



Original Contribution

Adiposity, Physical Activity, and Pancreatic Cancer in the National Institutes of Health–AARP Diet and Health Cohort**Rachael Z. Stolzenberg-Solomon¹, Kenneth Adams¹, Michael Leitzmann¹, Catherine Schairer²,
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Obesity and lack of physical activity have been inconsistently associated with pancreatic cancer. Using data from a self-administered baseline questionnaire (1995–1996), the authors investigated the association between adiposity and physical activity and pancreatic cancer in 495,035 participants of the National Institutes of Health–AARP Diet and Health Study who were aged 50–71 years. To avoid the influence of subclinical disease, follow-up time started 1 year after baseline, and subjects with a body mass index (BMI) of <18.5 kg/m² were excluded. A subcohort ($n = 302,060$) completed a second questionnaire with information about physical activity and waist and hip circumference. During follow-up through 2000, 654 pancreatic cancer cases were identified. The authors used Cox proportional hazard models to generate adjusted hazard ratios and 95% confidence intervals. Compared with those with a BMI of 18.5– <25 , those with a BMI of ≥ 35 had a 45% greater pancreatic cancer risk (95% confidence interval (CI): 1.04, 2.02; $p_{\text{trend}} = 0.02$). Significant positive associations for BMI were observed among nonsmokers (for BMI ≥ 35 : hazard ratio = 1.70, 95% CI: 1.14, 2.53; $p_{\text{trend}} = 0.004$) but not recent smokers ($p_{\text{interaction}} = 0.08$). Waist circumference was positively associated with pancreatic cancer (fourth vs. first quartile: hazard ratio = 2.53, 95% CI: 1.13, 5.65; $p_{\text{trend}} = 0.04$) in women but not men. The authors observed no association with physical activity. Their results suggest a positive association between adiposity and pancreatic cancer.

adenocarcinoma; adiposity; body mass index; cohort studies; exercise; pancreatic neoplasms; smoking; waist-hip ratio

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent; NIH, National Institutes of Health.

Pancreatic cancer ranks fourth for cancer mortality for men and women, respectively, in the United States and has a 5-year survival rate of 4.3 percent (1). In addition to cigarette smoking (2), diabetes mellitus and glucose intolerance are among the few consistent and potentially modifi-

able risk factors for pancreatic cancer (3). One biologically plausible mechanism whereby type 2 diabetes may be related to pancreatic carcinogenesis is through the growth-promoting effects of insulin (4). This hypothesized mechanism is supported indirectly by positive associations between

obesity (5–11) and lack of physical activity (12, 13) and pancreatic cancer in some but not all epidemiologic studies (6, 13–24). Obesity, particularly central or abdominal adiposity, may lead to metabolic changes including higher glucose and insulin concentrations, insulin resistance, and type 2 diabetes (25).

The evidence from cohort and case-control studies more consistently supports obesity as a risk factor for pancreatic cancer (5–7, 9–11, 24) than physical activity (12–14, 18–24, 26). Recent meta-analyses reported weak but significant positive associations between increasing body mass index (BMI) and pancreatic cancer, with associations being slightly stronger for cohort than case-control studies and men than women (10, 19). Five cohort studies have examined some aspect of abdominal obesity (e.g., waist circumference or waist/hip ratio, central torso weight gain) and pancreatic cancer (14, 15, 18, 19, 23) with four showing positive associations (14, 15, 19, 23). Although most studies examining physical activity and pancreatic cancer have not shown significant associations (7, 12–14, 18–24, 26), three studies have shown significant inverse associations with greater physical activity in substrata of subjects (12, 13, 22). None of the pancreatic cancer studies that evaluated interactions of BMI and physical activity reported statistically significant interactions (7, 12, 14, 15, 19, 22, 24); however, one study showed that overweight and obese subjects with low physical activity had greater pancreatic cancer risks compared with those with more physical activity and normal weight (12). The lack of consistent associations between these factors and pancreatic cancer may reflect methodological difficulties including reverse causation, recall, and proxy reporting biases from data collected in case-control studies and the small number of incident cases in many cohort studies, resulting in limited power to observe associations. Age-related variation in lean mass (muscle and skeletal mass) may reduce the validity of body mass index (weight (kg)/height (m)²) as a measure of body fatness, and waist circumference may more accurately reflect body fatness in older persons (27). The positive relation between BMI and pancreatic cancer risk may be stronger in non-smokers (15, 26) than in smokers (22). However, few studies have considered effect modification of BMI by smoking status (7, 14, 15, 19, 24, 26).

We conducted an analysis in a large cohort, the National Institutes of Health (NIH)–AARP Diet and Health Study, to examine the association between adiposity, as reflected by BMI, waist circumference, and waist/hip ratio and pancreatic cancer. We also examined physical activity as a risk factor for pancreatic cancer. The NIH–AARP cohort has a larger number of incident pancreatic cancer cases compared with most previous cohort studies (10), which allowed us to examine sex-specific associations and interactions by smoking status.

MATERIALS AND METHODS

Study population

The NIH–AARP Diet and Health Study is a large prospective study of AARP members established in 1995–1996

(28). Self-administered questionnaires eliciting information on demographic characteristics, dietary intake, and numerous health-related behaviors were mailed to AARP members aged 50 and 71 years, who resided in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). The questionnaire was returned by 617,119 members, and 567,169 subjects completed the questionnaire satisfactorily (28). The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and informed consent was obtained from all participants.

We excluded subjects with duplicate representation ($n = 179$), who moved out of the eight areas included in our study before returning the baseline questionnaire ($n = 321$), who died before study entry ($n = 261$), or who withdrew ($n = 1$). We also excluded subjects who had questionnaires completed by proxy respondents ($n = 15,760$), prevalent cancers as determined by the cancer registry data ($n = 8,552$), extreme energy intake outside the normal distribution of the cohort by sex ($n = 4,793$), missing height or weight ($n = 12,927$), and missing smoking data ($n = 16,810$). We further excluded subjects who had a BMI of $<18.5 \text{ kg/m}^2$ ($n = 5,601$) and those censored during the first year of follow-up ($n = 6,929$; number of pancreatic cancer cases = 127) to avoid reverse causation bias. Our final baseline analytical cohort consisted of 495,035 individuals (293,562 men, 201,473 women).

Six months after the baseline questionnaire was sent, baseline respondents were sent a second questionnaire that queried information about physical activity during the past 10 years and measurement of waist and hip (28). Among subjects in our baseline analytical cohort, 302,060 subjects completed the second questionnaire. We included all subjects with complete physical activity ($n = 294,609$) data or who provided waist, hip, or both waist and hip measurements ($n = 228,080$, 217,930, and 217,119, respectively); therefore, the number of subjects in each subcohort analysis varies slightly.

Cohort follow-up and case ascertainment

Cancer cases were identified by linking cohort members to state cancer registries and to the US National Death Index between 1995 through 2000 and are estimated to be about 90 percent complete (29). The vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File. For these analyses, we included incident primary adenocarcinoma of the exocrine pancreas (*International Classification of Diseases for Oncology*, Third Edition (ICD-O-3), codes C250–C259). Our case definition excluded endocrine pancreatic tumors (histology types 8150, 8151, 8153, 8155, and 8240), because the etiology of these cancers is thought to be different. A total of 654 incident pancreatic cancer cases (429 men and 225 women) were identified among the baseline analytical cohort and included in the BMI analyses. In the subcohort, 399 (252 men and 147 women) cases had complete physical activity data, and 312 (212 men and 100 women) cases or 290 (191 men and 99 women) cases had complete waist or hip data, respectively.

Assessment of height, weight, diet, and other risk factors

At baseline, study subjects completed a self-administered questionnaire that included questions on current weight and height, diet, demographic factors, medical history, and other health-related behaviors (28). The dietary questionnaire assessed the usual frequency of consumption and portion size of 124 food items and included 21 questions on low-fat, high-fiber foods and food preparation over the previous 12 months. Details of the questionnaire have been published elsewhere (30–32). BMI was calculated from self-reported height and weight (kg/m^2).

In the second questionnaire, subjects were queried “how often (never, rarely, weekly: <1, 1–3, 4–7, or >7 hours) did you participate in light or moderate and vigorous activities” during the past 10 years. Examples were provided for “light” (i.e., bowling, golf riding in a cart, table tennis, slow walking/slow dancing, light calisthenics, light gardening, fishing, horseshoes/croquet, and light housework) and “moderate/vigorous” (i.e., tennis, golf walking, biking, swimming, heavy gardening, weight lifting, basketball/baseball, football/soccer, cheerleading/drill team, handball/racquetball) activities. Validation studies of similar physical activity questionnaires suggest that the reliability and validity of our questionnaire are comparable to those used in other studies (33). With detailed instructions, subjects were asked to record their waist and hip measurements.

We developed a physical activity score using literature-based relative metabolic equivalent (MET) values for moderate and vigorous activities (34). MET values were calculated by averaging the 11 examples of light (3.5 METs) and 13 examples of moderate/vigorous (6.0 METs) activities described in the physical activity question, respectively, and multiplying these two averages by the number of hours that individuals reported participating in each type of activity (never = 0; rarely = 0.33; weekly: <1 = 0.67, 1–3 = 2, 4–7 = 5.5, or >7 hours = 8 hours, respectively).

Statistical analysis

Within and across the BMI categories by sex in table 1, we calculated means for the continuous-population-characteristic variables and frequency proportions for dichotomous characteristics. To avoid the influence of subclinical disease, we started follow-up time 1 year after the date of receipt of the baseline questionnaire through December 2000, diagnosis of pancreatic cancer, or death. Cox proportional hazard models, with age as the underlying time metric, were used to generate hazard ratios and 95 percent confidence intervals. Entry time was defined as the subjects’ age in days at the return of the questionnaire plus 1 year. Exit time was defined as the subjects’ age in days at cancer diagnosis or censoring.

Body mass index was categorized to be consistent with the World Health Organization obesity classifications or 18.5–<25 (normal), 25–<30 (overweight), 30–<35 (moderate obesity), and $\geq 35 \text{ kg}/\text{m}^2$ (severe obesity) (35). Waist and hip measurements (centimeters) and the waist/hip ratio were categorized on the basis of the cohort sex-specific

distribution with quintiles and quartiles for men and women, respectively. We also calculated the continuous hazard ratios for BMI for our results. Metabolic equivalent units were categorized on the basis of sex-specific and cohort distributions. Trend tests were calculated using a score variable for each quantile or category. The dietary variables were energy adjusted by use of the density method. We created a compound smoking variable to control for confounding, on the basis of risk estimates from our data, that integrated never, former (including time since having quit smoking), and current smoking, as well as smoking dose (never, quit ≥ 10 years ago, quit 5–9 years ago, quit 1–4 years ago, quit <1 year ago or current and smoked ≤ 20 or > 20 cigarettes/day).

We evaluated confounding by individually entering potential confounding variables into the model. Variables remained in the model if they changed the risk estimate ≥ 10 percent or were putative risk factors for pancreatic cancer. The variables investigated and included in the multivariable models for BMI and abdominal obesity were smoking; race (Caucasian, Black, Hispanic, Asian, Pacific Islander or American Indian/Alaskan Native, and missing); total caloric intake (kcal/day); and total fat intake (g/1,000 kcal/day), self-reported diabetes, and sex (sex combined models). Self-reported diabetes (yes/no), a putative pancreatic cancer risk factor, is potentially on the causal pathway between BMI and pancreatic cancer; therefore, we show the BMI models with and without the inclusion of diabetes. For waist, hip, and the waist/hip ratio, we additionally adjusted for height to control for measurement error and for BMI to evaluate associations independent of fat-free mass. The physical activity models were adjusted for smoking, race, BMI, diabetes, and sex (sex-combined models). Physical activity, alcohol consumption, and folate and protein intakes did not confound any association and were not included in our final regression models.

We evaluated interactions by smoking status, diabetes, physical activity, and BMI by including cross-product terms in multivariable models using the trend score variables and joint analysis. To provide an adequate number of cases in strata to evaluate smoking interactions, we combined never smokers and former smokers who had quit ≥ 10 years ago as pancreatic cancer risk is similar in these two groups (2, 36–45). Previous studies have demonstrated a rapid reduction in pancreatic cancer risk among former smokers with risks approaching that of never smokers within 5–15 years after smoking cessation (36, 37). Effect modification by length of follow-up was tested using a time-dependent interaction term (<2 years and ≥ 2 years) and analyses stratified by follow-up time. All statistical analyses were performed with Statistical Analysis Systems (version 8.2; SAS Institute, Inc., Cary, North Carolina) software, and the *p* values for statistical tests were two tailed.

RESULTS

For both men and women (table 1), weight, energy and total and saturated fat intakes, and the proportions of subjects who were former smokers, are African American, or had a history of diabetes mellitus were directly related to greater BMI. In contrast, age, height, alcohol consumption,

TABLE 1. Selected age-adjusted characteristics of the National Institutes of Health–AARP Diet and Health Study cohort (*n* = 495,035) by body mass index category means and proportions, United States, 1995–2000*

Characteristics	Body mass index			
	Normal weight (18.5–<25.0 kg/m ²)	Overweight (25.0–29.9 kg/m ²)	Moderate obesity (30.0–34.9 kg/m ²)	Severe obesity (≥35.0 kg/m ²)
Men (<i>n</i> = 293,562)				
Body mass index (kg/m ²)	23.2	27.2	31.9	38.7
Age (years)	62.7	62.3	61.7	60.9
Height (cm)	178.5	178.0	178.3	177.5
Weight (kg)	73.9	86.3	101.6	122.1
Smoking history (%)				
Never smoker	34.2	29.8	27.0	26.9
Ever smoker	65.8	70.2	73.0	73.1
Former smoker	52.3	60.6	64.2	65.1
Quit >10 years ago	41.7	47.0	48.1	48.3
Current smoker	13.5	9.6	8.8	8.0
Education, college graduate or postgraduate (%)	51.5	44.5	38.6	35.3
African American (%)	2.0	2.6	3.5	3.9
Self-reported diabetes (%)	6.3	9.3	15.7	24.8
Heavy leisure activity, ≥5 times per week (%)	26.7	21.1	15.5	10.2
Heavy work activity (%)	23.2	21.7	17.8	13.0
Dietary intake†				
Energy (kcal)	1,975	1,998	2,078	2,199
Fat (g/1,000 kcal)	32.3	33.8	35.5	37.0
Saturated fat (g/1,000 kcal)	10.0	10.5	11.2	11.7
Multivitamin use (%)	63.2	58.4	54.0	51.8
Alcohol (g)	17.0	17.0	16.1	13.7
Women (<i>n</i> = 201,473)				
Body mass index (kg/m ²)	22.5	27.2	32.1	40.2
Age (years)	61.9	62.1	61.8	61.0
Height (cm)	163.6	163.3	162.6	162.2
Weight (kg)	60.2	72.8	85.0	105.9
Smoking history (%)				
Never smoker	44.2	45.7	47.6	47.5
Ever smoker	55.8	54.3	52.5	52.5
Former smoker	38.5	41.0	41.8	44.0
Quit >10 years ago	26.5	26.7	27.1	29.4
Current smoker	17.4	13.3	10.7	8.5
Education, college graduate or postgraduate (%)	34.5	28.2	25.6	24.2
African American (%)	2.7	5.9	8.1	10.1
Self-reported diabetes (%)	2.9	6.9	13.6	22.3
Heavy leisure activity, ≥5 times per week (%)	20.7	14.8	10.6	7.0
Heavy work activity (%)	20.7	14.8	10.6	7.0
Dietary intake†				
Energy (kcal)	1,527	1,564	1,621	1,721
Fat (g/1,000 kcal)	32.1	33.4	34.9	36.3
Saturated fat (g/1,000 kcal)	9.9	10.3	10.8	11.4
Multivitamin use (%)	71.8	66.3	62.5	58.8
Alcohol (g)	7.4	5.6	3.8	2.7

* Generalized linear models were used to estimate means for the continuous variables and frequencies for proportions calculated within each body mass index category.

† Dietary variables were adjusted for energy except for multivitamin and alcohol use.

TABLE 2. Age- and multivariable-adjusted hazard ratios and 95% confidence intervals of baseline body mass index and according to smoking history in the National Institutes of Health–AARP Diet and Health Study cohort, United States, 1995–2000*

	Body mass index				<i>P</i> _{trend}	Continuous, per unit increase in body mass index
	Normal weight (18.5–<25.0 kg/m ²)	Overweight (25.0–29.9 kg/m ²)	Moderate obesity (30.0–34.9 kg/m ²)	Severe obesity (≥35.0 kg/m ²)		
Nonstratified models						
Men†						
No. of cases/no. of person-years	110/298,804	227/512,801	66/170,950	26/48,226		
Age-adjusted HR‡ (95% CI)§	1.00 (referent)	1.25 (0.99, 1.56)	1.15 (0.85, 1.56)	1.74 (1.13, 2.67)	0.04	1.02 (1.00, 1.04)
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.21 (0.96, 1.52)	1.04 (0.76, 1.42)	1.48 (0.96, 2.30)	0.10	1.01 (0.99, 1.03)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.22 (0.97, 1.54)	1.09 (0.80, 1.48)	1.61 (1.05, 2.49)	0.07	1.02 (1.00, 1.04)
Women†						
No. of cases/no. of person-years	84/309,597	84/235,383	38/105,613	19/62,093		
Age-adjusted HR (95% CI)§	1.00 (referent)	1.30 (0.96, 1.76)	1.34 (0.91, 1.96)	1.22 (0.74, 2.01)	0.14	1.02 (1.00, 1.03)
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.31 (0.96, 1.77)	1.33 (0.90, 1.97)	1.19 (0.71, 1.99)	0.20	1.01 (1.00, 1.03)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.33 (0.98, 1.81)	1.40 (0.95, 2.07)	1.29 (0.78, 2.16)	0.09	1.01 (1.00, 1.03)
Combined						
No. of cases/no. of person-years	194/608,401	311/748,184	104/276,563	45/110,319		
Age-adjusted HR (95% CI)§	1.00 (referent)	1.26 (1.05, 1.51)	1.21 (0.95, 1.54)	1.47 (1.07, 2.04)	0.01	1.02 (1.00, 1.03)
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.24 (1.03, 1.49)	1.14 (0.89, 1.46)	1.33 (0.95, 1.86)	0.08	1.01 (1.00, 1.03)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.26 (1.05, 1.52)	1.20 (0.94, 1.52)	1.45 (1.04, 2.02)	0.02	1.02 (1.00, 1.04)
Smoking-stratified models						
Men†						
<i>Never smoker or former smoker who had quit ≥10 years ago at baseline</i>						
No. of cases/no. of person-years	68/228,236	156/394,927	43/128,769	18/36,273		
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.28 (0.96, 1.70)	1.07 (0.72, 1.57)	1.62 (0.95, 2.76)	0.20	1.02 (0.99, 1.04)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.29 (0.97, 1.72)	1.11 (0.75, 1.63)	1.76 (1.04, 2.98)	0.11	1.02 (1.00, 1.05)
<i>Current smoker or former smoker who had quit <10 years ago at baseline</i>						
No. of cases/no. of person-years	42/70,569	71/117,874	23/42,181	8/11,953		
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.08 (0.73, 1.59)	0.99 (0.59, 1.66)	1.22 (0.56, 2.64)	0.78	1.00 (0.96, 1.04)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.09 (0.74, 1.61)	1.03 (0.62, 1.74)	1.33 (0.63, 2.86)	0.60	1.01 (0.97, 1.05)
Women†, **						
<i>Never smoker or former smoker who had quit ≥10 years ago at baseline</i>						
No. of cases/no. of person-years	41/219,618	58/171,001	42/127,031			
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.75 (1.17, 2.62)	1.74 (1.11, 2.72)		0.01	1.02 (1.00, 1.04)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.79 (1.20, 2.68)	1.88 (1.21, 2.92)		0.003	1.03 (1.01, 1.04)
<i>Current smoker or former smoker who had quit <10 years ago at baseline</i>						
No. of cases/no. of person-years	43/89,979	26/64,382	15/40,675			
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	0.87 (0.53, 1.42)	0.81 (0.44, 1.50)		0.45	1.00 (0.96, 1.04)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	0.88 (0.53, 1.44)	0.84 (0.46, 1.54)		0.52	1.00 (0.96, 1.04)
Combined†						
<i>Never smoker or former smoker who had quit ≥10 years ago at baseline</i>						
No. of cases/no. of person-years	109/447,854	214/565,928	71/207,889	32/84,184		
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	1.43 (1.13, 1.81)	1.30 (0.96, 1.77)	1.55 (0.99, 2.32)	0.02	1.02 (1.00, 1.04)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	1.45 (1.15, 1.84)	1.37 (1.01, 1.85)	1.70 (1.14, 2.53)	0.004	1.02 (1.01, 1.04)
<i>Current smoker or former smoker who had quit <10 years ago at baseline</i>						
No. of cases/no. of person-years	85/160,547	97/182,256	33/68,674	13/26,135		
Multivariable-adjusted HR (95% CI)¶	1.00 (referent)	0.98 (0.73, 1.32)	0.91 (0.60, 1.38)	1.00 (0.55, 1.83)	0.79	1.00 (0.97, 1.03)
Multivariable-adjusted HR (95% CI)#	1.00 (referent)	0.99 (0.74, 1.34)	0.95 (0.63, 1.44)	1.09 (0.60, 1.97)	0.97	1.00 (0.98, 1.03)

* Follow-up started 1 year after cohort baseline with 654 cases, 495,035 cohort subjects, 1,743,467 person-years, 429 male cases, 293,562 male cohort subjects, 225 female cases, and 201,473 female cohort subjects.

† *P*_{interaction} by gender is 0.84 for the main body mass index association and by smoking history for men is 0.58, for women is 0.03, and for genders combined is 0.09 for both multivariable models.

‡ HR, hazard ratio; CI, confidence interval.

§ Cox proportional hazard models were used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric.

¶ Models were additionally adjusted for smoking (never, quit ≥10 years ago, quit 5–9 years ago, quit 1–4 years ago, quit <1 year ago or current, and smoked ≤20 or >20 cigarettes/day); race (Caucasian, Black, Hispanic, Asian, Pacific Islander or American Indian/Alaskan Native, and missing); energy (quintiles); energy-adjusted total fat (quintiles); self-reported diabetes (yes, no); and sex (in gender-combined models).

Multivariable models adjusted for all the variables above except self-reported diabetes.

** The highest body mass index category for women was collapsed to ≥30 kg/m² because of small numbers.

and the proportions of subjects who are current smokers, have a college or postgraduate education, report multivitamin use, or engage in heavy leisure or work physical activity ≥ 5 times per week were inversely associated with BMI. The proportion of subjects who were ever smokers was positively associated with BMI among men; however, it was inversely associated with BMI among women.

Compared with normal weight, severe obesity was significantly and positively associated with pancreatic cancer in men but not in women (table 2). Among men and women combined, overweight and severe obesity ($p_{\text{trend}} = 0.02$) were significantly associated with increased pancreatic cancer risk. Weak, positive, borderline-significant associations were observed per unit increase in BMI, and the hazard ratios per 5-unit BMI increase were 1.08 (95 percent confidence interval (CI): 0.97, 1.19), 1.08 (95 percent CI: 1.00, 1.16), and 1.08 (95 percent CI: 1.01, 1.15) for men, women, and men and women combined, respectively (data not shown). These associations were slightly attenuated (7–8 percent risk reduction) with adjustment for history of diabetes. There were no significant interactions of the BMI associations by sex, history of diabetes, or follow-up time ($p_{\text{interaction}} > 0.40$). Height was not associated with pancreatic cancer among men or women in any models (smoking-, BMI-, race-adjusted model: men ≥ 183 cm compared with < 170 cm: hazard ratio (HR) = 1.14, 95 percent CI: 0.82, 1.60; $p_{\text{trend}} = 0.46$; women ≥ 168 cm compared with < 157 cm: HR = 0.77, 95 percent CI: 0.52, 1.12; $p_{\text{trend}} = 0.24$; data not shown).

The association between BMI and pancreatic cancer was not significantly different according to smoking status among men (table 2); however, in women there were significant positive risks and a trend with increasing BMI among nonsmokers but not among recent smokers ($p_{\text{interaction}} = 0.02$). A pattern similar to that observed in women was observed in sex-combined models. Among never smokers, positive associations with increasing BMI were observed only in women (refer to supporting documentation). In joint analyses of BMI and smoking that used normal BMI among nonsmokers as the referent category, pancreatic cancer risks were increased for all BMI categories within recent smokers (figure 1).

Waist, hip, or the waist/hip ratio was not associated with pancreatic cancer among men (table 3). Among women, increasing waist circumference was significantly associated with pancreatic cancer (fourth vs. first quartile: HR = 2.53, 95 percent CI: 1.13, 5.65; $p_{\text{trend}} = 0.04$). Significant risk associated with greater hip circumference was attenuated and nonsignificant with adjustment for BMI, and the waist/hip ratio was not associated with pancreatic cancer. No significant associations were observed between low or high intensity physical activity or METs and pancreatic cancer by sex or in sex-combined models (table 4). The waist, hip, waist/hip ratio, and physical activity associations were not modified by smoking, history of diabetes, BMI, or follow-up time ($p_{\text{interaction}} > 0.05$).

DISCUSSION

We observed significant increased pancreatic cancer risks among NIH–AARP Diet and Health Study cohort members with severe obesity (BMI: ≥ 35 kg/m²), compared with those

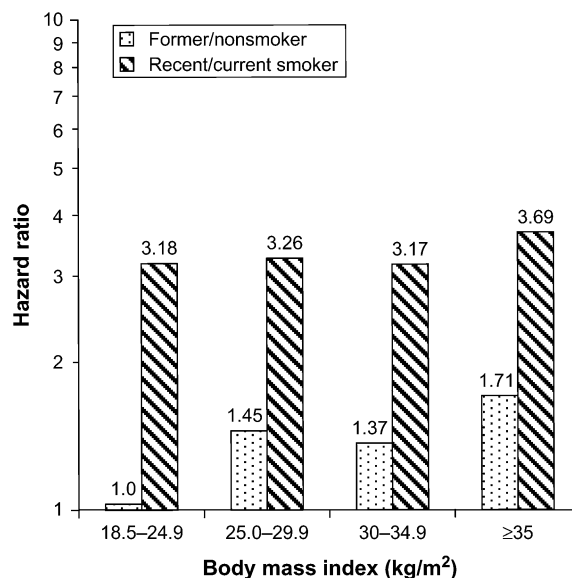


FIGURE 1. Hazard ratios for body mass index and pancreatic cancer by smoking status among men and woman combined, United States, 1995–2000. $p_{\text{interaction}} = 0.09$. Compared with the referent, all hazard ratios were statistically significant; the confidence interval does not include 1.00. “Nonsmoker” refers to a never/former smoker who quit ≥ 10 years ago, and “recent smoker” refers to a current/former smoker who quit < 10 years ago. All models should be considered adjusted for age because age is the time metric. Models were additionally adjusted for smoking within smoking strata, race (Caucasian, Black, Hispanic, Asian, Pacific Islander or American Indian/Alaskan Native, and missing), energy, energy-adjusted total fat (continuous), and sex.

with normal weight, which was more apparent in men than women. Among nonsmokers, however, stronger risks were observed with increasing BMI, particularly among women, but no significant associations were evident among current smokers or those who quit < 10 years before. Greater waist circumference was associated with a greater than twofold pancreatic cancer risk in women, but no association was observed in men. Physical activity was not associated with pancreatic cancer in our study.

Our BMI results are consistent with and similar in magnitude to two recent meta-analyses of obesity and pancreatic cancer (6, 10). The first meta-analysis based on six case-control studies and eight cohort studies showed a weak but statistically significant summary relative risk of 1.02 (95 percent CI: 1.01, 1.03) per unit increase of BMI and estimated a 19 percent (95 percent CI: 1.10, 1.29) increased pancreatic cancer risk for obese compared with nonobese subjects (6). The second meta-analysis based on 21 cohort studies had a summary relative risk of 1.12 (95 percent CI: 1.06, 1.17) per 5-unit BMI increase. Among all the prospective studies (5, 10, 11, 23, 26, 46), 13 studies have shown significant associations for pancreatic cancer, with relative risks ranging from 1.25 to 3.10 for high or > 30 -kg/m² BMI among men (5, 11, 14, 15, 24, 26, 46–50), among women (11, 12, 14, 50), or among men and women combined (12, 14, 15, 42, 46, 50).

TABLE 3. Multivariable-adjusted hazard ratios and 95% confidence intervals of waist, hip, and waist/hip ratio and pancreatic cancer by gender in the National Institutes of Health–AARP Diet and Health Study cohort, United States, 1995–2000

	Quantile					<i>P</i> _{trend}
	1	2	3	4	5	
Men						
Waist (<i>N</i> = 212 cases)						
	<88.9 cm	88.9–<93.3 cm	93.3–<98.4 cm	98.4–<106.0 cm	≥106.0 cm	
No. of cases/no. of person-years	40/110,286	35/80,768	39/102,340	46/97,118	52/110,309	
Age-adjusted HR* (95% CI)†	1.00 (referent)	1.15 (0.73, 1.81)	1.00 (0.64, 1.56)	1.23 (0.81, 1.85)	1.26 (0.84, 1.91)	0.24
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.11 (0.70, 1.75)	0.95 (0.61, 1.48)	1.14 (0.74, 1.76)	1.07 (0.69, 1.64)	0.77
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	1.00 (0.62, 1.61)	0.81 (0.49, 1.32)	0.96 (0.58, 1.58)	0.95 (0.54, 1.67)	0.91
Hip (<i>N</i> = 191 cases)						
	<95.9 cm	95.9–<100.3 cm	100.3–<104.1 cm	104.1–<109.2 cm	≥109.2 cm	
No. of cases/no. of person-years	31/89,411	37/102,589	49/94,716	35/85,564	39/93,936	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.01 (0.62, 1.63)	1.44 (0.92, 2.26)	1.15 (0.71, 1.86)	1.18 (0.74, 1.89)	0.45
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.02 (0.63, 1.65)	1.41 (0.89, 2.22)	1.09 (0.66, 1.78)	1.04 (0.64, 1.70)	0.93
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	0.96 (0.59, 1.56)	1.23 (0.76, 2.00)	0.92 (0.54, 1.58)	0.92 (0.51, 1.67)	0.72
Waist/hip ratio (<i>N</i> = 191 cases)						
	<0.90	0.90–<0.93	0.93–<0.96	0.96–<1.00	≥1.00	
No. of cases/no. of person-years	31/92,851	33/93,341	33/92,082	38/83,106	56/103,215	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.02 (0.62, 1.66)	1.02 (0.62, 1.67)	1.30 (0.81, 2.09)	1.59 (1.03, 2.47)	0.01
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.00 (0.61, 1.63)	0.97 (0.59, 1.58)	1.20 (0.74, 1.92)	1.34 (0.86, 2.08)	0.10
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	0.97 (0.59, 1.59)	0.94 (0.57, 1.54)	1.16 (0.71, 1.87)	1.30 (0.82, 2.05)	0.15
Women						
Waist (<i>N</i> = 100 cases)						
	<74.9 cm	74.9–<83.2 cm	83.2–<92.1 cm	≥92.1 cm		
No. of cases/no. of person-years	14/78,206	24/74,451	28/75,769	34/75,795		
Age-adjusted HR (95% CI)†	1.00 (referent)	1.68 (0.87, 3.25)	1.86 (0.98, 3.53)	2.29 (1.22, 4.27)		0.01
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.79 (0.92, 3.47)	1.99 (1.04, 3.80)	2.52 (1.33, 4.77)		0.006
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	1.74 (0.89, 3.41)	1.88 (0.92, 3.85)	2.53 (1.13, 5.65)		0.04
Hip (<i>N</i> = 99 cases)						
	<95.9 cm	95.9–<101.6 cm	101.6–<109.2 cm	≥109.2 cm		
No. of cases/no. of person-years	13/68,617	31/84,571	30/73,951	25/76,056		
Age-adjusted HR (95% CI)†	1.00 (referent)	1.91 (1.00, 3.65)	2.08 (1.09, 4.00)	1.75 (0.89, 3.42)		0.18
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	2.17 (1.13, 4.18)	2.48 (1.28, 4.82)	2.07 (1.03, 4.14)		0.08
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	2.03 (1.04, 3.96)	2.10 (1.00, 4.42)	1.62 (0.67, 3.93)		0.45
Waist/hip ratio (<i>N</i> = 99 cases)						
	<0.76	0.76–<0.81	0.81–<0.86	≥0.86		
No. of cases/no. of person-years	19/75,083	25/76,171	27/75,053	28/75,652		
Age-adjusted HR (95% CI)†	1.00 (referent)	1.20 (0.66, 2.17)	1.25 (0.69, 2.25)	1.25 (0.69, 2.24)		0.49
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.20 (0.66, 2.18)	1.22 (0.68, 2.20)	1.19 (0.66, 2.15)		0.63
Multivariable-adjusted HR (95% CI)§	1.00 (referent)	1.13 (0.62, 2.07)	1.09 (0.60, 1.99)	1.00 (0.54, 1.87)		0.91

* HR, hazard ratio; CI, confidence interval.

† Cox proportional hazard models were used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric.

‡ Models were additionally adjusted for smoking (never, quit ≥10 years ago, quit 5–9 years ago, quit 1–4 years ago, quit <1 year ago or current, and smoked ≤20 or >20 cigarettes/day); race (Caucasian, Black, Hispanic, Asian, Pacific Islander or American Indian/Alaskan Native, and missing); energy (quintiles); energy-adjusted total fat (quintiles); self-reported diabetes (yes, no); and sex (in gender-combined models).

§ Multivariable models were additionally adjusted for body mass index (World Health Organization obesity categories).

TABLE 4. Hazard ratios and 95% confidence intervals for low intensity and vigorous activity and metabolic equivalents in the National Institutes of Health–AARP Diet and Health Study cohort, United States, 1995–2000

	Physical activity category					<i>P</i> _{trend}
Men						
	Low intensity activity (<i>N</i> = 252 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
No. of cases/no. of person-years	26/60,886	21/53,345	61/154,012	71/162,618	73/174,840	
Age-adjusted HR* (95% CI)†	1.00 (referent)	0.93 (0.53, 1.66)	0.91 (0.57, 1.44)	0.96 (0.61, 1.50)	0.87 (0.56, 1.37)	0.62
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	0.94 (0.53, 1.67)	0.94 (0.59, 1.48)	1.00 (0.63, 1.56)	0.90 (0.58, 1.42)	0.74
	Vigorous activity (<i>N</i> = 252 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
No. of cases/no. of person-years	34/85,634	33/63,815	56/152,973	64/157,319	65/145,961	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.34 (0.84, 2.18)	0.93 (0.61, 1.42)	1.01 (0.67, 1.53)	1.06 (0.70, 1.61)	0.88
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.41 (0.88, 2.28)	1.02 (0.67, 1.57)	1.15 (0.76, 1.75)	1.22 (0.80, 1.86)	0.57
	METs* (<i>N</i> = 252 cases)					
	<13.2	13.2–<30.0	30.0–<49.2	49.2–<61.0	≥61.0	
No. of cases/no. of person-years	50/115,488	41/106,093	52/140,978	57/130,415	52/112,727	
Age-adjusted HR (95% CI)†	1.00 (referent)	0.86 (0.57, 1.30)	0.82 (0.56, 1.21)	0.94 (0.64, 1.37)	0.95 (0.64, 1.40)	0.91
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	0.90 (0.60, 1.37)	0.89 (0.60, 1.32)	1.04 (0.71, 1.52)	1.05 (0.71, 1.56)	0.52
Women						
	Low intensity activity (<i>N</i> = 147 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
No. of cases/no. of person-years	7/20,591	7/25,112	36/90,852	38/120,326	59/176,065	
Age-adjusted HR (95% CI)†	1.00 (referent)	0.84 (0.30, 2.40)	1.17 (0.52, 2.64)	0.90 (0.40, 2.01)	0.93 (0.42, 2.03)	0.58
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	0.85 (0.30, 2.42)	1.22 (0.54, 2.75)	0.94 (0.42, 2.11)	0.92 (0.45, 2.16)	0.72
	Vigorous intensity activity (<i>N</i> = 147 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
No. of cases/no. of person-years	26/61,817	12/46,277	42/111,182	42/111,536	25/102,134	
Age-adjusted HR (95% CI)†	1.00 (referent)	0.64 (0.32, 1.26)	0.92 (0.56, 1.49)	0.89 (0.55, 1.46)	0.57 (0.33, 0.99)	0.15
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	0.65 (0.33, 1.29)	0.94 (0.58, 1.54)	0.93 (0.57, 1.54)	0.60 (0.35, 1.04)	0.20

Table continues

We found that waist circumference was positively associated with pancreatic cancer in women but not in men. The 2.5-fold risk in women was independent of BMI, suggesting that adiposity independent of fat-free body mass may account for our observed association. Four cohort studies examined waist circumference or the waist/hip ratio (15, 18, 19, 23), with three reporting positive associations for increasing waist circumference (15, 19, 23) or the waist/hip ratio (19) in men and women and two being statistically significant (19, 23). The American Cancer Society cohort demonstrated a marginally significant positive association for pancreatic cancer with the self-reported tendency for abdominal compared with peripheral weight gain (14).

The magnitude of our positive association between higher BMI and pancreatic cancer was slightly attenuated (7–8 percent risk reduction) with adjustment for history of diabetes. There is evidence to suggest that type 2 diabetes is etiologically involved in pancreatic carcinogenesis (3, 51), as well as the result of subclinical malignancy (52–54). The attenuation of our BMI association after adjustment for di-

abetes may be due to the inability to completely remove diabetes because of latent pancreatic cancer, despite the fact that we designed our study to minimize reverse causation. Prospective cohort studies with extended follow-up have reported positive associations between higher glucose concentrations, biochemically defined diabetes, and pancreatic cancer (47, 55–59). A recent epidemiologic study also showed a positive pancreatic cancer association with increasing glucose and insulin concentrations that was stronger among subjects with follow-up of >10 years (58). Experimental studies demonstrate that insulin has mitogenic effects on pancreatic cancer cell lines (60), and peripheral insulin resistance promotes ductal pancreatic carcinogenesis in animals (61–64). A history of diabetes is associated with higher BMI in our cohort, and subjects with type 2 diabetes exhibit higher insulin concentrations and insulin resistance during the early stages of their disease (25); therefore, the reduction in pancreatic cancer risk with adjustment for diabetes may be related to type 2 diabetes being in the causal pathway of the obesity and pancreatic cancer association.

TABLE 4. Continued

	Physical activity category					<i>P</i> _{trend}
	METs (<i>N</i> = 147 cases)					
	<14.3	14.3–<31.3	31.3–<50.3	50.3–<61.0	≥61.0	
No. of cases/no. of person-years	25/71,470	45/110,464	16/60,248	38/98,594	23/92,171	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.13 (0.69, 1.84)	0.74 (0.40, 1.39)	1.04 (0.63, 1.73)	0.67 (0.38, 1.18)	0.12
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.16 (0.71, 1.90)	0.78 (0.42, 1.47)	1.09 (0.66, 1.81)	0.70 (0.40, 1.24)	0.16
Combined						
	Low intensity activity (<i>N</i> = 399 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
	No. of cases/no. of person-years	33/81,477	28/78,457	97/244,864	109/282,944	
Age-adjusted HR (95% CI)†	1.00 (referent)	0.91 (0.55, 1.50)	0.99 (0.67, 1.47)	0.93 (0.63, 1.37)	0.89 (0.60, 1.30)	0.48
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	0.92 (0.56, 1.52)	1.02 (0.69, 1.51)	0.97 (0.66, 1.43)	0.93 (0.63, 1.36)	0.65
	Vigorous intensity activity (<i>N</i> = 399 cases)					
	Never/rarely	<1 hour/week	1–3 hours/week	4–7 hours/week	>7 hours/week	
	No. of cases/no. of person-years	60/147,450	45/110,092	98/264,155	106/268,855	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.04 (0.70, 1.52)	0.92 (0.67, 1.28)	0.96 (0.70, 1.32)	0.86 (0.62, 1.19)	0.32
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.08 (0.74, 1.60)	0.99 (0.72, 1.37)	1.05 (0.77, 1.45)	0.95 (0.68, 1.32)	0.75
	METs (<i>N</i> = 399 cases)					
	<14.3	14.3–<31.3	31.3–<50.3	50.3–<61.0	≥61.0	
	No. of cases/no. of person-years	76/197,685	104/253,971	53/158,498	91/223,595	
Age-adjusted HR (95% CI)†	1.00 (referent)	1.04 (0.77, 1.40)	0.85 (0.60, 1.20)	1.01 (0.74, 1.37)	0.88 (0.64, 1.22)	0.39
Multivariable-adjusted HR (95% CI)‡	1.00 (referent)	1.08 (0.80, 1.46)	0.91 (0.64, 1.30)	1.08 (0.80, 1.47)	0.96 (0.69, 1.32)	0.74

* HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent.

† Cox proportional hazard models were used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric.

‡ Models were additionally adjusted for smoking (never, quit ≥10 years ago, quit 5–9 years ago, quit 1–4 years ago, quit <1 year ago or current, and smoked ≤20 or >20 cigarettes/day); body mass index (World Health Organization obesity categories); race (Caucasian, Black, Hispanic, Asian, Pacific Islander or American Indian/Alaskan Native, and missing); self-reported diabetes; and sex (in gender-combined models).

In our study, BMI appeared to be more clearly associated with pancreatic cancer risk among subjects that were never smokers/quitters for >10 years. Although we do not observe significant interactions by smoking status in men, we observe significant interactions by smoking in women. Some studies have shown stronger BMI-associated pancreatic cancer risk in never smokers compared with that observed in the overall population (5, 49, 50). Five of six cohort studies that evaluated effect modification of BMI and pancreatic cancer risk by smoking status (14, 15, 19, 22, 24) did not report significant interactions by smoker status, which contrasts one study in a Japanese cohort that reported an elevated risk with increase in BMI among current smokers but not nonsmokers (26). Similar to our study (figure 1), a pooled analysis of Swedish women and men showed positive associations for BMI and pancreatic cancer, independent of smoking; however, all associations in current smokers were significantly higher than that of the nonsmokers (15). Our study and the latter (15) suggest that the carcinogenic effect of cigarette smoke on the pancreas appears stronger than that of BMI and may mask the BMI–pancreatic cancer association among the current smokers or recent quitters.

Although we hypothesized a protective relation, we did not observe an association between greater physical activity

and pancreatic cancer, which is consistent with most studies (12, 14, 18–21, 24, 26). Three previous studies found some evidence for a protective effect with greater physical activity. One case-control study observed an inverse association with a composite variable for greater moderate and strenuous activity in men but not in women (13). A pooled analysis of health professionals and nurses observed an inverse association between greater metabolic equivalents of moderate activity but no association with greater total or vigorous activity (12). In a cohort study of male smokers, men with sedentary leisure activity had significant protective associations with greater occupational activity, although no association was observed overall for occupational or leisure physical activity (22). We did not observe a statistically significant interaction between BMI and physical activity, which is consistent with the other studies (7, 12, 14, 15, 19, 22, 24). Physical activity is a complex behavior that encompasses multiple domains (e.g., occupation, leisure, household, transportation) and characteristics (frequency, intensity, and duration) and is not precisely measured in most epidemiologic studies. Measurement imprecision may contribute to the lack of association observed in most studies. Alternatively, the lack of association between physical activity and pancreatic cancer may possibly suggest an

etiologic mechanism related to adiposity, not influenced by physical activity that contributes to pancreatic cancer.

The strength of our study is its large prospective nature with body weight and physical activity being assessed prior to cancer diagnosis, thereby reducing biases and the influence of reverse causality. It also has a larger number of cases compared with many previous prospective studies (6, 14–19, 48, 65), providing greater power to detect differences in risk and the ability to stratify analyses by sex and by smoking status. Our study has internal validity, as the cases arose from the cohort that includes the noncases and therefore does not have control selection bias, has relatively good follow-up of members and outcome assessment, and includes adjustment for confounders. The NIH–AARP cohort includes both sexes and never, former, and current smokers; therefore, results may be generalizable to many older adults. Our cohort is limited because of a relatively short follow-up time (up to 5 years), and our associations may become stronger with extended follow-up. Although most cohort studies with longer follow-up time than our cohort show positive associations between BMI and pancreatic cancer, the majority are not statistically significant and a third have less magnitude (10). Our case definition includes nonmicroscopically confirmed cancer, which could contribute to misclassification of case status and attenuated risk estimates (11). Measurement error related to self-reported measurements (66, 67) and physical activity assessment is likely present and could contribute to spurious or attenuated associations.

In conclusion, our results from this large prospective study support the hypothesis that adiposity may increase the risk of developing pancreatic cancer in older persons. Our results, as well as those of others, may have important implications for cancer prevention particularly related to the avoidance of obesity.

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