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Physical activity and pancreatic cancer risk among urban Chinese: Results from two prospective cohort studies

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Abstract

Background—Associations between physical activity and pancreatic cancer risk are unclear.

Methods—In two prospective cohort studies: the Shanghai Women's Health Study and Shanghai Men's Health Study, physical activity and other information were collected at the baseline interview of 72,451 women and 60,037 men. Participants were followed up through annual linkage with cancer registry in combination with in-person interviews taking place every 2-4 years.

Results—We identified 225 female and 159 male cases during a median follow up of 16.1 and 10.3 years, respectively. Adult exercise participation was significantly associated with a decreased pancreatic cancer risk in men [hazard ratio (HR), 95% confidence interval (CI): 0.71 (0.50-1.00)]. Meeting the recommended minimum exercise threshold to achieve health benefits of 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity exercise was associated with further decreased pancreatic cancer risk [HR (95% CI): 0.59 (0.40-0.87)]. We also observed an inverse association between adolescent physical activity and pancreatic cancer risk in men [HR (95% CI): 0.54 (0.33-0.90)]. Exercise throughout one's lifetime was associated with a 68% decrease in pancreatic cancer risk [HR (95% CI): 0.32 (0.16-0.66)]. No significant association was found in women. Adult non-exercise daily activity and occupational activity were not associated with pancreatic cancer risk in either men or women.

Conclusions—Adult exercise and adolescent physical activity were significantly associated with a decreased pancreatic cancer risk in men but not in women.

Impact—These findings underscore the importance of investigating the possible modification by sex on the exercise and pancreatic cancer risk association.

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Keywords

physical activity; pancreatic cancer; association; Chinese; prospective cohort

Introduction

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States, with an estimated 43,090 deaths in 2017 (1). In China, there were 90,100 estimated new pancreatic cancer cases and 79,400 estimated deaths due to pancreatic cancer in 2015 (2). Most pancreatic cancers are already metastasized at diagnosis, resulting in a five-year survival rate of only 7% (3). It is critical to better understand the risk factors and etiology of pancreatic cancer in order to identify effective prevention strategies to reduce its public health burden.

The etiology of pancreatic cancer is largely unknown. Cigarette smoking (4,5), type 2 diabetes (6,7), family history of pancreatic cancer (8), and pancreatitis (9) are the few known risk factors for pancreatic cancer. Several epidemiologic studies suggest that physical activity may also be associated with risk of pancreatic cancer. For example, in the Japan Public Health Center-based Prospective Study, Inoue et al. observed that high levels of total physical activity were associated with decreased pancreatic cancer risk in men (10). With respect to leisure time physical activity (LTPA), a significant inverse association between high LTPA and pancreatic cancer risk was suggested in the Netherlands Cohort Study (11), the Canadian National Enhanced Cancer Surveillance System study among men (12), and a central European multicenter case–control study (13). Isaksson et al. also observed a significant inverse association between occupational physical activity (OPA) and pancreatic cancer risk in the Swedish Twin Registry study (14). Despite these observations, however, a potential beneficial role of physical activity was not detected in many other studies (15,16); in fact, one showed an opposite effect. In the College Alumni Health Study, moderate intensity physical activity was associated with increased risk of pancreatic cancer [RR (95% CIs): 1.37 (1.00-1.87)] (17). It is possible that different types of physical activity, including LTPA, OPA, and daily living physical activity (DPA), may be associated with pancreatic cancer risk differentially; however, few studies have systematically assessed their effects separately. Also, little is known as to whether physical activity during adolescence is associated with pancreatic cancer risk in later life. There is thus a critical need to conduct a study evaluating associations of both adult and adolescent physical activity, including the different subtypes (LTPA, OPA, and DPA), to better characterize the relationship between physical activity and pancreatic cancer.

The Shanghai Women’s Health Study (SWHS) and the Shanghai Men’s Health Study (SMHS), two large population-based prospective cohort studies of approximately 75,000 women and 61,500 men in China, collected detailed information on different types of physical activity during both adulthood and adolescence. These two cohort studies thus provide an excellent opportunity to characterize the relationship between adult and adolescent physical activity and pancreatic cancer risk.

Materials and Methods

Study population

The SWHS and SMHS are population-based prospective cohort studies that recruited 74,941 Chinese women (aged 40-70 years) from December 1996 to May 2000, and 61,480 Chinese men (aged 40-74 years) from 2002 to 2006, in eight urban communities of Shanghai, China (participation rate: 92.7% and 74.0%, respectively). Detailed information on the study design and recruitment strategies has been described elsewhere (18,19). Briefly, at baseline, in-person recruitment was implemented and interviews were conducted using structured questionnaires. Information including participants' socio-demographics, lifestyle, medical history, occupation history and dietary intake was collected. In addition, anthropometric measurements were taken using standardized protocols. The SWHS and SMHS have been approved by the institutional review boards of participating institutions (Shanghai Cancer Institute and Vanderbilt University Medical Center) and all participants have provided written informed consent. This research was conducted in accordance with the Belmont Report.

Physical activity information collection

Information on physical activity was collected using a validated physical activity questionnaire (20-22). For adult physical activity, information for LTPA, DPA, and OPA was collected. For LTPA, participants were asked whether they had engaged in regular exercise/sports (at least once a week for three months continuously) during the past five years. Participants were then asked to report details for up to three types of exercise/sports (including type, hours/week, and years of participation). For DPA, participants were asked about their average daily time spent on walking, stair climbing, bicycling, and housework in the year before the interview (20). OPA data were derived by energy level and sitting time based on the title of the longest held job (22,23).

Energy expenditure in standard metabolic equivalent values (METs) was used to estimate the intensity of LTPA, DPA, and OPA. LTPA energy expenditure was estimated by calculating the weighted average of energy expended in all activities reported during the five years preceding the interview (METs hours/week/year). DPA activities were estimated using the following standard MET values: housework, 2.0 METs; walking, 3.3 METs; stair climbing, 9.0 METs; and bicycling, 4.0 METs (20-22). For OPA, participants were classified into high (>12 kJ/min), medium (8-12 kJ/min), or low levels (<8 kJ/min) of energy expenditure, using the occupation titles (24). Each participant was also categorized into low (<2 hours/day), medium (2-6 hours/day), or high (>6 hours/day) levels of sitting time.

For physical activity during adolescence, LTPA participation between the ages of 13 and 19 years was collected in the SWHS, and LTPA/physical labor participation from the ages of 13 to 15 years was collected in the SMHS. Briefly, women were asked if they participated in exercise activities regularly, and men were asked if they participated in exercise and/or physical labor activities regularly, both of which were defined as participating at least once a week, for more than three months continuously. Information on the intensity and duration of these physical activities, as well as participation in sports tournaments and on sports teams

(yes or no) was also collected. Energy expenditure in METs was used to estimate intensity, similar to the method we used to determine adult physical activity. The validity of the physical activity questionnaires used for the two cohorts has been assessed previously and found to be reasonable (25,26).

Assessment of demographic, dietary, and anthropometric variables

Demographic information on age, level of education, per capita yearly income, smoking status, alcohol consumption, history of diabetes, gallstone and gallbladder surgery, and family history of pancreatic cancer was collected at study enrollment using baseline structured questionnaires. Dietary intake information was collected using validated food frequency questionnaires (27,28). Total energy and nutrient intake (kcals/day) were estimated based on amount of food intake and nutrient content from the Chinese Food composition tables. Anthropometric measurements, including weight, height, and circumferences of waist and hips were taken by trained interviewers according a standard protocol.

Cohort follow-up and outcome ascertainment

Participants of the SWHS/SMHS were followed up through annual record linkage to the population-based Shanghai Cancer Registry and Shanghai Vital Statistics Registry, supplemented by in-person interviews taking place every 2-4 years. Identified cancer diagnoses were verified through review of medical charts obtained from the diagnostic hospital.

Statistical analyses

After excluding participants with cancer before baseline (N=1,598 women; subjects with a history of cancer were excluded from the SMHS at baseline), those with abnormal total energy intake (<500 kcal/day or >3500 kcal/day) (N=122 women and 353 men), and those with follow-up shorter than 2 years (N=769 women and 1,088 men), 72,451 women in the SWHS and 60,037 men in the SMHS remained for the current study.

Differences in socio-demographic characteristics and potential risk factors by pancreatic cancer outcome status and range of adult LTPA and DPA were evaluated using t-test/ANOVA for continuous variables and chi-square test for categorical variables. Cox proportional hazards analyses using age as time-scale were performed to estimate the association of pancreatic cancer risk with physical activity variables, including the joint effect of adult and adolescent physical activity. Entry time into the model was age at enrollment and exit time was age at cancer diagnosis, censoring at death, or the date of last follow up (December 31, 2014), whichever occurred first. We adjusted for potential confounders identified in our study population and suggested risk/protective factors for pancreatic cancer reported in the literature including education (elementary school or less, middle school, high school, college or more), income (low, middle, high), WHR in quartiles, smoking status (never smokers, former smokers, current smokers), alcohol consumption (never, ever), family history of pancreatic cancer (yes, no), gallstone history (yes, no), gallbladder surgery history (yes, no), and diabetes history (yes, no). Additional adjustment for BMI in the models did not change the results materially. Similarly, in the SMHS,

additionally adjusting for smoking pack-years did not substantially change the results. Thus, results without adjustment of BMI/pack-years are reported. For analysis of adult LTPA, a cutoff of 1.07 MET-h/day/year (~7.5 MET-h/week) based on the recommended minimum threshold for health benefits by the 2008 US federal physical activity guidelines and the 2010 World Health Organization (WHO) guidelines was used for categorization. We examined potential non-linear effects of physical activity variables using restricted cubic splines with five knots. We evaluated possible violations of the proportional hazard assumption by including time-dependent covariates in the Cox model and found no evidence of violation of the assumption. The hazard ratios (HRs) and 95% CIs are reported. All analyses were performed using SAS (Version 9.4; SAS Institute) and R version 3.3.2.

Results

There were 225 pancreatic cancer cases in the SWHS after a median follow-up time of 16.1 years (range: 2 to 18 years) and 159 cases in the SMHS after a median follow-up time of 10.3 years (range: 2 to 13 years). In women, pancreatic cancer cases and controls were similar regarding distributions by family history of cancer, family history of pancreatic cancer, alcohol consumption, and total energy intake (Table 1). Female cases were more likely to be older, have a lower education level, have a low income, have a higher BMI, have a history of pancreatitis, diabetes, gallstone and gallbladder surgery, to smoke, and to eat less fat and red meat (Table 1). In men, pancreatic cancer cases and controls were similar regarding distributions by education, income, BMI, WHR, family history of cancer, family history of pancreatic cancer, gallstone history, gallbladder surgery history, alcohol consumption, energy intake, and intake of fat (Table 1). Compared with male controls, male cases were more likely to be older, be former or never smokers, have a history of diabetes, and to eat less red meat (Table 1). For both women and men, a majority of the baseline characteristics tended to differ by ranges of adult LTPA and DPA categories (Table 2), except for pancreatitis history and family history of pancreatic cancer for women, and family history of pancreatic cancer for men (Table 2).

After adjusting for covariates, adult LTPA participation was significantly associated with pancreatic cancer risk in men (Table 3), with an HR of 0.71 (95% CI 0.50-1.00). According to the 2008 Physical Activity Guidelines for Americans from the Office of Disease Prevention and Health Promotion (29) and the 2010 World Health Organization (WHO) guidelines (30,31), an LTPA higher than 1.07 MET-h/day/year (corresponding to 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity exercise) is the recommended minimum threshold to obtain health benefits. Compared with no LPTA, we found that this higher LTPA level was associated with a 41% reduced pancreatic cancer risk (HR=0.59, 95% CI 0.40-0.87). This inverse association persisted when treating LTPA as a continuous variable in analysis. Restricted cubic spline analysis showed no statistical evidence of a non-linear relationship (P=0.17). In analyses restricted to male never smokers (N=18,258), the statistically significant inverse association between adult exercise and pancreatic cancer risk persisted (HR=0.49, 95% CI 0.26-0.93). Similarly, adolescent LTPA/physical labor was also associated with decreased pancreatic cancer risk in men, with an HR of 0.54 (95% CI 0.33-0.90) for adolescent LTPA/physical labor participation and 0.51 (95% CI 0.30-0.86) for an adolescent LTPA/physical labor higher than 1 MET-h/day/year. In an

analysis of never smokers only, an inverse association was also suggested [HR=0.56 (95% CI 0.23-1.40) for adolescent LTPA/physical labor participation; HR=0.47 (95% CI 0.18-1.24) for adolescent LTPA/physical labor higher than 1 MET-h/day/year]. Mutual adjustment of adult and adolescent PA did not change the results. Neither adult nor adolescent LTPA was significantly associated with pancreatic cancer risk in women (Table 3). No significant association between DPA/OPA and pancreatic cancer risk was found in either men or women (Table 3).

We further examined whether the associations with physical activity differed by subgroup of subjects who reported having at least one of the following risk factors: gallstone history, gall surgery history, diabetes history, family history of pancreatic cancer, current smoking, or obesity, and by the subgroup of subjects with none of these risk factors. Similar association patterns were observed in both subgroups of men and women. Stratified analyses according to history of diabetes or hypertension or coronary artery disease also suggested similar patterns in both men and women.

Additionally, we assessed the influence of joint adult LTPA and adolescent LTPA/physical labor on pancreatic cancer risk (Table 4). Compared with men who did not exercise regularly during adulthood and did not participate in exercise or physical labor activities regularly during adolescence, men who exercised regularly during adulthood, and engaged in LTPA/physical labor during adolescence had a 62% decreased pancreatic cancer risk (HR=0.38, 95% CI 0.19-0.77). Again, we did not find a significant association for joint adult and adolescent LTPA on pancreatic cancer risk in women.

Discussion

In these two large prospective cohort studies in urban Chinese, we found that both adult LTPA and adolescent LTPA/physical labor were significantly associated with a decreased risk of pancreatic cancer in men but not in women. Men who exercised throughout life had a 62% reduced risk of pancreatic cancer compared to lifetime non-exercisers. We did not find that DPA and OPA were related to the risk of pancreatic cancer.

LTPA has been previously linked to pancreatic cancer risk but results were not entirely consistent (32,33). In two case-control studies and one cohort study (11-13), for example, LTPA was significantly and inversely associated with pancreatic cancer risk. However, null results were reported from several other studies (34-37). Recently published meta-analyses suggested that LTPA might be associated with a reduced pancreatic cancer risk, although there was some evidence of a low-to-moderate heterogeneity across the studies (15,16). Farris et al. synthesized association estimates of 25 cohort studies and eight case-control studies and reported an association between the highest category of LTPA and a decreased pancreatic cancer risk (relative risk (RR) (95% CI): 0.96 (0.90-1.02) in cohort studies and 0.69 (0.59-0.81) in case-control studies) compared to the lowest category (15). Behrens et al. identified a pooled RR (95% CI) of 0.95 (0.90-1.01) in 31 cohort studies and 0.71 (0.55-0.93) in ten case-control studies comparing high versus low level of LTPA (16). Our finding of an inverse association between LTPA and pancreatic cancer in men is generally consistent with the literature. Although the exact underlying biological mechanism for the

potential link between LTPA and pancreatic cancer remains unclear, several possible explanations have been proposed. A high level of LTPA has been suggested to counteract the effects of overweight, adiposity and diabetes on influencing pancreatic cancer risk (16). In our study, however, this appears to be a less likely mechanism, because the association estimates were adjusted for diabetes and WHR, and additional adjustment for BMI did not alter the associations. Another potential explanation is that LTPA may lower fasting insulin and C-peptide levels and increase adiponectin levels (38-40) thus reducing insulin resistance, a factor thought to potentially cause pancreatic cancer (41,42). Alternatively, it may be due to that physical activity can reduce chronic inflammation, as indicated by lowering levels of leptin, interleukin-6, and C-reactive protein (40,43), or that physical activity can prevent DNA damage through activating cellular stress response signaling and antioxidant defense capacity (44,45). Interestingly, in men, it has been shown that exercise can increase dihydrotestosterone (46), which is decreased in pancreatic cancer patients (47). The reason for a null association of LTPA among women in our study is unknown. A sex-specific association has not been previously reported. In women, exercise is reported to potentially decrease levels of estrogen (48). Several epidemiological studies have reported a potential link between increased estrogen exposure and decreased pancreatic cancer risk (49-55). High estrogen levels have also been shown to inhibit the growth of preneoplastic pancreatic lesions and transplanted pancreatic carcinoma in animal models (56,57). We speculate that the counteracting effect of lower estrogen level and the non-estrogen mediated anti-cancer properties of LTPA may explain the null association found for women. On the other hand, it is worth noting that typical epidemiologic tools for assessing physical activity, including those used in our study, may engender misclassification of physical activity. Future research incorporating measurements of biomarkers of the above-mentioned potential mechanisms is needed to better understand the role of LTPA in pancreatic cancer development.

Our study has several strengths. To the best of our knowledge, this is one of the first attempts to evaluate the relationship between physical activity variables and pancreatic cancer risk in a Chinese population using a prospective cohort design. Besides evaluating adult LTPA, we also assessed the association of adolescent physical activity, which has rarely been explored before. The high participation rate, along with the population-based design of our study, reduce potential selection bias. Availability of a wide range of covariates allowed us to perform comprehensive analyses to minimize the confounding from these factors.

Several limitations also need to be acknowledged for an appropriate interpretation of our findings. First, as with all observational studies, measurement errors are unavoidable for self-reported exposure information, particularly for adolescent physical activity, since the average age of cohort participants at enrollment was 52 for women and 54 for men. However, our validation studies show that the questionnaires we used have good reliability and validity (25,26). In addition, these measurement errors are likely to be non-differential. Second, individuals with a pre-symptomatic disease or at high risk of developing a disease may change their pattern of physical activity (i.e., reverse causation). In our study we excluded subjects with less than two years of follow up, a protocol that would be expected to reduce the potential influence of reverse causality. Third, we cannot infer causality from the identified associations due to the observational nature of our study.

In conclusion, we found in two large prospective cohort studies that adult LTPA and adolescent LTPA/physical labor were significantly associated with a decreased pancreatic cancer risk in men but not in women. Biomarker-based studies are needed to better understand the biological mechanisms underlying the observed association, particularly the potential modification by sex.

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Table 1

Comparison between participants with and without pancreatic cancer on demographic and known pancreatic cancer risk factors, the Shanghai Women's Health Study (1996–2014) and Shanghai Men's Health Study (2002–2014)

Characteristic	Shanghai Women's Health Study		P	Shanghai Men's Health Study		P
	With pancreatic cancer (n=225)	Without pancreatic cancer (n=72,226)		With pancreatic cancer (n=159)	Without pancreatic cancer (n=59,878)	
Age, years (mean ± SD)	60.0 ± 8.1	52.4 ± 9.0	<0.0001	61.7 ± 9.7	55.2 ± 9.7	<0.0001
Education (%)			<0.0001			0.69
≤ Elementary school	43.6	21.1		8.3	6.5	
Middle school	27.6	37.3		34.4	33.5	
High school	18.2	28.1		32.5	36.3	
> High school	10.7	13.6		24.8	23.8	
Income (%)			0.006			0.09
Low	21.3	16.0		6.9	12.5	
Middle	74.2	74.4		83.7	77.7	
High	4.4	9.6		9.4	9.8	
Smoking			0.03			0.0005
Never (%)	95.1	97.3		33.3	30.4	
Former (%)	0	0.4		19.5	10.8	
Current (%)	4.9	2.3		47.2	58.8	
Pack-years (mean ± SD)	0.9 ± 4.7	0.3 ± 3.0	0.06	19.0 ± 21.2	16.9 ± 17.5	0.21
Body mass index (kg/m^2) continuous (mean ± SD)	24.6 ± 3.4	24.0 ± 3.4	0.0054	24.0 ± 3.1	23.7 ± 3.1	0.23
Waist to hip ratio continuous (mean ± SD)	0.8 ± 0.1	0.8 ± 0.1	<0.0001	0.9 ± 0.1	0.9 ± 0.1	0.27
Having a family history of cancer (%)	26.7	26.5	0.96	29.6	28.4	0.74
Having a history of pancreatitis (%)	1.8	0.7	0.05	NA	NA	NA
Having a history of diabetes (%)	8.9	4.2	0.0005	11.3	6.2	0.007
Alcohol consumption (ever, %)	1.8	2.3	0.63	29.6	33.7	0.27
Having a family history of pancreatic cancer (%)	1.8	0.9	0.18	1.9	1.2	0.46
Having a history of gallstone (%)	21.8	11.1	<0.0001	10.1	7.5	0.21
Having a history of gallbladder surgery (%)	12.0	4.3	<0.0001	4.4	2.7	0.19
Fat intake (g/day)	27.2 ± 12.0	29.4 ± 13.0	0.01	33.0 ± 14.4	34.3 ± 15.0	0.26
Red meat intake (g/day)	46.1 ± 34.0	50.9 ± 36.1	0.04	56.7 ± 37.0	62.7 ± 42.6	0.04

Characteristic	Shanghai Women's Health Study		P	Shanghai Men's Health Study		P
	With pancreatic cancer (n=225)	Without pancreatic cancer (n=72,226)		With pancreatic cancer (n=159)	Without pancreatic cancer (n=59,878)	
Total energy (Kcal/day)	1645.5 ± 373.5	1674.6 ± 393.9	0.27	1841.1 ± 452.7	1900.8 ± 462.0	0.10

NA: not available

Table 2

Baseline characteristics by ranges of adult leisure time physical activities and daily living activities, the Shanghai Women's Health Study (1996–2014) and Shanghai Men's Health Study (2002–2014)

	Adult leisure time physical activities				Adult daily living activities				
Females									
Characteristic	0	<1.28	≥1.28	*p*-value	Q1 (lowest)	Q2	Q3	Q4 (highest)	*p*-value
Number (%)	47101 (65.0)	12593 (17.4)	12757 (17.6)		18057 (24.9)	18166 (25.1)	18099 (25.0)	18129 (25.0)	
Age, years (mean ± SD)	50.4 ± 8.5	54.2 ± 8.8	58.2 ± 8.5	<0.0001	52.8 ± 9.1	52.9 ± 9.0	52.6 ± 9.1	51.6 ± 8.9	<0.0001
Education (%)				<0.0001					<0.0001
≤ Elementary school	16.8	23.1	35.4		18.5	21.2	23.0	21.9	
Middle school	41.6	29.8	29.0		29.1	34.6	39.2	46.2	
High school	29.2	29.2	22.7		30.6	29.0	27.0	25.5	
> High school	12.5	17.9	13.0		21.7	15.2	10.8	6.4	
Income (%)				<0.0001					<0.0001
Low	15.4	14.9	19.3		15.2	15.8	15.7	17.3	
Middle	74.8	73.9	73.5		71.8	74.0	75.6	76.3	
High	9.8	11.2	7.2		13.0	10.3	8.6	6.5	
Smoking status (%)				<0.0001					0.22
Never	97.4	97.6	96.5		97.0	97.5	97.3	97.3	
Former	0.3	0.4	0.7		0.4	0.4	0.4	0.4	
Current	2.3	2.0	2.8		2.6	2.2	2.4	2.3	
Pack-years (mean ± SD)	0.3 ± 3.0	0.3 ± 2.8	0.4 ± 3.3	0.0002	0.4 ± 3.4	0.3 ± 2.9	0.3 ± 2.9	0.3 ± 2.8	0.0016
Body mass index (kg/m^2)				<0.0001					<0.0001
continuous (mean ± SD)	23.8 ± 3.4	24.1 ± 3.4	24.5 ± 3.5	<0.0001	23.9 ± 3.4	24.0 ± 3.5	24.1 ± 3.4	24.1 ± 3.4	<0.0001
Waist to hip ratio				<0.0001					<0.0001
continuous (mean ± SD)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	<0.0001	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	<0.0001
Having a family history of cancer (%)	26.1	28.3	26.4	<0.0001	27.9	26.5	26.3	25.3	<0.0001
Having a history of pancreatitis (%)	0.7	0.7	0.8	0.12	0.7	0.7	0.7	0.7	0.78
Having a history of diabetes (%)	3.3	4.9	7.1	<0.0001	5.2	4.5	4.1	3.0	<0.0001
Alcohol consumption (ever, %)	2.0	2.5	3.0	<0.0001	2.5	2.1	2.2	2.2	0.13
Having a family history of pancreatic cancer (%)	0.9	1.0	0.8	0.22	0.9	1.0	1.0	0.9	0.68

	Adult leisure time physical activities				Adult daily living activities				
Having a history of gallstone (%)	9.4	12.2	16.1	<0.0001	12.3	11.7	10.8	9.6	<0.0001
Having a history of gallbladder surgery (%)	3.5	4.5	7.1	<0.0001	4.6	4.5	4.3	3.8	0.0006
Fat intake (g/day)	29.1 ± 13.1	29.7 ± 12.6	30.0 ± 13.2	<0.0001	29.2 ± 12.9	29.4 ± 12.7	29.2 ± 13.0	29.7 ± 13.5	0.0002
Red meat intake (g/day)	52.2 ± 36.8	49.3 ± 34.1	47.8 ± 35.4	<0.0001	50.3 ± 36.0	50.6 ± 34.6	50.7 ± 36.1	52.1 ± 37.6	<0.0001
Total energy (Kcal/day)	1669.7 ± 395.0	1676.6 ± 385.5	1689.9 ± 397.0	<0.0001	1625.6 ± 383.2	1665.8 ± 381.9	1682.9 ± 391.4	1723.4 ± 411.7	<0.0001
Males									
Characteristics	0	<1.99	≥1.99	*p*-value	Q1 (lowest)	Q2	Q3	Q4 (highest)	*p*-value
Number (%)	38796 (64.6)	10136 (16.9)	11105 (18.5)		15001 (25.0)	15000 (25.0)	14978 (25.0)	15058 (25.1)	
Age, years (mean ± SD)	52.6 ± 8.5	57.0 ± 9.6	63.0 ± 9.1	<0.0001	53.7 ± 9.4	54.9 ± 9.6	55.7 ± 9.8	56.8 ± 9.7	<0.0001
Education (%)				<0.0001					<0.0001
≤ Elementary school	4.8	6.1	12.9		5.4	5.3	6.5	8.8	
Middle school	36.3	26.6	30.1		29.5	31.7	34.3	38.4	
High school	39.2	33.2	28.6		36.2	36.7	36.8	35.4	
> High school	19.8	34.1	28.4		28.9	26.3	22.4	17.4	
Income				<0.0001					<0.0001
Low	14.9	8.9	7.6		11.2	10.8	12.5	15.6	
Middle	76.0	78.0	83.3		74.5	78.4	79.4	78.4	
High	9.1	13.1	9.1		14.2	10.9	8.0	6.0	
Smoking status (%)				<0.0001					<0.0001
Never	24.0	38.6	45.2		25.4	30.8	32.4	33.1	
Former	7.8	13.5	19.0		10.1	10.2	10.9	12.3	
Current	68.1	48.0	35.8		64.6	59.0	56.8	54.7	
Pack-years (mean ± SD)	18.6 ± 17.1	14.0 ± 16.8	14.0 ± 18.6	<0.0001	19.2 ± 18.0	16.7 ± 17.1	16.1 ± 17.3	15.9 ± 17.2	<0.0001
Body mass index (kg/m^2) continuous (mean ± SD)	23.6 ± 3.1	23.9 ± 3.0	24.0 ± 3.0	<0.0001	23.9 ± 3.1	23.7 ± 3.0	23.6 ± 3.0	23.7 ± 3.1	<0.0001
Waist to hip ratio continuous (mean ± SD)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.02	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	<0.0001
Having a family history of cancer (%)	28.3	29.9	27.2	<0.0001	29.1	28.4	28.0	28.1	0.15
Having a history of diabetes (%)	4.8	7.7	9.7	<0.0001	6.9	5.8	6.2	5.8	0.0002
Alcohol consumption (ever, %)	35.2	30.1	31.5	<0.0001	33.8	32.8	33.8	34.3	0.04
Having a family history of pancreatic cancer (%)	1.2	1.4	1.1	0.08	1.4	1.3	1.2	1.1	0.18
Having a history of gallstone (%)	6.4	8.4	10.3	<0.0001	7.6	7.8	7.5	6.9	0.01
Having a history of gallbladder surgery (%)	2.3	2.8	4.0	<0.0001	2.8	2.8	2.6	2.6	0.73

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	Adult leisure time physical activities				Adult daily living activities				
Fat intake (g/day)	34.0 ± 15.1	35.0 ± 14.4	35.0 ± 14.8	<0.0001	33.8 ± 15.3	34.2 ± 14.4	34.7 ± 14.7	34.7 ± 15.5	<0.0001
Red meat intake (g/day)	64.7 ± 43.6	61.0 ± 41.0	57.3 ± 40.1	<0.0001	62.7 ± 44.2	62.1 ± 41.1	63.1 ± 41.6	62.8 ± 43.4	0.22
Total energy (Kcal/day)	1895.9 ± 467.5	1904.3 ± 444.4	1913.8 ± 458.4	0.001	1821.4 ± 451.4	1883.9 ± 445.6	1926.1 ± 458.4	1970.7 ± 478.8	<0.0001

Table 3

Type of physical activity and pancreatic cancer risk in the Shanghai Women's Health Study (1996–2014) and Shanghai Men's Health Study (2002–2014)

	SWHS (N=72,451)			SMHS (N=60,037)		
	Cases (no.)	**Hazard ratio***	**95% confidence interval**	**Cases (no.)**	**Hazard ratio***	**95% confidence interval**
Adult LTPA participation						
None	116	1 (ref.)		93	1 (ref.)	
Yes	109	1.06	0.81-1.38	66	**0.71**	**0.50-1.00**
Adult LTPA (MET-h/day/yr)						
None	116	1 (ref.)		93	1 (ref.)	
≤1.07#	37	1.05	0.72-1.53	21	1.09	0.67-1.76
>1.07	72	1.06	0.78-1.44	45	**0.59**	**0.40-0.87**
p for treating as continuous variable		0.57			**0.02**	
p for non-linear association (using 5 knots)		0.38			0.17	
Physical activity during adolescence ##						
None	96	1 (ref.)		21	1 (ref.)	
Yes	129	1.26	0.82-1.94	138	**0.54**	**0.33-0.90**
Physical activity during adolescence ## (MET-h/day/yr###)						
None	96	1 (ref.)		21	1 (ref.)	
≤ 0.28 / 1	63	1.44	0.92-2.26	72	0.59	0.35-1.01
>0.28 / 1	66	1.02	0.62-1.67	66	**0.51**	**0.30-0.86**
p for treating as continuous variable		0.44			0.21	
p for non-linear association (using 5 knots)		0.26			0.74	
Adult daily activity (MET-h/wk/yr)						
Q1	50	1 (ref.)		40	1 (ref.)	
Q2	55	1.07	0.73-1.57	26	0.58	0.36-0.96
Q3	61	1.19	0.82-1.74	45	0.96	0.62-1.47
Q4	59	1.28	0.87-1.87	48	0.95	0.62-1.46
p for trend		0.18			0.58	
p for non-linear association (using 5 knots)		0.47			0.11	
Occupation physical activity (sitting time **)						
High	33	1 (ref.)		24	1 (ref.)	

	SWHS (N=72,451)			SMHS (N=60,037)		
	Cases (no.)	**Hazard ratio***	**95% confidence interval**	**Cases (no.)**	**Hazard ratio***	**95% confidence interval**
Medium	91	1.07	0.72-1.60	73	1.20	0.75-1.91
Low	98	1.06	0.69-1.62	60	1.22	0.75-1.99
p for trend		0.85			0.48	
Occupation physical activity (energy***)						
Low	80	1 (ref.)		51	1 (ref.)	
Medium	135	1.09	0.78-1.52	94	1.25	0.85-1.84
High	7	0.52	0.23-1.17	12	1.42	0.72-2.80
p for trend		0.47			0.22	

‡MET, metabolic equivalent; Q, Quartile; LTPA, leisure time physical activity

#LTPA cutoff 1.07 MET-h/day/yr is based on recommended minimum threshold for health benefits by the 2008 US federal physical activity guidelines and the 2010 World Health Organization (WHO) guidelines;

##Physical activity during adolescence represents adolescent LTPA for females and adolescent LTPA or physical labor for males

###median values of adolescent LTPA for females (0.28 MET-h/day/yr) and adolescent LTPA/physical labor for males (1 MET-h/day/yr) were used as cutoff

*Hazard ratios adjusted for education (elementary school or less, middle school, high school, college or more), income (low, middle, high), WHR quartile (female, Q1: WHR<0.77, Q2: 0.77≤WHR< 0.81, Q3: 0.81≤WHR< 0.84; Q4: WHR≥0.84; male, Q1: WHR<0.86, Q2: 0.86≤ WHR< 0.9, Q3: 0.9≤ WHR< 0.94; Q4: WHR≥0.94), smoking status (never smokers, former smokers, current smokers), alcohol consumption (never, ever), family history of pancreatic cancer (yes, no), gallstone history (yes, no), gallbladder surgery history (yes, no), and diabetes history (yes, no)

**The high, medium and low categories of sitting time correspond to >6 hours/day, 2-6 hours/day, and <2 hours/day respectively; N=72,115 for SWHS and 59,373 for SMHS with sitting time information

***The low, medium and high categories of energy correspond to <8 kJ/min, 8-12 kJ/min, and >12 kJ/min respectively; N=72,115 for SWHS and 59,373 for SMHS with energy information

Table 4

Joint analysis for adult and adolescence physical activity on pancreatic cancer risk in the Shanghai Women's Health Study (1996–2014) and Shanghai Men's Health Study (2002–2014)

Category[#]	SWHS (N=72,451)			SMHS (N=60,037)		
	Cases (no.)	Hazard ratio[*]	95% confidence interval	Cases (no.)	Hazard ratio[*]	95% confidence interval
adult LTPA: 0 / physical activity during adolescence: 0	44	1 (ref.)		10	1 (ref.)	
adult LTPA: 0 / physical activity during adolescence: >0	72	1.32	0.81-2.22	83	0.54	0.27-1.08
adult LTPA: >0 / physical activity during adolescence: 0	52	1.10	0.74-1.65	11	0.69	0.29-1.64
adult LTPA: >0 / physical activity during adolescence: >0	57	1.34	0.81-2.22	55	**0.38**	**0.19-0.77**

[#]All units in MET-h/day/year; physical activity during adolescence represents adolescent LTPA for females and adolescent LTPA or physical labor for males

[*]Hazard ratios adjusted for education (elementary school or less, middle school, high school, college or more), income (low, middle, high), WHR quartile (female, Q1: WHR<0.77, Q2: 0.77≤ WHR< 0.81, Q3: 0.81≤ WHR< 0.84; Q4: WHR≥0.84; male, Q1: WHR<0.86, Q2: 0.86≤WHR< 0.9, Q3: 0.9≤ WHR< 0.94; Q4: WHR≥0.94), smoking status (never smokers, former smokers, current smokers), alcohol consumption (never, ever), family history of pancreatic cancer (yes, no), gallstone history (yes, no), gallbladder surgery history (yes, no), and diabetes history (yes, no)