol use, dietary quality, body mass index, and physical activity. Participants received 1 point if they had any of the following behaviors: never smokers or quit smoking 10 years or longer, limited alcohol use, adherent to an alternate Mediterranean dietary pattern (excluding alcohol), body mass index (calculated as weight in kilograms divided by height in meters squared) ≥18 and <25, or regular physical activity.

Table 3. Relative Risk of Pancreatic Cancer in Relation to Single Lifestyle Factors in Men and Women

Healthy Lifestyle Factor	Score	Men			Women			Men and Women			
		Case	RR[a] (95% CI)	RR[b] (95% CI)	Case	RR[a] (95% CI)	RR[b] (95% CI)	Case	RR[a] (95% CI)	RR[b] (95% CI)	PAR,[c] %
Smoking	0	216	1 [Reference]	1 [Reference]	145	1 [Reference]	1 [Reference]	361	1 [Reference]	1 [Reference]	14
	1	459	0.57 (0.48-0.67)	0.60 (0.51-0.71)	237	0.56 (0.46-0.69)	0.56 (0.45-0.69)	696	0.57 (0.50-0.65)	0.59 (0.51-0.67)	
Alcohol use	0	147	1 [Reference]	1 [Reference]	51	1 [Reference]	1 [Reference]	198	1 [Reference]	1 [Reference]	3
	1	528	0.69 (0.57-0.83)	0.78 (0.64-0.95)	331	1.02 (0.76-1.38)	1.11 (0.82-1.51)	859	0.78 (0.67-0.91)	0.86 (0.73-1.01)	
Dietary quality	0	437	1 [Reference]	1 [Reference]	239	1 [Reference]	1 [Reference]	676	1 [Reference]	1 [Reference]	5
	1	238	0.78 (0.67-0.93)	0.89 (0.76-1.05)	143	0.92 (0.75-1.14)	0.98 (0.79-1.21)	381	0.84 (0.74-0.95)	0.92 (0.81-1.05)	
BMI	0	488	1 [Reference]	1 [Reference]	210	1 [Reference]	1 [Reference]	698	1 [Reference]	1 [Reference]	8
	1	187	0.84 (0.70-0.99)	0.84 (0.71-0.99)	172	0.96 (0.78-1.18)	0.95 (0.77-1.17)	359	0.88 (0.78-1.00)	0.88 (0.77-0.99)	
Physical activity	0	342	1 [Reference]	1 [Reference]	224	1 [Reference]	1 [Reference]	566	1 [Reference]	1 [Reference]	3
	1	333	0.87 (0.74-1.01)	0.93 (0.80-1.08)	158	0.89 (0.73-1.10)	0.94 (0.77-1.16)	491	0.88 (0.78-0.99)	0.94 (0.83-1.06)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; PAR, population attributable risk; RR, relative risk.

[a] Adjusted for age, race/ethnicity, educational achievement level, and marital status. For men and women combined model, adjusted also for sex.

[b] Adjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), and other lifestyle factors including smoking status, alcohol use, dietary quality, BMI, and physical activity (binary variable). For men and women combined model, adjusted also for sex.

[c] Population attributable risk of pancreatic cancer according to each single factor in all participants, adjusted for age, total energy intake (log-transformed), and other risk factors including smoking status, alcohol use, dietary quality, BMI, and physical activity (binary variable).

duced risk. We observed a 27% reduced risk with a high no-alcohol aMDS (7-8 points) compared with a low no-alcohol aMDS (0-1 points) (P=.06). The PAR for pancreatic cancer explained by smoking (ie, current smoking and smoking cessation for <10 years) was 14%, which was the largest PAR among the 5 single lifestyle factors.

Table 4 gives the combined healthy lifestyle score in relation to pancreatic cancer risk. Compared with the least healthy score (0 points), the combination of the 5 healthy lifestyle factors (5 points) was statistically significantly associated with a 59% risk reduction (RR [95% CI]) in men (0.41 [0.24-0.71], P_{trend} <.001), a nonsignificant 53% risk reduction in women (0.47 [0.19-1.15], P_{trend} <.001), and a 58% risk reduction in all participants (0.42 [0.26-0.66], P_{trend} <.001). The PAR for pancreatic cancer was 27% for having a combined lifestyle score of less than 5 points. Because there was a relatively smaller number of participants with the lowest and highest scores, we combined the lower (0-1 points) and higher (4-5 points) scores. The RR for having a higher score compared with a lower score was 0.64 (95% CI, 0.45-0.91; P_{trend}=.003) in women. The PAR for pancreatic cancer was 29% for having a combined lifestyle score of fewer than 4 points. The associations between the score and risk of pancreatic cancer did not vary significantly by sex ($P_{interaction}$=.49) or age ($P_{interaction}$=.89).

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Table 4. Relative Risk of Pancreatic Cancer in Relation to Combined Healthy Lifestyle Score

Healthy Lifestyle Score[a]	Men			Women			Men and Women		
	Case	Person-Year	RR[b] (95% CI)	Case	Person-year	RR[b] (95% CI)	Case	Person-Year	RR[b] (95% CI)
0	20	29 034	1 [Reference]	6	13 576	1 [Reference]	26	42 610	1 [Reference]
1	88	179 315	0.72 (0.44-1.16)	43	116 734	0.82 (0.35-1.92)	131	296 053	0.73 (0.48-1.12)
2	219	450 132	0.69 (0.43-1.09)	119	333 804	0.75 (0.33-1.70)	338	783 937	0.69 (0.46-1.03)
3	213	519 575	0.55 (0.35-0.88)	119	372 156	0.65 (0.28-1.47)	332	891 731	0.57 (0.38-0.85)
4	95	352 406	0.34 (0.21-0.56)	72	253 226	0.56 (0.24-1.29)	167	700 528	0.40 (0.27-0.61)
5	40	120 516	0.41 (0.24-0.71)	23	97 035	0.47 (0.19-1.15)	63	217 551	0.42 (0.26-0.66)
P_{trend}[c]			<.001			<.001			<.001
0-1	108	208 349	1 [Reference]	50	130 310	1 [Reference]	157	338 663	1 [Reference]
2-3	432	969 707	0.81 (0.66-1.01)	238	705 960	0.83 (0.61-1.13)	670	1 675 668	0.81 (0.68-0.97)
4-5	135	472 922	0.48 (0.37-0.63)	95	350 261	0.64 (0.45-0.91)	230	918 079	0.54 (0.44-0.66)
P_{trend}[c]			<.001			.003			<.001

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Healthy lifestyle score (range, 0-5 points) was calculated by summing the binary exposure factors (0, 1) including smoking, alcohol use, dietary quality, body mass index (calculated as weight in kilograms divided by height in meters squared), and physical activity. Participants received 1 point if they had any of the following behaviors: never smokers or quit smoking 10 years or longer, limited alcohol use, healthy dietary quality, body mass index ≥18 and <25, or regular physical activity.

[b] Adjusted for age, race/ethnicity, educational achievement level, marital status, and total energy intake (log-transformed). For men and women combined model, adjusted also for sex.

[c] *P* values for linear trend of relative risk.

Table 5. Relative Risk of Pancreatic Cancer for Most Common Lifestyle Pattern in Each Score Category

Healthy Lifestyle Score	Percentage	No. of Cases	Score for Healthy Lifestyle Factor[a]					RR[b] (95% CI)		
			Smoking	Alcohol Use	Dietary Quality	Body Mass index	Physical Activity	Men	Women	Men and Women
0	1.5	26	0	0	0	0	0	1 [Reference]	1 [Reference]	1 [Reference]
1	6.0	73	0	1	0	0	0	0.63 (0.36-1.11)	1.04 (0.43-2.51)	0.77 (0.49-1.24)
2	14.6	151	1	1	0	0	0	0.57 (0.34-0.95)	0.68 (0.29-1.60)	0.61 (0.40-0.94)
3	9.9	106	1	1	0	0	1	0.46 (0.27-0.76)	0.62 (0.25-1.54)	0.50 (0.32-0.78)
4	9.1	80	1	1	1	0	1	0.28 (0.16-0.50)	0.70 (0.28-1.73)	0.40 (0.25-0.64)
5	7.6	63	1	1	1	1	1	0.35 (0.19-0.66)	0.53 (0.21-1.35)	0.41 (0.25-0.69)
Total	**48.7**	**499**	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .

Abbreviations: CI, confidence interval; ellipsis, not applicable; RR, relative risk.

[a] The score of 1 point indicated nonsmoking, limited alcohol use, healthy dietary quality, normal body weight, and regular physical activity for the respective factors.

[b] For healthy lifestyle score equals 1 point, the RR was adjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), scores for smoking, dietary quality, body mass index (calculated as weight in kilograms divided by height in meters squared), and physical activity. For healthy lifestyle score equals 2 points, the RR was adjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), scores for dietary quality, body mass index, and physical activity. For healthy lifestyle score equals 3 points, the RR was adjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), scores for dietary quality, and body mass index. For healthy lifestyle score equals 4 points, the RR was adjusted for age, race/ethnicity, educational achievement level, marital status, total energy intake (log-transformed), and body mass index score. For healthy lifestyle score equals 5 points, the RR was adjusted for age, race/ethnicity, educational achievement level, marital status, and total energy intake (log-transformed). For the men and women combined model, the RR was adjusted for sex.

We identified 32 healthy lifestyle patterns derived from various combinations of the lifestyle score factors. For simplicity, we present the most common pattern in each score category (**Table 5**). The risk decreased with the addition of each lifestyle factor in the following order: limited alcohol use, nonsmoking, regular physical activity, healthy dietary quality, and normal BMI, when the other factors in the pattern were adjusted in the respective models. The addition of normal BMI to the most common 4-factor pattern (nonsmoking, limited alcohol use, healthy diet quality, and regular physical active) reduced the risk in women but not in men. However, the association between the lifestyle pattern and risk of pancreatic cancer did not differ by sex ($P = .09 \sim .72$, Wald test).

In sensitivity analyses, when 5-point scores were compared with 0-point scores, the RR (95% CI) was 0.39 (0.24-0.62) in a 2-year lag analysis based on 925 cases, 0.40 (0.24-0.64) in an analysis based on 922 cases identified from cancer registries only, and 0.41 (0.25-0.66) in participants without a self-reported history of cancer based on 947 cases.

COMMENT

In this large prospective study in older individuals in the United States, we found that the risk of pancreatic cancer was significantly lower in participants who had the highest combined lifestyle score compared with participants who had the lowest score. Approximately 14% of cases may have been prevented if all participants were nonsmokers, whereas 27% of cases may have been pre-

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vented if all participants were nonsmokers and had limited alcohol use, healthy dietary quality, normal weight, and regular physical activity. There was a significant trend of risk reduction with increment in the number of healthy lifestyle factors.

In the analyses of single lifestyle factors, consistent with findings of previous studies,[1,17] nonsmoking and normal BMI had inverse associations with pancreatic cancer. Although nonsmoking showed the strongest effect, the combination with other factors rendered a further risk reduction. We found that the lack of further risk reduction by adding normal BMI to the most common 4-factor pattern was solely driven by the risk estimate in men aged 62 years or older. For example, we did not observe a risk reduction in older men when normal BMI was added to the less common 3-factor pattern (including nonsmoking, limited alcohol use, and healthy dietary quality), whereas the risk reduction was observed in younger men and women regardless of age. We examined alcohol use as a separate factor because we found that limited alcohol use was a significant protective factor for pancreatic cancer in men. Most epidemiologic studies have not shown an association between physical activity and pancreatic cancer.[2] We found that the addition of regular physical activity to the most common 2-factor pattern (nonsmoking and limited alcohol use) further reduced the risk. If these observations are true, it may reflect the interactions among these lifestyle factors.

Two studies have examined the association between risk of pancreatic cancer and dietary patterns as determined by data-driven factor analysis. A population-based study including 585 patients and 4779 control individuals showed a significant inverse association with a high fruit and vegetable dietary pattern in men but not in women.[18] A pooled prospective analysis including 366 cases found no association of either a western (high fat and meat intake) or prudent (high fruit and vegetable intake) dietary pattern with incident pancreatic cancer.[19] We used adherence to the no-alcohol aMDS to evaluate the diet quality because in 3 US studies, the Mediterranean dietary pattern has been associated with reduced risk of colorectal adenoma in men[20,21] and reduced all-cause and cancer mortality.[14] We also observed a reduced risk associated with a high no-alcohol aMDS. Among the food groups in the Mediterranean diet, fruits and vegetables have been associated with reduced risk of pancreatic cancer,[18] whereas red meat intake[22] has been associated with increased risk.

Several studies have shown the beneficial effects of adopting a healthy lifestyle on total mortality[16] and coronary heart disease.[23] To our knowledge, no study has evaluated the combined lifestyle factors in relation to cancer incidence. The mechanism by which the combined factors reduce risk of pancreatic cancer likely involves multiple pathways. For example, lifestyle with nonsmoking would mean less exposure to tobacco carcinogens.[24] Inflammation may be a common etiologic factor for chronic diseases, which may create a microenvironment that fosters pancreatic tumor growth.[25] Alternatively, the combined healthy lifestyle could influence pancreatic cancer risk via energy balance.[26,27]

The strengths of the present study include the large sample size, the prospective study design, and a wide range of dietary intake and detailed exposure information. Health behaviors are complex and consist of multiple dimensions; thus, using a lifestyle pattern analysis may capture the influence of multiple health behaviors better than an analysis based on single health behaviors. We observed a stronger risk reduction in the lifestyle pattern–based analysis than that observed in a single risk factor–based analysis, which would support the use of lifestyle pattern in risk assessment. The use of the simple score algorithm facilitated study interpretation and provided equivalent risk estimates compared with the weighted lifestyle score, which considers the unequal contribution of each factor in risk reduction in various lifestyle patterns. Our study findings may be generalizable to other study settings and could have implications for the prevention of other lifestyle-related cancers.

The present study has some limitations. First, to produce an adequate number of participants in each of 32 lifestyle patterns, we dichotomized 5 factors to maintain a lower data dimension. However, the dichotomization could result in loss of study power. The cutoff points we used were based on public health recommendations rather than pancreatic cancer–specific cutoff points. This could further reduce the magnitude of associations and result in loss of study power. Second, we had only 1 baseline measure of the factors that contributed to our healthy lifestyle score, which did not take into account lifestyle changes before or after assessment. Third, the combined score did not include all possible lifestyles, occupational exposure, or medical history that could be risk factors for pancreatic cancer. With these additional factors, the PAR might be larger and the prediction of pancreatic cancer might be stronger. Our study findings should be confirmed in other studies with refined exposure information to give a comprehensive evaluation of lifestyle patterns and pancreatic cancer risk.

In conclusion, the combined healthy lifestyle factors including nonsmoking, adherence to US alcohol use recommendation, healthy dietary quality as defined by adherence to the Mediterranean diet pattern excluding alcohol consumption, normal weight, and regular physical activity may have direct implications for pancreatic cancer prevention in older individuals in the United States. Although further searching for cancer-causing factors or mechanisms may contribute to innovative preventive strategies, the examination of combined known modifiable factors in cancer risk assessment is an appropriate way to translate analytic epidemiologic findings to primary cancer prevention, especially for the prevention of pancreatic cancer for which both early diagnosis and effective treatment remain challenging.

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Correspondence: Li Jiao, MD, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd, Executive Plaza S, Room 3032, Rockville, MD 20852 (jiaol@mail.nih.gov or stolzenr@mail.nih.gov).
Author Contributions: Dr Jiao had full access to all of the data in the study and takes full responsibility for the

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integrity of the data and the accuracy of the data analysis. Drs Mitrou and Reedy contributed equally to this study. *Study concept and design:* Jiao, Mitrou, Reedy, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. *Acquisition of data:* Jiao, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. *Analysis and interpretation of data:* Jiao, Mitrou, Reedy, Graubard, Schatzkin, and Stolzenberg-Solomon. *Drafting of manuscript:* Jiao, Mitrou, Reedy, and Stolzenberg-Solomon. *Critical revision of the manuscript for important intellectual content:* Jiao, Reedy, Mitrou, Graubard, Hollenbeck, Schatzkin, and Stolzenberg-Solomon. *Statistical analysis:* Jiao, Mitrou, Reedy, Graubard, and Stolzenberg-Solomon. *Obtained funding:* Hollenbeck and Schatzkin. *Administrative, technical, and material support:* Hollenbeck, Schatzkin, and Stolzenberg-Solomon. *Study supervision:* Schatzkin and Stolzenberg-Solomon.

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