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Healthy lifestyle index and risk of pancreatic cancer in the Women's Health Initiative

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Abstract

Purpose—Lifestyle factors such as smoking, alcohol, body weight, physical activity, and diet quality have been associated with the risk of pancreatic cancer. However, studies of their combined association in women are limited.

Methods—Data on smoking habits, alcohol intake, diet composition, recreational physical activity, body weight, and waist circumference, obtained at recruitment for 136,945 postmenopausal women (aged 50–79 years) participating in the Women's Health Initiative study,

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by institutional review boards at all 40 clinical centers and at the coordinating center.

Informed consent All participants in the WHI gave written-informed consent.

were categorized separately, with higher scores for each variable assigned to the categories representing healthier behaviors. The combined healthy lifestyle index (HLI) score, created by summing the scores for each risk factor, was grouped into quartiles. We used multivariable-adjusted Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for pancreatic cancer risk in association with the HLI.

Results—Over an average follow-up period of approximately 16.0 years, 1,119 incident cases of pancreatic cancer were ascertained. Compared to women in the lowest HLI quartile, those in the upper quartiles (*qt*) had a reduced risk of pancreatic cancer (multivariable-adjusted HRqt_3^{rd} 0.83, 95% CI 0.74–0.99; and HRqt_4^{th} 0.74, 95% CI 0.62–0.88, respectively, $p\ trend = 0.001$). Use of waist circumference instead of BMI in the HLI score yielded similar results. Among women who were either non-diabetic or non-smokers, high HLI was also associated with reduced risk HRqt_4^{th} 0.78, 95% CI 0.65–0.85 and HRqt_4^{th} 0.80, 95% CI 0.66–0.97, respectively). Stratification by BMI categories (18.5− < 25.0, 25.0− < 30.0 and > 30.0 kg/m^2) showed similar results in all groups.

Conclusions—Our findings suggest that in postmenopausal women, a healthy lifestyle is associated with reduced risk of pancreatic cancer.

Keywords

Healthy lifestyle index; Pancreatic cancer; Postmenopausal women; Propspective cohort study

Introduction

Pancreatic ductal adenocarcinoma is the 7th most common type of cancer in the US and the 14th worldwide [1, 2]. In its early stages, the disease is often asymptomatic, so that in the majority of cases, detection and diagnosis occur at an advanced stage, when resection and treatment options are limited [3, 4], resulting in a high fatality rate associated with this malignancy [2]. Increasing age, family history, diabetes, and chronic pancreatitis are major contributors to pancreatic cancer incidence [5, 6]. In addition, several potentially modifiable risk factors such as tobacco smoking, obesity, heavy alcohol consumption, and certain dietary patterns have also been linked to increased pancreatic cancer occurrence [6, 7].

Tobacco smoking has been consistently linked with pancreatic cancer, with increased risk in current smokers, in former smokers up to 20 years after quitting [8, 9], and in those exposed to second-hand smoke [10]. Obesity and overweight in childhood and throughout adulthood have been associated with increased risk of pancreatic precancerous lesions [11] and pancreatic cancer [12]. Dietary patterns, including relatively high intake of red and processed meat, fat, and sugar, have been linked to elevated risk of pancreatic cancer in some studies [13–15], while there are indications that whole-plant foods may inhibit pancreatic carcinogenesis and reduce the risk of pancreatic cancer [16, 17]. Despite some inconsistencies, several prospective cohort studies have found a positive dose-dependent association between alcohol intake, particularly distilled spirits such as liquor, and increased risk of pancreatic cancer [18]. The association between physical activity and pancreatic cancer has been the focus of several case–control and cohort studies, which have shown a potential protective effects of physical activity if practiced consistently over time [19].

Both the International Agency for Research on Cancer and the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) have identified these factors as targets to improve primary prevention and reduce the burden of pancreatic cancer [20]. A study focused on the population attributable fraction (PAF) of pancreatic cancer based on nationally representative data on exposures and outcome prevalence estimated a PAF for pancreatic cancer of approximately 25% due to these modifiable risk factors, in the US population [21]. Similar estimates were found in the analysis of two distinct cohorts with a total of 140,000 individuals with detailed information on these factors and pancreatic cancer occurrence [22].

The healthy lifestyle index (HLI) is a composite score which combines information on body mass index (BMI), smoking, alcohol intake, diet quality, and physical activity and has been linked to the incidence of and mortality from several chronic diseases including cardiovascular disease and some types of cancer, as well as to life expectancy and quality of life [23–27]. However, only two studies have used a combined index score of these modifiable risk factors to assess the impact of a healthy lifestyle on the risk of pancreatic cancer [28, 29]. Therefore, given the paucity of studies to date, we evaluated the association of this lifestyle-related composite index with risk of pancreatic cancer in the Women's Health Initiative (WHI) cohort.

Methods

The WHI study is a large prospective study designed to advance understanding of the determinants of major chronic disease in postmenopausal women. The study includes 161,808 postmenopausal women aged 50–79 at enrollment, representing major racial/ethnic groups recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. The WHI comprises an observational component and 4 overlapping clinical trials, including 2 hormone therapy trials, a dietary modification trial, and a calcium plus vitamin D supplementation trial. Details of the selection criteria, study design, and trial interventions have been extensively reported [30, 31]. The original WHI study was completed in 2005 and was followed by two extension studies (2005–2010 and 2010–2020) with the purpose of gathering additional outcome information. Regular contact (through visits, phone calls, or mailings) with participants occurred throughout the follow-up period to oversee the study participation and the occurrence of health-related outcomes. The study was approved by institutional review boards at all 40 clinical centers and at the coordinating center. All participants in the WHI gave written-informed consent.

Exposure information and covariates

Information on demographic, health and reproductive characteristics, medication use, and lifestyle factors was collected at enrollment. Selection and categorization of the variables included in the HLI was based on WCRF/AIRC recommendation and on previous studies in this cohort [24, 32]. Dietary intake was assessed using a validated food frequency questionnaire administrated at the baseline examination [33] and was used to calculate the Alternate Healthy Eating Index (AHEI-2010), a diet quality index previously used by this and other studies [34, 35]. The AHEI is a composite score based on the intake

of vegetables, fruit, nuts and soy protein, red and processed meat, *trans* fat, the ratio of polyunsaturated to saturated fat, and multivitamin use, with higher score values assigned to more healthy dietary habits [36]. The total AHEI-2010 score was categorized into quintiles. A self-administered questionnaire on frequency and duration of mild, moderate, and vigorous intensity recreational physical activity was completed at baseline by all study participants. A metabolic equivalent (MET) value was assigned to each category of physical activity, and the total weekly MET hours of activity was computed by multiplying the MET of each category by the duration (hours) and then summing the values (MET hours/week (h/wk)) [37]; quintiles of MET-h/wk were created. Smoking status was categorized based on smoking history and cigarette amount (*never*, *former* ≤ 15 *pack years* (number of packs of cigarettes smoked per day by the number of years the person had smoked), *former* > 15 *pack years, current* ≤ 15 *pack years*, and *current* > 15 *pack years*). Alcohol intake was calculated from the food frequency questionnaire for beer, wine, and liquor, converted to total grams (g) (12.8 g of ethanol for 360 ml (12 oz) of regular beer, 11.3 g for 360 ml (12 oz) of light beer, 11.0 g for 120 ml (4 oz) of wine, and 14.0 g for 45 ml (1.5 oz) of liquor) and categorized as < 6.0, 6.0– < 12.0, 12.0– < 24.0, 24.0– < 60.0, and ≥ 60.0 g a day (g/d). Measurements of weight (kg), height (cm), and waist circumference (cm) were obtained at baseline by trained personal. BMI was computed as measured weight divided by the square of height (kg/m^2) and categorized into three groups (*normal*, 18.5– < 25.0; *overweight*, 25.0– < 30.0; and *obese* ≥ 30.0 kg/m^2); women with a BMI < 18.5 kg/m^2 were excluded, to reduce the likelihood of reverse causality due to an effect of pancreatic cancer on BMI. Waist circumference was categorized into three groups (< 80 cm, 80– < 88 cm, and ≥ 88 cm).

The combined HLI score included diet quality, level of physical activity, smoking, alcohol intake, and either body mass index or, alternatively, waist circumference, as a marker of abdominal obesity [38]. A description of each component of the HLI and the HLI$_{WST}$ (which included waist circumference instead of BMI) and their distribution is presented in Supplementary Table 1. The total HLI score ranged from 0 to 18 with the highest score representing the healthiest combination of factors (highest quintiles of AHEI and level of physical activity, *never* smoked, < 6 g/d of alcohol consumption, and *normal* BMI, or waist circumference < 80 cm).

Information on education, race and ethnicity, marital status, total non-alcohol energy intake, history of type 2 diabetes, history of pancreatitis, and use of hormone replacement therapy was collected at baseline. Type 2 diabetes status was updated throughout the follow-up based on information collected at each visit or via phone contact regarding receipt of a diagnosis of diabetes, use of oral glucose lowering medications or insulin, report of diabetes-related diet and exercise modifications, and hospitalization due to diabetes complications [39].

Analytic sample

For the present study, we included all participants in the observational and clinical trial components, except women randomized to the dietary intervention arm (n = 19,541) of the dietary modification trial, as well as those missing follow-up information (n = 450). In addition, we excluded underweight women (BMI < 18.5 kg/m^2, n = 1,328). Some

of the participants had missing data on various components of the HLI and HLI_{WST} (Supplementary Table 1), leaving a total of 136,945 women with complete data on the HLI and 139,556 on the HLI_{WST}.

Case ascertainment

Information of cancer occurrence was collected every 6 to 12 months by mailed or telephone questionnaires. Self-reported cancer cases were verified by centralized review of medical records and pathology reports when a biopsy or resection were available [40]. Final adjudication and histology coding were used to identify primary pancreatic adenocarcinoma cases using the National Cancer Institute's Surveillance, Epidemiology, and End Results coding system (including codes C25.0–C25.3 and C25.7–C25.9—International Classification of Diseases for Oncology (ICD)-2, and ICD-O-3 histology codes: 8000, 8010, 8021, 8140, 8144, 8150, 8240, 8246, 8260, 8323, 8440, 8470, 8480, 8481, 8490, 8500, 8503, 8560, 8570, 8800, and 8801).

Statistical analysis

The study population was categorized into quartiles of the HLI score based on its distribution among non-cases. Descriptive statistical analyses were conducted to compare the study population baseline characteristics by HLI quartiles using Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. Cox-proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations between the HLI quartiles and risk of pancreatic cancer using the lowest quartile as referent group; a similar approach was used for analyses based on the HLI_{wst}. Follow-up time was used as the timescale and was calculated from the date of study entry until the date of cancer diagnosis for the cases, and until the date of death (as reported during the study follow-up and confirmed using the Vital Status from the National Death Index), withdrawal from the study, loss to follow-up, or the end of follow-up (02/28/2020) for the non-cases. No violation of the proportional hazards assumption for HLI quartiles was found on the basis of examination of Schoenfeld residuals (p value = 0.08). To test for linear trend in the risk of pancreatic cancer across the quartiles of the HLI or HLI_{wst}, the quartile levels were included in the model as an ordinal variable and Wald test p values were reported. To evaluate whether HLI_{wst} provided similar results to those obtained using BMI in the HLI, we compared the HR estimates associated with increments of 1 standard deviation of the HLI and HLI_{WST}. Selection of the variables included in the multivariable model was based on their association with pancreatic cancer and whether these factors acted as confounders by altering the estimates of association for the main exposure by more than 10%. The models were adjusted for education, race/ethnicity, marital status, total non-alcohol energy intake, hormone replacement therapy, participation in the calcium and vitamin D trial, the dietary modification trial (no-intervention arm only), and/or the hormone replacement therapy trials, diabetes status and use of diabetes medications, and history of pancreatitis. In addition, when the HLI_{wst} score was used, height was also included in the model.

We conducted several additional analyses. First, we conducted a sensitivity analysis excluding women with less than two years of follow-up to reduce the possibility of an effect

of an undiagnosed pancreatic cancer on risk factors such as BMI and waist circumference. Second, type 2 diabetes is an established risk factor for pancreatic cancer [41] and is often associated with elevated BMI [42], and a diet high in fat and low in whole grain, fruits, and vegetables [43]. Therefore, we carried out analyses excluding women with type 2 diabetes to test whether the association between HLI and pancreatic cancer was mainly driven by diabetes. All diabetes-free women at baseline (n = 135,264) were included in this analysis and censored at the time they reported having diabetes, if their diabetes status changed [44]. Third, analyses were also conducted excluding women who were current smokers at baseline (n = 6,733). Fourth, to test if the association between HLI and pancreatic cancer was modified by BMI level, we carried out analyses stratified by BMI categories using HRT_{WST} quartiles. The p value for the interaction term between HLI_{WST} quartiles and BMI categories was obtained by comparing the likelihood ratio of the full regression model, including the cross-product of the HLI_{WST} and BMI terms, versus the reduced model without this term. Finally, we evaluated the association of the individual components of HLI with risk of pancreatic cancer by removing one component at a time from the composite score and adjusting for it in the model. Women with missing values for any of the HLI components were excluded from the main analysis, but they were included in the analyses of the individual components for which they did not have missing values.

The analyses were conducted using STATA version 17 (Stata Corp LP, College Station, TX). All p values were two sided.

Results

Over an average follow-up period of 16.2 years (standard deviation, 7.0 years), a total of 1,119 confirmed cases of incident pancreatic cancer were ascertained among women with complete information on all the HLI components and 1,141 cases were ascertained among women with complete information on HLI_{WST}. Baseline characteristics examined by HLI quartiles showed that women with higher HLI scores were more likely to be older, to be White, to have a higher level of education, to be married or in a marriage-like relationship, to be enrolled in the observational study component of WHI, and to have a lower total non-alcohol energy intake, and that they were less likely to have diabetes and to take diabetes medication at baseline (Table 1).

Compared to women in the lowest quartile of the HLI, those in the upper quartiles had lower risk of pancreatic cancer (multivariable-adjusted $HR_{qt_3^{rd}}$ 0.83, 95% CI 0.74–0.99; and $HR_{qt_4^{th}}$ 0.74, 95% CI 0.62–0.88, respectively, $p\ trend$ = 0.001). There was an 11% reduction in risk of pancreatic cancer per standard deviation increase in the HLI (SD = 2.9 HLI) (HR 0.89, 95% CI 0.84–0.95) (Table 2). Excluding women with less than two years of follow-up from the analysis did not change the risk estimates ($HR_{qt_4^{th}}$ 0.73, 95% CI 0.60–0.84). Use of waist circumference instead of BMI in the HLI score yielded similar results, with a lower risk of pancreatic cancer for those in the higher HLI_{WST} quartiles compared to the lowest quartile ($HR_{qt_2^{nd}}$ 0.84, 95% CI 0.70–0.99; $HR_{qt_3^{rd}}$ 0.80, 95% CI 0.68–0.95; and $HR_{qt_4^{th}}$ 0.72, 95% CI 0.61–0.85, respectively, $p\ trend$ = 0.001), and a similar reduction in risk associated with a one SD (3.0 HLI_{WST}) increment (HR 0.91, 95% CI 0.85–0.99) (Table 2). A total of 20,994 (15.5%) women developed type 2 diabetes over an average period of 6.1

years. Analysis restricted to women who remained diabetes-free during the follow-up period yielded similar results (HR qt_4^{th} 0.78, 95% CI 0.64–0.95). Also, the results were similar when the analysis was restricted to non-current smokers (HR qt_4^{th} 0.80, 95% CI 0.66–0.97).

Analyses stratified by categories of BMI showed that among women with normal BMI, a relatively high HLI_{WST} was associated with a reduced risk of pancreatic cancer (HR qt_4^{th} 0.65, 95% CI 0.47–0.90), while among overweight and obese women, there was also a reduction in risk, although the confidence intervals included an HR of one, presumably due to the smaller sample size in these two strata. No overall effect modification by BMI on the association of HLI_{WST} quartiles with pancreatic cancer risk was observed (*p value* for interaction term = 0.739) (Table 3).

Additional analyses in which each lifestyle component was excluded in turn from the overall HLI score showed that compared to women in the lowest quartile of HLI, those in the uppermost quartile had a significantly reduced risk of pancreatic cancer independently of the component excluded (Table 4).

Discussion

In this large multicenter population-based study of postmenopausal women, we found that a healthy lifestyle index, represented by having a normal BMI or a waist circumference less than 80 cm, no cigarette smoking, low alcohol intake, undertaking at least moderate levels of physical activity, and a diet rich in vegetables, fruits, nuts, and low in red meat, trans fat, and with a high polyunsaturated to saturated fat ratio, was associated with a reduced risk of pancreatic cancer over an average follow-up period of 16 years. The results were similar regardless of whether we used the HLI or the HLI_{WST} scores, and when the analysis was restricted to non-diabetics, non-smokers, and women with normal BMI (Table 4).

Several epidemiological studies have examined the association between modifiable risk factors and the risk of pancreatic cancer, although only two studies have evaluated a combined healthy lifestyle score. A study conducted in the National Institutes of Health-AARP Diet and Health study cohort of approximately 450,000 participants (41.5% women), aged 50–71, used dichotomized scores (healthy behavior no/yes) for each of the 5 factors. Over a follow-up period of approximately 7 years, a total of 1,057 cases (382 in women) of pancreatic cancer were identified. The study showed that compared to the lowest score (0–1 points), the highest composite score (4–5) was associated with a reduction in pancreatic cancer risk (HR 0.48, 95% CI 0.37–0.63 in men, and HR 0.64, 95% CI 0.45–0.91 and in women) [28]. A second study used data from approximately 400,000 participants (age range of 35–70 years) in the European Prospective Investigation into Cancer and Nutrition and constructed a HLI using dose-dependent scores (0–4) to quantify the level of smoking status, alcohol intake, waist-to-hip ratio, and diet based on the intake of cereal fiber, vegetables and fruits, red and processed meat, polyunsaturated to saturated fat ratio, trans fat, and glycemic load [29]. Over 15 years of follow-up, a total of 1,113 cases of pancreatic cancer (634 in women) were diagnosed, and an inverse association was found between the highest HLI score (> 15 points) and risk of pancreatic cancer (HR 0.79, 95% CI 0.73–0.86, using as the reference group the second lowest HLI category (5–9 points)). Among women, each

1 standard deviation increment in the HLI score was associated with a 21% reduction in the risk of pancreatic cancer (HR 0.79, 95% CI 0.73–0.86). The results of our study are in line with those of previous studies, indicating that a healthy lifestyle score based on several modifiable factors is associated with reduced risk of pancreatic cancer.

There is a complex relationship between type 2 diabetes and pancreatic cancer. Diabetes of long duration (> 3 years) is a major risk factor for pancreatic cancer [45] and is associated with a 50–150% increased risk. However, evidence suggests that for individuals who received a diabetes diagnosis less than two years before the diagnosis of pancreatic cancer, a reverse temporal relationship between these two diseases might have occurred [46]. In the present study, we showed for the first time that a healthy lifestyle is associated with a lower risk of pancreatic cancer among non-diabetic women. Information on type 2 diabetes was available at baseline and throughout the study follow-up and was used to define time-at-risk for participants who developed diabetes subsequent to the baseline exam. This approach reduced the possibility that the observed lower risk of pancreatic cancer in women with high healthy lifestyle index was due to the association of HLI with type 2 diabetes [27]. Additional studies are needed to confirm whether a healthy lifestyle may lower the risk of pancreatic cancer in women without diabetes over a prolonged period. There were too few cases of pancreatic cancer among diabetic women to allow us to examine the association between HLI and pancreatic cancer in this sub-group. As with non-diabetics, a healthy lifestyle was associated with a reduction in risk of pancreatic cancer among women who were non-smokers. Cigarette smoking is an established risk factor for pancreatic cancer and is estimated to account for approximately 20–25% of cases [45]. In the WHI cohort, only 7% of participants were current smokers. In analyses stratified by BMI categories, we showed that among women with normal BMI, there was a statistically significant inverse association between the HLI upper quartile and pancreatic cancer risk, while in overweight and obese women, the results were not significant. These findings may be due to small sample sizes within the higher BMI categories. The results obtained with the exclusion of each individual component in turn from the HLI composite score showed that the protective effect of high HLI does not depend upon one particular factor but rather on the combination of multiple lifestyle components. However, we recognize that characteristics such as smoking and high BMI may have a stronger association than the other components of the HLI with this outcome.

The present study, the largest with respect to the number of participating women and the number of incident pancreatic cancer cases, was based on a well characterized cohort with detailed information on risk factors, a prospective design, and an average follow-up period of 16 years. The relative higher incidence rate of pancreatic cancer observed in this cohort compared to other studies [28, 29] was likely due to the higher median age of this cohort at enrollment and the extended duration of follow-up. Objective anthropometric measurements were obtained during the study baseline exam for all participants, while previous studies relied on self-reported data in part or in full [28, 29]. Cancer cases were confirmed centrally by trained physicians according to standard guidelines. The healthy lifestyle index was based on a multilevel risk score, which allowed us to evaluate the association of HLI with the outcome in a dose-dependent manner. Although the estimates of association were adjusted for several risk factors, we cannot exclude the possibility of residual confounding.

Furthermore, we did not have repeated measurements of lifestyle factors throughout follow-up, which would have allowed for better characterization and control for lifestyle factors changes.

In conclusion, we found that in this cohort of postmenopausal women, a relatively high healthy lifestyle index is associated with reduced risk of pancreatic cancer over a follow-up period of more than a decade. Pancreatic cancer remains one of the deadliest types of malignancy in the United States and worldwide. The results of our study suggest that promoting smoking cessation and limiting alcohol consumption, along with undertaking regular physical activity, consuming a healthy diet rich in fruits, vegetables, and whole grains and low in saturated and trans fats, and maintaining a healthy body weight, may be important steps to lower the risk of this lethal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data are available through the WHI online resource, https://www.whi.org/researchers/data/Pages/Home.aspx, and the WHI remains funded indefinitely through BioLINCC, https://biolincc.nhlbi.nih.gov/studies/whi_ctos/.

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Table 1

Baseline characteristics of participants in the Women's Health Initiative by Healthy Lifestyle Index

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p* value[b]**
N	31,301	32,131	33,902	39,611	
HLI range	0–9	10–11	12–13	≥ 14	
Characteristics					
Age at enrollment,[a] years	62.3 (7.1)	63.3 (7.2)	63.7 (7.3)	63.8 (7.3)	< 0.001
Age at diagnosis,[c] years	77.5 (8.6)	79.3 (8.5)	80.2 (8.5)	80.7 (8.4)	< 0.001
Ethnicity, %					
White	79.0	81.3	84.0	85.6	< 0.001
Black	13.9	10.2	7.5	4.9	
Others	7.1	8.5	8.4	9.5	
Education, %					
≤ High school	30.9	26.1	21.1	14.7	< 0.001
Some college	41.0	39.3	37.1	33.7	
≥ College degree	26.0	32.1	38.7	47.1	
Marital status, %					
Single, divorced, separated, widow	42.4	38.9	35.8	33.9	< 0.001
Married or marriage-like relationship	57.6	61.1	63.2	66.1	
WHI study enrollment, %					
Observational study	54.4	60.0	67.0	76.7	< 0.001
Calcium and vitamin D trial	24.6	21.9	18.5	21.8	< 0.001
Dietary modification trial[d]	28.3	25.2	19.8	12.9	< 0.001
Hormone therapy trial	23.4	19.3	15.9	11.8	< 0.001
Estrogen-alone intervention arm	5.0	4,0	3.0	1.9	< 0.001
Estrogen + Progesterone intervention arm	6.9	5.9	5.0	4.1	< 0.001
History of type 2 diabetes, %	2.0	1.6	1.4	1.1	< 0.001
Diabetes medications, %	1.1	0.8	0.6	0.5	< 0.001
History of pancreatitis, %	0.9	0.9	0.8	0.6	< 0.001
Total non-alcohol dietary energy,[a] kcal/day	1747.6 (792.0)	1618.4 (732.5)	1564.8 (699.2)	1523.4 (638.5)	< 0.001

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p* value[b]**
Body mass index,[a] kg/m^2	31.2 (6.4)	29.1 (5.9)	27.3 (5.3)	25.0 (4.1)	, < 0.001
Waist circumference,[a] cm	81.9 (17.5)	76.2 (16.0)	71.5 (14.3)	65.4 (11.4)	< 0.001
Alcohol,[a] g/day	8.3 (16.5)	5.1 (10.6)	4.6 (8.1)	3.5 (5.5)	< 0.001
Diet score (AHEI-2010), highest quintile, %	1.6	7.1	18.3	46.2	< 0.001
Never Smoker, %	26.6	49.6	55.2	67.0	< 0.001
Physical activity,[a] MET-hours/week	3.1	6.8	12.6	23.0	< 0.001

HLI healthy lifestyle index, *MET* metabolic energy equivalent

[a]Data represent mean (standard deviation)

[b]*p* value based on Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables

[c]Mean age at diagnosis among pancreatic cancer cases

[d]Among women in the control arm of the trial

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Table 2

Incidence rates and hazard ratios (95% confidence intervals) for risk of pancreatic cancer in association with the Healthy Lifestyle Index

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p trend*** [a]
Total study population					
N	31,301	32,131	33,902	39,611	
Pancreatic cancer cases	267	262	285	305	
Incidence rate per 1000 person-years[b]	0.56	0.51	0.51	0.45	
HR (95% CI)	1.00	0.84 (0.71–0.99)	0.81 (0.68–0.96)	0.70 (0.60–0.83)	< 0.001
HR (95% CI)[c]	1.00	0.85 (0.71–1.01)	0.83 (0.74–0.99)	0.74 (0.62–0.88)	0.001
HR (95% CI) for 1 SD increase in HLI[c, d]	0.89 (0.84–0.95)				
Using waist circumference in the HLI [e]					
N	33,995	32,551	33,761	39,249	
Pancreatic cancer cases	297	268	279	297	
Incidence rate per 1000 person-years[b]	0.58	0.52	0.50	0.44	
HR (95% CI)	1.00	0.83 (0.71–0.98)	0.78 (0.66–0.92)	0.69 (0.58–0.81)	< 0.001
HR (95% CI)[c, f]	1.00	0.84 (0.70–0.99)	0.80 (0.68–0.95)	0.72 (0.61–0.85)	0.001
HR (95% CI) for 1 SD increase in HLI[c, d]	0.91 (0.85–0.98)				
Excluding women with follow-up < 2 years					
N	30,696	31,685	33,510	39,241	
Pancreatic cancer cases	248	241	275	286	
Incidence rate per 1000 person-years[b]	0.52	0.47	0.50	0.43	
HR (95% CI)	1.00	0.83 (0.69–0.99)	0.84 (0.70–0.99)	0.71 (0.60–0.84)	< 0.001
HR (95% CI)[c]	1.00	0.84 (0.69–1.00)	0.86 (0.72–1.02)	0.73 (0.61–0.88)	0.002
HR (95% CI) for 1 SD increase in HLI[c, d]	0.90 (0.84–0.96)				
Non-diabetics					
N	30,818	31,725	33,499	39,222	
Pancreatic cancer cases	190	209	240	270	
Incidence rate per 1000 person-years[b]	0.47	0.46	0.48	0.43	

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p trend*** [a]
HR (95% CI)	1.00	0.90 (0.7–1.10)	0.90 (0.74–1.09)	0.79 (0.68–0.96)	0.018
HR (95% CI)[c]	1.00	0.90 (0.71–1.10)	0.89 (0.73–1.08)	0.78 (0.64–0.95)	0.015
HR (95% CI) for 1 SD increase in HLI[c, d]	0.91 (0.85–0.97)				
Non-smokers					
N	24,383	30,635	33,328	39,615	
Pancreatic cancer cases	194	250	277	304	
Incidence rate per 1000 person-years[b]	0.52	0.51	0.50	0.45	
HR (95% CI)	1.00	0.93 (0.77–1.12)	0.89 (0.74–1.07)	0.79 (0.66–0.94)	0.006
HR (95% CI)[c]	1.00	0.94 (0.78–1.13)	0.91 (0.75–1.09)	0.80 (0.66–0.97)	0.017
HR (95% CI) for 1 SD increase in HLI[c, d]	0.92 (0.86–0.99)				

HR hazard ratio, *CI* confidence interval, *SD* standard deviation

Hazard ratios and 95% confidence intervals estimates adjusted for age at enrollment

[a] *p* value based on Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables

[b] Unadjusted incidence rate

[c] Model adjusted for age, education, marital status, hormone replacement therapy clinical trial participation and arm, calcium plus vitamin D clinical trial participation and arm, dietary modification clinical trial non-intervention arm, diabetes status and medication, pancreatitis, and total non-alcohol dietary energy

[d] Hazard ratio and 95% confidence interval associated with an increase in the HLI of one standard deviation

[e] The HLI score includes waist circumference categories (score *0*: ≥ 88 cm; *1*: 80– < 88 cm; 2: < 80 cm) instead of BMI

[f] Model adjusted as for model[a] plus height

Table 3

Incidence rates and hazard ratios (95% confidence intervals) for risk of pancreatic cancer in association with the HLI_{wst} by body mass index categories

	Healthy lifestyle index quartile[a]				
	1st	**2nd**	**3rd**	**4th**	***p trend***
BMI 18.5–<25.0 *(kg/m²)*					
N	5,729	8,421	12,650	22,437	
Pancreatic cancer cases	49	70	108	164	
Incidence rate per 1000 person-years[b]	0.57	0.51	0.51	0.42	
HR (95% CI)	1.00	0.83 (0.58–1.20)	0.80 (0.57–1.12)	0.66 (0.48–0.91)	0.006
HR (95% CI)[c]	1.00	0.84 (0.58–1.20)	0.80 (0.56–1.12)	0.65 (0.47–0.90)	0.006
BMI 25.0– <30.0 *(kg/m²)*					
N	11,177	12,026	12,742	12,066	
Pancreatic cancer cases	102	99	108	102	
Incidence rate per 1000 person-years[b]	0.59	0.51	0.51	0.50	
HR (95% CI)	1.00	0.82 (0.62–1.08)	0.79 (0.60–1.04)	0.78 (0.59–1.02)	0.083
HR (95% CI)[c]	1.00	0.81 (0.61–1.07)	0.79 (0.60–1.04)	0.78 (0.58–1.03)	0.091
BMI> 30.0 *(kg/m²)*					
N	16,780	11,779	7,903	3,833	
Pancreatic cancer cases	141	97	52	27	
Incidence rate per 1000 person-years[b]	0.57	0.54	0.42	0.44	
HR (95% CI)	1.00	0.89 (0.69–1.15)	0.68 (0.50–0.94)	0.71 (0.47–1.07)	0.012
HR (95% CI)[c]	1.00	0.91 (0.70–1.18)	0.72 (0.52–0.99)	0.77 (0.50–1.17)	0.045
Interaction term between BMI group*HLI quartiles *p value* = 0.739					

HLI healthy lifestyle index, *wst* waist circumference, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index

All models were adjusted for age at enrollment in the study

[a] Healthy lifestyle index calculated using categories of waist circumference (score 0: ≥ 88 cm; *1*: 80− < 88 cm; 2: < 80 cm) instead of BMI

[b] Unadjusted incidence rate

[c] Model adjusted for age, height, education, marital status, hormone replacement therapy clinical trial participation and arm, calcium plus vitamin D clinical trial participation and arm, dietary modification clinical trial non-intervention arm, diabetes status and medication, pancreatitis, and total non-alcohol energy intake

Table 4

Hazard ratios (95% confidence intervals) for risk of pancreatic cancer in association with the Healthy Lifestyle Index, excluding each lifestyle component in turn

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p* trend**
HLI without smoking					
Incidence rate per 1000 person-years[a]	0.54	0.51	0.53	0.46	
HR (95% CI)[b]		0.89 (0.75–1.06)	0.89 (0.76–1.05)	0.78 (0.65–0.92)	0.005
HR (95% CI)[c,d]	1.00	0..91 (0.77–1.09)	0.93 (0.78–1.10)	0.83 (0.69–0.99)	0.059
HR (95% CI) for 1 SD increase in HLI[b,c,d,e]	0.94 (0.89–1.00)				
HLI without diet					
Incidence rate per 1000 person-years[a]	0.58	0.47	0.49	0.47	
HR (95% CI)[b]	1.00	0.77 (0.63–0.92)	0.79 (0.68–0.92)	0.73 (0.62–0.86)	< 0.001
HR (95% CI)[c,f]	1.00	0.77 (0.64–0.93)	0.81 (0.70–0.95)	0.76 (0.64–0.90)	0.002
HR (95% CI) for 1 SD increase in HLI[b,d,e,f]	0.88 (0.83–0.94)				
HLI without physical activity					
Incidence rate per 1000 person-years[a]	0.61	0.53	0.47	0.47	
HR (95% CI)[b]	1.00	0.81 (0.67–0.97)	0.69 (0.58–0.83)	0.66 (0.54–0.80)	< 0.001
HR (95% CI)[c,g]	1.00	0.81 (0.67–0.97)	0.70 (0.58–0.84)	0.67 (0.55–0.82)	< 0.001
HR (95% CI) for 1 SD increase in HLI[b,d,e,g]	0.87 (0.82–0.93)				
HLI without alcohol					
Incidence rate per 1000 person-years[a]	0.54	0.50	0.50	0.49	
HR (95% CI)[b]	1.00	0.85 (0.72–.1.00)	0.82 (0.70–0.97)	0.80 (0.68–0.94)	0.006
HR (95% CI)[c,h]	1.00	0.87 (0.74–1.02)	0.84 (0.71–0.99)	0.83 (0.70–0.99)	0.035
HR (95% CI) for 1 SD increase in HLI[b,c,e,h]	0.89 (0.84–0.96)				
HLI without body mass index					
Incidence rate per 1000 person-years[a]	0.54	0.54	0.50	0.46	
HR (95% CI)[b]	1.00	0.93 (0.78–1.10)	0.83 (0.70–0.99)	0.76 (0.64–0.90)	0.001

	Healthy lifestyle index quartile				
	1st	**2nd**	**3rd**	**4th**	***p* trend**
HR (95% CI)[c,i]	1.00	0.91 (0.76–1.08)	0.84 (0.71–1.00)	0.78 (0.65–0.94)	0.006
HR (95% CI) for 1 SD increase in HLI[b,c,e,i]	0.89 (0.83–0.94)				

[a] Unadjusted incidence rate

[b] Model adjusted for age at enrollment in the study

[c] Model adjusted for age, education, marital status, hormone replacement therapy clinical trial participation and arm, calcium plus vitamin D clinical trial participation and arm, dietary modification clinical trial non-intervention arm, diabetes status and medication, pancreatitis, and total no-alcohol energy intake

[d] Model additionally adjusted for smoking categories

[e] Hazard ratio and 95% confidence interval associated with an increase in the HLI of one standard deviation

[f] Model additionally adjusted for quintiles of diet score (AHEI-2010)

[g] Model additionally adjusted for quintiles of physical activity

[h] Model additionally adjusted for alcohol intake categories

[i] Model additionally adjusted for body mass index categories