Published in final edited form as:

Cancer Causes Control. 2010 August ; 21(8): 1305–1314. doi:10.1007/s10552-010-9558-x.

Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts

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Conflict of Interest No conflict of interest is declared.

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Abstract

Objective—To investigate whether the positive association of body mass index (BMI, kg/m²) with risk of pancreatic cancer is modified by age, sex, smoking status, physical activity, and history of diabetes.

Methods—In a pooled analysis of primary data of seven prospective cohorts including 458,070 men and 485,689 women, we identified 2,454 patients with incident pancreatic cancer during an average 6.9 years of follow-up. Cox proportional hazard regression models were used in data analysis.

Results—In a random-effects meta-analysis, for every 5 kg/m² increment in BMI, the summary relative risk (RR) was 1.06 (95% confidence interval (CI) 0.99–1.13) for men and 1.12 (95% CI 1.05–1.19) for women. The aggregate analysis showed that compared with normal weight (BMI: 18.5 to <25), the adjusted RR was 1.13 (95% CI 1.03–1.23) for overweight (BMI: 25 to <30) and 1.19 (95% CI 1.05–1.35) for obesity class I (BMI: 30 to <35). Tests of interactions of BMI effects by other risk factors were not statistically significant. Every 5 kg/m² increment in BMI was associated with an increased risk of pancreatic cancer among never and former smokers, but not among current smokers (*P*-interaction = 0.08).

Conclusion—The present evidence suggests that a high BMI is an independent risk factor of pancreatic cancer.

Keywords

Pancreatic cancer; Body mass index; Pooled analysis; Prospective cohort; Effect modification

Introduction

Age, genetic predisposition, and cigarette smoking are well-established risk factors for pancreatic cancer. The positive association between a high body mass index (BMI, weight in kg divided by height in m²) and risk of pancreatic cancer has been observed in at least 19 of 29 prospective studies and 3 meta-analyses, although not all showed a statistically significant association. The magnitude of the association varied from 10 to 45% increased risk for every 5 kg/m² increase in BMI [1–3]. There are sparse data on whether the association between BMI and pancreatic cancer risk is modified by age, sex, smoking, physical activity and history of diabetes [4–6]. We therefore conducted a pooled analysis using primary data from seven prospective cohorts to explore associations that individual studies may lack the power to investigate. We hypothesized that the association between BMI and risk of pancreatic cancer is modified by age, smoking, physical activity and history of diabetes. This analysis is instructive about whether the association between BMI and pancreatic cancer is dependent on other risk factors. We also aimed to determine the magnitude and dose–response of the association of BMI with pancreatic cancer risk.

Materials and methods

Study participants

The present study was comprised of seven prospective cohorts that are studied in collaborative investigations by National Cancer Institute and extramural researchers. Each of these seven cohorts collected body weight and height information and had more than 50 incident pancreatic cancer cases after excluding prevalent pancreatic cancer. Among the studies, the National Institutes of Health-AARP Diet and Health Study (AARP), Agricultural Health Study (AHS), Breast Cancer Detection Demonstration Project (BCDDP), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), and the US Radiologic Technologists Study (USRT) are cohorts in the United States; the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) is a cohort of Finnish male smokers; and the Shanghai Women's Health Study (SWHS) is a cohort of Chinese women. The association of BMI with pancreatic cancer risk previously has been investigated in the AARP and ATBC cohorts with less follow-up time than the current analysis. From a total of 1,042,625 participants and 2,828 patients identified, we excluded 45,175 without BMI information, 18,033 with proxy respondents, 239 censored

before entry to the study, and 26,684 with extreme body mass values (3 times the interquartile range below or above the quartile values). After these exclusions, we had 952,494 participants and 2,639 patients with incident pancreatic cancer. We included only pancreatic adenocarcinoma with the International Classification of Disease (ICD) for Oncology 3 code C25 or ICD 8 or 9 code 157, excluding C25.4 and 157.4, respectively, which are endocrine cases. The Human Subjects Institutional Review Boards overseeing each study approved the use of the data.

Exposure assessment and data aggregation

At baseline, all participants in each cohort completed questionnaires, either self-administered or through in-person interviews (for ATBC and SWHS), that elicited information on demographics (age, sex, race, and educational achievement level), smoking history, physical activity, and history of diabetes. Dietary intake information was collected in the AARP, PLCO, BCDDP, ATBC, and SWHS cohorts. We calculated BMI using height and weight information that was either measured in the ATBC [6] and SWHS [7] or self-reported in all other cohorts. Information on the history of diabetes was not collected at baseline in the USRT study. We created cohort-specific definitions of low versus high levels of physical activity based on the individual cohort questionnaires using expert judgment. Before aggregating the primary data, we compiled a standardized variable list and recoded the exposure variables in a uniform manner.

Cohort follow-up and case ascertainment

Follow-up time was calculated from 1 year after the completion of the baseline questionnaire (age at entry) to the date of pancreatic cancer diagnosis or death, death from any other cause, or last date of follow-up, whichever came first. We excluded the first year of follow-up to reduce the potential bias due to subclinical-disease-related weight loss. Vital status was ascertained by linkage to the US Social Security Administration Death Master File (for AARP) [8], State Death Registry or the National Death Index (for AHS, BCDDP, PLCO, and USRT) [9–12]; Register of Causes of Death (for ATBC) [13], or Shanghai Vital Statistics Unit (for SWHS) [14]. Incident pancreatic cancer cases were identified from cancer registries or National Death Index (AARP, AHS, ATBC, BCDDP, PLCO, and USRT) [8–10,14,15]. All of the PLCO cases, 62% of the ATBC cases, and a small portion of self-reported cases (<10%) in BCDDP were confirmed by medical records or pathological reports [10,15]. Incident cases in the SWHS were identified through biennial in-person interviews and linkage to the Shanghai Cancer Registry. Histology codes were documented for 79% of the cases.

Statistical analysis

Cox proportional hazard regression models using the attained age as the underlying time metric were used to calculate sex-specific and sex-combined relative risks (RRs) and 95% confidence intervals (CIs) of pancreatic cancer in association with BMI and other risk factors. BMI was modeled continuously (per 5 kg/m² increment) and categorically, grouped according to the World Health Organization categories of underweight (16.5 to <18.5), normal weight (18.5 to <25), overweight (25 to <30), obesity class I (30 to <35), and obesity class II or greater (≥35) with normal weight being the referent category [16]. We used STATA 9.0 software (STATA corporation, College Station, Texas) to perform the analysis. All *P* values were based on two-sided tests, and a value of <0.05 was considered statistically significant. We tested the proportional hazards assumption for all variables included in the model using the *stptest* command in STATA. We performed meta-analysis [17] of the individual data and as well the aggregate analysis using the aggregated individual data.

First, RRs and 95% CIs of pancreatic cancer in relation to BMI were calculated separately in each cohort with adjustment for age, sex (for sex-combined model), and smoking history (never

smokers, former smokers with ≤ 10 cigarettes per day, former smokers with >10 –20 cigarettes per day, former smokers with >20 –30 cigarettes per day, former smokers with >30 –40 cigarettes per day, former smokers with >40 cigarettes per day, current smokers with ≤ 10 cigarettes per day, current smokers with >10 –20 cigarettes per day, current smokers with >20 –30 cigarettes per day, current smokers with >30 –40 cigarettes per day, current smokers with >40 cigarettes per day, and missing). A summary RR estimate was then computed by combining the cohort-specific relative risks using a random-effects model [18]. We tested the between-study heterogeneity using a Mantel–Haenszel test and with the I^2 statistic [19]. To investigate the influence of individual studies on the summary RR, an influence analysis was conducted by removing one cohort at a time and calculating the corresponding summary RR.

Second, we aggregated the primary data of the seven cohorts into one dataset to estimate overall risk. Because there was no between-study heterogeneity and the risk estimates from the meta-analysis and aggregate analysis were essentially the same, we present the results of the aggregate analyses. We assessed the association of BMI (categorical) and pancreatic cancer risk using two models: the first model adjusted for age, sex (in the sex-combined model) and cohort; the second model additionally adjusted for smoking history. To test for a linear trend in risk with increasing BMI, we treated categorical BMI as a continuous term in the regression models and used the Wald χ^2 test to test for statistical significance. Using the five US cohorts, we calculated the age-, cohort-, sex-, and smoking-adjusted population attributable risk (PAR) to estimate the percentage of cases that would have been eliminated had all participants had normal weight ($18.5 \leq \text{BMI} < 25$), assuming a causal relationship between BMI and pancreatic cancer risk [20].

As dietary intakes (saturated fat, fruit, and vegetables) did not confound the association between BMI and risk of pancreatic cancer, we did not include dietary variables in the models. Total energy intake is intimately related to BMI, but such information was not available for all cohorts. Nevertheless, adjustment of energy intake in the AARP, ATBC, and SWHS cohorts did not change the risk estimates ($<5\%$ change). Adjustments for race, education, history of diabetes, body height, and physical activity also did not change the risk estimates in general. Therefore, these variables were not included in the models.

Effect modification was evaluated using the stratified analyses according to age at entry (<60 vs. ≥ 60 years old), baseline calendar year (before 1995 vs. after 1995), smoking status (never vs. former vs. current smoker), physical activity (low vs. high), and history of diabetes (no vs. yes). To examine the significance of interaction, we generated cross product terms for the continuous BMI variable (per 5 kg/m² increment) by these factors. We used the Wald χ^2 test to test the statistical significance of interaction. The sensitivity analyses were done by excluding the first 2 years of follow-up based on 2,257 cases, or participants with self-reported history of cancer based on 2,203 cases. We also limited the analysis to 1,938 patients with pathologically confirmed pancreatic adenocarcinoma.

Results

The characteristics of all participants are presented in Table 1. The AHS, SWHS, and USRT cohorts had a younger mean age at entry than the other cohorts. The mean age of diagnosis was 69 years for both men and women. The majority of the US study participants were non-Hispanic whites (84.6%). The AARP and PLCO cohorts had the highest mean BMI, whereas the SWHS and USRT cohorts had the lowest mean BMI. After excluding 8,735 participants with less than 1 year of follow-up, we had 943,759 participants (458,070 men and 485,689 women) and 2,454 pancreatic cancer cases (1,548 men and 906 women) with a mean follow-up of 6.9 years and the follow-up was up to 20 years.

Table 2 presents the selected characteristics of men and women at baseline across the BMI categories. The mean BMI was 27.0 (± 3.7 SD) in men and 25.8 (± 4.9 SD) in women. In both men and women, a higher BMI was related to being African American, having lower levels of physical activity, or having a history of diabetes. Individuals with higher BMI were less likely to be current smokers, but they were more likely to be former smokers. Among former and current smokers, the proportion of men smoking more than 30 cigarettes per day was higher among obese men and the proportion of women smoking more than 20 cigarettes per day was higher among obese women.

In the aggregate data, compared with never smokers, the adjusted RR of pancreatic cancer was 1.23 (95% CI 1.10–1.38) for former smokers and 2.16 (95% CI 1.88–2.48) for current smokers. The RR was 1.05 (95% CI 1.01–1.11) for history of diabetes. High levels of physical activity were associated with significantly reduced risk for all the participants (RR 0.90; 95% CI 0.82–0.99, adjusting for sex, BMI, smoking history, cohort and diabetes), but not for never smokers (RR 1.04; 95% CI 0.88–1.24). Height was not associated with pancreatic cancer risk (RR 0.98; 95% CI 0.79–1.21, highest versus lowest quintile with the lowest cut-off point of 0.91 meter and the highest cut-off point of 1.80 meter) (data not shown in tables).

Figure 1 shows that every 5 kg/m² increment of BMI was associated with an increased risk of pancreatic cancer. The summary RR from the random-effects meta-analysis was 1.08 (95% CI 1.03–1.14) for all participants, 1.06 (95% CI 0.99–1.13) for men and 1.12 (95% CI 1.05–1.19) for women. The risk estimates across cohorts were similar in magnitude. The exclusion of the AARP study, the largest study, did not change the summary RR substantially (RR 1.10; 95% CI 1.02–1.18). The exclusion of the ATBC or/and the SWHS study did not change the risk estimate. The test for heterogeneity among cohorts was not statistically significant ($P = 0.997$). We observed essentially similar associations per 5 kg/m² increment of BMI in the sensitivity analysis. For example, for all participants, the adjusted summary RR of pancreatic cancer was 1.10 (95% CI 1.05–1.16) when we excluded participants with less than 2 years of follow-up. Figure 2 shows the linear relation of increment of every 2.5 kg/m² of BMI and risk of pancreatic cancer (P -trend 0.02). We plotted the 8% increased risk per 5 kg/m² increment of BMI on this association. It shows that the summary risk estimate on a continuous scale was an approximation of the risk estimates on a categorical scale.

Table 3 shows the results of the aggregate analysis. Compared with normal weight, overweight and obesity class I were associated with statistically significant increased risk of pancreatic cancer. The association between BMI and pancreatic cancer risk did not differ by sex (P -interaction = 0.44) and age at entry (P -interaction = 0.32) (Table 3), nor did risk vary significantly by calendar year of entry (P -interaction = 0.67). In the five US cohorts, compared with $18.5 \leq \text{BMI} < 25$, the RR for those with $\text{BMI} \geq 25$ was 1.18 (95% CI 1.07–1.30) and the RR for those with $25 \leq \text{BMI} < 30$ was 1.16 (95% CI 1.05–1.28). The adjusted PAR for BMI ≥ 25 was 7.8% (95% CI 2.1–13.4%). It was noted that overweight explained the majority of the PAR because 68.8% were overweight among the participants whose BMI was no less than 25.

Table 4 shows the joint effects of BMI (per 5 kg/m² increment) and smoking, physical activity, or history of diabetes on risk of pancreatic cancer. Every 5 kg/m² of increment in BMI was associated with increased risk for never smokers (RR 1.15; 95% CI 1.06–1.25) and former smokers (RR 1.11; 95% CI 1.03–1.20), but not for current smokers (RR 1.00; 95% CI 0.91–1.11) (P -interaction = 0.08). The association of BMI with pancreatic cancer risk did not differ statistically significantly by physical activity (P -interaction = 0.61) and history of diabetes (P -interaction = 0.56).

Discussion

High BMI, both overweight and obesity, increased risk of pancreatic cancer in men and women. For every 5 kg/m² increment in BMI, the association was borderline significant in men and statistically significant in women. We observed an overall 6% increase in risk for men and 12% for women, which were similar to the magnitude reported by a recent meta-analysis of 16 prospective cohorts³ that showed 7% increase in risk for men and 12% for women. Along with two recent meta-analyses of prospective studies [2,3], we showed no evidence for an effect modification by sex. We estimated that in the US study population, 7.8% of pancreatic cancer would be eliminated if normal weight was maintained. The effect of BMI on pancreatic cancer risk was not modified by age at entry, sex, smoking status, physical activity, and history of diabetes. There was no between-study heterogeneity for the seven cohorts.

Several mechanisms have been proposed for the link between obesity and cancer [21]. Obesity has been related to glucose intolerance, insulin resistance, hyperinsulinemia, and type 2 diabetes. These progressive physical conditions have also been associated with an increased risk in pancreatic cancer [22–24]. Obesity has an inverse association with concentration of adiponectin, which is an insulin-sensitizing and anti-diabetic hormone. Higher adiponectin concentration had an inverse association with the development of pancreatic cancer in a male smoker cohort [25]. An alternative mechanism by which high BMI may increase the risk of pancreatic cancer is the formation of DNA adducts caused by endogenous lipid peroxidation. A positive association between plasma levels of lipid peroxidation and obesity has been reported in healthy individuals [26]. BMI was the only significant predictor of lipid peroxidation-related adducts levels in adjacent normal pancreatic tissue from pancreatic cancer patients [27].

We found that the association between BMI and pancreatic cancer risk was slightly stronger among participants whose age at entry was younger than 60 years. It has been suggested that higher BMI early in life may be a better predictor for future pancreatic cancer development than BMI later in life. The latency period between obesity and onset of pancreatic cancer development is likely to be long [28]. Alternatively, a greater misclassification due to misreporting in older individuals may have attenuated the risk estimates. Individuals older than 60 years have been shown to more likely underestimate their current weight than individuals younger than 60 years of age [29–31]. Nevertheless, the test of interaction by age at entry was not statistically significant.

We did not find a significant interaction of BMI and smoking status in modifying risk of pancreatic cancer. Seven studies found a higher risk of pancreatic cancer among obese never smokers, but not among obese ever-smokers compared with non-obese never smokers [5,6, 32–36]. Among smokers, tobacco carcinogens may be a more dominant etiologic mechanism than obesity-related metabolic disturbances and may mask the effect of the latter on pancreatic cancer development [6,8]. In addition, in the short term, nicotine increases energy expenditure and is positively associated with satiety [37]. Smoking can increase metabolic rate and decrease metabolic efficiency and caloric absorption [38]. However, in the long term, smoking is associated with high plasma insulin concentrations independent of other factors known to influence insulin sensitivity [39]. Some tobacco carcinogens may accumulate in adipose tissue [40]. A Japanese cohort study found that obese smokers had a higher risk of pancreatic cancer than non-obese smokers and suggested an additive effect of BMI and smoking in pancreatic cancer development [41]. While the statistical interaction was not significant, there was a suggestion that the association was limited to never and former smokers. Former smokers, especially those who quit smoking for more than 10 years, had a risk of pancreatic cancer that was equivalent to that of never smokers [42]. Further investigation on the smoking–BMI–pancreatic cancer association is warranted.

We did not find physical activity modifies the association between BMI and risk of pancreatic cancer. Physical activity plays a role in reducing glucose intolerance. The joint effect of BMI and physical activity on risk of pancreatic cancer is plausible. Michaud et al. [43] detected a statistically non-significant interaction between BMI and physical activity by showing total physical activity reduced risk among overweight and obese individuals but not among normal weight individuals. Other studies did not show such an association [6,8,33,44–46]. Our data suggested that an increasing BMI was associated with pancreatic cancer risk regardless of levels of physical activity.

There was no interaction of BMI and history of diabetes in modifying risk of pancreatic cancer. However, we found that a high BMI was associated with a greater risk of pancreatic cancer among non-diabetics. The similar association has been reported in two other studies [5,34]. This observation suggests that hyperglycemia but not necessarily clinically evident diabetes could exert an effect on pancreatic cancer and supports the hypothesis that insulin resistance plays a role in pancreatic cancer etiology. Although diabetes was associated with risk of pancreatic cancer in our study, we did not observe an association between high BMI and risk of pancreatic cancer among diabetics. Diabetes may be a potential intermediate variable because it could be in the causal pathway of obesity and pancreatic cancer. At baseline, participants reporting to be diabetic might have been at a different stage in the disease course and no longer synthesize insulin endogenously. In addition, interventions including diet, weight loss, and medications could contribute to the lack of association. In the present study, we were not able to distinguish type 1 versus type 2 diabetes; we did not know the time of diagnosis of diabetes; and we did not have updated information on diabetes during the follow-up. These limitations precluded us to investigate the diabetes and weight change in association with pancreatic cancer risk. Further study should investigate whether weight change in diabetics affects the risk of pancreatic cancer. The medications used to control the symptoms of diabetes may also modify the risk of pancreatic cancer [47,48]. Finally, low statistical power among the small group of diabetics may account for the lack of associations.

The present study has several limitations. As BMI was calculated based mostly on self-reported information, the potential measurement error might have led to an inaccurate relative risk estimate [49]. The information on self-reported physical activity was also subjected to measurement error. We might not have captured critical windows of lifetime weight change that may confer a higher risk of pancreatic cancer, particularly among former smokers. Central adiposity may be a more relevant measure than BMI for risk of pancreatic cancer [8,44,45, 50–52]. AARP, BCDDP, and SWHS collected waist and hip circumference information, but the number of cases in the BCDDP or SWHS cohorts with such data was small (<60) so that the associations with central adiposity would be driven by the AARP study, for which a positive association was previously reported for women but not for men [8]. Because the majority of the cohort members were non-Hispanic whites, we could not perform analyses stratified by racial group. The information on smoking duration and therefore pack-year was not available in some of the cohorts. Therefore, the confounding effects by smoking could not be fully adjusted and the residual confounding effects may have biased the risk estimate toward the null. One of the advantages of aggregating primary data compared to literature-based meta-analysis is that it allows categorize the major exposure variables and covariates in the same way and adjust analysis in the same fashion. The present analysis allowed us to detect a statistically significant association that could have been missed by any single study. For example, other than the AARP cohort, none of the individual cohorts detected a significant association between BMI and pancreatic cancer. On the other hand, we detected a significant association with the same magnitude in the pooled analysis of six cohorts without the AARP cohort. The study findings may be most generalizable to the US population than a single study because five of the seven cohorts were from the United States. Consistent with a previous study conducted in Shanghai [53], we observed a slightly elevated risk among obese Shanghai women

using the World Health Organization cutoff point. With the transition to a Western lifestyle pattern, the concurrent rising obesity in the Chinese population raises an opportunity for preventing pancreatic cancer, as well as for preventing other obesity-related diseases.

In summary, the adjusted PAR for pancreatic cancer associated with overweight and obesity was 7.8% in the US population, which was lower than 26.9% that was reported by a previous study. The relative risk associated with overweight or obesity was higher in the previous study than in the present study [54]. Nevertheless, given a substantial increase in the proportion of the population that is overweight or obese, reversal of the obesity epidemic offers an opportunity for primary prevention of pancreatic cancer. The relationship between obesity and risk of pancreatic cancer appears to be independent of age, sex, smoking, physical activity, and diabetes. Further epidemiologic investigations on body composition in early life, central adiposity, and weight change and their associations with other modifying factors of pancreatic cancer risk may provide new insight into pancreatic cancer pathogenesis.

Acknowledgments

The authors thank Jerome Mabie, Joe Barker, Matthew Butcher, Jeremy Miller, and Anne Taylor from the Information Management System for their help with data management.

Financial Support The funding source of this pooled analysis is the Intramural Research Program of the National Cancer Institute, Division of Cancer Epidemiology and Genetics; and National Institute of Environment Health Sciences, Epidemiology Branch, National Institutes of Health.

Abbreviation

AARP	National Institutes of Health-AARP Diet and Health Study
AHS	Agricultural Health Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BCDDP	Breast Cancer Detection Demonstration Project
BMI	Body mass index
CI	Confidence interval
NCI-DCEG	National Cancer Institute-Division of Cancer Epidemiology and Genetics
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
SD	Standard deviation
SWHS	Shanghai Women's Health Study
RR	Relative risk
USRT	United States Radiologic Technologists Study

References

1. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer* 2003;89:519–523. [PubMed: 12888824]
2. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. *Int J Cancer* 2007;120:1993–1998. [PubMed: 17266034]
3. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–578. [PubMed: 18280327]

4. Luo J, Iwasaki M, Inoue M, et al. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan-The JPHC study. *Cancer Causes Control* 2007;18:603–612. [PubMed: 17401636]
5. Fryzek JP, Schenk M, Kinnard M, et al. The association of body mass index and pancreatic cancer in residents of southeastern Michigan, 1996–1999. *Am J Epidemiol* 2005;162:222–228. [PubMed: 15987732]
6. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, et al. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). *Cancer Causes Control* 2002;13:417–426. [PubMed: 12146846]
7. Rosenthal AD, Jin F, Shu XO, et al. Body fat distribution and risk of diabetes among Chinese women. *Int J Obes Relat Metab Disord* 2004;28:594–599. [PubMed: 14770196]
8. Stolzenberg-Solomon RZ, Adams K, Leitzmann M, et al. Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. *Am J Epidemiol* 2008;167:586–597. [PubMed: 18270373]
9. Koutros S, Lynch CF, Ma X, et al. Heterocyclic aromatic amine pesticide use and human cancer risk: results from the U.S. Agricultural Health Study. *Int J Cancer* 2009;124:1206–1212. [PubMed: 19058219]
10. Calton BA, Stolzenberg-Solomon RZ, Moore SC, et al. A prospective study of physical activity and the risk of pancreatic cancer among women (United States). *BMC Cancer* 2008;8:63. [PubMed: 18307811]
11. Boice JD Jr, Mandel JS, Doody MM, et al. A health survey of radiologic technologists. *Cancer* 1992;69:586–598. [PubMed: 1728391]
12. Freedman DM, Ron E, Ballard-Barbash R, et al. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes (Lond)* 2006;30:822–829. [PubMed: 16404410]
13. The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. *Ann Epidemiol* 1994;4:1–10. [PubMed: 8205268]
14. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol* 2005;162:1123–1131. [PubMed: 16236996]
15. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, et al. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. *Cancer Res* 2009;69:1439–1447. [PubMed: 19208842]
16. World Health Organization. WHO Technical Report Series No. 894. WHO; Geneva: 2000.
17. Smith-Warner SA, Spiegelman D, Ritz J, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. *Am J Epidemiol* 2006;163:1053–1064. [PubMed: 16624970]
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188. [PubMed: 3802833]
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–1558. [PubMed: 12111919]
20. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control* 2007;18:571–579. [PubMed: 17387622]
21. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc* 2001;60:91–106. [PubMed: 11310428]
22. Gapstur SM, Gann PH, Lowe W, et al. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000;283:2552–2558. [PubMed: 10815119]
23. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* 2005;294:2872–2878. [PubMed: 16352795]
24. Michaud DS, Wolpin B, Giovannucci E, et al. Prediagnostic plasma C-peptide and pancreatic cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev* 2007;16:2101–2109. [PubMed: 17905943]
25. Stolzenberg-Solomon RZ, Weinstein S, Pollak M, et al. Prediagnostic adiponectin concentrations and pancreatic cancer risk in male smokers. *Am J Epidemiol* 2008;168:1047–1055. [PubMed: 18801887]

26. Olusi SO. Obesity is an independent risk factor for plasma lipid peroxidation and depletion of erythrocyte cytoprotective enzymes in humans. *Int J Obes Relat Metab Disord* 2002;26:1159–1164. [PubMed: 12187391]
27. Wang M, Abbruzzese JL, Friess H, et al. DNA adducts in human pancreatic tissues and their potential role in carcinogenesis. *Cancer Res* 1998;58:38–41. [PubMed: 9426054]
28. Michaud DS, Fuchs CS. Obesity and pancreatic cancer: overall evidence and latency period. *Cancer Epidemiol Biomarkers Prev* 2005;14:2678–2679. 2678. author reply. [PubMed: 16284397]
29. Nawaz H, Chan W, Abdulrahman M, et al. Self-reported weight and height: implications for obesity research. *Am J Prev Med* 2001;20:294–298. [PubMed: 11331120]
30. Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Am Diet Assoc* 2001;101:28–34. [PubMed: 11209581]
31. Gillum RF, Sempos CT. Ethnic variation in validity of classification of overweight and obesity using self-reported weight and height in American women and men: the Third National Health and Nutrition Examination Survey. *Nutr J* 2005;4:27. [PubMed: 16209706]
32. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–1638. [PubMed: 12711737]
33. Nothlings U, Wilkens LR, Murphy SP, et al. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control* 2007;18:165–175. [PubMed: 17219012]
34. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362, 552 Swedish men. *Cancer Causes Control* 2006;17:901–909. [PubMed: 16841257]
35. Anderson LN, Cotterchio M, Gallinger S. Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada. *Cancer Causes Control* 2009;20:825–834. [PubMed: 19194662]
36. Pan SY, Johnson KC, Ugnat AM, et al. Association of obesity and cancer risk in Canada. *Am J Epidemiol* 2004;159:259–268. [PubMed: 14742286]
37. Jessen A, Buemann B, Toubro S, et al. The appetite-suppressant effect of nicotine is enhanced by caffeine. *Diabetes Obes Metab* 2005;7:327–333. [PubMed: 15955118]
38. Hofstetter A, Schutz Y, Jequier E, et al. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med* 1986;314:79–82. [PubMed: 3941694]
39. Ronnema T, Ronnema EM, Puukka P, et al. Smoking is independently associated with high plasma insulin levels in nondiabetic men. *Diabetes Care* 1996;19:1229–1232. [PubMed: 8908385]
40. Obana H, Hori S, Kashimoto T, et al. Polycyclic aromatic hydrocarbons in human fat and liver. *Bull Environ Contam Toxicol* 1981;27:23–27. [PubMed: 7296033]
41. Lin Y, Kikuchi S, Tamakoshi A, et al. Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. *Int J Cancer* 2007;120:2665–2671. [PubMed: 17304505]
42. Jiao L, Silverman DT, Schairer C, et al. Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 2009;169:1043–1051. [PubMed: 19299403]
43. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 2001;286:921–929. [PubMed: 11509056]
44. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 2006;15:879–885. [PubMed: 16702364]
45. Patel AV, Rodriguez C, Bernstein L, et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. *Cancer Epidemiol Biomarkers Prev* 2005;14:459–466. [PubMed: 15734973]
46. Eberle CA, Bracci PM, Holly EA. Anthropometric factors and pancreatic cancer in a population-based case-control study in the San Francisco Bay area. *Cancer Causes Control* 2005;16:1235–1244. [PubMed: 16215874]
47. Wang F, Gupta S, Holly EA. Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. *Cancer Epidemiol Biomarkers Prev* 2006;15:1458–1463. [PubMed: 16896032]

48. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009;301:2553–2562. [PubMed: 19549972]
49. Gorber SC, Tremblay M, Moher D, et al. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007;8:307–326. [PubMed: 17578381]
50. Luo J, Margolis KL, Adami HO, et al. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). *Br J Cancer* 2008;99:527–531. [PubMed: 18628761]
51. Larsson SC, Permert J, Hakansson N, et al. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer* 2005;93:1310–1315. [PubMed: 16288300]
52. Ansary-Moghaddam A, Huxley R, Barzi F, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev* 2006;15:2435–2440. [PubMed: 17164367]
53. Ji BT, Hatch MC, Chow WH, et al. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Int J Cancer* 1996;66:432–437. [PubMed: 8635856]
54. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4:579–591. [PubMed: 15286738]

Fig. 1.

Relative risk of pancreatic cancer per 5 kg/m² increment in body mass index in the individual studies with the summary relative risk estimates. Diamonds indicate the summary relative risk and its 95% confidence interval. Test of between-study heterogeneity: $P = 0.997$, 0.628 , and 0.899 for all participants, men and women, respectively

Fig. 2.

Relative risk of pancreatic cancer per 2.5 kg/m² increment of body mass index using 22.5–25 as the referent group (P for trend 0.02). The number of cases was 17, 41, 294, 520, 705, 404, 250, 131, 71, and 21 for each BMI category along the X axis from left to right. We placed the dots for 8% increase of risk per 5 kg/m² increment in body mass index at 18.8, 23.8, 28.8, 33.8, 38.8 and 43.8 of body mass index and drew a super-imposed dashed line. This figure shows that in the aggregate analysis, the summary relative risk per 5 kg/m² increment of body mass index is the approximation to the risk estimate by the categorical analysis

Table 1

Characteristics of all participants in the pooled analysis of body mass index and risk of pancreatic cancer

Cohorts	Baseline (calendar year)	Follow-up through	No. of Participants ^a	No. of cases	No. with diabetes	Men (%)	African American (%)	Current smokers (%)	Age at entry (mean)	Years of follow-up (mean)	BMI (mean)
AARP	1995–1996	12/2003	516,827	1,426	46,329	60.1	3.8	11.7	62.2	7.3	27.0
AHS	1993–1997	12/2005	67,245	95	1,790	56.8	1.5	12.2	47.4	10.3	26.9
ATBC	1985–1988	04/2005	29,114	338	1,240	100	0	100.0	57.2	14.3	26.3
BCDDP	1987–1989	12/1997	46,903	124	2,575	0	3.8	12.4	62.2	8.4	25.1
PLCO	1993–2001	04/2006	138,799	444	10,347	49.0	4.9	10.4	62.6	8.4	27.1
SWHS	1997–2000	12/2005	74,875	75	3,297	0	0	2.4	52.1	7.2	24.0
USRT	1983–1989	12/2003	78,731	137	NA	22.4	2.4	23.8	39.0	16.7	23.7
All			952,494	2,639	65,578	48.9	3.2	13.6	58.3	8.6	26.4

AARP National Institutes of Health–AARP Diet and Health Study, AHS Agricultural Health Study, ATBC Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, BCDDP Breast Cancer Detection Demonstration Project, BMI body mass index, NA Not available, PLCO Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, SWHS Shanghai Women’s Health Study, USRT United States Radiologic Technologists Study

^aWith complete data on body mass index and with the first year of follow-up

Table 2

Baseline characteristics of men and women across categories of body mass index in the aggregate dataset of the seven cohorts

Characteristics	Body mass index (kg/m ²)				
	16.5 to 18.5	18.5 to <25	25 to <30	30 to <35	≥35
<i>Men (n = 458,070)</i>					
Participants (%)	0.5	30.0	50.3	16.5	2.7
Age at entry (mean)	62	61	61	61	60
African American (%)	2.8	2.2	2.6	3.4	4.1
Smoking status (%)					
Never	28.0	32.8	30.3	28.1	28.9
Former	41.6	43.4	51.8	55.3	54.4
Current	25.3	19.4	13.7	12.1	11.8
Missing	5.0	4.4	4.3	4.5	4.9
Cigarette smoked per day (%) ^a					
>0–10	13.5	14.3	12.9	11.6	10.9
>10–20	24.9	25.0	23.5	20.6	18.5
>20–30	16.7	14.3	15.5	16.2	15.2
>30–40	8.6	7.3	9.5	12.2	12.8
≥40	5.0	3.6	5.3	8.1	10.0
Missing	3.3	2.7	3.0	3.2	3.7
High level of physical activity (%) ^b					
44.1	50.5	52	46.4	37.7	30.2
Self-reported diabetes (%)	6.1	5.2	7.9	13.3	19.0
<i>Women (n = 485,689)</i>					
Participants (%)	1.6	49.8	31.2	12.0	5.5
Age at entry (mean)	55	50	60	61	60
African American (%)	1.8	1.4	4.6	7.2	9.8
Asian (%)	20.4	34.5	16.1	6.9	2.4
Smoking status (%)					
Never	65.0	58.5	57.1	53.8	51.1
Former	15.5	26.1	30.1	34.4	38.2
Current	18.4	13.9	10.9	9.6	8.2

Characteristics	Body mass index (kg/m ²)					
	16.5 to 18.5	18.5 to <25	25 to <30	30 to <35	>=35	
Missing	1.1	1.6	1.9	2.2	2.5	
Cigarette smoked per day (%) ^a						
>0–10	11.4	14.5	14.3	14.7	15.3	
>10–20	13.5	14.5	14.1	14.4	14.0	
>20–30	6.8	7.3	7.4	8.2	8.4	
>30–40	1.1	2.3	3.4	4.3	5.4	
≥40	0.8	1.0	1.5	2.2	3.1	
Missing	1.4	1.9	2.2	2.4	2.7	
High level of physical activity (%) ^b	32.6	41.7	40.0	32.2	23.8	
Self-reported diabetes (%)	1.8	2.4	5.9	11.4	18.8	

^aNot including never smokers

^bDefined according to cohort-specific questions by expert opinion

Table 3

Relative risk (RR) and 95% confidence interval (CI) of pancreatic cancer in relation to body mass index in all participants and in participants according to sex and age at entry (aggregate analysis)

Groups	Body mass index (kg/m ²)					Continuous (per 5 kg/ m ² increment)
	16.5 to 18.5 (underweight)	18.5 to <25 (normal weight)	25 to 30 (overweight)	30 to <35 (obesity class I)	≥35 (obesity class II and over)	
All participants						
Cases	17	855	1109	381	92	
Person-years	91,763	3,114,608	2,837,129	969,934	279,645	
RR(95% CI) ^a	0.94 (0.58–1.53)	1.00	1.10 (1.01–1.21)	1.17 (1.03–1.32)	1.16 (0.93–1.43)	0.005
RR(95% CI) ^b	0.89 (0.55–1.44)	1.00	1.13 (1.03–1.23)	1.19 (1.05–1.35)	1.19 (0.96–1.48)	0.001
Men						
Cases	7	465	793	240	43	
Person-years	16,325	1,061,807	1,719,626	548,296	90,314	
RR(95% CI) ^a	0.92 (0.44–1.94)	1.00	1.09 (0.97–1.22)	1.10 (0.94–1.28)	1.34 (0.98–1.83)	0.05
RR(95% CI) ^b	0.88 (0.42–1.86)	1.00	1.11 (0.99–1.25)	1.11 (0.95–1.30)	1.34 (0.98–1.84)	0.03
Women						
Cases	10	390	316	141	49	
Person-years	75,438	2,052,801	1,117,503	421,638	189,330	
RR(95% CI) ^a	0.96 (0.51–1.81)	1.00	1.12 (0.97–1.31)	1.29 (1.06–1.57)	1.04 (0.77–1.40)	0.04
RR(95% CI) ^b	0.91 (0.48–1.70)	1.00	1.15 (0.99–1.34)	1.34 (1.11–1.64)	1.09 (0.81–1.47)	0.01
Age at entry						
<60 years						
Cases	3	242	281	121	33	
Person-years	64,319	1,574,785	960,845	325,461	104,744	
RR(95% CI) ^a	0.55 (0.18–1.71)	1.00	1.08 (0.90–1.29)	1.33 (1.06–1.66)	1.34 (0.93–1.94)	0.02
RR(95% CI) ^b	0.52 (0.16–1.61)	1.00	1.10 (0.92–1.32)	1.36 (1.09–1.70)	1.40 (0.97–2.02)	0.007
≥60 years						
Cases	16	769	1017	353	81	
Person-years	37,581	1,918,956	2,258,218	778,480	214,110	
RR(95% CI) ^a	1.00 (0.61–1.64)	1.00	1.10 (0.99–1.20)	1.19 (1.05–1.36)	1.14 (0.90–1.44)	0.006
						1.07 (1.02–1.12)

Groups	Body mass index (kg/m ²)					P for trend ^c	Continuous (per 5 kg/ m ² increment)
	16.5 to 18.5 (underweight)	18.5 to <25 (normal weight)	25 to 30 (overweight)	30 to <35 (obesity class I)	≥35 (obesity class II and over)		
RR(95% CI) ^b	0.95 (0.58–1.56)	1.00	1.11 (1.01–1.23)	1.21 (1.07–1.38)	1.17 (0.93–1.48)	0.002	1.08 (1.03–1.14)

^a RR was adjusted for age, sex, and cohort

^b RR was adjusted for age, sex, cohort, smoking habit (never smokers, former smokers with ≤10 cigarettes per day, former smokers with >10–20 cigarettes per day, former smokers with >20–30 cigarettes per day, former smokers with >30–40 cigarettes per day, current smokers with ≤10 cigarettes per day, current smokers with >10–20 cigarettes per day, current smokers with >20–30 cigarettes per day, current smokers with >30–40 cigarettes per day, and missing)

^c P for trend was tested using the Wald test treating the BMI category as a continuous variable

Table 4

Joint effects of body mass index and smoking status, levels of physical activity, and history of diabetes in modifying risk of pancreatic cancer (aggregate analysis)

	No. of cases	RR (95% CI) ^a	<i>P</i> value for interaction
Smoking status			
Never	711	1.15 (1.06–1.25)	0.08
Former	980	1.11 (1.03–1.20)	
Current	623	1.00 (0.91–1.11)	
Level of physical activity			
High	801	1.10 (1.00–1.20)	0.61
Low	1240	1.08 (1.01–1.15)	
History of diabetes			
No	1975	1.07 (1.02–1.13)	0.56
Yes	284	0.98 (0.86–1.12)	

The interaction was examined using the BMI on the continuous scale (per 5 kg/m² increment)

^aRR was adjusted for age, sex, cohort, and smoking history (never smokers, former smokers with ≤10 cigarettes per day, former smokers with >10–20 cigarettes per day, former smokers with >20–30 cigarettes per day, former smokers with >30–40 cigarettes per day, former smokers with >40 cigarettes per day, current smokers with ≤10 cigarettes per day, current smokers with >10–20 cigarettes per day, current smokers with >20–30 cigarettes per day, current smokers with >30–40 cigarettes per day, current smokers with >40 cigarettes per day, and missing). For the joint effect by smoking status, the number of cigarettes smoked per day (never, >0–10, >10–20, >20–30, >30–40, ≥40, and missing) was adjusted