Obesity, Recreational Physical Activity, and Risk of Pancreatic Cancer In a Large U.S. Cohort

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Abstract

Background: **Obesity and physical activity, in part through their effects on insulin sensitivity, may be modifiable risk factors for pancreatic cancer.**
Methods: **The authors analyzed data from the American Cancer Society Cancer Prevention Study II Nutrition Cohort to examine the association between measures of adiposity, recreational physical activity, and pancreatic cancer risk. Information on current weight and weight at age 18, location of weight gain, and recreational physical activity were obtained at baseline in 1992 via a self-administered questionnaire for 145,627 men and women who were cancer-free at enrollment. During the 7 years of follow-up, 242 incident pancreatic cancer cases were identified among these participants. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) and to adjust for potential confounding factors including personal history of diabetes and smoking.**
Results: **We observed an increased risk of pancreatic cancer among obese [body mass index (BMI) ≥30] men and women compared with men and women of normal BMI [<25; RR, 2.08; 95% confidence interval (95% CI), 1.48-2.93, P_{trend} = 0.0001]. After adjustment for between BMI, risk of pancreatic cancer was independently increased among men and women who reported a tendency for central weight gain compared with men and women reporting a tendency for peripheral weight gain (RR, 1.45; 95% CI, 1.02-2.07). We observed no difference in pancreatic cancer incidence rates between men and women who were most active (>31.5 metabolic equivalent hours per week) at baseline compared with men and women who reported no recreational physical activity (RR, 1.20; 95% CI, 0.63-2.27).**
Conclusion: **This study, along with several recent studies, supports the hypothesis that obesity and central adiposity are associated with pancreatic cancer risk.** (Cancer Epidemiol Biomarkers Prev 2005;14(2):459–66)

Introduction

Pancreatic cancer is the fourth leading cancer cause of death among U.S. men and women (1). Over 31,000 new cases and an equal number of deaths due to pancreatic cancer are estimated to occur in 2004 (1). Cigarette smoking and diabetes are the only risk factors that have been consistently associated with pancreatic cancer (2-6). In addition, insulin resistance and abnormal glucose metabolism, without a diagnosis of diabetes, may also be risk factors in pancreatic cancer etiology (7-9). There is a direct relationship between body mass index (BMI) and insulin production, and there is sufficient evidence that obesity, especially intra-abdominal fat, is related to the development of insulin resistance (10). Physical activity may increase insulin sensitivity through reduction of intra-abdominal fat deposits; additionally, physical activity, independent of its effects on weight, has been associated with improved glucose metabolism, increased insulin sensitivity, and decreased plasma insulin levels (10). Therefore, we hypothesized that obesity, through BMI and abdominal weight gain, and physical activity may be modifiable risk factors for pancreatic cancer.

Results of previous observational studies on the association between obesity, physical activity, and pancreatic cancer risk have been inconsistent. Of the 20 studies (12 prospective cohorts, refs. 3, 7, 11-20; and eight case-control studies, refs. 21-28) that have reported on the association between BMI and pancreatic cancer risk, 10 report a positive association (7, 11, 13, 16, 17, 19, 21-24) and 10 report no association (3, 5, 12, 14, 15, 18, 20, 25-28). Most early reports that observed no relationship between increasing BMI and risk of pancreatic cancer had limited power to examine a wide range of BMI (3, 15, 18, 20, 25-27), used proxy respondents for case patients (25-28), or did not adjust for important factors, such as smoking, that may significantly modify the association between obesity and pancreatic cancer risk (3, 18, 25, 27). However, more recent studies (since 1995), including a few large prospective cohorts, suggest that obese (BMI $\geq$ 30) individuals may have a higher risk of developing pancreatic cancer (11, 13, 16, 17, 19, 23, 24). One previous study (15) examined the association between pancreatic cancer risk and adult weight gain and reported a nonstatistically significant positive association. To our knowledge, no previous study has examined the association between location of weight gain and pancreatic cancer risk.

Of the seven studies (five prospective cohorts, refs. 3, 12, 14-16; two case-control studies, refs. 22, 29) that have reported on the association between recreational physical activity and pancreatic cancer, four studies found an inverse association (15, 16, 22, 29) and three found no association (3, 12, 14) between physical activity and pancreatic cancer risk. However, in most positive studies, a lower risk of pancreatic cancer generally was observed only with high levels of moderate to vigorous physical activity (15, 22, 29). Only one previous study (16), analyzing data from the Health Professionals Follow-up Cohort and Nurses' Health Study, observed a significant inverse association with moderate-intensity activities or walking/hiking for men and women; but this study found no association with vigorous activity. Consequently, the frequency, intensity, and type of physical activity necessary to influence pancreatic cancer risk remain unclear.

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We examined the association of BMI, weight gain, location of weight gain, recreational physical activity, and risk of pancreatic cancer among men and women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the United States. It should be noted that 38% of pancreatic cancer cases (49 cases in men and 44 cases in women) in this study were also included in the previous publication by Calle et al. (13) on obesity and cancer mortality using the larger CPS-II Mortality Cohort.

Materials and methods

Study Population. Men and women in this analysis were drawn from the 184,190 participants in the CPS-II Nutrition Cohort, which was established in 1992 by the American Cancer Society as a subgroup of the larger 1982 CPS-II baseline mortality cohort (30). Nearly all participants were ages 50 to 74 years at enrollment in 1992, and they completed a 10-page self-administered questionnaire that included questions on demographic, medical, reproductive, behavioral, environmental, and dietary factors. Beginning in 1997, follow-up questionnaires have been sent to cohort members every 2 years to update exposure information and to ascertain newly diagnosed cancers. Questionnaire response rates among living cohort members have been at least 90%. Cohort members who died are identified by routine linkage of the entire cohort with the National Death Index (31).

This analysis is based on 7 years of follow-up. We excluded participants who were lost to follow-up from 1992 to 1999 (n = 8,223), who reported prevalent cancer (except nonmelanoma skin cancer) at baseline (n = 20,934), who had missing or extreme (lowest and highest 0.1%) values of BMI (n = 4,794), who left the baseline recreational physical activity section blank (n = 2,180), or who had missing information on smoking status (n = 1,575). We also excluded individuals who died from any cause within the first year of follow-up to reduce the possibility of undiagnosed disease at baseline (n = 852) and those with an unverified date of diagnosis of pancreatic cancer (n = 5). After all exclusions, the final analytic cohort consisted of 145,627 men and women with a mean age at study entry of 62.9 years (±6.4 SD).

Case Ascertainment. We identified a total of 242 incident pancreatic cancers that occurred between the date of enrollment and August 31, 1999, among those cohort members eligible for analysis. Seventy-nine percent of incident pancreatic cancers (n = 190) were initially identified through automated linkage of the cohort with the National Death Index where pancreatic cancer was listed as a primary or contributory cause of death (International Classification of Diseases, Ninth Revision codes 157 to 157.9 or International Classification of Diseases, Tenth Revision codes C25-C25.9; refs. 32, 33). Additional information for 141 of these interval deaths was obtained through linkage with state cancer registries. Pancreatic cancer cases (n = 41) were also initially identified by self-report on one of the two follow-up questionnaires (1997 and 1999) and subsequently verified by medical records (n = 26) or linkage with state cancer registries (n = 15). A previous study linking cohort participants with state cancer registries has shown that the Nutrition Cohort participants are highly accurate (93% sensitivity) in reporting any past cancer diagnoses (34). Finally, an additional 11 pancreatic cancer cases were reported by the participant as another cancer but were found to be pancreatic cancer upon examination of medical or registry records.

Measures of Obesity and Physical Activity. BMI (weight in kg/height in m^2) at baseline was calculated using self-reported weight and height and categorized as follows: 18.5 to 24.9, 25 to 29.9, and ≥30. According to the WHO definition for obesity, a BMI <25 is considered ''normal weight,'' 25 to 29.9 is ''grade 1 overweight,'' 30 to 39.9 is ''grade 2 overweight,'' and 40 or more is ''grade 3 overweight'' (35). In this analysis, we refer to BMI of 25 to 29.9 as ''overweight'' and BMI of ≥30 as ''obese.'' We also categorized BMI at age 18 (using recalled weight at age 18 reported in 1992) as <21, 21 to 22.9, and ≥23. BMI <25 in 1992 and BMI <21 at age 18 were the reference groups in their respective analyses.

We categorized adult weight change in kilograms (kg) between age 18 and weight at baseline and categorized as lost >2.27 kg, lost 2.27 kg to gained 4.54 kg (reference group), gained 4.55 to 9.07 kg, gained 9.08 to 13.61 kg, and gained ≥13.62 kg. Lastly, we categorized location of weight gain using the question ''When you gain weight, where on your body do you mainly add the weight: chest and shoulders, waist, hips and thighs, other part of the body, equally all over, or don't gain weight?.'' Central weight gain was defined as reported weight gain in chest and shoulders or waist, and peripheral weight gain was defined as reported weight gain in hips and thighs or equally all over. The vast majority of individuals categorized as central weight gainers reported weight gain on the waist only (84.2% of men and 80.3% of women), and a small percent of those included as central weight gainers gained weight on the waist and chest and shoulders (13.7% of men and 17.2% of women). Most men (95%) categorized as peripheral weight gainers reported weight gain equally all over, whereas reported weight gain in hips and thighs or equally all over was approximately equal in women categorized as peripheral weight gainers. Men and women with other responses that could not be clearly categorized into one of these two groups were excluded from analyses examining location of weight gain.

Baseline recreational physical activity information was collected using the question ''During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?.'' Response to each activity could be ''none,'' ''1 to 3 h/wk,'' ''4 to 6 h/wk,'' or ''7+ h/wk.'' Summary metabolic equivalent (MET) hours per week were calculated for each participant. A MET is the ratio of metabolic rate during a specific activity to resting metabolic rate (36). The summary MET score for each participant was calculated by multiplying the hours spent engaged in each activity (0 for none, 1 for 1-3 h/wk, 4 for 4-6 h/wk, and 7 for 7+ h/wk) times the MET score estimated for each activity according to the Compendium of Physical Activities (36). Due to the older age of this population, MET-hours per week were calculated using the lowest value in a category of hours spent and moderate intensity MET values for each activity to provide conservatively estimated summary measures. The following MET scores were used (36): 3.5 for walking, 7 for jogging/running, 7 for lap swimming, 6 for tennis or racquetball, 4 for bicycling/stationary biking, 4.5 for aerobics/calisthenics, and 3.5 for dancing.

In 1992, we also asked participants to recall recreational physical activity at age 40 based on the question, ''At age 40, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?.'' MET-hours per week at age 40 were then summarized using the same method as baseline recreational activity described above. Recreational physical activity at baseline and age 40 were categorized into MET-hours per week as none, >0 to 7, >7 to 17.5, >17.5 to 31.5, or >31.5. People who reported no recreational physical activity were used as the reference group. Another measure of past physical activity was available using the historical 1982 CPS-II questionnaire data, where participants reported behavior 10 years before baseline. In 1982, participants were asked ''How much exercise do you get (work or play): none, slight,

moderate, heavy?.'' Exercise in 1982 was categorized as none/slight, moderate, or heavy; people who responded ''none'' and ''slight'' were combined due to small numbers and were used as the reference group. Physical activity at age 40 (as recalled in 1992) and exercise reported in 1982 were combined with baseline 1992 exposure information to assess whether risk of pancreatic cancer was reduced among participants who consistently reported being physically active.

Statistical Analysis. We calculated age-standardized pancreatic cancer incidence rates for measures of obesity (BMI at baseline and age 18, adult weight gain, location of weight gain) and recreational physical activity (MET-hours in 1992 and age 40, exercise level in 1982) standardized to the sex-specific age distribution of CPS-II Nutrition Cohort participants. We used Cox proportional hazards modeling (37) to calculate hazards rate ratios (RR) and corresponding 95% confidence intervals (CI) to examine the relationship between measures of obesity, recreational physical activity, and pancreatic cancer. For each BMI and physical activity exposure variable, we assessed risk in two models, one adjusted only for age and the other adjusted for age and potential confounding factors. All Cox models were stratified on exact year of age at enrollment. Potential confounders included in the multivariate models smoking status (never, current, former) and time since quitting for former smokers (<10, 10-19, and >20 years), height (quintiles), alcohol intake (never,<1 drink per day, 1 drink per day, >1 drink per day, missing), education (≤high school graduate, some college, college graduate and above, missing), first-degree family history of pancreatic cancer (yes, no), personal history of gallbladder disease (yes, no), personal history of diabetes at baseline (yes, no), total caloric intake (quartiles), fruit and vegetable intake (quartiles), and gender (male, female). Furthermore, all multivariate models were mutually adjusted for BMI and physical activity.

Trend tests for BMI, adult weight gain, and physical activity were conducted by assigning the mean BMI, weight change (in lb) or MET value, respectively, within each category to that category. To test whether any of the above-described potential confounders significantly modified the association between measures of obesity or recreational physical activity and pancreatic cancer risk, we constructed multiplicative interaction terms between each main exposure variable and all covariates. We also constructed interaction terms between measures of obesity and recreational physical activity to test for effect modification between these factors. Due to small numbers in some strata, categories of potential effect modifiers were collapsed. To test for any violation of the Cox proportional hazard assumption, we created interaction terms between measures of obesity and recreational physical activity with time. Statistical interaction and the Cox proportional hazard assumption were assessed in multivariate models using the likelihood ratio test and $P < 0.05$ was considered statistically significant (38).

Results

The mean baseline BMI in this study population was 26.4 (±3.5 SD) among men and 25.6 (±4.4 SD) among women. Thirty-five percent (n = 34,734) of men and 32% (n =24,582) of women were overweight (BMI 25-29.9) and 14% (n = 9,915) of men and 15% (n = 11,740) of women were obese (BMI ≥ 30). Approximately 12% (n = 8,345) of men and 9% (n = 6,908) of women reported no recreational physical activity at baseline (Table 1). Among participants who reported any recreational physical activity at baseline, the median MET expenditure was 14 MET-h/wk for men and 9.5 MET-h/wk for women, which corresponds to ~4 and 3 hours, respectively, of moderately paced walking per week. Active participants at all levels of MET expenditure engaged primarily in activities judged to be of low intensity (walking biking, aerobics/calisthenics, or dancing) rather than activities judged to be of moderate/high intensity (jogging/running, swimming, or tennis/racquetball). As expected, physical activity and body mass were inversely correlated, with physically active participants more likely to be leaner. Leaner and more physically active participants also were more likely to report being nonsmokers, not having gained weight since age 18 years, drink alcohol, have no history of diabetes, and have higher educational attainment.

Men and women with a BMI >30 had a relative risk of pancreatic cancer of 2.08 (95% CI 1.48-2.93, P_{trend} = 0.0001) compared with men and women of normal weight (Table 2). The association between BMI and pancreatic cancer risk was somewhat stronger in men (RR, 2.38; 95% CI, 1.50-3.78 for BMI ≥30 versus <25) than women (RR, 1.73; 95% CI, 1.02-2.92 for BMI ≥30 versus <25). Risk of pancreatic cancer was 33% higher among men and women who reported BMI >23 at age 18 compared with BMI <21 even after adjustment for baseline BMI in 1992 (RR, 1.33; 95% CI, 0.95-1.85, P_{trend} = 0.11).

After adjustment for baseline BMI, location of weight gain also was associated independently with risk of pancreatic cancer. Men and women who reported ''central'' weight gain had a relative risk of pancreatic cancer of 1.45 (95% CI, 1.02-2.07) compared with men and women who reported peripheral weight gain (Table 2). Similar to the observed BMI association, the risk was greater in men (RR, 1.51; 95% CI, 0.92-2.50) than in women (RR, 1.36; 95% CI, 0.80-2.30). We observed no independent association between adult weight change (age 18 to 1992) and pancreatic cancer in this population.

We observed no association between baseline recreational physical activity and risk of pancreatic cancer in this study. Men and women in the highest category of MET-hours per week (>31.5 MET-h/wk) had a relative risk of pancreatic cancer of 1.20 (95% CI, 0.63-2.27) compared with men and women who reported no physical activity at baseline (Table 3). Tests for trend including participants who reported no recreational physical activity (P_{trend} = 0.97) and excluding participants who reported no recreational physical activity (P_{trend} = 0.82) were not statistically significant. The lack of association also did not differ when we restricted the analysis to participants engaging in at least some moderate/heavy physical activity compared with those who reported no physical activity or only low-intensity physical activity (data not shown). We also examined the association between pancreatic cancer risk and recreational physical activity at age 40 (reported retrospectively at baseline). Physical activity at age 40 was not associated with risk of pancreatic cancer.

Additionally, we examined the association between pancreatic cancer risk and historically collected exercise levels reported in 1982. Moderate physical activity in 1982 was inversely associated with risk (RR, 0.74; 95% CI, 0.56-0.99; Table 3). Pancreatic cancer risk was not associated among individuals who reported being physically active across multiple time points compared with individuals who reported no recreational physical activity at each time point (data not shown). There also was no statistical interaction between measures of obesity and recreational physical activity levels.

We examined risk of pancreatic cancer in a stratified analysis by smoking status because residual confounding due to smoking has the potential to impact the relationship between BMI and pancreatic cancer risk (13). Risk of pancreatic cancer risk among men and women with BMI ≥ 30 compared with <25 was similar when restricting the analysis to never smokers (RR, 1.70; 95% CI, 0.95-3.06). Residual confounding by smoking in relation to BMI and pancreatic cancer risk in this cohort was minimal because there were few smokers. Only nine percent of cohort members reported smoking at baseline

Table 1. Selected study participant characteristics in relation to BMI and recreational physical activity at baseline among 145,627 men and women in the CPS-II Nutrition Cohort, 1992-1999

Characteristic	BMI [weight (kg)/height (m)^2]					
	Men			Women		
	<25	25 to <30	30+	<25	25 to <30	30+
No. participants	24,940	34,734	9,915	39,716	24,582	11,740
Age at baseline (mean ± SE)	64.8 ± 0.04	63.6 ± 0.03	62.5 ± 0.06	62.1 ± 0.03	62.3 ± 0.04	61.3 ± 0.06
Smoking status (%)						
Never	36.2	31.3	28.6	53.7	56.6	59
Current	10.7	8.3	7.6	9.6	7.7	5.6
Former	53.1	60.4	63.8	36.7	35.7	35.3
MET-hours per week (mean ± SE)	14.8 ± 0.08	13.0 ± 0.07	10.1 ± 0.13	13.4 ± 0.06	11.3 ± 0.08	9.3 ± 0.11
Height, cm (mean ± SE)	178.82 ± 0.05	178.31 ± 0.03	178.05 ± 0.08	164.34 ± 0.03	163.83 ± 0.05	162.56 ± 0.05
Weight change, kg (age 18 to 1992; mean ± SE)	7.89 ± 0.06	15.83 ± 0.06	27.12 ± 0.10	6.62 ± 0.04	16.69 ± 0.05	28.58 ± 0.07
≥College graduate, %	53.9	45.3	35.6	35.6	28.2	24.3
Family history of pancreatic cancer, %	4.1	4.4	4.5	4.3	4.6	4.6
Personal history of diabetes, %	7.2	9.1	15.5	3.9	7	13.1
Personal history of gallbladder disease, %	6	8.3	10.5	10.2	17.4	26
No alcohol intake in last year, %	31.1	31.8	37.7	39.6	47.8	58.6
Caloric intake, kcal (mean ± SE)	1,754 ± 4	1,807 ± 3.4	1,911 ± 6.5	1,321 ± 2.5	1,379 ± 3.1	1,460 ± 4.5

Characteristic	Recreational leisure-time activity (MET-hours per week)					
	Men			Women		
	None	>0 to 17.5	17.5+	None	>0 to 17.5	17.5+
No. participants	8,345	40,905	20,339	6,908	50,531	18,599
Median MET-hours per week	0	7.8	29.6	0	7.6	28.8
Moderate/high-intensity activities,* %	—	9.8	23.4	—	6.6	19.2
Age at baseline (mean ± SE)	63.4 ± 0.07	63.9 ± 0.03	64.3 ± 0.04	61.9 ± 0.08	62.0 ± 0.03	62.2 ± 0.05
Smoking status (%)						
Never	25.9	33	34.6	51.6	56.9	52.9
Current	16.9	8.4	7	13.5	7.9	7.7
Former	57.1	58.6	58.3	34.9	35.2	39.4
BMI [weight (kg)/height (m^2); mean ± SE]	27.2 ± 0.04	26.5 ± 0.02	26.0 ± 0.02	26.9 ± 0.05	25.7 ± 0.02	24.8 ± 0.03
Height, cm (mean ± SE)	178.31 ± 0.08	178.31 ± 0.03	178.56 ± 0.05	163.83 ± 0.08	163.83 ± 0.01	163.83 ± 0.05
Weight change, kg (age 18 to 1992; mean ± SE)	17.01 ± 0.12	15.01 ± 0.05	12.79 ± 0.08	16.60 ± 0.13	13.65 ± 0.05	10.98 ± 0.08
≥College graduate, %	29.6	48.2	51.6	23.3	31.2	35.1
Family history of pancreatic cancer, %	4	4.3	4.5	4.5	4.4	4.4
Personal history of diabetes, %	11.1	9.4	8.5	8.4	6.3	5.7
Personal history of gallbladder disease, %	8.2	8	7.1	18	15.1	13.4
No alcohol intake in last year, %	40	32.2	29.8	53.8	46	40
Caloric intake, kcal (mean ± SE)	1,901 ± 7	1,770 ± 3.1	1,828 ± 4.5	1,379 ± 6	1,354 ± 2.2	1,374 ± 3.6

NOTE: All values (except age) are standardized to the age distribution of the study population.
*Low-intensity activities are defined as those with MET scores <4.5 (walking, biking, aerobics/calisthenics, or dancing), and moderate/high-intensity activities are defined as those with MET scores >4.5 (jogging/running, swimming, or tennis/racquetball).

and former smokers had a median of 22 years since quitting. There also was no statistical interaction between measures of obesity or baseline recreational physical activity and any of the other potential risk factors examined in this analysis (data not shown).

Discussion

Results from this prospective study support the hypothesis that obesity is associated with approximately a doubling of risk of pancreatic cancer. Higher risk of pancreatic cancer was observed among men and women with higher BMI at baseline and at age 18. The present findings also are consistent in direction and magnitude with six (7, 11, 13, 16, 17, 19) of twelve (3, 7, 11-20) prospective cohort studies, including results included in the large CPS-II Mortality Study (13), and four (21-24) of eight (21-28) case-control studies that found a positive association between BMI and pancreatic cancer risk. There are several possible explanations for the inconsistent findings of obesity and pancreatic cancer risk across previous studies. First, studies that observed a positive association generally examined higher levels of BMI (≥30) and had larger sample sizes (at least 10 cases in the highest BMI category). Seven (11, 13, 16, 17, 19, 23, 24) of eight (11, 13, 15-17) previous studies that examined an association with BMI of ≥30 found an increased risk of pancreatic cancer ranging from 20% to 180% (Fig. 1). The one previous study (15) that reported no association with BMI of ≥30 and pancreatic cancer risk had limited power with only four cases of pancreatic cancer classified as obese.

A second possible explanation for the lack of association observed in early case-control studies may be due to the use of proxy respondents. If proxy respondents systematically underreported weight for case patients, this would bias results toward the null. Four (21-24) of eight (21-28) case-control studies used only direct patient interviews, and all four studies found a positive association between BMI and pancreatic cancer risk. Third, many studies that did not observe an association with obesity also did not properly control for smoking history (3, 18, 25, 27). Residual confounding by smoking due to the lack of proper (or any) adjustment for smoking may bias the association between obesity and pancreatic cancer risk toward the null.

Our results also support a role of central adiposity, independent of BMI, on pancreatic cancer carcinogenesis, an association that previously has not been examined in observational studies. There is a direct linear relationship between intra-abdominal fat deposits, insulin production, and

Table 2. RR and 95% CI for measure of obesity at various times during a participant's lifetime and pancreatic cancer, CPS-II Nutrition Cohort, 1992-1999

	BMI [weight (kg)/height (m)^2] at baseline (1992)					
	<25	25 to <30	30+	P_{trend}*		
Men						
No. cases/person-years	44/155,031	57/218,536	36/62,047			
Age-standardized rate	29.01	29	67.71			
RR‡ (95% CI)	1 (reference)	1.00 (0.67-1.48)	2.43 (1.55-3.80)			
RR§ (95% CI)	1 (reference)	0.99 (0.66-1.47)	2.38 (1.50-3.78)	0.0004		
Women						
No. cases/person-years	50/250,570	33/154,594	22/73,572			
Age-standardized rate	21.84	22.91	35.19			
RR‡ (95% CI)	1 (reference)	1.07 (0.69-1.66)	1.66 (1.00-2.74)			
RR§ (95% CI)	1 (reference)	1.09 (0.70-1.70)	1.73 (1.02-2.92)	0.06		
Men + women						
RR§,‖ (95% CI)	1 (reference)	1.03 (0.76-1.38)	2.08 (1.48-2.93)	0.0001		
	BMI (weight (kg)/height (m^2) at age 18¶					
	<21	21 to <23	23+	P_{trend}*		
Men						
No. cases/person-years	48/175,978	32/117,073	56/136,460			
Age-standardized rate†	28.41	28.95	49.53			
RR‡ (95% CI)	1 (reference)	1.07 (0.68-1.67)	1.70 (1.15-2.50)			
RR§,**	1 (reference)	1.06 (0.67-1.67)	1.43 (0.94-2.19)	0.09		
Women						
No. cases/person-years	59/294,896	25/107,363	17/71,824			
Age-standardized rate†	21.87	25.13	27.95			
RR‡ (95% CI)	1 (reference)	1.18 (0.74-1.88)	1.25 (0.73-2.15)			
RR§,** (95% CI)	1 (reference)	1.15 (0.71-1.85)	1.06 (0.59-1.89)	0.77		
Men + women						
RR§,‖,** (95% CI)	1 (reference)	1.07 (0.77-1.49)	1.33 (0.95-1.85)	0.11		
	Adult weight change (age 18 to 1992)¶, kg					
	>−2.27	−2.27 to +4.54	+4.55 to +9.07	+9.08 to +13.61	+13.62 or more	P_{trend}*
Men						
No. cases/person-years	11/15,891	12/61,242	21/71,901	15/76,014	77/204,464	
Age-standardized rate†	75.48	20.97	31.55	22.98	40.64	
RR‡ (95% CI)	3.67 (1.62-8.32)	1 (reference)	1.50 (0.74-3.04)	1.02 (0.48-2.17)	1.99 (1.08-3.65)	
RR§,** (95% CI)	3.54 (1.56-8.03)	1 (reference)	1.49 (0.73-3.04)	0.97 (0.45-2.11)	1.59 (0.82-3.08)	0.36
Women						
No. cases/person-years	4/21,168	20/86,920	18/86,513	21/83,551	38/195,931	
Age-standardized rate†	19.80	25.11	21.93	28.42	21.70	
RR‡ (95% CI)	0.79 (0.27-2.32)	1 (reference)	0.93 (0.49-1.75)	1.12 (0.61-2.08)	0.87 (0.50-1.49)	
RR§, (95% CI)	0.71 (0.24-2.08)	1 (reference)	0.89 (0.47-1.68)	0.95 (0.50-1.80)	0.50 (0.25-1)	0.22
Men + women						
RR†,‖,** (95% CI)	1.74 (0.94-3.22)	1 (reference)	1.12 (0.70-1.79)	0.97 (0.60-1.58)	0.96 (0.61-1.52)	0.16
	Location of weight gain ††					
	Peripheral weight gain	Central weight gain				
Men						
No. cases/person-years	18/71,964	103/275,518				
Age-standardized rate†	25.88	41.21				
RR‡ (95% CI)	1 (reference)	1.53 (0.92-2.52)				
RR§,** (95% CI)	1 (reference)	1.51 (0.92-2.50)				
Women						
No. cases/person-years	38/193,587	24/86,474				
Age-standardized rate†	24.17	27.76				
RR‡ (95% CI)	1 (reference)	1.21 (0.73-2.02)				
RR§,** (95% CI)	1 (reference)	1.36 (0.80-2.30)				
Men + women						
RR§,‖,** (95% CI)	1 (reference)	1.45 (1.02-2.07)				

*Trend tests conducted in multivariate models.
†Age-standardized incidence rates per 100,000 standardized to the sex-specific distribution of Nutrition Cohort participants.
‡Age-adjusted RR and corresponding 95% CI.
§Multivariate-adjusted hazard RR and 95% CI adjusted for: age, smoking status, years since quitting smoking among former smokers, education, family history of pancreatic cancer, personal history of gallbladder disease, personal history of diabetes, height, total caloric intake, and MET-hours per week in 1992.
‖Also adjusted for gender.
¶One case in men (6,103 person-years) and four cases in women (4,653 person-years) not included due to missing BMI at age 18.
**Also adjusted for BMI in 1992.
††Sixteen cases in men (88,132 person-years) and 43 cases in women (198,675 person-years) not included due to report of inconsistent or other locations of weight gain. Central weight gain defined as weight gain in ''waist'' or ''chest and shoulders'' and peripheral weight gain defined as ''hips and thighs'' or ''equally all over.''

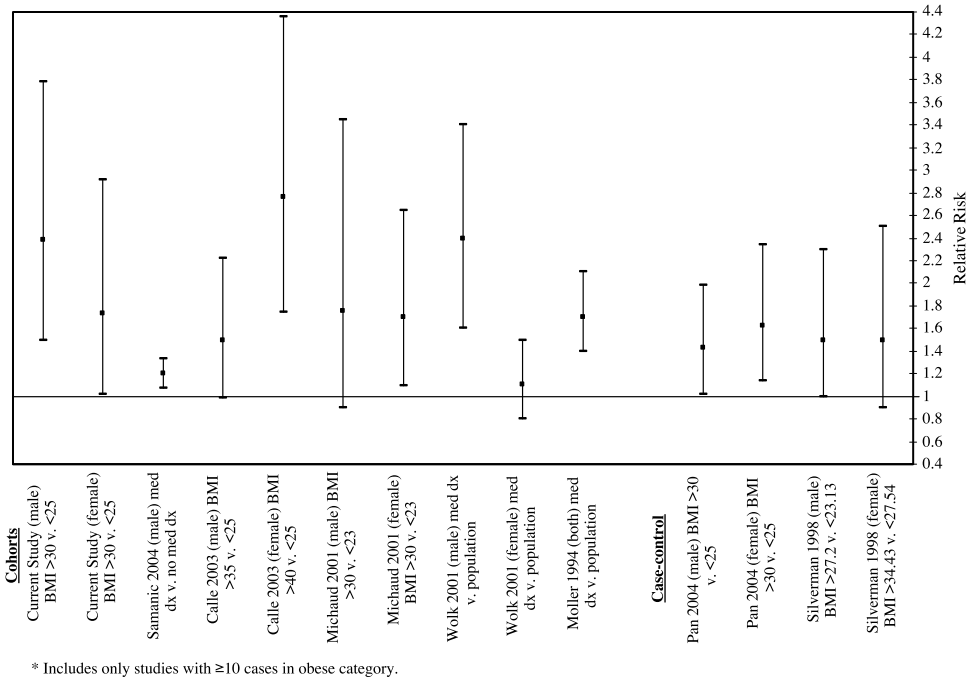
Table 3. RR and 95% CI for measures of recreational physical activity at various points in time and pancreatic cancer, CPS-II Nutrition Cohort, 1992-1999

	MET-hours per week (1992)					
	None	>0-7	>7-17.5	>17.5-31.5	>31.5	P_{trend}*
Men						
No. cases/person-years	12/51,179	44/130,056	42/126,302	32/97,277	7/30,801	
Age-standardized rate†	27.97	37.33	36.35	33.95	24.11	
RR‡ (95% CI)	1 (reference)	1.39 (0.73-2.63)	1.33 (0.70-2.53)	1.29 (0.66-2.51)	0.91 (0.36-2.30)	
RR§ (95% CI)	1 (reference)	1.45 (0.76-2.75)	1.43 (0.74-2.73)	1.41 (0.72-2.77)	1.01 (0.39-2.60)	0.84 (0.52 among active)
Women						
No. cases/person-years	12/42,852	41/163,528	23/154,903	20/88,987	9/28,466	
Age-standardized rate†	35.10	28.22	15.33	22.55	35.49	
RR‡ (95% CI)	1 (reference)	0.89 (0.47-1.69)	0.52 (0.26-1.05)	0.78 (0.38-1.59)	1.13 (0.48-2.69)	
RR§ (95% CI)	1 (reference)	1 (0.52-1.91)	0.62 (0.30-1.25)	0.92 (0.44-1.89)	1.42 (0.59-3.41)	0.73 (0.65 among active)
Men + women						
RR§,‖	1 (reference)	1.24 (0.79-1.96)	1 (0.62-1.61)	1.17 (0.72-1.91)	1.20 (0.63-2.27)	0.97 (0.82 among active)
	MET-hours per week (age 40)¶					
	None	>0-7	>7-17.5	>17.5-31.5	>31.5	P_{trend}*
Men						
No. cases/person-years	22/72,196	37/109,549	29/99,756	36/94,278	12/54,225	
Age-standardized rate†	36.79	36.24	31.06	39.42	25.81	
RR (95% CI)‡	1 (reference)	1.09 (0.64-1.85)	0.94 (0.54-1.64)	1.18 (0.69-2)	0.70 (0.35-1.42)	
RR (95% CI)§	1 (reference)	1.09 (0.64-1.85)	0.95 (0.54-1.65)	1.19 (0.70-2.02)	0.69 (0.34-1.41)	0.40 (0.32 among active)
Women						
No. cases/person-years	16/68,685	37/138,625	23/130,086	16/83,851	11/49,870	
Age-standardized rate†	25.17	29.92	20.53	19.96	23.88	
RR‡ (95% CI)	1 (reference)	1.12 (0.62-2.02)	0.76 (0.40-1.43)	0.78 (0.39-1.55)	0.94 (0.44-2.02)	
RR§ (95% CI)	1 (reference)	1.15 (0.64-2.07)	0.77 (0.41-1.46)	0.77 (0.38-1.53)	0.94 (0.44-2.03)	0.38 (0.41 among active)
Men + women						
RR§,‖ (95% CI)	1 (reference)	1.15 (0.78-1.70)	0.88 (0.58-1.34)	1.03 (0.67-1.56)	0.81 (0.48-1.36)	0.24 (0.19 among active)
	Exercise (1982)**					
	None/slight	Moderate	Heavy	P_{trend}*		
Men						
No. cases/person-years	45/112,960	73/268,276	19/51,413			
Age-standardized rate†	48.71	28.86	36.57			
RR‡ (95% CI)	1 (reference)	0.62 (0.43-0.90)	0.89 (0.52-1.52)			
RR§ (95% CI)	1 (reference)	0.70 (0.48-1.02)	1.12 (0.64-1.95)	0.69 (0.75 among active)		
Women						
No. cases/person-years	30/128,524	67/319,625	6/24,935			
Age-standardized rate†	27.53	22.55	24.77			
RR‡ (95% CI)	1 (reference)	0.79 (0.51-1.22)	0.91 (0.38-2.18)			
RR§ (95% CI)	1 (reference)	0.84 (0.54-1.29)	0.97 (0.40-2.35)	0.59 (0.43 among active)		
Men + women						
RR§,‖ (95% CI)	1 (reference)	0.74 (0.56-0.99)	1.04 (0.65-1.65)	0.38 (0.34 among active)		

*Trend tests conducted in multivariate models.
†Age-standardized incidence rates per 100,000 standardized to the sex-specific distribution of Nutrition Cohort participants.
‡Age-adjusted RR and corresponding 95% CI.
§Multivariate-adjusted hazard RR and 95% CI adjusted for: age, smoking status, years since quitting smoking among former smokers, education, family history of pancreatic cancer, personal history of gallbladder disease, personal history of diabetes, height, total caloric intake, and MET-hours per week in 1992.
‖Also adjusted for gender.
¶One case in men (5,610 person-years) and two cases in women (7,618 person-years) not included due to missing information on physical activity at age 40.
**No cases in men (2,966 person-years) and two cases in women (5,652 person-years) not included due to missing 1982 exercise information.

the development of insulin resistance (reviewed in ref. 10). *In vitro* studies have shown that insulin binds to the insulin-like growth factor-I receptor and has growth-promoting effects in the pancreas (39). A hyperinsulinemic state also allows increased levels of insulin to pass through pancreatic exocrine cells, bind to the insulin receptor, and trigger mitotic activity (7, 9, 40). Increased insulin also can down-regulate insulin-like growth factor binding protein-I, leaving more bioavailable insulin-like growth factor-I that has been shown to *in vitro* stimulate cell proliferation (41, 42). As many women tend to gain weight more peripherally, the lack of or weaker magnitude of association observed in some studies in women compared with men (7, 17) may be explained by the role of central adiposity in pancreatic carcinogenesis.

In contrast with several previous studies, we did not observe a relationship between recreational physical activity at baseline and pancreatic cancer risk. The low prevalence of high-intensity activities reported by participants in this cohort may account for the lack of an observed association. In this cohort, we could not examine the more vigorous physical activities that have been associated with reduced risk of pancreatic cancer in previous studies (15, 22, 29). The low-intensity physical activity reported by study participants may be insufficient to improve insulin sensitivity. It is also plausible that the lack of association in our study is due to the timing of the physical activity measure. Pancreatic cancer is generally diagnosed at advanced stages (1), and as a result of the relatively short follow-up period (7 years), pancreatic carcinogenesis may have been initiated before exposure assessment. We evaluated the association after excluding the first 2 years of follow-up and found no differences in risk estimates. Additionally, we evaluated pancreatic cancer risk according to



* Includes only studies with ≥10 cases in obese category.

Figure 1. Previous studies (includes only studies with ≥10 cases in obese category) of obesity (BMI ≥ 30 or medical diagnosis) and pancreatic cancer risk.

physical activity in 1982 (10 years before baseline) due to the potential for change in physical activity in 1992 due to preclinical disease. We observed a 26% decrease in pancreatic cancer incidence among men and women engaging in moderate physical activity in 1982 compared with men and women engaging in no/slight physical activity in 1982. This finding is consistent with another large prospective cohort study that reported an association with moderate, but not vigorous, physical activity and pancreatic cancer risk (16). Thus, moderate physical activity may be inversely associated with pancreatic cancer risk.

There are a few limitations of our study that should be mentioned. In addition to the limited range of recreational physical activities commonly done by our participants, the lack of individual information on intensity of activities may increase the potential for misclassification of true energy expenditure. Another limitation is that obesity and physical activity measures are self-reported. Furthermore, our physical activity questions have not been validated but physical activity has been previously associated with breast (43) and colon cancer (44) in this cohort. Another limitation is the limited statistical power to examine detailed effect modification between BMI, central weight gain, recreational physical activity, and other covariates, such as smoking or personal history of diabetes. There are many strengths of this study that should also be noted. The prospective design eliminates differential reporting of past exposure information. We were able to control for potential confounding by most known or hypothesized pancreatic cancer risk factors. We had the ability to examine the association between adiposity and pancreatic cancer across a wide range of BMI.

In summary, we observed independent associations between both obesity and the tendency for central weight gain and pancreatic cancer risk. However, we did not observe an association between recreational physical activity and risk of pancreatic cancer in our population of elderly adults. Sufficient biological plausibility exists to warrant additional research to better understand the potential role of physical activity in pancreatic carcinogenesis and the amount, frequency, and intensity of physical activity needed to impact insulin response and other hormonal changes in relation to pancreatic cancer risk. Although evidence recognizing pancreatic cancer as an obesity-related cancer previously has been considered insufficient (10), findings from this study, along with other recent studies, strongly support the role of obesity in pancreatic cancer development.

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