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Physical Activity, Obesity, Height, and the Risk of Pancreatic Cancer

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CANCER OF THE PANCREAS REPRESENTS the fifth leading cause of cancer-related mortality in the United States.¹ Nonetheless, other than cigarette smoke, few environmental factors have been linked to the risk of pancreatic cancer.^{2,3} An association between diabetes and pancreatic cancer has been shown in many studies. In a meta-analysis including more than 20 epidemiologic studies, the pooled relative risk (RR) of pancreatic cancer among those diagnosed with diabetes for at least 5 years was 2.0 (95% confidence interval [CI], 1.3-2.2).⁴ Recently, a positive association between postload plasma glucose concentration and pancreatic cancer risk was found in 2 studies, supporting the hypothesis that impaired glucose tolerance, insulin resistance, and hyperinsulinemia play a role in pancreatic cancer etiology.^{5,6}

Obesity has been linked to significant metabolic abnormalities including insulin resistance, glucose intolerance, and diabetes mellitus.⁷⁻¹⁰ Epidemiologic findings on obesity and the risk of pancreatic cancer have been conflicting.^{5,11-18} To date, suggestive associations have been observed for height and pancreatic cancer risk in 3 studies.¹⁵⁻¹⁷ Height has been associated with elevated risks of other cancers¹⁹⁻²¹ and may be a

For editorial comment see p 967.

Context Diabetes mellitus and elevated postload plasma glucose levels have been associated with an increased risk of pancreatic cancer in previous studies. By virtue of their influence on insulin resistance, obesity and physical inactivity may increase risk of pancreatic cancer.

Objective To examine obesity, height, and physical activity in relation to pancreatic cancer risk.

Design and Setting Two US cohort studies conducted by mailed questionnaire, the Health Professionals Follow-up Study (initiated in 1986) and the Nurses' Health Study (initiated in 1976), with 10 to 20 years of follow-up.

Participants A total of 46648 men aged 40 to 75 years and 117041 women aged 30 to 55 years who were free of prior cancer at baseline and had complete data on height and weight.

Main Outcome Measures Relative risk of pancreatic cancer, analyzed by self-reported body mass index (BMI), height, and level of physical activity.

Results During follow-up, we documented 350 incident pancreatic cancer cases. Individuals with a BMI of at least 30 kg/m² had an elevated risk of pancreatic cancer compared with those with a BMI of less than 23 kg/m² (multivariable relative risk [RR], 1.72; 95% confidence interval [CI], 1.19-2.48). Height was associated with an increased pancreatic cancer risk (multivariable RR, 1.81; 95% CI, 1.31-2.52 for the highest vs lowest categories). An inverse relation was observed for moderate activity (multivariable RR, 0.45; 95% CI, 0.29-0.70 for the highest vs lowest categories; *P* for trend <.001). Total physical activity was not associated with risk among individuals with a BMI of less than 25 kg/m² but was inversely associated with risk among individuals with a BMI of at least 25 kg/m² (pooled multivariable RR, 0.59; 95% CI, 0.37-0.94 for the top vs bottom tertiles of total physical activity; *P* for trend = .04).

Conclusion In 2 prospective cohort studies, obesity significantly increased the risk of pancreatic cancer. Physical activity appears to decrease the risk of pancreatic cancer, especially among those who are overweight.

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marker for exposure levels to growth factors or a proxy for net energy intake during childhood and early adolescence.

Because physical activity improves glucose tolerance, even in the absence of weight loss,^{22,23} we hypothesized that physical activity would reduce the risk of pancreatic cancer. However, to our knowledge no study has examined the association between physical activity and pancreatic cancer risk.

We therefore examined the relationship between body mass index (BMI), height, and physical activity and the risk

of pancreatic cancer in 2 large prospective cohort studies of men and women. In both studies, weight and physical activity data were measured prior to pancreatic cancer detection, thus avoiding potential biases that may occur when obtaining such information from pancreatic cancer patients and next-of-kin.

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METHODS

Cohorts

Two ongoing cohort studies provided data for our analyses, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). The HPFS was initiated in 1986 when 51 529 US men aged 40 to 75 years responded to a mailed questionnaire. The NHS began in 1976 when 121 700 female registered nurses aged 30 to 55 years responded to a mailed questionnaire. Detailed information on individual characteristics and habits was obtained from the mailed questionnaires at baseline and subsequently every 2 years. Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonrespondents; this method has been shown to have a sensitivity of 98%.²⁴

For those analyses using anthropometric measurements, a total of 46 648 HPFS men and 117 041 NHS women were eligible after excluding participants diagnosed with cancer (other than nonmelanoma skin cancer) prior to baseline or with missing weight data at baseline. In the NHS, detailed data on physical activity were not obtained until 1986. A total of 77 559 women completed the physical activity questions on the 1986 questionnaire and were free of cancer.

Assessment of Anthropometric Variables

Baseline height, current weight, weight at 21 years old, and weight change in past 5 years were reported by men participating in the HPFS in 1986. Similarly, women in the NHS reported their baseline height and current weight in 1976. Weight at 18 years old was collected in 1980. In addition, participants of the 2 cohorts reported their current weight on the biennial mailed questionnaires. We estimated BMI from weight and height (weight in kilograms divided by square of height in meters) as a measure of total adiposity. We evaluated the precision of self-reported anthropometric measures among 123

HPFS participants by having trained technicians visit those participants twice (6 months apart) to measure current weight.²⁵ After adjustment for age and within-person variability, the Pearson correlation between self-report and the average of the 2 technician measurements was 0.97 for weight. Among women in the NHS, the correlation between self-reported and measured weight was 0.96, although self-reported weight averaged 1.5 kg less than directly measured weight.²⁵

Assessment of Physical Activity

In 1986, the questionnaires mailed to the 2 cohorts included a section assessing physical activity. Participants were asked to average the time spent per week in each of the following 8 activities over the previous year: walking or hiking outdoors; jogging (<10 minutes per mile); running (≥ 10 minutes per mile); bicycling (including on stationary machines); lap swimming; tennis; squash or racquetball; and calisthenics (use of a rowing machine [HPFS] or aerobics, aerobic dance [NHS]). A total of 10 possible answers were available for each of the exercises, ranging from 0 to 11 or more hours per week. In addition, individuals reported their usual walking pace (<2.0, 2.0-2.9, 3.0-3.9, or ≥ 4.0 mph [<3.2 , 3.2-4.6, 4.8-6.2, or ≥ 6.4 km/h]) and the number of flights of stairs climbed daily. Our calculations did not include household activities or occupational physical activity. The reliability and validity of the assessment of physical activity as used in these 2 cohorts were tested among 147 participants of the Nurses' Health Study II, a similar cohort to the NHS but participants were younger nurses. The correlation between physical activity reported on the questionnaire and that recorded in the 4 1-week diaries was 0.62.²⁶ The validity of the physical activity questionnaire used in the HPFS in 1986 was assessed among 238 randomly selected participants by comparisons with 4 1-week activity diaries, 4 1-week activity recalls, and resting and postexercise pulse rates.²⁷ The correlation for vigorous physical

activity with the activity diaries was 0.58. Vigorous activity assessed by the questionnaire was correlated with resting pulse ($r=-0.45$) and postexercise pulse ($r=-0.41$).

A weekly physical activity score expressed in metabolic equivalent tasks (METs) was derived by multiplying the time spent in each activity per week by its typical energy-expenditure requirements.²⁸ The MET is the caloric expenditure per kilogram of body weight per hour of activity divided by the equivalent per hour at rest. One MET, which is the energy expended by sitting quietly, is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute for a 70-kg adult. Body weight was excluded from the derivation of energy expenditure from physical activity to avoid confounding the expenditure variable by body weight. We further classified activities into vigorous (≥ 6 METs) and moderate (<6 METs). Accordingly, moderate activities included walking or hiking outdoors and stair climbing, and all other activities were classified as vigorous (eg, MET values of 7 were assigned to swimming and bicycling).

Smoking History and Other Risk Factors

Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires in both cohorts. Current smokers also reported intensity of smoking (average number of cigarettes smoked per day) on each questionnaire. Past smokers reported when they last smoked and time since quitting was also calculated for those who quit during follow-up. In a previous publication,²⁹ we examined the relationship between smoking and pancreatic cancer risk in detail; the strongest associations were observed in analyses of pack-years smoked within the previous 15 years.

Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. In 1986 (HPFS) and in 1982 (NHS), and biennially thereafter, participants were asked about their history of cholecystectomy.

Identification of Pancreatic Cancer Cases

In both cohorts, participants were asked to report specified medical conditions including cancers that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next-of-kin for decedents) reported a diagnosis of pancreatic cancer, we asked for permission to obtain related medical records or pathology reports. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or telephone call to the participant. If the primary cause of death as reported on a death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records, or at least to confirm the diagnosis of pancreatic cancer. In the HPFS cohort, we were able to obtain pathology reports confirming the diagnosis of pancreatic cancer for 95% of cases. For the other 5% of cases, we obtained confirmation of the self-reported cancer from a secondary source (eg, death certificate, physician, or telephone interview of a family member). In the NHS cohort, we were able to obtain pathology reports confirming the diagnosis of pancreatic cancer for 85% of cases. For the other 15% of cases, we obtained confirmation of the self-reported cancer from a secondary source (eg, death certificate, physician, or telephone interview of a family member). In both cohorts, all medical records had complete information on histology (hospitals were recontacted if the original information sent was incomplete). In our analyses, associations were examined including and excluding cases with missing medical records; because no differences were observed between these 2 types of analyses, we included cases without medical records.

In the HPFS cohort, 140 confirmed incident cases of pancreatic cancer were diagnosed between 1986 and 1998 (after exclusions); 139 cases were available with data on physical activity at baseline. In the NHS, 210 confirmed incident pancreatic cancer cases, diag-

nosed between 1976 and 1996, were available for the anthropometric analyses (after exclusions); 110 confirmed cases were available for analyses on physical activity (1986-1996).

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (January 31, 1998, for men and June 30, 1996, for women), whichever came first. Incidence rates of pancreatic cancer were calculated by dividing the number of incident cases by the number of person-years in each category of exposure. We computed the RR for each of the upper categories by dividing the rates in these categories by the rate in the lowest category.

We estimated the power to detect trends across quintiles for specified RRs comparing highest vs the lowest quintile, assuming a linear relationship and fixing the 2-tailed $\alpha = .05$.³⁰ We found an 80% power to detect an RR of 1.5 between the highest and lowest quintiles; a 95% power to detect an RR of 1.75 between the highest and lowest quintiles; and a greater than 99% power to detect an RR of 2.0 between the highest and lowest quintiles.

For each cohort, RRs adjusted for potential confounders were estimated using pooled logistic regression analyses with 2-year time increments. With short intervals between questionnaires and the low rates of events, this approach yields results similar to those of a Cox regression analysis with time-varying covariates.³¹ In these models, age was categorized into 5-year age groups and cigarette smoking was categorized as follows (based on a previous analysis of these cohorts²⁹): never smoker, quit more than 15 years ago, quit less than 15 years ago and smoked less than 25 pack-years in past 15 years, quit less than 15 years ago and smoked more than 25 pack-years in past 15 years, current smoker with less than 25 pack-years in past 15 years, and current smoker with more than 25 pack-years in past 15 years (age and smoking

variables were updated biennially). In addition, we controlled for history of diabetes and cholecystectomy updating these variables biennially in the analyses.^{4,32,33} We categorized men and women into 5 groups of BMI using whole number cutpoints that included widely used definitions of overweight and obesity.^{34,35} BMI was not updated in the main analyses because pancreatic cancer is frequently associated with profound weight loss. In addition, we performed analyses with a 2-year lag to exclude preclinical cases at baseline. We used quintiles of total, vigorous, and moderate physical activity in both cohorts and did not update these variables over time since preclinical symptoms could affect activity levels. For height, whole cutpoints were made to approximate increments of 2.54 to 5.08 cm and keeping person-years fairly evenly distributed across the categories. All *P* values are based on 2-sided tests.

We pooled the data from the 2 cohorts using a random-effects model for the log of the RRs.³⁶ Tests of heterogeneity using the *Q* statistic³⁶ were obtained for continuous variables to evaluate the overall trend before pooling. All statistical procedures were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). The Human Research Committee at the Brigham and Women's Hospital approved the NHS and the Harvard School of Public Health Human Subjects Committee approved the HPFS.

RESULTS

We examined BMI and physical activity in relation to potential confounders for both men and women (TABLE 1). History of diabetes or cholecystectomy was higher among individuals with elevated BMI or with low physical activity. Men and women with low BMI or low physical activity were more likely to be current smokers, although men with high BMI had smoked more cigarettes in the past. Height and age were not substantially different by BMI or physical activity level. Caloric intake was slightly higher and percentage of total calories from fat was slightly lower among those in the top quintile

of physical activity. As expected, physically active individuals tended to be leaner whereas heavier individuals tended to be more sedentary.

During 2800837 person-years of follow-up from the 2 cohorts, we identified 140 men and 210 women who were diagnosed as having pancreatic cancer. A statistically significant association between BMI and the risk of pancreatic cancer was observed in both cohorts (TABLE 2). After adjusting for known risk factors, men and women with a BMI of 30 or higher had a 72% increase in the risk of pancreatic cancer compared with men and women with a BMI of less than 23. In multi-

variable analyses, an increment of 1 BMI unit (1 kg/m²) was associated with a 5% increased risk of pancreatic cancer in the HPFS (RR, 1.05; 95% CI, 1.00-1.11) and a 3% increased risk in the NHS (RR, 1.03; 95% CI, 1.00-1.07). Of all the pancreatic cancer cases, only 24 women and 14 men were diabetic prior to diagnosis. Controlling for smoking history using cumulative (lifetime) pack-years did not change the results for BMI and pancreatic cancer risk.

To eliminate preclinical cases that might have experienced weight loss before completing the baseline questionnaires, we performed analyses that excluded the first 4 years of follow-up. In

both cohorts, associations with BMI were strengthened in lag analyses in top vs bottom category comparison (multivariable RR, 1.94; 95% CI, 1.26-2.98 in women and multivariable RR, 2.03; 95% CI, 0.90-4.57 in men).

In each cohort, we examined the effect of body size at a younger age using BMI at ages 18 years (NHS) and 21 years (HPFS). Women with a BMI of 24 or greater at age 18 years had a nonsignificant elevation in the risk of pancreatic cancer when compared with a BMI of less than 20 among women at age 18 years (RR, 1.45; 95% CI, 0.92-2.31). After adjusting for current BMI and other risk factors, the risk of pancreatic cancer asso-

Table 1. Baseline Characteristics Among Men in the HPFS and Women in the NHS Cohorts According to Category of BMI or Physical Activity*

Characteristic	Health Professionals Follow-up Study			Nurses' Health Study		
	<23.0	BMI, kg/m ² † 23.0-29.9	≥30.0	<23.0	BMI, kg/m ² † 23.0-29.9	≥30.0
No. of individuals	8477	34 348	3823	60 567	46 606	9868
Age, y, mean (SD)	53.9 (10)	54.4 (9.7)	54.0 (9.0)	41.6 (7.1)	44.1 (7.1)	44.4 (6.9)
Height, cm, mean (SD)	178.3 (6.9)	178.3 (6.6)	176.8 (10.4)	164.1 (6.1)	163.6 (6.1)	163.1 (6.1)
BMI, kg/m ² , mean (SD)	21.7 (1.0)	25.7 (1.7)	32.6 (3.0)	21.0 (1.3)	25.4 (1.9)	33.6 (3.5)
MET, h/wk, mean (SD)‡	24.3 (30)	20.0 (25)	12.9 (22)	15.6 (23)	12.9 (19)	9.9 (16)
History of diabetes, %	2.7 (16)	2.9 (17)	5.7 (23)	1.0 (10)	1.7 (13)	5.9 (24)
Cholecystectomy, %	1.9 (13)	3.0 (17)	4.9 (21)	3.6 (18)	6.7 (25)	14.7 (36)
Current smokers, %	10.5 (30)	9.3 (29)	9.1 (29)	36.8 (48)	30.6 (46)	25.0 (43)
Pack-years of cigarettes, mean (SD)§	11.2 (18)	13.2 (19)	16.7 (22)	6.5 (8.5)	5.9 (8.5)	5.3 (8.5)
Daily intake, mean (SD)						
Calories, kcal	2006 (609)	1977 (618)	2018 (654)	1565 (498)	1560 (502)	1604 (527)
Total fat, % of kcal	30.7 (6.8)	32.1 (6.2)	33.9 (12)	38.8 (1.6)	38.9 (7.9)	39.5 (8.0)
Alcohol, g	10.7 (14)	11.6 (15)	10.2 (16)	7.5 (11)	5.6 (10.2)	3.1 (7.8)

Characteristic	Health Professionals Follow-up Study			Nurses' Health Study		
	Physical Activity, quintiles ≤2.8	2.9-33.9	≥34.0	Physical Activity, quintiles ≤2.0	2.1-21.7	≥21.8
No. of individuals	9015	27 760	9340	13 538	48 638	15 383
Age, y, mean (SD)	54.9 (9.7)	54.6 (9.7)	53.2 (9.6)	52.9 (7.1)	52.9 (7.2)	53.0 (7.2)
Height, cm, mean (SD)	177.8 (8.6)	178.1 (8.4)	178.1 (8.6)	163.6 (8.4)	163.8 (8.1)	163.8 (7.6)
BMI, kg/m ² , mean (SD)	26.2 (3.6)	25.5 (3.1)	24.8 (2.8)	24.5 (4.8)	23.7 (4.0)	23.1 (3.6)
MET, h/wk, mean (SD)‡	1.20 (0.8)	13.8 (8.4)	57.2 (35)	0.72 (0.4)	8.6 (5.7)	43.3 (31)
History of diabetes, %	4.2 (20)	3.1 (17)	2.2 (14)	5.0 (22)	4.0 (19)	3.0 (17)
Cholecystectomy, %	3.9 (20)	2.8 (17)	2.6 (15)	11.6 (32)	9.6 (29)	8.0 (27)
Current smokers, %	14.5 (35)	9.1 (29)	6.4 (25)	28.8 (45)	20.5 (40)	17.5 (38)
Pack-years of cigarettes, mean (SD)§	16.5 (23)	12.9 (19)	10.7 (17)	7.2 (9.4)	5.6 (8.1)	5.2 (7.5)
Daily intake, mean (SD)						
Calories, kcal	1933 (618)	1983 (613)	2049 (636)	1704 (538)¶	1774 (520)¶	1798 (533)¶
Total fat, % of kcal	33.3 (6.3)	32.0 (6.2)	30.5 (8.4)	33.9 (5.9)	32.8 (5.5)	31.5 (5.8)
Alcohol, g	10.8 (16)	11.2 (15)	12.2 (15)	5.9 (12)	6.0 (10)	7.0 (11)

*All variables (except age) are age-standardized means. BMI indicates body mass index; and MET, metabolic equivalents.

†Baseline: 1986 for HPFS, 1976 for NHS (dietary values from 1980 food frequency questionnaire).

‡MET, h/wk, sum of the average time/week spent in each activity times MET value of each activity (1986 for NHS).

§Pack-years are calculated for current and past smokers.

¶Baseline: 1986 for both cohorts. Physical activity was categorized according to quintile 1, quintile 2 through 4, and quintile 5.

||Caloric intake is higher on average in the 1986 questionnaire because the food frequency questionnaire had more items than in the 1980 food frequency questionnaire.

ciated with BMI at age 18 years was attenuated (multivariable RR, 1.09; 95% CI, 0.66-1.80). Men with a BMI of 27 or higher at age 21 years had an RR of 1.80 (95% CI, 0.97-3.34) compared with men who had a BMI of less than 21 at age 21 years, but controlling for current BMI also attenuated the association (multivariable RR, 1.50; 95% CI, 0.75-3.00).

We also examined the relation of weight loss to risk of pancreatic cancer. Compared with individuals whose weight had not changed by more than 2.25 kg between 2 consecutive biennial questionnaires, individuals who reported losing 6.75 or more kg between 2 consecutive biennial questionnaires had an RR of 4.56 (95% CI, 2.35-8.84) among men and 2.44 (95% CI, 1.46-4.06) among women. In both cohorts, only recent weight loss was associated with risk suggesting an influence of preclinical disease. Compared with those who had not lost 6.75 kg, the

RR of pancreatic cancer was 3.66 (95% CI, 2.00-6.70) and 2.60 (95% CI, 1.53-4.40) in men and women, respectively, for a 6.75-kg weight loss within the past 2 years.

We observed an association between height and risk of pancreatic cancer in both cohorts (Table 2). Although cut-points for the categories of height were different for men and women, both cohorts had similar increases in RR when comparing the highest and lowest categories. When men and women were combined, individuals in the highest vs lowest category of height had an RR of 1.81 (95% CI, 1.31-2.52) adjusting for potential confounders and BMI. The age-adjusted RRs were very similar, however, and including BMI in the multivariable model did not change the association. In multivariable analyses, an additional 2.54 cm of height increased the risk of pancreatic cancer by 6% in the HPFS (RR, 1.06; 95% CI, 0.99-1.12) and

by 10% in the NHS (RR, 1.10; 95% CI, 1.04-1.16).

A total of 1 277 183 person-years and 249 pancreatic cancer cases (139 men, 110 women) were available for the physical activity analyses. We detected a slight inverse association between total physical activity and pancreatic cancer risk, but associations were not statistically significant in either cohort (TABLE 3). Vigorous activity was not related to the risk of pancreatic cancer in men or women in the multivariable models. In contrast, we observed inverse associations for moderate activity and pancreatic cancer risk in both cohorts. In the multivariable pooled analysis, men and women in the highest quintile of moderate activity had a significant reduction in the risk of pancreatic cancer (RR, 0.45; 95% CI, 0.29-0.70; $P < .001$ for trend) compared with those in the lowest quintile (Table 3). Additional control for total fat, pro-

Table 2. Relative Risk (RR) for Pancreatic Cancer by Height and Body Mass Index (BMI) in the NHS and HPFS*

	Category					P Value for Trend
	1	2	3	4	5	
	BMI, kg/m²					
	<23.0	23.0-24.9	25.0-26.9	27.0-29.9	≥30.0	
Men						
Cases/person-years	19/95 809	32/149 749	44/143 405	29/97 164	16/43 370	
Age-adjusted RR†	1.00	1.06 (0.60-1.87)	1.45 (0.85-2.49)	1.41 (0.79-2.51)	1.83 (0.94-3.56)	.04
Multivariable RR‡	1.00	1.07 (0.61-1.89)	1.48 (0.86-2.54)	1.38 (0.77-2.48)	1.76 (0.90-3.45)	.05
Women						
Cases/person-years	85/1 178 921	41/437 651	29/264 451	24/201 117	31/189 200	
Age-adjusted RR†	1.00	1.05 (0.73-1.53)	1.16 (0.76-1.78)	1.25 (0.79-1.97)	1.77 (1.17-2.68)	.01
Multivariable RR‡	1.00	1.10 (0.75-1.59)	1.18 (0.77-1.80)	1.25 (0.79-1.99)	1.70 (1.09-2.64)	.02
Pooled multivariable RR‡	1.00	1.09 (0.79-1.49)	1.29 (0.92-1.80)	1.30 (0.91-1.87)	1.72 (1.19-2.48)	.003
	Height, cm					
	≤172.7	175.3	177.8-180.3	182.9	≥185.4	
Men						
Cases/person-years	34/140 138	14/62 516	45/162 667	18/72 553	29/91 623	
Age-adjusted RR†	1.00	1.00 (0.54-1.87)	1.34 (0.86-2.10)	1.32 (0.75-2.35)	1.88 (1.14-3.10)	.01
Multivariable RR‡	1.00	1.01 (0.54-1.88)	1.34 (0.86-2.10)	1.34 (0.75-2.38)	1.88 (1.14-3.11)	.01
Women						
Cases/person-years	36/513 468	20/274 705	41/384 421	63/638 454	50/460 291	
Age-adjusted RR†	1.00	1.04 (0.60-1.80)	1.59 (1.02-2.49)	1.51 (1.00-2.27)	1.76 (1.14-2.70)	.006
Multivariable RR‡	1.00	1.04 (0.60-1.79)	1.61 (1.03-2.51)	1.52 (1.01-2.29)	1.77 (1.15-2.72)	.006
Pooled multivariable RR‡	1.00	1.03 (0.68-1.53)	1.47 (1.07-2.02)	1.46 (1.04-2.03)	1.81 (1.31-2.52)	.001

*NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; and CI, confidence interval.

†Data presented as RR (95% CI).

‡Relative risks are from a multivariable model that included height, BMI (assessed at baseline), age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy.

tein, fruit and vegetables, and coffee or alcohol intakes did not alter the associations reported in Table 2 or Table 3.

Walking or hiking outdoors accounted for an average of 70% of the METs associated with moderate activ-

ity in each cohort. In both cohorts, we observed inverse associations between hours per week of walking or

Table 3. Relative Risk (RR) for Pancreatic Cancer in Relation to Physical Activity in the NHS and HPFS*

	Quintiles					P Value for Trend
	1	2	3	4	5	
Total Physical Activity, MET, h/wk						
	≤2.8	2.9-7.7	7.8-16.9	17.0-33.9	≥34.0	
Men						
Cases/person-years	31/102 119	34/102 525	29/107 012	26/107 418	19/108 111	
Age-adjusted RR†	1.00	1.06 (0.65-1.72)	0.89 (0.54-1.48)	0.84 (0.50-1.42)	0.65 (0.37-1.14)	.07
Multivariable RR‡	1.00	1.10 (0.68-1.80)	0.95 (0.57-1.59)	0.92 (0.54-1.55)	0.72 (0.40-1.27)	.15
Women						
Cases/person-years	24/143 775	27/155 886	20/150 791	21/148 463	18/151 083	
Age-adjusted RR†	1.00	1.02 (0.59-1.77)	0.79 (0.44-1.43)	0.84 (0.47-1.50)	0.70 (0.38-1.30)	.21
Multivariable RR‡	1.00	1.00 (0.56-1.77)	0.84 (0.46-1.55)	0.84 (0.45-1.55)	0.78 (0.42-1.47)	.40
Pooled multivariable RR‡	1.00	1.06 (0.73-1.54)	0.91 (0.61-1.34)	0.88 (0.59-1.32)	0.74 (0.49-1.14)	.10
Vigorous Activity, MET, h/wk						
	0	0.1-3.4	3.5-11.9	12.0-29.9	≥30.0	
Men						
Cases/person-years	61/191 529	20/87 822	28/83 120	19/84 325	11/80 389	
Age-adjusted RR†	1.00	0.84 (0.51-1.39)	1.29 (0.83-2.03)	1.00 (0.59-1.67)	0.68 (0.36-1.30)	.32
Multivariable RR‡	1.00	0.84 (0.51-1.40)	1.40 (0.89-2.20)	1.11 (0.66-1.87)	0.77 (0.40-1.48)	.59
Women						
Cases/person-years	62/346 628	11/102 850	10/87 299	13/115 069	14/98 151	
Age-adjusted RR†	1.00	0.67 (0.35-1.27)	0.70 (0.36-1.36)	0.68 (0.37-1.24)	0.88 (0.49-1.56)	.69
Multivariable RR‡	1.00	0.66 (0.34-1.29)	0.64 (0.31-1.35)	0.76 (0.41-1.43)	1.06 (0.57-1.96)	.80
Pooled multivariable RR‡	1.00	0.77 (0.51-1.15)	1.00 (0.47-2.14)	0.95 (0.64-1.43)	0.91 (0.58-1.42)	.74
Moderate Activity, MET, h/wk						
	<0.8	0.8-2.2	2.3-4.8	4.9-10.9	≥11.0	
Men						
Cases/person-years	33/98 894	26/108 961	38/107 632	22/105 927	20/105 770	
Age-adjusted RR†	1.00	0.74 (0.44-1.24)	0.95 (0.59-1.51)	0.53 (0.31-0.90)	0.41 (0.23-0.71)	<.001
Multivariable RR‡	1.00	0.75 (0.46-1.25)	0.95 (0.60-1.52)	0.52 (0.31-0.90)	0.41 (0.24-0.72)	<.001
Women						
Cases/person-years	24/124 288	26/154 031	22/164 935	23/159 687	15/147 057	
Age-adjusted RR†	1.00	0.97 (0.56-1.70)	0.72 (0.40-1.28)	0.77 (0.43-1.36)	0.51 (0.27-0.97)	.03
Multivariable RR‡	1.00	1.01 (0.56-1.81)	0.85 (0.47-1.55)	0.85 (0.46-1.57)	0.52 (0.26-1.05)	.05
Pooled multivariable RR‡	1.00	0.85 (0.58-1.25)	0.91 (0.63-1.32)	0.65 (0.41-1.04)	0.45 (0.29-0.70)	<.001
Walking or Hiking, per Week						
	<20 min	20-80 min	1.5-3 h	≥4 h		P Value for Trend
Men						
Age-adjusted RR†	1.00	0.93 (0.60-1.43)	0.58 (0.35-0.95)	0.43 (0.25-0.76)	<.001	
Multivariable RR‡	1.00	0.96 (0.62-1.49)	0.61 (0.37-1.00)	0.45 (0.26-0.80)	<.001	
Women						
Age-adjusted RR	1.00	0.66 (0.41-1.06)	0.57 (0.34-0.96)	0.46 (0.24-0.85)	.02	
Multivariable RR‡	1.00	0.79 (0.48-1.30)	0.65 (0.38-1.13)	0.48 (0.24-0.97)	.04	
Pooled multivariable RR‡	1.00	0.88 (0.64-1.22)	0.63 (0.43-0.91)	0.46 (0.30-0.72)	<.001	

*NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalents; and CI, confidence interval. The NHS analyses use 1986 as baseline.

†Data presented as RR (95% CI).

‡Relative risks are from a multivariable model that included height, age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy. Moderate activity was included in the vigorous activity models.

hiking and pancreatic cancer risk. Among men and women, walking or hiking 4 or more hours per week was associated with a 54% lower risk of pancreatic cancer when compared with less than 20 minutes per week.

The potential inverse association between moderate activity and pancreatic cancer risk could be the result of early symptoms associated with the disease. To address this question, we performed 2-year lag analyses in each cohort (starting follow-up time in 1988) to avoid including individuals who were diagnosed as having pancreatic cancer within 2 years of having responded to the physical activity questions. Associations in these analyses were not substantially different for total physical activity, vigorous activity, or moderate activity (pooled multivariable RR, 0.48; 95% CI, 0.25-0.92 top vs bottom quintile comparison).

To explore the possibility of an interaction between physical activity and BMI, we examined the risk of pancreatic cancer according to both total physical activity (in tertiles) and BMI (<25.0, 25.0-29.9, and ≥ 30.0 kg/m²) among men and women combined. After adjusting for potential confounders, the association between total physical activity level and the pancreatic cancer risk was modified by BMI (FIGURE). Among nonoverweight participants (BMI <25 kg/m²), total physical activity was not related to the risk of pancreatic cancer, but total physical activity was inversely associated with risk among overweight individuals (pooled multivariable RR, 0.59; 95% CI, 0.37-0.94 for top vs bottom tertile of total physical activity among individuals with BMI ≥ 25 kg/m²; *P* = .04 for trend). Individuals with a BMI of 30 kg/m² or higher in the lowest tertile of exercise had twice the risk of pancreatic cancer compared with individuals who had a BMI of lower than 25 kg/m² in the highest tertile of total physical activity.

While the Figure presents data for the pooled analysis, findings were homogeneous across the 2 cohorts with the exception of a greater increase in risk in the high BMI and low physical activity category in men than women, compared with the reference (HPFS:

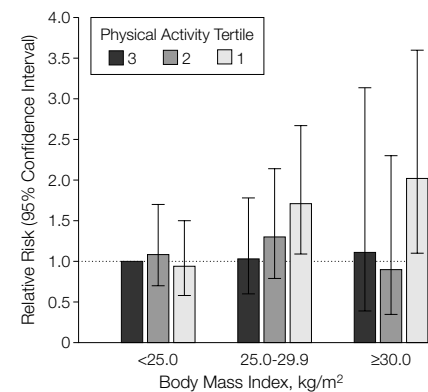
multivariable RR, 2.43; 95% CI, 1.13-5.23; NHS: multivariable RR, 1.57; 95% CI, 0.65-3.82). The nature of the association between physical activity and BMI appears to be an example of a "joint exposure" in which elevated risk of pancreatic cancer is only apparent in individuals who have combined exposures (high BMI and low physical activity). However, the multiplicative interaction reported in the Figure was not statistically significant. Removing current smokers from these analyses resulted in similar findings.

COMMENT

In 2 prospective cohort studies, we found a consistent and significant excess risk of pancreatic cancer among obese men and women (BMI ≥ 30 kg/m² compared with <23 kg/m²). A direct association between height and the risk of pancreatic cancer was also observed in these 2 cohorts. Both cohorts demonstrated strong inverse associations for moderate physical activity, specifically for walking or hiking outdoors. Although total physical activity was not significantly related to the risk of pancreatic cancer overall, it was inversely associated with risk among overweight individuals (BMI ≥ 25 kg/m²). Physical activity appeared to have no effect on risk among nonoverweight participants (<25 kg/m²). Moreover, BMI had no apparent influence on risk among men and women who were exercising (top 2 tertiles of physical activity).

Several case-control studies have examined BMI or weight and pancreatic cancer risk, but findings have been inconsistent. A total of 4^{16-18,37} of 7^{14-18,37-39} case-control studies reported no association for BMI or weight and the risk of pancreatic cancer. The largest study to date,^{38,39} based only on direct interviews with cases, showed a 50% to 60% increase in the risk of pancreatic cancer in obese individuals that was consistent by sex and race. Obesity was associated with increased risk of pancreatic cancer in 3 studies in which weight was determined prior to the detection of pancreatic cancer¹¹⁻¹³ in men, but not women, in a recent mortality cohort

Figure. Pancreatic Cancer According to Physical Activity and Body Mass Index From the NHS and HPFS Cohorts



NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

study.⁵ A prospective cohort study of pancreatic cancer in elderly persons did not detect any association for BMI.⁴⁰

There are several possible explanations for the discrepancies across studies on obesity and pancreatic cancer risk. Because pancreatic cancer is highly fatal, numerous case-control studies had to obtain information on cases through indirect interviews¹⁵⁻¹⁸ or did not obtain weight on deceased cases.^{14,38,39} These methods may have led to biased findings, if, for example, leaner individuals had higher survival rates. In retrospective studies, prediagnostic weight loss associated with pancreatic cancer may have biased weight recall. Among previous studies, cutpoints for the top categories of BMI may not have been set high enough to detect an association with BMI, as risk appears to be most elevated among men and women with a BMI of 30 or higher. In 2 studies in which no influence of BMI was observed, the cutpoints of the top categories were relatively low: 23.2 in women, 23.9 in men,⁴⁰ and 26.5 in both sexes.¹⁶

Previous studies have also examined the association of height and pancreatic cancer risk. Although findings have not been entirely consistent,^{14-17,37} at least 2 studies reported nonsignificant positive associations for height.^{16,17} In a third study conducted in the Netherlands, a sig-

nificant positive association was reported among women.¹⁵ An association between height and cancer risk at other sites has been reported in the HPFS cohort and in other studies.¹⁹⁻²¹ Height may serve as a proxy for net energy intake or exposure levels to growth factors such as insulin and insulin-like growth factor 1 during childhood.

To our knowledge, this was the first epidemiologic study to examine the relation between physical activity and the risk of pancreatic cancer. Thus, further studies are needed. Nonetheless, the consistency in the associations for moderate physical activity observed in 2 entirely separate cohorts argues strongly against the role of chance as an explanation for our findings.

Our findings related to BMI and physical activity may be explained, biologically, within the axis of abnormal glucose intolerance and hyperinsulinemia. In a recent prospective study, a 2-fold elevation in fatal pancreatic cancer was detected among individuals with high prediagnostic postload plasma glucose levels (>200 mg/dL [>11.1 mmol/L]) compared with low levels (<119 mg/dL [<6.6 mmol/L]).⁵ Abnormal glucose metabolism and hyperinsulinemia have been proposed as underlying mechanisms that might explain the positive association between diabetes mellitus and the risk of pancreatic cancer.⁴ Hyperinsulinemia has been shown to increase local blood flow and cell division within the pancreas.^{41,42} By causing the downregulation of insulin-like growth factor binding protein 1, excess insulin may also result in an increase in exposure to free insulin-like growth factor 1, which has been shown to promote growth in human pancreatic cell lines.⁴³⁻⁴⁵

Physical activity has long been known to reduce glucose intolerance and an elevated BMI is associated with an increase in risk of hyperinsulinemia and diabetes. In addition, studies have demonstrated that weight loss is not necessary to benefit from the effects of physical activity on glucose tolerance and insulin clearance rates.^{23,46} Our findings are consistent because we ob-

served an inverse association between physical activity and pancreatic cancer risk, especially among those who were obese. Moreover, since the obese group is more likely to include persons with glucose abnormalities than the overweight group, evidence for a stronger inverse association with activity in the obese is consistent with a mechanism involving glucose tolerance.

An alternative mechanism for the association between BMI and pancreatic cancer may be related to DNA adduct formation.⁴⁷ Comparing pancreatic tissue from healthy individuals (organ donors) and cancer patients, DNA adduct levels were reported to be significantly higher in cancer patients. Positive correlations were found between BMI and the levels of lipid peroxidation-related DNA adducts and total adduct levels in cancer patients, which persisted after controlling for age, sex, and smoking. Thus, an increase in DNA damage to the pancreas caused by increased lipid peroxidation in individuals with elevated BMIs may be an alternative explanation for the observed association with BMI.

Our findings observed a strong association for moderate activity in both cohorts, but not for vigorous activity. One possible explanation is related to the modifying effect of obesity. Because men and women who are overweight or obese appear to benefit the most from physical activity but are less likely to participate in vigorous exercise, the effect of physical activity may be most apparent for moderate activity.

An alternative explanation for our findings is related to energy expenditure vs cardiorespiratory fitness. A recent study demonstrated that regular exercise at low intensity may be more important than cardiorespiratory fitness obtained with vigorous exercise in reducing glucose intolerance.⁴⁸ In both our cohorts, the level of vigorous activity was much lower among those with BMI of 30 kg/m² or higher compared with a BMI of lower than 30 (for vigorous activities: 13.0 vs 6.3 METs for BMI <30 vs BMI ≥ 30 in HPFS; 7.1 vs 4.5 METs for BMI <30 vs BMI ≥ 30 in

NHS). In contrast, the difference in METs for moderate activity was substantially lower (7.8 vs 6.3 METs for BMI <30 vs BMI ≥ 30 in HPFS; 7.3 vs 5.5 METs for BMI <30 vs BMI ≥ 30 in NHS). Although the average level of METs expended in vigorous and moderate activities is similar for individuals with elevated BMIs, less time is spent exercising for those performing vigorous exercise, given that METs reflect time exercising and intensity level (intensity is higher). It is therefore possible that low activity exercising (moderate activity) is more successful at reducing risk in overweight individuals because, on average for those individuals, more time is spent exercising.

Alternatively, we cannot exclude the possibility that vigorous and moderate exercisers may have differed on other characteristics that were not considered in this article, possibly explaining the relationship reported for physical activity. However, certain dietary factors are unlikely to account for the relationships given that we observed no association for either coffee or alcohol intakes and pancreatic cancer risk,⁴⁹ and that adjusting for total fat intake did not change the associations.

The strengths of this study include a prospective design, large sample size, data from 2 completely separate cohorts, and detailed information on potential risk factors of pancreatic cancer. The prospective design precluded recall bias and the need to use next-of-kin respondents. Moreover, because exposure data were collected before the diagnosis of any cases of pancreatic cancer, any error in recall (nondifferential misclassification) would have attenuated rather than exaggerated a true association. Differential follow-up is unlikely to have made a material contribution to these findings, since follow-up was high.⁵⁰

In summary, we observed an increased risk of pancreatic cancer among obese men and women in 2 prospective cohorts. Walking or hiking 1.5 hours or more per week was associated with a 50% reduction in pancreatic cancer risk in men and women. The inverse associa-

tion of physical activity with the risk of pancreatic cancer was most apparent among obese individuals who were more likely to have glucose abnormalities and who may thus benefit from an improved glucose response associated with exercising. While our findings require confirmation, they provide support for a role of insulin resistance and hyperinsulinemia in the pathogenesis of pancreatic cancer.

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