American Journal of Epidemiology
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Vol. 182, No. 3
DOI: 10.1093/aje/kwv041
Advance Access publication:
June 17, 2015

Systematic Reviews and Meta- and Pooled Analyses

Circulating Leptin and Risk of Pancreatic Cancer: A Pooled Analysis From 3 Cohorts

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Initially submitted October 9, 2014; accepted for publication February 6, 2015.

Adiposity is associated with pancreatic cancer; however, the underlying mechanism(s) is uncertain. Leptin is an adipokine involved in metabolic regulation, and obese individuals have higher concentrations. We conducted a pooled, nested case-control study of cohort participants from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, and the Cancer Prevention Study II Nutrition Cohort to investigate whether prediagnostic serum leptin was associated with pancreatic cancer. A total of 731 pancreatic adenocarcinoma cases that occurred between 1986 and 2010 were included (maximum follow-up, 23 years). Incidence density–selected controls ($n = 909$) were matched to cases by cohort, age, sex, race, and blood draw date. Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals. Sex-specific quintiles were based on the distribution of the controls. Overall, serum leptin was not associated with pancreatic cancer (quintile 5 vs. quintile 1: odds ratio = 1.13, 95% confidence interval: 0.75, 1.71; $P_{trend} = 0.38$). There was a significant interaction by follow-up time ($P = 0.003$), such that elevated risk was apparent only during follow-up of more than 10 years after blood draw (quintile 5 vs. quintile 1: odds ratio = 2.55, 95% confidence interval: 1.23, 5.27; $P_{trend} = 0.004$). Our results support an association between increasing leptin concentration and pancreatic cancer; however, long follow-up is necessary to observe the relationship. Subclinical disease may explain the lack of association during early follow-up.

adiposity; insulin resistance; leptin; pancreatic cancer

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CPS-II, Cancer Prevention Study II Nutrition Cohort; OR, odds ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. As there are no effective screening methods for detection of this malignancy, it is typically diagnosed at advanced stages, which contributes to a 5-year survival rate of 6.7% (1). Cigarette smoking, diabetes mellitus, and adiposity are among the few consistent and potentially modifiable risk factors for pancreatic cancer (2–5). Diabetes as defined by fasting glucose and glucose intolerance has been consistently associated with pancreatic cancer in prospective epidemiologic studies (3, 6, 7); however, associations between blood markers related to diabetes (e.g., C-peptide, adiponectin, advanced glycation end products, insulin-like growth factor 1 axis, C-reactive protein) that may mediate these associations have been less consistent (3, 4, 6, 8–14).

Leptin is a highly pleiotropic adipokine that is synthesized primarily in white adipose tissue (15). It is important in neurological regulation of physiological processes and behaviors including appetite, metabolism, and body weight (15), and it also plays a role in glucose homeostasis (16). Although leptin lessens food intake and body weight, blood concentrations of leptin are positively correlated with adipose stores (16). Similar to other physiological signaling pathways, leptin regulates its own receptor and signaling (16); however, obesity creates a pathological state whereby high leptin concentrations downregulate leptin receptors and signaling, thus fostering leptin resistance and contributing to greater adiposity (16). Leptin has been shown to enhance tumor vascularization, promote cellular proliferation, migration,

Table 1. Selected Baseline Characteristics of Case and Control Participants From the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985–1988), Cancer Prevention Study II Nutrition Cohort (1998–2001), and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (1992–2001)

Characteristic	ATBC				CPS-II			
	Cases ($n = 352$)		Controls ($n = 352$)		Cases ($n = 90$)		Controls ($n = 90$)	
	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%
Age at blood draw, years[a]	57 (53–61)		57 (54–61)		70 (67–73)		70 (67–73)	
Age at diagnosis, years[a]	69 (64–73)		69 (64–73)		73 (69–77)		73 (69–77)	
Time from blood draw to diagnosis, years[a]	11.4 (7.1–16.4)				2.9 (1.6–4.6)			
Leptin concentration, ng/mL[a]								
Male	5.5 (2.9–9.3)		4.7 (2.8–8.6)		7.0 (5.0–11.0)		8.9 (5.2–15.3)	
Female					27.0 (14.7–49.3)		30.4 (13.7–52.0)	
Male sex		100.0		100.0		52.2		52.2
Race/ethnicity								
White		100.0		100.0		96.7		97.8
Black								
Asian						1.1		1.1
Other						2.2		1.1
Cigarette smoking status								
Never smoker						50.0		48.9
Former smoker						44.4		50.0
Current smoker		100.0		100.0		5.6		1.1
Body mass index[b]								
<25		35.5		37.8		46.7		33.3
25.0 to <30		46.9		44.3		38.9		43.3
≥30		17.6		17.9		14.4		20.0
Missing data								3.3
Body mass index[a,b]	26.2 (23.9–28.5)		26.2 (23.9–28.9)		25.5 (23.3–27.7)		26.4 (23.3–29.3)	
Diabetes mellitus		6.0		5.7		14.4		8.9
Daily intake[a]								
Alcohol, g	10.8 (2.3–27.8)		10.7 (2.9–25.1)		3.7 (0.5–11.2)		2.3 (0.2–11.7)	
Total fat, g	116.6 (93.8–142.0)		116.4 (94.1–147.1)		52.8 (41.0–71.3)		54.3 (43.1–68.0)	
Saturated fat, g	49.8 (37.4–62.3)		49.4 (37.1–62.6)		17.1 (13.3–23.4)		18.0 (13.1–21.4)	

Table continues

and invasion, and inhibit apoptosis of tumor cells (17), raising the possibility that the epidemiologic association between overweight/obesity and pancreatic cancer might in part be mediated by leptin. To the best of our knowledge, no prospective epidemiologic study has examined the association between blood concentrations of leptin and risk of pancreatic cancer.

We conducted a pooled, nested case-control study of participants from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), and Cancer Prevention Study II Nutrition Cohort (CPS-II) to investigate whether prediagnostic circulating leptin concentrations were associated with pancreatic cancer. We hypothesized that higher leptin concentrations would be positively associated with pancreatic cancer.

METHODS

Study design and population

This pooled, nested case-control study included data from the ATBC (18), CPS-II (19), and PLCO (20). Details about the nested case-control sets from the ATBC and PLCO study have been published previously (14). Written, informed consent was obtained from all individuals within their respective studies. Each study was approved by its local institutional review boards, the National Cancer Institute Special Studies Institutional Review Board for the ATBC and PLCO cohorts (18, 20), and the Emory University Institutional Review Board for CPS-II. In addition, the ATBC was approved by the institutional review boards at the National Public Health Institute in Finland, and the PLCO was approved by each of its 10 participating screening centers.

Table 1. Continued

Characteristic	PLCO				All Cohorts Combined			
	Cases ($n = 289$)		Controls ($n = 467$)		Cases ($n = 731$)		Controls ($n = 909$)	
	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%
Age at blood draw, years[a]	65 (61–69)		66 (61–69)		62 (56–67)		63 (57–67)	
Age at diagnosis, years[a]	72 (68–76)		71 (68–76)		71 (66–75)		71 (66–75)	
Time from blood draw to diagnosis, years[a]	7.7 (4.5–10.0)				8.3 (4.2–12.2)			
Leptin concentration, ng/mL[a]								
Male	7.3 (4.0–12.0)		6.7 (4.3–11.2)		6.1 (3.3–10.3)		5.9 (3.4–10.4)	
Female	21.7 (12.3–32.5)		21.2 (13.1–32.1)		22.8 (12.6–38.9)		22.4 (13.2–36.6)	
Male sex		61.2		62.7		78.8		76.1
Race/ethnicity								
White		90.0		90.1		95.6		94.7
Black		3.1		3.0		1.2		1.5
Asian		5.2		5.1		2.2		2.8
Other		1.7		1.7		0.9		1.0
Cigarette smoking status								
Never smoker		38.8		47.8		21.5		29.4
Former smoker		43.3		44.8		22.6		27.9
Current smoker		18.0		7.5		56.0		42.7
Body mass index[b]								
<25		33.6		34.7		36.1		35.8
25.0 to <30		42.9		45.8		44.3		45.0
≥30		22.8		19.1		19.3		18.7
Missing data		0.7		0.4		0.3		0.6
Body mass index[a,b]	26.6 (24.1–29.8)		26.6 (24.0–28.8)		26.2 (23.9–29.1)		26.4 (23.9–28.9)	
Diabetes mellitus		12.5		8.1		9.6		7.3
Daily intake[a]								
Alcohol, g	1.5 (0.3–11.2)		0.9 (0.3–9.4)		6.1 (0.5–20.1)		3.8 (0.4–16.5)	
Total fat, g	61.9 (43.7–83.9)		62.4 (44.8–88.6)		87.0 (58.2–122.3)		82.6 (53. 4–116.1)	
Saturated fat, g	21.0 (14.3–28.8)		20.7 (14.7–30.5)		31.4 (19.0–50.3)		28.4 (17.8–46.3)	

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; IQR, interquartile range; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

[a] Median (interquartile range, 25%–75%).

[b] Expressed as weight (kg)/height $(m)^2$.

Cases were incident primary pancreatic adenocarcinomas (*International Classification of Diseases for Oncology, Third Edition* (ICD-O-3), codes C250–C259, C25.0–C25.3, or C25.7–C25.9, and *International Classification of Diseases, Ninth Revision* (ICD-9), code 157.0). Endocrine pancreatic tumors (ICD-O-3 code C25.4; histology codes 8150, 8151, 8153, 8155, and 8240; ICD-9 code 157.4) were excluded because the etiology of these cancers is thought to be different. Case ascertainment varied between studies but included linking participants to cancer registries (ATBC, PLCO, CPS-II), self- and next-of-kin reports (PLCO, CPS-II), and use of national death indices (ATBC, PLCO, CPS-II) (18, 19, 21).

Controls were selected with a 1:1 control:case ratio (ATBC, CPS-II, PLCO) or a 2:1 control:case ratio (PLCO) and were alive and free from pancreatic cancer on the date their matched case was diagnosed. Data from cases and controls from the previously published ATBC and PLCO nested case-control studies (13, 14, 22) were included in the present analysis. Controls were matched to cases on age and calendar date of blood draw (+30 days), sex, and race. The final analytical data set included 731 cases and 909 controls from these 3 cohorts: 352 cases and 352 controls from ATBC, 90 cases and 90 controls from CPS-II, and 289 cases and 467 controls from PLCO. Cases were diagnosed between 1986 and 2009 in the ATBC cohort, between 1999 and 2006 in the CPS-II cohort, and between 1995 and 2010 in the PLCO cohort.

Data on lifestyle, demographics, and possible confounders were collected. Detailed descriptions of data collection methods

have been published previously for the individual studies (18–21). Information was obtained from each cohort on sex, age, race, body mass index, history of cigarette smoking, self-reported diabetes, diet, and alcohol use, and the data were harmonized.

Measurement of leptin

ATBC participants provided a blood sample at their pre-randomization visit (1985–1988) after an overnight fast, and serum was stored at −70°C. Nonfasting blood samples were collected from PLCO (1992–2001) (20) and CPS-II (1998–2001) (19) participants. Frozen serum samples from all studies were sent to Dr. Michael Pollak's laboratory at the Lady Davis Institute for Medical Research, Montreal Quebec, Canada. Serum leptin was analyzed by enzyme-linked immunosorbent assay with reagents from R&D Systems, Inc. (Minneapolis, Minnesota). 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, and blinded replicate quality control samples from each respective study were placed in each batch within each cohort and comprised 10% of each batch.

Using a nested components-of-variance analysis, with logarithmically transformed quality-control leptin measurements across all batches (23), we found that the overall coefficient of variation (intra- and interbatch) was 8.0%, with values of 4.7%, 6.9%, and 6.0% within the ATBC, PLCO, and CPS-II studies, respectively. The intra- and interassay coefficients of variation, respectively, in each cohort were 4.0% and 2.4% in ATBC, 1.0% and 6.0% in CPS-II, and 4.4% and 5.3% in PLCO.

Statistical analysis

Medians, intraquartile ranges, and proportions of selected characteristics were determined for the cases and controls overall and by each cohort. We calculated sex-specific quintiles based on the distribution of leptin among the controls (<2.89, 2.89 to <4.80, 4.80 to <7.22, 7.22 to <11.67, and ≥11.67 ng/mL for men and <10.82, 10.82 to <17.43, 17.43 to <26.55, 26.55 to <40.78, and ≥40.78 ng/mL for women). Generalized linear models were used to calculate means for continuous variables adjusting for cohort, and frequencies were used to calculate proportions (percentages) for categorical variables to describe characteristics among the controls across leptin quintiles. Dietary nutrients and foods highly correlated with energy were energy adjusted by using the residual method (24). The variables assessed as potential confounders in risk models included age; smoking status (never, former quit ≥15 years ago, former quit <15 years ago, or current smoking); height; weight; body mass index (8 categories, missing); history of diabetes (yes, no, missing); nutrients from foods (energy, carbohydrate, total and saturated fat); total or red meat intake; alcohol; and physical activity. As serum levels of C-peptide (4), adiponectin (22, 25), and transforming growth factor β1 (26) have been reported to be associated with pancreatic cancer, they were also evaluated as potential confounders. Variables were evaluated as confounders in models built within each cohort and overall and were included in the final model if they were associated with both leptin and pancreatic cancer and changed risk estimates more than 10% or were established risk factors for pancreatic cancer. Leptin was analyzed both categorically and continuously. The continuous analysis was based on the standard deviation of leptin (7.34 ng/mL for men and 23.12 ng/mL for women). Trend tests were based on a −2 log-likelihood test comparing a model with a continuous leptin measure (standard deviation) with a model without a continuous measure.

We used conditional logistic regression to calculate odds ratios and 95% confidence intervals for pancreatic cancer with the lowest quintile of serum leptin as the referent category. Our multivariable model was adjusted for age, smoking, body mass index, and diabetes.

Interactions were evaluated in stratified analyses by sex, age, smoking status (never, former, current), body mass index expressed as weight (kg)/height $(m)^2$ (<25 vs. ≥25), diabetes, and cohort. Statistical significance was tested by using a multiplicative risk model. Analyses stratified by follow-up time (<5 years, 5 to <10 years, and 10 years or more) were also performed to evaluate the potential influence of preclinical disease on risk estimates. Conditional logistic regression was used to calculate odds ratios stratified by sex, age, cohort, and follow-up time, while unconditional logistic regression, additionally adjusting for matching factors, was used for the other stratified analyses.

All statistical analyses were performed by using Statistical Analysis Systems (SAS), version 9.3, software (SAS Institute, Inc., Cary, North Carolina), and statistical tests were 2-tailed.

RESULTS

The characteristics of cases and controls in each cohort and combined are shown in Table 1. The interval between serum collection and diagnosis was up to 22.8 years for ATBC, up to 14.5 years for PLCO, and up to 7.4 years for CPS-II. The median time between serum collection and diagnosis was 8.3 years overall (11.4 years for ATBC, 7.7 years for PLCO, and 2.9 years for CPS-II). The median age at pancreatic cancer diagnosis was 71 years. The range of leptin concentrations varied across cohorts with participants in the ATBC cohort having slightly lower concentrations compared with male participants in the PLCO and CPS-II cohorts. As expected, leptin concentrations were about 3-fold higher among women than among men in the CPS-II and PLCO cohorts. The characteristics of cases and controls did not differ greatly, except for the higher proportion of current smokers among cases than among controls.

Table 2 shows the means and proportions of selected baseline characteristics among the controls according to quintile of leptin concentrations, adjusted for cohort. Increasing leptin concentrations were directly related to male sex, former smoker status, higher body mass index, history of diabetes, less alcohol use, higher fat intake, higher C-peptide and transforming growth factor β1 concentrations, and lower total adiponectin concentrations.

In analyses including the entire follow-up period, leptin was not associated with risk of pancreatic cancer (Table 3). However, the association between leptin concentrations and risk of pancreatic cancer differed by follow-up time, with

Table 2. Selected Baseline Characteristics of Control Participants From the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985–1988), Cancer Prevention Study II Nutrition Cohort (1998–2001), and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (1992–2001) Cohorts by Sex-Specific Quintile of Leptin Concentration[a]

Characteristic	Sex-Specific Quintile of Serum Leptin Concentration[b]									
	1		2		3		4		5	
	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean
Leptin concentration, ng/mL										
Male		1.9		4.1		6.3		9.7		19.6
Female		6.7		14.0		21.8		32.2		63.7
Age at blood draw, years		64		64		63		64		65
Male sex	70.6		72.1		77.1		78.8		80.0	
Race/ethnicity										
White	91.2		93.6		94.0		98.1		95.1	
Black	0.7		1.9		1.5		0.9		2.7	
Asian	7.4		2.5		3.0		0.9		1.1	
Other	0.7		2.1		1.5		0		1.1	
Cigarette smoking history										
Never smoker	36.8		30.9		27.1		23.6		30.5	
Former smoker	19.8		22.9		30.7		34.2		29.1	
Current smoker	43.4		46.2		42.2		42.2		40.3	
Body mass index[c]										
<25	76.7		53.5		30.1		18.5		1.1	
25.0 to <30	23.3		42.7		56.1		54.9		43.1	
≥30	0		1.5		12.7		26.7		55.8	
Missing data	0		2.3		1.2		0		0	
Body mass index[c]		22.8		24.4		26.1		27.8		31.1
History of diabetes mellitus	4.9		7.2		5.0		3.9		16.5	
Daily intake, g										
Alcohol		12.7		12.0		14.3		10.5		10.7
Total fat		81.5		84.0		82.2		81.9		90.0
Saturated fat		31.1		31.3		29.9		30.7		34.5
C-peptide concentration, ng/mL										
Male		2.0		2.2		3.0		3.3		4.1
Female		2.1		2.1		3.3		3.6		3.7
Total adiponectin concentration, ng/mL										
Male		11,433		9,738		9,165		8,865		8,046
Female		16,438		17,290		14,810		13,814		14,545
TGF-β concentration, ng/mL										
Male		26.5		26.8		28.2		27.7		29.5
Female		29.2		29.5		29.2		31.0		31.4

Abbreviation: TGF-β, transforming growth factor β.

[a] Means and proportions standardized for cohort.

[b] Sex-specific quintiles were <2.9, 2.9 to <4.8, 4.8 to <7.2, 7.2 to <11.7, and ≥11.7 ng/mL for men and <10.8, 10.8 to <17.4, 17.4 to <26.6, 26.6 to <40.8, and ≥40.8 ng/mL for women. Generalized linear models adjusted for cohort were used to estimate the means for continuous variables. Direct adjustment for cohort was used to estimate the frequencies for proportions within each leptin quintile.

[c] Expressed as weight (kg)/height $(m)^2$.

suggestion of an inverse association during the first 5 years of follow-up (continuous odds ratio (OR) = 0.79, 95% confidence interval (CI): 0.61, 1.03), no apparent association during follow-up between 5 and 10 years (continuous OR = 1.12, 95% CI: 0.88, 1.41), and a positive association during follow-up occurring more than 10 years after baseline (continuous OR = 1.44, 95% CI: 1.11, 1.88). The *P* value for difference in association by follow-up time was 0.003 (calculated

Table 3. Odds Ratios and 95% Confidence Intervals for Leptin Concentration and Pancreatic Cancer by Follow-up Time in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985–2009), Cancer Prevention Study II Nutrition Cohort (1998–2006), and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (1992–2010)

	Follow-up Period[a]															
	Overall[b]				<5 Years				5 to <10 Years				≥10 Years[b]			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Total Population[c]																
Crude OR																
Q1[d]	149	181	1.00	Referent	45	52	1.00	Referent	45	53	1.00	Referent	59	76	1.00	Referent
Q2	138	181	0.96	0.70, 1.31	37	58	0.82	0.46, 1.48	43	55	0.98	0.55, 1.74	58	68	1.12	0.69, 1.81
Q3	137	183	0.96	0.70, 1.32	45	52	1.05	0.58, 1.90	44	69	0.79	0.45, 1.39	48	62	1.00	0.60, 1.68
Q4	160	181	1.17	0.86, 1.60	47	55	1.14	0.62, 2.07	49	81	0.76	0.45, 1.31	64	45	1.94	1.13, 3.33
Q5	147	183	1.06	0.78, 1.45	46	81	0.70	0.40, 1.22	47	61	1.01	0.58, 1.76	54	41	1.72	1.00, 2.94
P_{trend}[e]				0.60				0.10				0.69				0.03
Per SD[b,f]	731	909	1.03	0.93, 1.13	220	298	0.86	0.72, 1.04	228	319	1.04	0.87, 1.23	283	292	1.22	1.01, 1.47
Adjusted OR																
Q1[d]	149	181	1.00	Referent	45	52	1.00	Referent	45	53	1.00	Referent	59	76	1.00	Referent
Q2	138	181	0.95	0.68, 1.33	37	58	0.81	0.52, 2.12	43	55	0.98	0.52, 1.84	58	68	1.16	0.69, 1.95
Q3	137	183	0.98	0.68, 1.40	45	52	1.05	0.52, 2.12	44	69	0.77	0.40, 1.47	48	62	1.05	0.58, 1.90
Q4	160	181	1.20	0.84, 1.74	47	55	1.16	0.56, 2.40	49	81	0.77	0.40, 1.49	64	45	2.21	1.18, 4.13
Q5	147	183	1.13	0.75, 1.71	46	81	0.65	0.30, 1.39	47	61	1.08	0.50, 2.33	54	41	2.55	1.23, 5.27
P_{trend}[e]				0.38				0.07				0.36				0.004
Per SD[b,f]	731	909	1.06	0.93, 1.22	220	298	0.79	0.61, 1.03	228	319	1.12	0.88, 1.42	283	292	1.44	1.11, 1.88
ATBC Cohort																
Crude OR																
Q1[d]	87	91	1.00	Referent	22	14	1.00	Referent	23	16	1.00	Referent	42	61	1.00	Referent
Q2	75	86	0.93	0.61, 1.43	14	18	0.51	0.18, 1.44	18	14	0.90	0.33, 2.46	43	54	1.24	0.71, 2.17
Q3	60	65	0.99	0.62, 1.57	12	13	0.58	0.19, 1.81	13	12	0.77	0.28, 2.17	35	40	1.39	0.75, 2.58
Q4	74	57	1.40	0.88, 2.23	11	13	0.59	0.18, 1.94	16	16	0.80	0.31, 2.03	47	28	2.75	1.42, 5.31
Q5	56	53	1.13	0.69, 1.85	10	11	0.56	0.17, 1.85	4	16	0.18	0.05, 0.70	42	26	2.62	1.33, 5.19
P_{trend}[e]				0.29				0.65				0.01				0.006
Per SD[b,f]	352	352	1.09	0.93, 1.29	69	69	0.89	0.55, 1.46	74	74	0.59	0.37, 0.94	209	209	1.35	1.07, 1.71
Adjusted OR																
Q1[d]	87	91	1.00	Referent	22	14	1.00	Referent	23	16	1.00	Referent	42	61	1.00	Referent
Q2	75	86	0.89	0.57, 1.40	14	18	0.35	0.08, 1.41	18	14	0.81	0.28, 2.34	43	54	1.32	0.72, 2.42
Q3	60	65	0.95	0.57, 1.59	12	13	0.37	0.09, 1.65	13	12	0.61	0.19, 2.01	35	40	1.47	0.72, 2.98
Q4	74	57	1.50	0.87, 2.59	11	13	0.54	0.11, 2.71	16	16	0.62	0.18, 2.14	47	28	3.20	1.48, 6.94
Q5	56	53	1.33	0.70, 2.52	10	11	0.39	0.07, 2.08	4	16	0.13	0.02, 0.70	42	26	4.71	1.80, 12.3
P_{trend}[e]				0.15				0.69				0.006				0.001
Per SD[b,f]	352	352	1.18	0.94, 1.49	69	69	0.87	0.43, 1.75	74	74	0.41	0.21, 0.83	209	209	1.67	1.19, 2.35

Table continues

Table 3. Continued

	Follow-up Period[a]															
	Overall[b]				<5 Years				5 to <10 Years				≥10 Years[b]			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
								PLCO/CPS-II[g]								
Crude OR																
Q1[d]	62	90	1.00	Referent	23	38	1.00	Referent	22	37	1.00	Referent	17	15	1.00	Referent
Q2	63	95	0.99	0.63, 1.57	23	40	1.07	0.51, 2.23	25	41	1.09	0.51, 2.29	15	14	0.85	0.31, 2.35
Q3	77	118	0.93	0.60, 1.44	33	39	1.40	0.68, 2.86	31	57	0.89	0.44, 1.81	13	22	0.49	0.17, 1.36
Q4	86	124	1.03	0.66, 1.59	36	42	1.51	0.73, 3.10	33	65	0.84	0.42, 1.69	17	17	0.86	0.31, 2.36
Q5	91	130	1.01	0.67, 1.52	36	70	0.82	0.43, 1.58	43	45	1.64	0.83, 3.24	12	15	0.76	0.30, 1.97
P_{trend}[e]				0.94			0.12					0.08				0.62
Per SD[b,f]	379	557	1.09	0.93, 1.29	151	229	0.86	0.70, 1.04	154	245	1.19	0.98, 1.45	74	83	0.91	0.61, 1.34
Adjusted OR																
Q1[d]	62	90	1.00	Referent	23	38	1.00	Referent	22	37	1.00	Referent	17	15	1.00	Referent
Q2	63	95	1.07	0.65, 1.78	23	40	1.27	0.55, 2.94	25	41	1.22	0.52, 2.85	15	14	1.08	0.31, 3.75
Q3	77	118	1.02	0.61, 1.71	33	39	1.67	0.71, 3.89	31	57	0.99	0.42, 2.35	13	22	0.49	0.13, 1.86
Q4	86	124	1.13	0.67, 1.89	36	42	1.71	0.71, 4.14	33	65	1.00	0.42, 2.37	17	17	1.59	0.45, 5.67
Q5	91	130	1.08	0.62, 1.90	36	70	0.80	0.32, 2.00	43	45	2.39	0.87, 6.56	12	15	1.45	0.38, 5.58
P_{trend}[e]				0.81				0.04				0.03				0.54
Per SD[b,f]	379	557	1.02	0.86, 1.22	151	229	0.75	0.56, 1.00	154	245	1.36	1.03, 1.81	74	83	1.20	0.68, 2.11

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; CPS-II, Cancer Prevention Study Nutrition Cohort; OR, odds ratio; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; Q, quintile; SD, standard deviation.

[a] *P* value for interaction with follow-up time (continuous measure) in overall models was 0.003. *P* value was based on a −2 log-likelihood test using a continuous leptin measure.

[b] $P_{heterogeneity}$ by cohort was 0.87 overall and 0.12 for >10 years. $P_{heterogeneity}$ was based on a −2 log-likelihood test with 2 df comparing a model with an interaction term for cohort and continuous leptin with a model without any interaction term.

[c] Conditional logistic regression. Crude models were conditioned on age, sex, race, cohort, and date of blood draw. Multivariable model was additionally adjusted for age, smoking, body mass index (8 categories), and diabetes.

[d] Sex-specific quintiles were <2.89, 2.89 to <4.80, 4.80 to <7.22, 7.22 to <11.67, and ≥11.67 ng/mL for men and <10.82, 10.82 to <17.43, 17.43 to <26.55, 26.55 to <40.78, and ≥40.78 ng/mL for women.

[e] P_{trend} was based on a −2 log-likelihood test comparing a model with a continuous leptin measure (standard deviation) with a model without a continuous measure.

[f] Standard deviations were 7.34 ng/mL for men and 23.12 ng/mL for women.

[g] Analyses combine the 2 US cohorts (PLCO and CPS-II) that were similar in demographics and calendar era.

Table 4. Odds Ratios and 95% Confidence Intervals for Leptin Concentration and Pancreatic Cancer by Body Mass Index and Follow-up Time in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (1985–2009), Cancer Prevention Study II Nutrition Cohort (1998–2006), and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (1992–2010)

	Follow-up Period[a]															
	Overall[b]				<5 Years				5 to <10 Years				≥10 Years[b]			
	Cases	Controls	OR[c]	95% CI	Cases	Controls	OR[c]	95% CI	Cases	Controls	OR[c]	95% CI	Cases	Controls	OR[c]	95% CI
BMI <25[d]																
Q1[e]	117	138	1.00	Referent	36	41	1.00	Referent	38	39	1.00	Referent	43	58	1.00	Referent
Q2	64	95	0.82	0.54, 1.25	19	28	0.82	0.36, 1.87	21	36	0.63	0.30, 1.30	24	31	1.03	0.52, 2.04
Q3	46	55	1.15	0.70, 1.88	17	17	1.35	0.54, 3.35	13	23	0.66	0.28, 1.57	16	15	1.37	0.58, 3.22
Q4	28	34	1.04	0.58, 1.88	12	7	2.11	0.64, 6.90	6	21	0.31	0.11, 0.91	10	6	2.23	0.74, 6.74
Q5	9	3	3.52	0.89, 13.9	4	2	2.23	0.34, 14.7	1	1	0.96	0.05, 19.4	4	0		
P_{trend}[f]				0.22				0.10				0.03				0.005
Per SD[b,g]	264	325	1.27	0.87, 1.86	88	95	1.83	0.87, 3.84	79	120	0.42	0.18, 0.99	97	110	2.96	1.35, 6.50
BMI ≥25[d]																
Q1[e]	32	43	1.00	Referent	9	11	1.00	Referent	7	14	1.00	Referent	16	18	1.00	Referent
Q2	74	83	1.15	0.66, 2.02	18	27	0.74	0.25, 2.20	22	19	2.59	0.84, 7.94	34	37	1.00	0.43, 2.31
Q3	91	126	1.02	0.59, 1.74	28	35	0.92	0.32, 2.60	31	45	1.62	0.57, 4.64	32	46	0.80	0.35, 1.83
Q4	130	147	1.29	0.76, 2.18	35	48	0.90	0.32, 2.49	42	60	1.54	0.55, 4.33	53	39	1.69	0.75, 3.84
Q5	138	180	1.08	0.62, 1.86	42	79	0.51	0.18, 1.43	46	60	1.83	0.64, 5.28	50	41	1.50	0.64, 3.51
P_{trend}[f]				0.94				0.02				0.31				0.27
Per SD[b,g]	465	579	0.99	0.87, 1.13	132	200	0.74	0.57, 0.96	148	198	1.13	0.89, 1.44	185	181	1.13	0.91, 1.41

Abbreviations: BMI, body mass index; CI, confidence interval; Q, quintile; SD, standard deviation.

[a] *P* value was based on a −2 log-likelihood test using a continuous leptin measure.

[b] $P_{heterogeneity}$ was based on a −2 log-likelihood test with 2 df comparing a model with an interaction term for categorical BMI and continuous leptin with a model without any interaction term. $P_{heterogeneity}$ was not significant overall or during follow-up of <10 years ($P > 0.05$); however, $P_{heterogeneity}$ at >10 years = 0.03.

[c] Odds ratios were adjusted for age, sex, race, cohort, date of blood draw, smoking (never, current, former), body mass index (8 categories), and diabetes. Unconditional logistic regression.

[d] Expressed as weight (kg)/height $(m)^2$.

[e] Sex-specific quintiles were <2.89, 2.89 to <4.80, 4.80 to <7.22, 7.22 to <11.67, and ≥11.67 ng/mL for men and <10.82, 10.82 to <17.43, 17.43 to <26.55, 26.55 to <40.78, and ≥40.78 ng/mL for women.

[f] P_{trend} was based on a −2 log-likelihood test comparing a model with a continuous leptin measure (standard deviation) with a model without a continuous measure.

[g] Standard deviations were 7.34 ng/mL for men and 23.12 ng/mL for women.

on the basis of continuous terms for both follow-up time and leptin concentration).

Because the overall associations between leptin and pancreatic cancer risk were limited to follow-up after 10 years, we conducted further sensitivity and interaction analyses focused on this time period. Adjustment for body mass index strengthened the association; that is, for models without body mass index (quintile 4 and quintile 5 vs. quintile 1: OR = 2.09, 95% CI: 1.20, 3.62 and OR = 1.84, 95% CI: 1.06, 3.20; $P_{trend} = 0.03$) and for continuous body mass index (OR = 1.24, 95% CI: 1.02, 1.50). Additional adjustment for C-peptide slightly increased the significance of the association (quintile 5 vs. quintile 1: OR = 3.25, 95% CI: 1.50, 7.05; $P_{trend} = 0.001$) and for continuous C-peptide (OR = 1.57, 95% CI: 1.18, 2.09), while adjustment for total adiponectin or transforming growth factor β1 did not change the association (data not shown).

There were no significant interactions by study, sex, age, smoking status, body mass index, or history of diabetes. Positive associations were strongest during follow-up 5–10 years for the CPS-II/PLCO participants (continuous OR = 1.36, 95% CI: 1.03, 1.81) and during follow-up more than 10 years for the ATBC participants (continuous OR = 1.67, 95% CI: 1.19, 2.35) (Table 4), men (continuous OR = 1.53, 95% CI: 1.15, 2.04), and current smokers (continuous OR = 1.25, 95% CI: 0.98, 1.60) (Web Table 1 available at http://aje.oxfordjournals.org/). Among cases that occurred more than 10 years after baseline, associations were stronger among participants with a body mass index of less than 25 (continuous OR = 2.96, 95% CI: 1.35, 6.50) than among those with a body mass index of ≥25 (continuous OR = 1.13, 95% CI: 0.91, 1.41; $P_{heterogeneity} = 0.03$).

DISCUSSION

This pooled, nested case-control study from 3 cohorts of middle-aged and older adults showed that higher prediagnostic circulating leptin concentrations were associated with an increased pancreatic cancer risk among those with longer follow-up. In particular, a statistically significant greater than 2-fold risk for pancreatic cancer was observed among participants in the top 2 quintiles compared with those in the lowest quintile for those who developed pancreatic cancer 10 or more years after blood collection. The positive association was present in all cohorts and was independent of race, sex, smoking history, body mass index, and diabetes. To the best of our knowledge, this is the first prospective epidemiologic study that has examined prediagnostic leptin and subsequent pancreatic cancer development.

The absence of a positive association between leptin and pancreatic cancer during the earlier years of follow-up may be explained by reverse causation. Pancreatic cancer is most often diagnosed at advanced stages with metastasis to distant organs and is preceded by significant weight loss which could affect circulating leptin concentrations. Even relatively modest weight loss has been shown to substantially reduce blood leptin levels (27). Four small clinic–based case-control studies and 1 case series have demonstrated that prevalent pancreatic cancer cases have lower leptin concentrations than do noncases (28–32). One of these studies examined results by stage at diagnosis and found that leptin concentrations were lower among cases with distant metastasis than among cases with local disease (30). Consistent with the results of these case-control studies, our results included some suggestion of an association between lower leptin concentrations and higher risk of a pancreatic cancer diagnosis within 5 years of blood collection overall and among the ATBC participants diagnosed less than 10 years after blood collection. Alternatively, there might be processes independent of body mass index related to latent pancreatic cancer that could explain our observations.

There are biologically plausible reasons why higher leptin concentrations may be associated with risk of pancreatic cancer. First, serum leptin could directly influence pancreatic carcinogenesis. Leptin can promote tumor vascularization, as well as the proliferation, migration, and invasion of tumor cells (17). In rodent models, obesity both promotes pancreatic carcinogenesis (33–36) and increases leptin concentrations, although obesity-related changes in other adipocytokines and growth factors have also been reported (33, 34). Notably, in a hamster model of pancreatic carcinogenesis, diet-induced obesity resulted in fatty infiltration of the pancreas, greater leptin expression in pancreatic tissue, 2-fold higher serum leptin concentrations, and a significant increase in the number of pancreatic tumors (36). Recently, fatty pancreas infiltration has been associated with central adiposity (37, 38), as well as pancreatic cancer (39) in humans, although to the best of our knowledge leptin expression has not been quantified in the pancreas. Alternatively, serum leptin concentration may be a more sensitive marker for intra-abdominal or visceral adiposity compared with body mass index and even independent of body mass index (40). With aging, body composition changes, such that muscle mass decreases while total fat mass and intra-abdominal or visceral fat stores increase, although body mass index may stay the same or even decrease (41). Given the older age of our study participants, this may help to explain why we observe stronger associations between leptin and risk of pancreatic cancer in participants with a body mass index of less than 25 with longer follow-up. Additionally, in middle-aged and older adults the distribution of white adipose shifts from subcutaneous to visceral fat stores (15). This shift contributes to greater cytokine production, insulin insensitivity, glucose intolerance, and leptin resistance (15). Intra-abdominal adiposity may be particularly relevant for pancreatic carcinogenesis, given the proximity of the pancreas to visceral adipose tissue (42), the greater potential for fatty pancreas infiltration (37, 38), and possibly lipotoxicity. Waist circumference and the waist:hip ratio, indicators of intra-abdominal fat, are positively and linearly associated with risk of pancreatic cancer (43).

In our study, the association between leptin and pancreatic cancer was apparent among smokers during follow-up occurring 10 or more years after blood draw. This contrasts with epidemiologic studies of body mass index and pancreatic cancer that generally report positive associations among nonsmokers but little or no association among smokers (43, 44). One possible explanation is that leptin may be more strongly correlated than body mass index is with intra-abdominal adiposity, particularly among smokers. Cigarette smoking has been associated with greater intra-abdominal adiposity as characterized by the waist and waist:hip ratio, independent of body mass index (45, 46). In addition, heavy smoking has been associated with intra-abdominal fat, but not subcutaneous fat, as quantified by X-ray computed tomography scans and

independent of age, physical activity, and alcohol intake (45). Significant positive associations were also observed between leptin and pancreatic cancer among PLCO/CPS-II participants (who are mostly nonsmokers) and never smokers during lesser follow-up times (Web Table 1).

Important strengths of our study include its prospective nested case-control design. As the cases and controls are from the same cohorts, our study has internal validity and no control selection bias. In addition, our study included a large number of pancreatic cancer cases occurring over a wide range of follow-up time, allowing us to detect differences in associations between the early years of follow-up, when reverse causation is plausible, and later follow-up, when it is less likely. Our case definition includes confirmed pancreatic adenocarcinoma cases, reducing the potential of misclassification of the outcome. Our study also has some limitations. A single measurement of leptin in adulthood may not represent long-term leptin concentrations, and changes in diet, smoking, and weight during follow-up were not measured and could influence the risk estimates. The influence of fasting status on our study results is unclear. Overnight fasting lowers leptin concentrations (47) and may have contributed to differences in median leptin levels between cohorts. At the time of blood draw, all ATBC participants, some PLCO participants, and few, if any, CPS-II participants were fasting.

Some PLCO participants were likely fasting at the time of blood draw in preparation for the colonoscopy scheduled the same day, but we are unable to determine which participants were fasting. It is possible that variation in fasting time attenuated results somewhat in PLCO and CPS-II. However, the association between leptin and pancreatic cancer risk did not vary significantly ($P_{\text{heterogeneity}} = 0.66$) between ATBC and PLCO/CPS-II. Of note, significant continuous associations and trends were observed in the PLCO/CPS-II participants during follow-up 5 to <10 years after their baseline blood collection. A smaller number of cases (74 in PLCO/CPS-II vs. 209 in ATBC) and inadequate power might also explain the nonsignificant positive associations observed in the PLCO/CPS-II participants with follow-up 10 years or more. Residual confounding by cigarette smoking is possible; however, there was no significant interaction of our association by smoking status, and positive associations were observed among never, former, and current smokers. Finally, our results may be generalizable to middle-aged and older Caucasian populations but not necessarily to other ethnic groups.

In conclusion, our results support an association between serum leptin concentration and higher risk of pancreatic cancer, although this association may be obscured by reverse causation during early years of follow-up. Our findings are relevant given the obesity and diabetes epidemics and could potentially have preventive implications along with other adipokines associated with pancreatic cancer (22, 25). Additional research is needed to confirm the association between serum leptin concentration and risk of pancreatic cancer and to clarify the underlying potential biological mechanisms.

ACKNOWLEDGMENTS

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This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, the Extramural Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute, and the American Cancer Society. Additionally, this research was supported by US Public Health Service contracts N01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN261201000006C from the National Cancer Institute, Department of Health and Human Services.

Conflict of interest: none declared.

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