Prediagnostic Adiponectin Concentrations and Pancreatic Cancer Risk in Male Smokers

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Adiponectin, a hormone secreted by adipocytes, has insulin-sensitizing, antidiabetic, antiinflammatory, and antiangiogenic properties. The authors conducted a nested case-control study in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, a cohort of male Finnish smokers aged 50–69 years at baseline, to test whether prediagnostic adiponectin concentrations are associated with pancreatic cancer. Between January 1985 and October 2004, 311 incident exocrine pancreatic cancer cases were diagnosed among cohort participants with serum samples. Controls ($n = 510$) were alive and free of cancer at the time the case was diagnosed and were matched to the cases by age and date of blood drawing. The authors used conditional logistic regression adjusted for smoking, blood pressure, and C-peptide level to calculate odds ratios and 95% confidence intervals for pancreatic cancer. Higher adiponectin concentrations were inversely associated with pancreatic cancer (for highest quintile (>9.8 μg/mL) vs. lowest (≤ 4.6 μg/mL), odds ratio $= 0.65$, 95% confidence interval: 0.39, 1.07; P-trend $= 0.04$). The inverse association was significant among cases diagnosed 5 or more years after blood collection ($n = 238$) (for highest quintile vs. lowest, odds ratio $= 0.55$, 95% confidence interval: 0.31, 0.98; P-trend $= 0.03$). These results support the hypothesis that higher adiponectin concentrations may be inversely associated with the development of pancreatic cancer.

adenocarcinoma; adiponectin; biological markers; case-control studies; diabetes mellitus; pancreatic neoplasms

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI, body mass index; CI, confidence interval; OR, odds ratio.

Pancreatic cancer ranks fourth for cancer mortality among men and women in the United States (1, 2). There is no effective screening test for the malignancy; therefore, it is often diagnosed at an advanced stage, which contributes to a 5-year survival rate of 4.3% (3). In addition to cigarette smoking (3), diabetes mellitus, higher glucose concentrations, and obesity are among the few consistent and potentially modifiable risk factors for pancreatic cancer (4–11).

Adiponectin is a hormone exclusively expressed and secreted by adipocytes (12). It is an insulin-sensitizing and antidiabetic hormone that also has antiinflammatory and antiangiogenic properties (12). In contrast to the case for other adipocytokines, circulating levels of adiponectin are decreased with obesity and type 2 diabetes (12, 13); prospective studies have shown low adiponectin concentrations preceding a decrease in insulin sensitivity (14). In addition, the adiponectin receptors AdipoR1 and AdipoR2 are expressed in human pancreatic β cells (15), potentially linking adiponectin to endocrine pancreatic function. Adiponectin concentrations have been inversely associated with risk for several malignancies that have been associated with either obesity or insulin resistance, including colorectal, gastric, endometrial, breast, and prostate cancers (12). One small case-control study showed pancreatic cancer cases ($n = 39$) to have significantly higher median adiponectin concentrations than controls ($n = 290$) (16); however, the results from that study could have been influenced by the weight loss associated with the disease or by reverse causation.

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We previously reported that higher prediagnostic glucose and insulin concentrations and biochemically defined diabetes were associated with a significant 2-fold increased risk of pancreatic cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a study of male smokers, with the risk estimates increasing and becoming more statistically significant with longer follow-up (8). We therefore evaluated whether prediagnostic adiponectin concentrations were associated with a decreased risk of incident pancreatic cancer. In order to reduce the potential influence of subclinical cancer on adiponectin concentrations, we stratified our analysis a priori according to time period of case occurrence (prior to or after 5 years of follow-up).

MATERIALS AND METHODS

Study population

The ATBC Study was a double-blind, placebo-controlled, 2×2 factorial-design primary prevention trial that tested whether α-tocopherol or β-carotene reduced cancer incidence in Finnish male smokers. The study rationale, design, and methods have been described previously (17). Between 1985 and 1988, 29,133 eligible men aged 50–69 years in southwestern Finland who smoked at least 5 cigarettes per day were randomized to receive active supplements or placebo. Men were excluded from the study if they had a history of malignancy other than nonmelanoma skin cancer or carcinoma in situ, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, or another medical condition that might limit long-term participation; if they were receiving anticoagulant therapy; or if they were using supplements containing vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or β-carotene (>6 mg/day). All study participants provided written informed consent prior to randomization, and the study protocol was approved by the institutional review boards of both the National Public Health Institute in Finland and the National Cancer Institute in the United States.

During a prerandomization baseline visit, participants completed questionnaires on general background characteristics, including medical, smoking, dietary, and physical activity histories (17). Trained study staff measured height, weight, and blood pressure at baseline using standard methods. Body mass index (BMI; weight (kg)/height $(m)^2$) was calculated from measured weight and height. Diet was assessed with a validated self-administered dietary history questionnaire which determined the frequency of consumption and usual portion size of 276 food items eaten during the past year, using a color picture booklet as a guide for portion size (18). Occupational activity was assessed by asking how much exercise and physical burden had been undertaken at work during the past year; responses could range from not working or sedentary to heavy physical work. Leisure-time activity was assessed by asking about the average level of activity engaged in during the past year; responses ranged from sedentary (reading, watching television) to moderate (walking, fishing, hunting, gardening regularly) to heavy or ''exercising to keep fit'' (running, jogging, or skiing regularly).

Case ascertainment and control selection

All cases of pancreatic cancer diagnosed between January 1985 and October 2004 were identified through the Finnish Cancer Registry, which provides almost complete case ascertainment in Finland (19). Because the etiology of islet cell carcinomas (*International Classification of Diseases*, Ninth Revision, code 157.4) may differ from that of exocrine tumors, only exocrine tumors (*International Classification of Diseases*, Ninth Revision, code 157) were included as the cancer outcome of interest. During the follow-up period, we identified 311 exocrine pancreatic cancer cases for which serum samples had been collected at baseline. The interval between serum collection and diagnosis extended to 19.1 years (median follow-up for case diagnosis, 9.4 years).

Controls were selected from ATBC Study participants who were alive and free of cancer (except nonmelanoma skin cancer) at the time the case was diagnosed. Controls were matched to each case by age (±5 years) and date of baseline blood drawing (±30 days). For the early cases, we used a nested case-control set created for our previous study that had a 2:1 ratio of controls to cases (20). For the cases that were identified later during follow-up, controls were selected at a 1:1 ratio.

Biomarkers

At their prerandomization visit, a blood sample was obtained from study participants after an overnight fast, and serum was stored at −70°C (17). Frozen baseline serum samples were sent to Dr. Michael Pollak's laboratory at Lady Davis Institute for Medical Research, Montreal, Quebec, Canada. Total adiponectin concentrations (duplicate measures) were analyzed by enzyme-linked immunosorbent assay with reagents from Millipore (formerly Linco Research, Inc.; St. Charles, Missouri). C-peptide was analyzed by enzyme-linked immunosorbent assay with reagents from Diagnostic Systems Laboratory (Webster, Texas). Case and control specimens were handled in the same standard manner, and the laboratory was blinded to case-control status. Matched serum case and control samples were analyzed consecutively within batches; blinded replicate ''phantom'' samples from 2 pooled samples were placed randomly in each batch and comprised 10% of each batch. Using a nested components-of-variance analysis with logarithmically transformed quality control measurements across all batches (21), the calculated overall (intra- and interbatch) coefficients of variation for adiponectin and C-peptide were 6.8% and 5.5%, respectively.

Statistical analysis

We compared the distributions of selected case and control characteristics using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. Adiponectin concentrations were categorized into quintiles based on the distribution in the controls. Generalized linear models were used to calculate mean values for continuous variables, and frequencies were used to calculate proportions (percentages) for the categorical variables to

describe control characteristics across adiponectin quintiles. Variables examined in the analyses and as potential confounders in the risk models were based on previous findings from the ATBC Study cohort or were associated with pancreatic cancer in the literature. Variables that have been associated with pancreatic cancer in the ATBC cohort include age; history of chronic bronchial asthma; diabetes; cigarette smoking habits; occupational and leisure activity; and folate, carbohydrate, and total and saturated fat intakes (8, 22–24). Additional variables examined as potential confounders included serum C-peptide concentration; education; living in a city; height, weight, and BMI; measured systolic and diastolic blood pressure; pancreatitis, peptic ulcer, and gallbladder disease; nutrient intake from foods (energy, calcium, vitamin D, and protein); alcohol use; and other variables presented in Table 1. Serum glucose and insulin levels were not examined in these analyses because they were not measured in controls. Data on dietary nutrients and foods highly correlated with energy intake were adjusted for energy using the residual method described by Willett and Stampfer (25).

Conditional logistic regression was used to calculate odds ratios for pancreatic cancer, with men in the lowest quintile serving as the reference category. Continuous adiponectin odds ratios were standardized to the average size of the 2 central quartiles, and the *P* value for the continuous odds ratio was used for the dose-response trend. Multivariable models were developed by individually entering potentially confounding variables into the model. Variables remained in the model if they were associated with both the disease and exposure, had a *P* value of 0.20 or less in the full model, and changed the risk estimate by more than 10%. Diastolic blood pressure and C-peptide level were confounders. Although smoking history did not influence the risk estimates, smoking duration was included in the model because smoking is a putative risk factor and has been associated with pancreatic cancer in the ATBC cohort. The final multivariable models included smoking duration, diastolic blood pressure, and C-peptide concentration (all continuous variables). Effect modification by trial intervention, BMI, smoking intensity and duration, diabetes history, and C-peptide concentration was evaluated with cross-product terms composed of continuous adiponectin and dichotomized variables (median split for BMI, smoking duration and dose, and C-peptide level) in multivariable models and stratified analyses. We stratified our analysis a priori by time period of case diagnosis (e.g., <5 years, ≥ 5 years, ≥ 5 and <10 years, ≥ 10 and <15 years after baseline) to assess the potential for reverse causation. All statistical analyses were performed using SAS software (SAS Institute Inc., Cary, North Carolina), and statistical tests were 2-tailed. Because cases and controls were matched, their median values, proportions, and all risk estimates should be interpreted as having been adjusted for the matching factors (i.e., age, month of blood drawing, and follow-up time).

RESULTS

Compared with the controls, cases tended to be taller, had lower systolic and diastolic blood pressures, had higher total and saturated fat intakes, and had different distributions of occupational activity (Table 1). Cases and controls did not significantly differ with respect to other characteristics. The mean adiponectin concentration was 7.41 μg/mL (standard deviation, 3.32; range, 1.64–27.6) for the cases and 7.46 μg/mL (standard deviation, 3.54; range, 2.1–27.6) for the controls.

Table 2 shows the means and percentages of selected baseline characteristics among the controls according to quintile of serum adiponectin concentration. Across increasing quintiles of serum adiponectin, the proportion of men who reported living in a city increased, while serum C-peptide concentration, diastolic blood pressure, BMI, protein intake, and the proportion of men reporting a history of diabetes or gallstones decreased (P-trend < 0.05). Men in the lowest quintile of adiponectin tended to have smoked for fewer years than those in the other quintiles. The Spearman correlation of adiponectin with C-peptide was -0.39.

Higher concentrations of adiponectin were not associated with pancreatic cancer in crude conditional logistic regression models (Table 3); however, they showed a nonsignificant inverse association with pancreatic cancer in multivariable adjusted models (for highest quintile vs. lowest, odds ratio (OR) = 0.65, 95% confidence interval (CI): 0.39, 1.07; P-trend = 0.04). The inverse association between adiponectin concentration and pancreatic cancer risk was significant among the cases diagnosed 5 or more years after baseline (for highest quintile vs. lowest, OR = 0.55, 95% CI: 0.31, 0.98; P-trend = 0.03) and was strongest among cases diagnosed 5–$<$10 years after baseline (for highest quintile vs. lowest, OR = 0.32, 95% CI: 0.11, 0.90; P-trend = 0.03). Among cases that occurred prior to 5 years of follow-up, adiponectin was not associated with pancreatic cancer. Similar associations were observed when participants with outlier adiponectin values ($>$22.0 μg/mL; $n = 3$) were excluded from the analysis (in adjusted model, for fifth quintile vs. first, overall OR = 0.63, 95% CI: 0.37, 1.05; P-trend = 0.06; for cases diagnosed 5 or more years after baseline, OR = 0.55, 95% CI: 0.31, 0.97; P-trend = 0.03). The association between adiponectin and pancreatic cancer was not modified by smoking habits, BMI, trial intervention, diabetes history, or C-peptide concentration overall or among cases that occurred 5 or more years after baseline (all P's > 0.15).

DISCUSSION

To our knowledge, this is the first study to show an association between higher prediagnostic adiponectin concentrations and reduced risk of pancreatic cancer. The association we observed was independent of C-peptide concentrations and was statistically significant among cases that were diagnosed 5 or more years following baseline blood collection.

No experimental study has examined the direct effect of adiponectin on pancreatic cancer; therefore, any molecular mechanism for an impact of adiponectin on pancreatic carcinogenesis is highly speculative. Among the prospective studies that have measured adiponectin concentrations, inverse associations have been observed for prostate, endometrial, colon, and postmenopausal breast cancer (with the

Table 1. Selected Baseline Characteristics of Case and Control Subjects, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1988

Characteristic	Cases (n = 311)		Controls (n = 510)		P Value[a]
	Median (IQR)	%	Median (IQR)	%	
Age, years	58.0 (55.0–62.0)		58.0 (55.0–62.0)		0.72
Adiponectin concentration, μg/mL[b]	6.77 (5.03–9.11)		6.74 (4.99–8.78)		0.79
Height, cm	173 (169–178)		173 (168–177)		0.04
Body mass index[c]	25.8 (23.7–28.0)		26.1 (23.8–28.7)		0.25
Systolic blood pressure, mm Hg	140.0 (130.0–152.0)		144.0 (132.0–158.0)		0.005
Diastolic blood pressure, mm Hg	88.0 (80.0–94.0)		90.0 (82.0–98.0)		0.001
Medical history					
Diabetes mellitus		7.1		6.1	0.57
Pancreatitis		1.6		1.6	0.97
Gallstones		4.8		4.9	0.96
Ulcers		17.4		14.5	0.27
Smoking history					
Total cigarettes smoked per day	20.0 (15.0–25.0)		20.0 (15.0–25.0)		0.56
Years of smoking	39.0 (32.0–43.0)		39.0 (34.0–43.0)		0.84
Primary school education or less		77.1		81.6	0.13
Living in city		44.7		43.1	0.66
Daily dietary intake[d]					
Energy, kcal	2,701 (2,228–3,200)		2,753 (2,230–3,220)		0.65
Total fat, g	102.4 (93.3–112.1)		100.6 (90.2–110.0)		0.04
Saturated fat, g	53.5 (45.6–63.5)		52.1 (42.5–61.4)		0.048
Carbohydrate, g	300.1 (271.9–325.5)		300.8 (270.6–331.4)		0.37
Protein, g	102.9 (95.4–111.9)		1.01.9 (94.3–109.4)		0.10
Physical activity					
Occupational activity					0.03
Sedentary		16.1		9.8	
Moderate		29.3		27.7	
Heavy		6.1		8.0	
Not working		48.6		54.5	
Leisure activity[e]					0.40
Sedentary		45.3		41.3	
Light or moderate		52.9		48.0	
Exercising to keep fit		5.8		6.7	

Abbreviation: IQR, interquartile range.

[a] P values for categorical variables were based on the chi-squared test or Fisher's exact test; P values for continuous variables were based on Wilcoxon's rank-sum test.

[b] For cases, the mean adiponectin concentration was 7.41 μg/mL (standard deviation, 3.32; range, 1.64–27.6); for controls, it was 7.46 μg/mL (standard deviation, 3.54; range, 2.1–27.6).

[c] Weight (kg)/height $(m)^2$.

[d] Dietary intake analysis was based on 300 cases and 473 controls. Data on all foods and nutrients except alcohol were adjusted for energy intake.

[e] Leisure activity variables were based on 310 cases and 510 controls.

later 3 reaching statistical significance); these are cancer sites that are also associated with obesity, hormones, or potentially inflammation (26–29). One mechanism by which higher adiponectin concentrations might influence pancreatic cancer risk is by increasing insulin sensitivity, decreasing insulin concentrations and facilitating glucose control. Epidemiologic and experimental studies support the biologic plausibility that greater insulin concentrations

Table 2. Selected Characteristics of Control Subjects by Quintile of Adiponectin Concentration, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2004

Characteristic	Quintile of Serum Adiponectin Concentration, μg/mL[a]				
	Q1 (≤4.59)	Q2 (>4.59 and ≤6.16)	Q3 (>6.16 and ≤7.41)	Q4 (>7.41 and ≤9.80)	Q5 (>9.80)
Mean adiponectin concentration, μg/mL	3.74	5.39	6.73	8.37	13.08
Mean age, years	57.0	58.7	58.7	58.3	58.6
Mean C-peptide concentration, ng/mL	2.91	1.97	2.06	1.76	1.72
Mean height, cm	173.0	172.5	173.0	172.9	171.8
Mean body mass index[b]	28.9	27.3	27.1	24.8	24.5
Mean systolic blood pressure, mm Hg	143.2	147.3	149.8	143.4	143.5
Mean diastolic blood pressure, mm Hg	89.8	90.5	92.2	88.0	87.1
Medical history, %					
Diabetes mellitus	17.7	5.9	2.0	2.9	2.0
Pancreatitis	0	4.0	0	2.9	1.0
Gallstones	5.9	10.8	4.9	1.0	2.0
Ulcers	16.7	17.7	9.8	15.7	12.8
Smoking history					
Total cigarettes smoked per day	20.1	19.2	20.2	20.8	19.7
Years of smoking	33.3	37.8	39.1	37.7	38.3
Primary school education or less, %	81.4	76.5	80.4	82.4	87.3
Living in city, %	36.3	38.2	36.3	54.9	50.0
Daily dietary intake[c]					
Energy, kcal	2716	2827	2799	2848	2878
Total fat, g	97.6	96.7	101.3	103.0	100.0
Saturated fat, g	51.9	50.0	52.4	53.6	51.2
Carbohydrate, g	302.6	311.5	300.8	301.4	297.6
Protein, g	107.9	103.8	104.6	99.7	99.4
Physical activity, %					
Occupational activity					
Sedentary	11.8	7.8	11.8	9.8	7.8
Moderate	31.4	22.6	23.5	30.4	30.4
Heavy	10.8	5.9	9.8	3.9	9.8
Not working	46.1	63.7	54.9	55.9	52.0
Leisure activity					
Sedentary	55.9	32.4	39.2	53.9	45.1
Light or moderate	36.3	64.7	56.9	38.2	44.1
Exercising to keep fit	7.8	2.9	3.9	7.8	10.8

Abbreviation: Q, quintile.

[a] Adiponectin quintiles were based on the distribution in all controls ($n = 510$).

[b] Weight (kg)/height $(m)^2$.

[c] Dietary intake analysis was based on 473 controls. Data on all foods and nutrients except alcohol were adjusted for energy intake.

or secretion and insulin resistance promote the development of pancreatic cancer (8, 30–33). The association between adiponectin and pancreatic cancer became significant after we controlled for C-peptide level; therefore, alternative mechanism(s) that are independent of insulin could possibly explain our findings. Adiponectin has been shown to directly suppress cell growth and proliferation in myelomonocytic, breast, and prostate cancer cell lines (34). These direct actions on malignant cells may be related to activation of downstream signaling pathways that could limit cell proliferation (34). Adiponectin may have direct effects on tumor vessels by activating the caspase cascade and inhibiting

Table 3. Age- and Multivariable-Adjusted Odds Ratios and 95% Confidence Intervals for the Relation Between Baseline Adiponectin Concentration and Pancreatic Cancer Risk Among 311 Cases and 510 Matched Controls, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2004

	Quintile of Serum Adiponectin Concentration, μg/mL					Continuous OR[a]	*P*-Trend[b]
	Q1 (≤4.59)	Q2 (>4.59 and ≤6.16)	Q3 (>6.16 and ≤7.41)	Q4 (>7.41 and ≤ 9.80)	Q5 (>9.80)		
No. of cases/no. of controls	60/102	71/102	48/102	70/102	62/102		
Crude OR (95% CI)[c]	1.00 (referent)	1.12 (0.72, 1.74)	0.76 (0.47, 1.23)	1.08 (0.68, 1.71)	1.00 (0.63, 1.56)	0.99 (0.91, 1.07)	0.78
Adjusted OR (95% CI)[d]	1.00 (referent)	0.96 (0.61, 1.53)	0.69 (0.41, 1.14)	0.80 (0.49, 1.31)	0.65 (0.39, 1.07)	0.91 (0.83, 1.00)	0.04
Cases diagnosed <5 years after baseline							
No. of cases/no. of controls	10/16	19/24	10/19	20/21	14/14		
Crude OR (95% CI)	1.00 (referent)	1.13 (0.42, 3.07)	0.77 (0.24, 2.46)	1.35 (0.48, 3.78)	1.43 (0.47, 4.34)	1.04 (0.86, 1.26)	0.68
Adjusted OR (95% CI)	1.00 (referent)	1.14 (0.41, 3.19)	0.79 (0.24, 2.52)	1.01 (0.34, 3.03)	0.98 (0.29, 3.21)	0.95 (0.77, 1.18)	0.65
Cases diagnosed ≥5 years after baseline							
No. of cases/no. of controls	50/86	52/78	38/83	50/81	48/88		
Crude OR (95% CI)	1.00 (referent)	1.13 (0.69, 1.86)	0.76 (0.45, 1.28)	1.01 (0.60, 1.70)	0.93 (0.56, 1.52)	0.98 (0.89, 1.07)	0.62
Adjusted OR (95% CI)	1.00 (referent)	0.91 (0.54, 1.53)	0.64 (0.37, 1.13)	0.73 (0.42, 1.27)	0.55 (0.31, 0.98)	0.89 (0.80, 0.99)	0.03
Cases diagnosed ≥5 and <10 years after baseline							
No. of cases/no. of controls	19/37	17/36	17/34	16/33	23/44		
Crude OR (95% CI)	1.00 (referent)	0.89 (0.40, 2.00)	0.93 (0.40, 2.19)	0.89 (0.38, 2.10)	0.99 (0.46, 2.14)	1.01 (0.88, 1.01)	0.86
Adjusted OR (95% CI)	1.00 (referent)	0.58 (0.22, 1.57)	0.57 (0.20, 1.65)	0.45 (0.16, 1.30)	0.32 (0.11, 0.90)	0.81 (0.68, 0.98)	0.03
Cases diagnosed ≥10 and <15 years after baseline							
No. of cases/no. of controls	25/44	24/34	18/42	29/44	18/34		
Crude OR (95% CI)	1.00 (referent)	1.41 (0.68, 2.89)	0.74 (0.36, 1.53)	1.13 (0.55, 2.32)	0.98 (0.47, 2.05)	0.97 (0.85, 1.11)	0.68
Adjusted OR (95% CI)	1.00 (referent)	1.21 (0.57, 2.56)	0.72 (0.34, 1.55)	0.94 (0.44, 2.00)	0.73 (0.32, 1.64)	0.92 (0.79, 1.07)	0.27
Cases diagnosed ≥5 and <15 years after baseline							
No. of cases/no. of controls	44/81	41/70	35/76	45/77	41/78		
Crude OR (95% CI)	1.00 (referent)	1.13 (0.66, 1.92)	0.82 (0.48, 1.43)	1.02 (0.59, 1.76)	0.98 (0.57, 1.67)	0.99 (0.90, 1.09)	0.85
Adjusted OR (95% CI)	1.00 (referent)	0.86 (0.49, 1.52)	0.66 (0.36, 1.21)	0.69 (0.38, 1.25)	0.54 (0.29, 0.98)	0.88 (0.79, 0.99)	0.03
Cases diagnosed ≥15 years after baseline							
No. of cases/no. of controls	6/5	11/8	3/7	5/4	7/10		
Crude OR (95% CI)	1.00 (referent)	1.02 (0.26, 4.05)	0.29 (0.04, 1.94)	0.81 (0.13, 5.10)	0.48 (0.10, 2.26)	0.91 (0.73, 1.15)	0.44
Adjusted OR (95% CI)	1.00 (referent)	2.82 (0.32, 24.97)	0.76 (0.07, 7.90)	2.08 (0.18, 24.68)	2.45 (0.19, 31.00)	1.01 (0.76, 1.35)	0.93

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quintile.

[a] Continuous variables were standardized to the average size of the 2 central quartiles. Therefore, this is the OR associated with a 25% change in serum adiponectin concentrations relative to the control distribution (per 1.96-μg/mL increase in adiponectin).

[b] *P*-trend for continuous odds ratio.

[c] The crude OR should be considered adjusted for matching factors (age at baseline and month of blood drawing).

[d] Adjusted for years of smoking, diastolic blood pressure, and C-peptide concentration.

the nuclear factor-κβ pathway in endothelial cells, which could consequently promote apoptosis and suppression of tumor angiogenesis (34). Nuclear factor-κβ activation occurs in both type 1 and type 2 diabetes (35, 36) and has been observed in pancreatic cancer cell lines, in animal models of exocrine pancreatic cancer, and in human pancreatic cancer tissue (37). Adiponectin may also regulate cell proliferation directly by selectively binding growth and angiogenic factors, thereby restricting their bioavailability; however, research on this is conflicting (12).

In many (but not all) epidemiologic studies, investigators have reported positive associations between obesity and pancreatic cancer, with recent meta-analyses supporting high BMI as a modest risk factor for pancreatic cancer (in cohort studies, the summary relative risk per 5-unit increase in BMI was 1.14 (95% CI: 1.07, 1.22) (11, 38–40)). Although BMI is inversely associated with adiponectin concentrations in our population of smokers, BMI is not associated with pancreatic cancer in our cohort (24) or in the present nested case-control study. In addition, the majority of the ATBC cohort participants are overweight (BMI > 25) (24), with a BMI distribution similar to that of populations that include nonsmokers in which positive BMI associations with pancreatic cancer have been observed (41, 42). Other investigators have also shown the association between BMI and pancreatic cancer to be less apparent in smokers (40, 43–45). It is possible that the carcinogenic effect of cigarette smoke on the pancreas may mask the association between BMI and pancreatic cancer. Historically, many studies have shown smokers to have lower body weights than nonsmokers; however, research also supports heavy smokers' having greater body weights and more central adiposity than light smokers and nonsmokers (46). The latter finding has been attributed to a clustering of unhealthy behaviors (i.e., poor diet, low physical activity, high alcohol intake, and smoking) and/or to smoking-related hormonal responses (e.g., cortisone, testosterone, or others) contributing to greater visceral fat accumulation and insulin resistance (46). In addition, age-related variation and reduction in lean mass (muscle and skeletal mass) may reduce the validity of BMI as a measure of body fatness in older persons (47). In comparison with BMI, intraabdominal body fat as measured by computed tomography is a stronger, more significant positive determinant of adiponectin level and an inverse predictor of insulin sensitivity (48). Therefore, it is possible that serum adiponectin concentration more accurately reflects intraabdominal body fat than does BMI in our middle-aged/older smoker population (48), with intraabdominal body fat accounting for our adiponectin association.

Alternatively, cigarette smoke-related bioactive chemicals could possibly affect adipose tissue and reduce adiponectin concentrations (49). In particular, nicotine has a lipolytic effect on adipose tissue, mediated via catecholamine release (50–52), that could affect adiponectin synthesis. Plasma adiponectin concentration has also been shown to be lower in smokers than in nonsmokers, independently of BMI (50, 53–56), percentage of body fat as measured by bioimpedence (55), and insulin resistance and sensitivity (49). The mean adiponectin concentration in our smoker population appears to be similar or slightly lower than concentrations observed in healthy nonsmoking men of similar age (13, 26, 27, 48, 50).

The strength of our study is its prospective nature, with serum adiponectin status being assessed up to 19 years prior to cancer diagnosis. The results we observed among the cases that occurred 5 or more years after blood collection are unlikely to have been a consequence of pancreatic cancer and are consistent with our previously reported associations between serum glucose and insulin concentrations, diabetes, and pancreatic cancer (8). Metabolic changes and associated weight loss that accompany subclinical pancreatic cancer probably contributed to the lack of an association among the cases that occurred early during follow-up. A limitation of our study is that we did not have repeated measurements taken over time; a single measurement of adiponectin may not reflect adiponectin concentrations over a lifetime, particularly since adiposity changes with aging ($>$15 years) (57).

Our study had internal validity because both cases and controls were derived from the same cohort. Residual confounding by amount of cigarette smoking is unlikely in our study, since all participants were current smokers at baseline and the smoking exposures were not confounders or effect modifiers of the adiponectin–pancreatic cancer association. Although our findings may not be generalizable to populations that include nonsmokers or women, our previous results for glucose concentration, biochemical diabetes, and insulin resistance being associated with pancreatic cancer are consistent with findings from other studies conducted in diverse populations (4–6, 8–10, 33); therefore, because adiponectin concentrations are known to be correlated with glucose control and inversely associated with diabetes and insulin resistance (13, 14, 34), similar associations between adiponectin and pancreatic cancer might be observed in nonsmoker populations. Different forms of adiponectin appear to have distinct biologic effects (12). In particular, high molecular weight adiponectin is a better indicator of insulin sensitivity and may have stronger associations with cancer than total adiponectin (12), which we measured in our study.

In conclusion, our results support the hypothesis that higher levels of adiponectin may play a protective role in pancreatic carcinogenesis among male smokers. Further research is needed to confirm our results in populations that include women and nonsmokers, particularly in cohorts with extended follow-up. In addition, the effect of adiponectin on molecular mechanisms underlying pancreatic carcinogenesis should be investigated experimentally. If the results of our study are confirmed and extended, adiponectin concentration may prove to be a novel predictor of pancreatic cancer risk, with potentially preventive implications.

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