

A Prospective Study of Plasma Adiponectin and Pancreatic Cancer Risk in Five US Cohorts

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Background The adipocyte-secreted hormone adiponectin has insulin-sensitizing and anti-inflammatory properties. Although development of pancreatic cancer is associated with states of insulin resistance and chronic inflammation, the mechanistic basis of the associations is poorly understood.

Methods To determine whether prediagnostic plasma levels of adiponectin are associated with risk of pancreatic cancer, we conducted a nested case-control study of 468 pancreatic cancer case subjects and 1080 matched control subjects from five prospective US cohorts: Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, and Women's Health Study. Control subjects were matched to case subjects by prospective cohort, year of birth, smoking status, fasting status, and month of blood draw. All samples for plasma adiponectin were handled identically in a single batch. Odds ratios were calculated with conditional logistic regression, and linearity of the association between adiponectin and pancreatic cancer was modeled with restricted cubic spline regression. All statistical tests were two-sided.

Results Median plasma adiponectin was lower in case subjects versus control subjects (6.2 vs 6.8 $\mu\text{g/mL}$, $P = .009$). Plasma adiponectin was inversely associated with pancreatic cancer risk, which was consistent across the five prospective cohorts ($P_{\text{heterogeneity}} = .49$) and independent of other markers of insulin resistance (eg, diabetes, body mass index, physical activity, plasma C-peptide). Compared with the lowest quintile of adiponectin, individuals in quintiles 2 to 5 had multivariable odds ratios ([ORs] 95% confidence intervals [CIs]) of OR = 0.61 (95% CI = 0.43 to 0.86), OR = 0.58 (95% CI = 0.41 to 0.84), OR = 0.59 (95% CI = 0.40 to 0.87), and OR = 0.66 (95% CI = 0.44 to 0.97), respectively ($P_{\text{trend}} = .04$). Restricted cubic spline regression confirmed a nonlinear association ($P_{\text{nonlinearity}} < .01$). The association was not modified by sex, smoking, body mass index, physical activity, or C-peptide (all $P_{\text{interaction}} > .10$).

Conclusions In this pooled analysis, low prediagnostic levels of circulating adiponectin were associated with an elevated risk of pancreatic cancer.

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Pancreatic cancer is the fourth leading cause of cancer death in the United States (1), yet little is known about its etiology. In addition to smoking, chronic pancreatitis, and diabetes mellitus, accumulating evidence has implicated obesity as an important risk factor for pancreatic cancer. The 2009 report from the World Cancer Research Fund concluded that the strength of the evidence supporting an association between obesity and pancreatic cancer is convincing (2). Multiple biological mechanisms have been proposed to explain this association, including insulin resistance and subsequent hyperinsulinemia, circulating insulin-like growth factors, and chronic inflammation (2), but the role of these mechanistic pathways remains poorly understood.

Discovered in 1995, adiponectin is a hormone primarily secreted by adipose tissue (3–6). Animal studies have shown that

adiponectin enhances insulin sensitivity and ameliorates insulin resistance (7–9). Consistent with this observation, in humans, circulating adiponectin is inversely correlated with plasma insulin and is reduced in individuals with insulin-resistant conditions such as obesity and type 2 diabetes mellitus (10). Low prediagnostic adiponectin levels are also associated with an increased risk of developing type 2 diabetes mellitus (11). In addition, prediagnostic plasma adiponectin levels have been inversely associated with several obesity-related cancers, including colorectal, endometrial, and postmenopausal breast cancers (12–15).

Given its essential role in mediating insulin sensitivity, adiponectin may be an important biological link in the development of obesity-associated malignancies, such as pancreatic cancer. Adiponectin receptors AdipoR1 and AdipoR2 are expressed on

human pancreatic beta cells (16) and pancreatic tumor cells (17). Animal studies of pancreatic cancer have shown that rapid tumor growth correlated inversely with serum adiponectin concentration (18). Interestingly, a recent genome-wide association study identified the nuclear receptor 5A2 (*NRS1A2*) gene, which is involved in transcriptional activation of the adiponectin gene (19), as an important predisposing factor for pancreatic cancer (20). These observations suggest a possible role for adiponectin in the development of pancreatic cancer. However, epidemiological data regarding circulating adiponectin and pancreatic cancer risk are limited and inconsistent (17,21–24). To investigate the role of adiponectin in the development of pancreatic cancer, we examined the association between prediagnostic plasma adiponectin and subsequent risk of pancreatic cancer in five US prospective cohorts with up to 26 years of follow-up since blood collection.

Methods

Study Participants

To obtain large numbers of prediagnostic blood samples for this analysis, we pooled the primary data from five US prospective cohorts. The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals aged 40 to 75 years in 1986. The Nurses' Health Study (NHS) enrolled 121,700 female nurses aged 30 to 55 years in 1976. The Physicians' Health Study I (PHS I) is a randomized clinical trial of aspirin and β -carotene and enrolled 22,071 healthy male physicians aged 40 to 84 years in 1982. The aspirin component of the trial ended in 1988, whereas the β -carotene component ended in 1995, and participants are followed as an observational cohort. The Women's Health Initiative (WHI) Observational Study enrolled 93,676 postmenopausal women aged 50 to 79 years between 1994 and 1998. The Women's Health Study (WHS) is a randomized, clinical trial of low-dose aspirin and vitamin E and enrolled 39,876 healthy, female, health professionals aged 45 years or older between 1992 and 1995. The trial was completed in 2004, and participants are followed as an observational cohort.

Individual characteristics and habits, including age at blood draw, sex, race/ethnicity, weight, height, smoking status, physical activity, history of diabetes, and current multivitamin use, were obtained from the baseline questionnaires at enrollment in PHS I, WHI, and WHS and from the questionnaires preceding the date of blood draw in HPFS and NHS. Details of these cohorts have been described previously (25–29). The current study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, Massachusetts, and participants provided informed consent.

Blood Collection and Plasma Assays

Blood samples were collected from 18,225 men in HPFS from 1993 to 1995, from 32,826 women in NHS from 1989 to 1990, from 14,916 men in PHS from 1982 to 1984, from 93,676 women in WHI from 1994 to 1998, and from 28,345 women in WHS from 1992 to 1995. Details on blood draw, transportation, and storage of plasma samples have been described previously (12,30–33).

Plasma adiponectin and 25-hydroxyvitamin D [25(OH)D] were assayed in the laboratory of Dr Nader Rifai (Children's Hospital,

Boston, MA), and C-peptide levels were assayed in the laboratory of Dr Michael Pollak (McGill University, Montreal, Canada). As previously described (34–36), plasma adiponectin was measured using an enzyme-linked immunosorbent assay from ALPCO Diagnostics (Salem, NH); plasma 25(OH)D was measured using the 25(OH)D enzyme immunoassay kit from Immunodiagnostic Systems (Fountain Hills, AZ); and plasma C-peptide was measured using an enzyme-linked immunosorbent assay from Diagnostic Systems Laboratory (Webster, TX). All samples for plasma adiponectin were shipped in a single batch to the reference laboratory, with laboratory personnel blinded to case, control, or quality control status. The mean intra-assay coefficients of variance for blinded, replicate quality control samples were 9.7% for adiponectin, 7.3% for C-peptide, and 4.7% for 25(OH)D.

Pancreatic Cancer Case Subjects and Matched Control Subjects

We included case subjects of pancreatic adenocarcinoma diagnosed through 2008 with blood samples and no prior history of cancer except nonmelanoma skin cancer. Incident case subjects were identified by self-report or during follow-up of a participant's death. Deaths were ascertained from next-of-kin or the US postal service and by searching the National Death Index. This method has been shown to capture more than 98% of deaths (37). Medical records of the case subjects were requested and reviewed by study physicians blinded to exposure data.

Eligible control subjects were cohort participants who provided a blood sample and were alive and free of cancer at the date of the case's diagnosis. We randomly selected up to three control subjects for each case subject, matching on year of birth, prospective cohort (which concurrently matched on sex), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw.

For the present analysis, 490 pancreatic cancer case subjects and 1136 matched control subjects were available. Because of failure of the assay, we removed three case subjects and 11 control subjects. For those three case subjects, we also removed their matched control subjects ($n = 7$). Because of concern about the possible influence of subclinical malignancy on body mass index (BMI), lifestyle choices, and plasma adiponectin levels, we further excluded pancreatic cancer case subjects diagnosed within 1 year of blood draw ($n = 19$) and their matched control subjects ($n = 38$), resulting in a total of 468 case subjects (HPFS: $n = 73$; NHS: $n = 103$; PHS I: $n = 69$; WHI: $n = 194$; WHS: $n = 29$) and 1080 control subjects (HPFS: $n = 175$; NHS: $n = 299$; PHS I: $n = 172$; WHI: $n = 380$; WHS: $n = 54$). Of these 468 case subjects, 463 (99%) were confirmed by review of medical records, tumor registry data, or death certificates.

Statistical Analysis

Median levels of adiponectin among case subjects and control subjects were compared using the Wilcoxon rank-sum test. We did a pooled analysis based on the primary data from five cohorts. Adiponectin was log transformed to improve normality, and participants were categorized into quintiles based on the distributions among all control subjects. Consistent with our prior analyses of the same dataset (35), we additionally performed separate analyses

in men and women using sex-specific quartiles (given fewer case subjects in each subgroup). To compute odds ratios (ORs) and 95% confidence intervals (CIs), we used conditional logistic regression conditioned on the matching factors, including year of birth, prospective cohort (HPFS, NHS, PHS I, WHI, WHS), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw. In multivariable models, we adjusted for established or suspected risk factors of pancreatic cancer, including race (white, black, other), multivitamin use (yes, no), and plasma 25(OH)D levels (quartiles). We additionally adjusted for other risk factors of pancreatic cancer including diabetes (yes, no), BMI (< 18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), physical activity (quartiles), and plasma C-peptide (quartiles), to see if the observed association was independent of factors related to insulin secretion and resistance. In no instance did including any of these covariates change the estimate by more than 10%. Further adjustment for alcohol intake (never/rare, 1–3 drinks per month, 1–6 drinks per week, ≥1 drink per day) and total calories (quartiles) did not change the estimate. *P* values for trend were calculated by the Wald test of a score variable that contained median values of quintiles.

To examine a possible nonlinear association between adiponectin and risk of pancreatic cancer, we used restricted cubic spline regression to flexibly model the association. For this analysis, individuals with extreme adiponectin levels (more than two standard deviations from the log-transformed mean of plasma adiponectin) were excluded to reduce the influence of extreme values. We evaluated nonlinearity by the likelihood ratio test, comparing the model fit including linear and cubic spline terms selected by a stepwise regression procedure with the model fit with only the linear term (38).

We also conducted a meta-analysis of individual study data. We calculated odds ratios for each cohort and then pooled these cohort-specific odds ratios to compute a summary odds ratio using the DerSimonian and Laird random effects model (39). Heterogeneity across studies was tested using the *Q* statistic (39).

To examine whether the association between adiponectin and risk of pancreatic cancer was modified by other risk factors of pancreatic cancer, we conducted preplanned subgroup analyses using unconditional logistic regression adjusted for the matching factors and other relevant covariates. We examined the association in subgroups defined by sex, age at blood draw, follow-up time of case subjects, fasting time, smoking status, BMI, physical activity, and C-peptide levels. Tests for interaction were performed by the Wald test of cross-product terms. To test the robustness of our results, we conducted a sensitivity analysis excluding individuals with diabetes. We also repeated the analyses excluding pancreatic cancer case subjects diagnosed within 2 or 4 years from the date of blood draw to further mitigate any effect of subclinical pancreatic cancer on plasma adiponectin levels.

All statistical analyses were performed with the SAS 9.1 statistical package (SAS Institute, Cary, NC). All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant.

Results

Median plasma adiponectin was lower in case subjects vs control subjects in the full population (6.2 vs 6.8 µg/mL, *P* = .009), among

men (4.6 vs 5.3 µg/mL, *P* = .006), and among women (7.4 vs 7.8 µg/mL, *P* = .07). Adiponectin levels were comparable across studies for men (HPFS and PHS I) and for women (NHS, WHI, and WHS). Among case subjects, median plasma adiponectin was 4.8 µg/mL (10th–90th percentile = 2.4–8.0) for HPFS, 4.4 µg/mL (10th–90th percentile = 2.2–10.3) for PHS I, 6.9 µg/mL (10th–90th percentile = 3.3–17.3) for NHS, 7.8 µg/mL (10th–90th percentile = 3.4–16.3) for WHI, and 6.4 µg/mL (10th–90th percentile = 3.5–14.6) for WHS. Among control subjects, median plasma adiponectin was 5.2 µg/mL (10th–90th percentile = 2.6–10.4) for HPFS, 5.3 µg/mL (10th–90th percentile = 2.9–9.2) for PHS I, 7.7 µg/mL (10th–90th percentile = 3.8–14.2) for NHS, 8.2 µg/mL (10th–90th percentile = 3.8–16.8) for WHI, and 7.1 µg/mL (10th–90th percentile = 4.5–11.0) for WHS. Individuals in the upper quintiles of adiponectin were less likely to have diabetes, more likely to use multivitamins, and had lower BMI and C-peptide levels (Table 1).

We observed a statistically significant inverse association between plasma adiponectin and risk of pancreatic cancer. In the base model conditioned on matching factors, compared with the lowest quintile of plasma adiponectin, individuals in quintiles 2 to 5 experienced odds ratios of 0.60 (95% CI = 0.43 to 0.85), 0.57 (95% CI = 0.41 to 0.80), 0.55 (95% CI = 0.38 to 0.78), and 0.60 (95% CI = 0.42 to 0.86), respectively, and the *P* value for trend was .004 (Table 2). Further adjustment for race, multivitamin use, plasma 25(OH)D, diabetes, BMI, physical activity, and plasma C-peptide yielded similar results. Compared with the lowest quintile of circulating adiponectin, individuals in quintiles 2 to 5 had multivariable odds ratios of 0.61 (95% CI = 0.43 to 0.86), 0.58 (95% CI = 0.41 to 0.84), 0.59 (95% CI = 0.40 to 0.87), and 0.66 (95% CI = 0.44 to 0.97), respectively (*P*_{trend} = .04) (Table 2).

We also performed separate analyses in men and women using gender-specific quartiles and observed similar inverse associations. Odds ratios for quartiles 2 to 4 were 0.76 (95% CI = 0.42 to 1.36), 0.66 (95% CI = 0.36 to 1.21), and 0.60 (95% CI = 0.32 to 1.12) for men (*P*_{trend} = .08) and 0.66 (95% CI = 0.45 to 0.96), 0.76 (95% CI = 0.51 to 1.13), and 0.78 (95% CI = 0.51 to 1.19) for women (*P*_{trend} = .30). There was no statistically significant heterogeneity due to sex (*P* = .36).

The restricted cubic splines showed a pattern similar to the quintile analysis (Figure 1, A); the multivariable odds ratio declined dramatically with increasing levels of adiponectin to approximately 5 µg/mL, but then flattened out (*P* for nonlinearity < .01). Similar patterns were observed among men and women, when analyzed separately (Figure 1, B and C). Thus for subsequent subgroup analyses, we categorized adiponectin by combining quintiles 2 to 5. The multivariable odds ratio comparing less than 4.4 µg/mL vs 4.4 µg/mL or greater was 0.62 (95% CI = 0.47 to 0.82) for the full population, 0.55 (95% CI = 0.35 to 0.86) for men, and 0.65 (95% CI = 0.45 to 0.95) for women (Table 3).

Furthermore, we observed similar odds ratios when analyzing each cohort separately (Figure 2), with no statistically significant heterogeneity across studies (*P* = .49). We conducted a meta-analysis to pool the cohort-specific odds ratios. Comparing less than 4.4 µg/mL vs 4.4 µg/mL or greater, the summary odds ratio of 0.62 (95% CI = 0.45 to 0.83) obtained by pooling the cohort-specific odds ratios (Figure 2) was the same as the odds ratio obtained by pooling the primary data from the five cohorts.

Table 1. Age- and study-standardized baseline characteristics according to plasma adiponectin levels among control subjects*

Characteristic	Quintiles of plasma adiponectin levels, µg/mL†				
	<4.4	4.4–5.8	5.9–7.8	7.9–10.8	≥10.9
Men					
No. of control subjects	112	97	71	43	24
Age at blood draw, y	59.3 (8.5)	60.1 (9.4)	60.8 (9.2)	63.6 (8.9)	61.6 (13.3)
Race, %					
White	91.5	92.6	92.6	92.7	89.7
Black	0.0	1.3	0.0	0.0	0.0
Other	8.5	6.1	7.4	7.3	10.3
Body mass index, kg/m ²	26.1 (3.3)	25.2 (2.7)	25.2 (3.2)	24.5 (2.3)	24.3 (2.6)
Physical activity, MET-hr/wk	21.9 (26.4)	30.4 (33.2)	36.4 (48.9)	31.4 (46.2)	25.0 (19.3)
Cigarette smoking, %					
Never	34.6	43.0	45.0	33.6	29.5
Past	50.3	45.3	37.4	49.7	56.8
Current	15.1	11.7	17.6	16.7	13.7
Missing	0.0	0.0	0.0	0.0	0.0
History of diabetes mellitus, %	6.2	0.9	2.8	0.0	2.9
Regular multivitamin use, %	28.9	33.6	37.0	37.7	40.8
Fasting time, h	7.4 (4.9)	6.9 (5.2)	7.7 (4.9)	6.1 (4.7)	7.8 (4.7)
Plasma C-peptide, ng/mL	2.8 (1.9)	2.6 (2.7)	2.3 (1.6)	2.1 (1.2)	2.5 (3.7)
Plasma 25(OH)D, nmol/L	69.1 (20.1)	69.0 (24.4)	74.5 (26.9)	78.8 (27.7)	70.6 (23.4)
Women					
No. of control subjects	103	120	145	173	192
Age at blood draw, y	62.4 (7.5)	63.2 (8.2)	63.9 (7.6)	62.7 (7.8)	64.5 (7.6)
Race, %					
White	84.1	94.7	93.8	93.4	94.9
Black	6.9	2.5	4.3	2.3	0.5
Other	9.0	2.9	1.9	4.3	4.7
Body mass index, kg/m ²	27.9 (5.2)	27.5 (5.2)	26.6 (5.3)	25.7 (4.5)	24.6 (4.5)
Physical activity, MET-hr/wk	17.6 (21.6)	15.5 (16.0)	14.7 (14.1)	15.7 (16.3)	16.1 (15.2)
Cigarette smoking, %					
Never	41.8	50.6	46.9	46.7	39.9
Past	44.3	38.7	44.5	39.7	47.3
Current	13.0	9.5	8.6	12.5	10.6
Missing	0.9	1.2	0.0	1.1	2.1
History of diabetes mellitus, %	9.4	3.3	4.8	1.4	2.8
Regular multivitamin use, %	27.6	56.6	43.6	37.0	46.8
Fasting time, h	12.1 (3.2)	11.5 (3.9)	11.6 (3.3)	11.7 (3.6)	12.1 (2.9)
Plasma C-peptide, ng/mL	2.3 (1.3)	2.2 (1.1)	2.0 (1.3)	1.9 (1.0)	1.6 (0.7)
Plasma 25(OH)D, nmol/L	57.5 (22.3)	58.2 (20.5)	60.1 (35.4)	63.7 (20.7)	66.1 (21.0)

* Data are mean (SD) unless otherwise noted. 25(OH)D = 25-hydroxyvitamin D; MET = metabolic equivalent.

† The quintiles were defined based on distribution among all control subjects.

Table 2. Odds ratios and 95% confidence intervals for pancreatic cancer according to quintiles of plasma adiponectin

Model	Quintiles of plasma adiponectin levels, µg/mL*					P _{trend} †
	<4.4	4.4–5.8	5.9–7.8	7.9–10.8	≥10.9	
No. of case subjects	135	83	79	79	92	
No. of control subjects	215	217	216	216	216	
Base model‡	1.00 (referent)	0.60 (0.43 to 0.85)	0.57 (0.41 to 0.80)	0.55 (0.38 to 0.78)	0.60 (0.42 to 0.86)	.004
Multivariable 1§	1.00 (referent)	0.60 (0.43 to 0.85)	0.58 (0.41 to 0.82)	0.57 (0.40 to 0.83)	0.63 (0.44 to 0.90)	.01
Multivariable 2	1.00 (referent)	0.61 (0.43 to 0.87)	0.57 (0.40 to 0.81)	0.57 (0.39 to 0.83)	0.63 (0.43 to 0.92)	.01
Multivariable 3¶	1.00 (referent)	0.61 (0.43 to 0.86)	0.58 (0.41 to 0.84)	0.59 (0.40 to 0.87)	0.66 (0.44 to 0.97)	.04

* The quintiles were defined based on distribution among all control subjects.

† P values were calculated by the Wald test of a score variable that contained median values of quintiles. All statistical tests were two-sided.

‡ Odds ratios and 95% confidence intervals were estimated by conditional logistic regression conditioned on the matching factors including year of birth, prospective cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, Women's Health Study), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw.

§ Base model further adjusted for race (white, black, other), history of diabetes mellitus (yes, no), current multivitamin use (yes, no), and plasma 25-hydroxyvitamin D levels (quartiles).

|| Multivariable 1 + body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²) and physical activity (quartiles).

¶ Multivariable 2 + plasma C-peptide levels (quartiles).

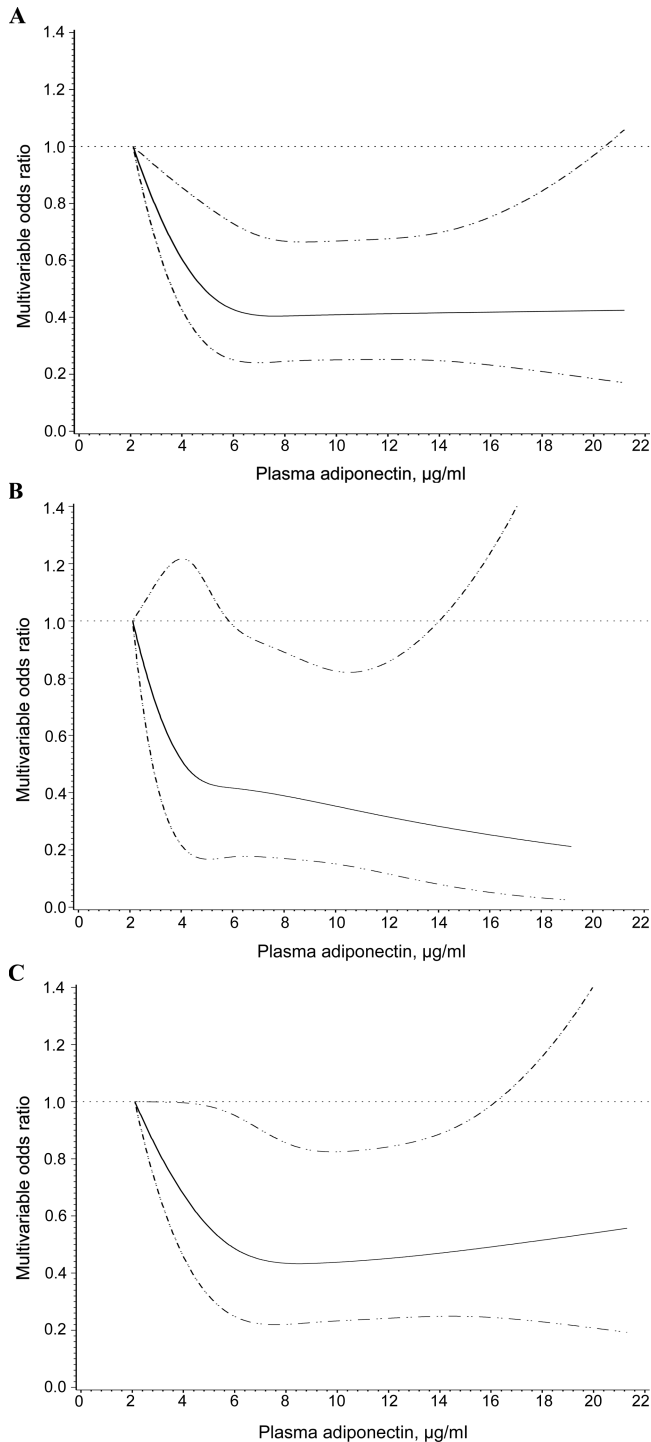


Figure 1. Nonparametric regression curve for the association between plasma adiponectin and risk of pancreatic cancer. **A)** Full population. **B)** Men. **C)** Women. Multivariable odds ratios were calculated by restricted cubic spline conditional logistic model. Odds ratios were conditioned on the matching factors including year of birth, prospective cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, Women's Health Study), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw, and adjusted for covariates in the multivariable model 3, including race (white, black, other), history of diabetes mellitus (yes, no), current multivitamin use (yes, no), plasma 25-hydroxyvitamin D levels (quartiles), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m²), physical activity (quartiles), and plasma C-peptide levels (quartiles). **Solid curve** represents point estimates and **dashed curves** represent 95% confidence intervals.

Similar odds ratios were observed comparing less than 4.4 $\mu\text{g}/\text{mL}$ vs 4.4 $\mu\text{g}/\text{mL}$ or greater when we excluded case subjects diagnosed within 2 years (multivariable OR = 0.60; 95% CI = 0.45 to 0.80) or 4 years (multivariable OR = 0.53; 95% CI = 0.38 to 0.74) from the date of blood draw or limited the analysis to nondiabetics (multivariable OR = 0.62; 95% CI = 0.46 to 0.82). No statistically significant interaction of plasma adiponectin and pancreatic cancer risk was seen for other potential risk factors for pancreatic cancer, including sex, age at blood draw, follow-up time of case subjects, fasting time, smoking status, BMI, physical activity, and C-peptide levels ($P > .10$ for all) (Table 3), and higher adiponectin remained inversely related to risk of pancreatic cancer across all subgroups (Table 3).

Discussion

In this prospective study of five large US cohorts, we observed a statistically significant inverse association between prediagnostic plasma adiponectin levels and the subsequent risk of pancreatic cancer. This inverse association persisted across all subgroups examined and was independent of smoking, diabetes, BMI, physical inactivity, plasma C-peptide levels, and other known or suspected risk factors for pancreatic cancer. Furthermore, the inverse association of plasma adiponectin with pancreatic cancer risk was consistently noted in all five individual prospective cohorts.

The association between circulating adiponectin and pancreatic cancer risk has been evaluated in three small, hospital-based, case-control studies with inconsistent results (17,21,22). Retrospective analyses are subject to bias because adiponectin levels are likely influenced by the profound weight loss often experienced by patients with pancreatic cancer (reverse causation). In contrast, prospective studies minimize this bias by obtaining plasma samples prior to the time of cancer diagnosis. One prospective nested case-control study of male, Finnish smokers found that high adiponectin levels were inversely associated with pancreatic cancer risk (multivariable OR = 0.65, 95% CI = 0.39 to 1.07, comparing extreme quintiles; $P_{\text{trend}} = .04$) (23). A second prospective study observed no overall association between circulating adiponectin and pancreatic cancer risk, although follow-up duration in the cohort was modest (mean follow-up of 5 years). Of note, this latter study reported an inverse association among never smokers (multivariable OR = 0.52, 95% CI = 0.27 to 1.01, comparing extreme quartiles; $P_{\text{trend}} = .03$) (24).

Several biological mechanisms might account for the association of circulating adiponectin with pancreatic cancer risk (40). Adiponectin has a central role in the regulation of glucose and lipid metabolism (7–9), and low plasma levels are associated with states of insulin resistance, including obesity and type 2 diabetes (10,11). Because impaired glucose processing (41–43), obesity (44,45), and type 2 diabetes (46) have been linked to incident pancreatic cancer, adiponectin may decrease pancreatic cancer risk by favorably modulating insulin resistance. Adiponectin also suppresses the synthesis of tumor necrosis factor and interferon γ and induces the production of anti-inflammatory cytokines such as interleukin 10 and interleukin 1 receptor antagonist (47). Because chronic inflammation is important in the development of pancreatic cancer (48,49), adiponectin might also reduce pancreatic cancer risk by

Table 3. Multivariable-adjusted odds ratios and 95% confidence intervals for pancreatic cancer by plasma adiponectin, among subgroups*

Characteristic	No. of case subjects	No. of control subjects	Plasma adiponectin levels, $\mu\text{g/mL}$		<i>P</i> _{interaction}
			<4.4	≥ 4.4	
All participants	468	1080	1.00 (referent)	0.62 (0.47 to 0.82)	
Sex					
Men	142	347	1.00 (referent)	0.55 (0.35 to 0.86)	.42
Women	326	733	1.00 (referent)	0.65 (0.45 to 0.95)	
Age at blood draw					
<63 y, median	201	496	1.00 (referent)	0.60 (0.40 to 0.91)	.90
≥ 63 y	267	584	1.00 (referent)	0.64 (0.43 to 0.94)	
Follow-up time of case subjects					
<5 y	110	246	1.00 (referent)	0.90 (0.48 to 1.68)	.66
5–9 y	176	387	1.00 (referent)	0.42 (0.26 to 0.68)	
≥ 10 y	182	447	1.00 (referent)	0.68 (0.44 to 1.05)	
Fasting time					
<8 h	104	255	1.00 (referent)	0.48 (0.27 to 0.84)	.57
≥ 8 h	364	825	1.00 (referent)	0.66 (0.48 to 0.92)	
Smoking status					
Never	195	471	1.00 (referent)	0.51 (0.33 to 0.80)	.57
Past/current	273	609	1.00 (referent)	0.66 (0.46 to 0.95)	
BMI					
<25 kg/m ²	211	518	1.00 (referent)	0.61 (0.39 to 0.96)	.78
25–29.9 kg/m ²	168	405	1.00 (referent)	0.64 (0.40 to 1.02)	
≥ 30 kg/m ²	89	157	1.00 (referent)	0.57 (0.31 to 1.06)	
Physical activity					
<6 MET-hr/wk, tertiles	160	301	1.00 (referent)	0.75 (0.43 to 1.31)	.11
6–17.9 MET-hr/wk	142	351	1.00 (referent)	0.59 (0.35 to 1.00)	
≥ 18 MET-hr/wk	166	428	1.00 (referent)	0.50 (0.32 to 0.78)	
C-peptide levels					
< 1.4 ng/mL, tertiles	156	355	1.00 (referent)	0.67 (0.35 to 1.27)	.21
1.4–2.1 ng/mL	113	398	1.00 (referent)	0.73 (0.42 to 1.26)	
≥ 2.2 ng/mL	199	327	1.00 (referent)	0.55 (0.37 to 0.83)	

* Odds ratios and 95% confidence intervals were estimated by unconditional logistic regression adjusted for the matching factors including age (continuous), prospective cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, Women's Health Study), smoking status (never, past, current), fasting time (0 to <4, 4 to <8, 8 to <12, ≥ 12 hours), and month of blood draw (2-month intervals), and other covariates in the multivariable model 3, including race (white, black, other), history of diabetes mellitus (yes, no), current multivitamin use (yes, no), plasma 25-hydroxyvitamin D levels (quartiles), body mass index (BMI) (<18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m²), physical activity (quartiles), and plasma C-peptide levels (quartiles), excluding the stratification variable. All statistical tests were two-sided. MET, metabolic equivalent.

blunting the protumorigenic effects of the inflammatory response. Alternatively, because adiponectin has been shown to inhibit tumor cell proliferation and promote apoptosis (50,51), adiponectin may directly impair tumor formation by promoting signaling through its receptors on tumor cells and cells in the tumor microenvironment (52). Laboratory studies suggest that harnessing the antitumor effects of adiponectin may provide a novel therapeutic approach to cancer (53,54).

The strengths of this study include its long follow-up period and large sample size, with participants from all geographic regions of the United States. The prospective design and exclusion of case subjects diagnosed within 1 year of blood draw minimized potential bias due to reverse causation. Furthermore, adiponectin was measured in a single laboratory as a single batch with low coefficients of variance for blinded, replicate quality control samples interspersed with participant samples. Extensive covariate data from all five cohorts allowed for rigorous control of potential confounding and evaluation of effect modification.

A limitation of this study is that adiponectin was measured only once at baseline, which may not fully reflect long-term plasma concentrations. However, repeated adiponectin measurements 1 year apart (55) and 3 years apart (56) demonstrated a high correlation of 0.85 and 0.73, respectively, suggesting that a single

adiponectin measurement is a reasonable proxy for intermediate-term levels and may be sufficient for risk assessment in epidemiological studies. We cannot rule out that our findings may be influenced in part by residual confounding. This may be more likely in an analysis involving multiple cohorts because not all covariate data are collected identically. However, we evaluated multiple possible confounding covariates and did not observe meaningful changes in our risk estimates. In addition, our study population consisted primarily of white participants, and we did not have adequate power to examine the association of plasma adiponectin in other ethnic groups. Further studies in non-white subjects are warranted.

In conclusion, we found that low prediagnostic adiponectin is associated with a statistically significantly increased risk of pancreatic cancer in this large, prospective study that combined five cohorts. Our data provide additional evidence for a biological link between obesity, insulin resistance, and pancreatic cancer risk and also suggest an independent role of adiponectin in the development of pancreatic cancer. In addition, because circulating adiponectin can be increased by a number of behavioral and drug interventions, such as weight loss (57,58), dietary modifications (59), caloric restriction (60), physical activity (61–63), and antidiabetic therapy (64,65), the observation in this study may help guide a preventive

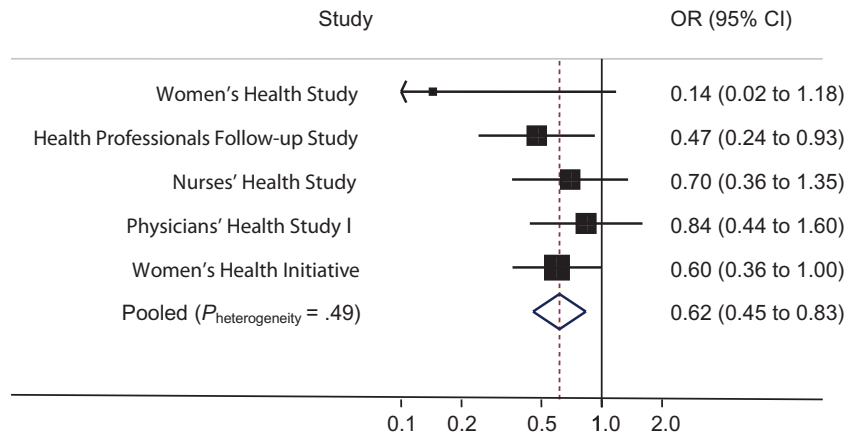


Figure 2. Cohort-specific and meta-analysis pooled odds ratios (ORs) of pancreatic cancer according to dichotomized plasma adiponectin levels (<4.4 vs ≥4.4 μg/mL). Cohort-specific multivariable odds ratios are conditioned on the matching factors including year of birth, prospective cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, Women's Health Study), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw, and adjusted for covariates in the multivariable model 3, including race (white, black, other), history of diabetes mellitus (yes, no), current multivitamin use (yes, no),

plasma 25-hydroxyvitamin D levels (quartiles), body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), physical activity (quartiles), and plasma C-peptide levels (quartiles). The pooled odds ratio is calculated by the DerSimonian and Laird random-effects model. The **solid squares** and **horizontal lines** correspond to the cohort-specific multivariable odds ratios and 95% confidence intervals (CIs), respectively. The area of the solid square reflects the cohort-specific weight (inverse of the variance). The **open diamond** represents the pooled multivariable odds ratio and 95% confidence interval. The **dashed vertical line** indicates the pooled odds ratio. The **solid vertical line** indicates an odds ratio of 1.0.

strategy for pancreatic cancer. Future studies need to further elucidate the molecular mechanisms through which adiponectin influences pancreatic carcinogenesis.

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