Serum C-Reactive Protein and Risk of Pancreatic Cancer in Two Nested, Case–Control Studies

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Abstract

Background: Many epidemiologic studies have examined the association between C-reactive protein (CRP) and risk of cancer with inconsistent results.

Methods: We conducted two nested, case–control studies in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) to test whether prediagnostic circulating CRP concentrations were associated with pancreatic adenocarcinoma. Between 1985 and 2004, 311 cases occurred in ATBC and between 1994 and 2006, 182 cases occurred in PLCO. Controls ($n = 510$ in ATBC, $n = 374$ in PLCO) were alive at the time the case was diagnosed and were matched by age, date of blood draw, sex, and race. We used conditional logistic regression adjusted for smoking to calculate OR and 95% CI for pancreatic cancer.

Results: CRP concentrations (ng/mL) tended to be inversely or not associated with pancreatic cancer risk in ATBC, PLCO, and combined analyses [per standardized quintile increase in CRP, continuous OR = 0.94 (95% CI, 0.89–0.99), OR = 0.99 (95% CI, 0.95–1.04), OR = 0.98 (95% CI, 0.95–1.01), respectively]. In combined analyses, we observed a significant interaction ($P_{\text{interaction}} = 0.02$) such that inverse associations were suggestive in younger (OR = 0.95; 95% CI, 0.90–1.01), but not older, participants.

Conclusion: Our results do not support the hypothesis that higher CRP concentrations are associated with incident pancreatic cancer.

Impact: Our results highlight the importance of investigating more specific biomarkers for inflammation that may reflect the biological mechanisms underlying pancreatic cancer in prospective cohort studies. *Cancer*

Introduction

Since Rudolf Virchow suggested in 1863 that cancer originated at sites of chronic inflammation, there has been increasing evidence that inflammation plays a key role in the pathogenesis of a number of cancers (1–7). Though acute inflammatory responses create a protective tissue microenvironment to recognize and repair cell damage, persistent inflammation may promote tumor formation (1, 2). However, epidemiologic data linking inflammation to cancer risk are relatively sparse.

Cytokines, inflammatory cells, and chemokines have an intricate involvement in carcinogenesis as they stimulate the proliferation and apoptosis of cancer cells (8). C-reactive protein (CRP) is an acute-phase protein produced in the liver and induced by interleukin-6 (IL-6), IL-1, and TNF-α (3, 4, 9). Production of CRP increases within 4 to 6 hours of inflammation, doubling every 8 hours thereafter, and peaks between 36 and 50 hours (9). A few epidemiologic studies have reported associations between CRP and risk of cancer, particularly colorectal cancer (3, 10–12). One relatively small study ($n = 14$ cases) reported a nonsignificant positive association between CRP and pancreatic cancer (13). In addition, previous pancreatic cancer research suggests that CRP correlates inversely with patient survival (14, 15).

We investigated whether serum CRP concentration is associated with pancreatic cancer risk. In accordance with the results from other cancer sites, we hypothesized that higher CRP concentration is associated with increased pancreatic cancer risk. We examined this hypothesis in 2 case–control studies nested within 2 cohorts, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) cohort and the Prostate, Lung, Colorectal,

and Ovarian Cancer Screening Trial (PLCO). To our knowledge, this is among the first studies evaluating the association between CRP and incident pancreatic cancer risk based on cohort data.

Materials and Methods

ATBC study population

The ATBC study tested whether α-tocopherol or β-carotene reduced cancer incidence in Finnish male smokers. The study was a double-blind, placebo-controlled, 2 × 2 factorial-design primary intervention trial. The methods have been described previously (16). Briefly, between 1985 and 1988, 29,133 eligible men ages 50 to 69 years in southwestern Finland who smoked at least 5 cigarettes per day were randomized to receive active supplements or placebo. Subjects 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. Also, subjects using supplements containing vitamin E (>20 mg/day), vitamin A (>20,000 IU/day), or β-carotene (>6 mg/day) were excluded. Written consent was provided by all study participants prior to randomization. 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 their prerandomization baseline visit, the men completed questionnaires on medical history, smoking habits, dietary intake, and physical activity (16). Trained study staff measured height and weight at baseline using standard methods. Validated self-administered dietary history questionnaires 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 (17).

PLCO study population

The PLCO screening trial is a randomized multicenter trial in the United States (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC) that has been previously described in detail (18). It sought to determine the effectiveness of early detection procedures for prostate, lung, colorectal, and ovarian cancers on disease-specific mortality. Study recruitment and randomization began in November 1993 and was completed in July 2001. The study cohort had 152,810 men and women ages 55 to 74 years old at baseline. Exclusion criteria included subjects with a history of 1 of the 4 PLCO cancers or those currently undergoing treatment for any cancer, except nonmelanoma of the skin, and those screened for prostate or colorectal cancer during the past 3 years. Participants were randomized to either an intervention arm or the control arm. The intervention arm participants had periodic cancer screening tests, which included prostate specific antigen (PSA) and digital rectal exams (men), chest X-ray, flexible sigmoidoscopy, or cancer antigen 125 and transvaginal ultrasound (women). Those in the control arm followed their usual medical care. Informed consent was obtained by all participants. The study was approved by the institutional review boards of all 10 screening centers and that of the U.S. National Cancer Institute.

The study participants completed self-administered questionnaires that queried information on dietary intake, medical history, family history of cancer, tobacco use, height, weight, physical activity, and other exposures. Diet was assessed using a food frequency questionnaire, which used a grid format to determine the frequency of 137 food items over the past 12 months, 77 of which inquired about usual portion size (19).

ATBC and PLCO case and control selection

Details about the nested case–control sets used in this study have been published previously (20–22). Cases included incident primary pancreatic adenocarcinomas [*International Classification of Diseases*, *Ninth Revision* (*ICD-9*), code 157 or ICD-O-3 code C250-C259 or C25.0-C25.3, C25.7-C25.9] for the ATBC and PLCO studies, respectively. Endocrine pancreatic tumors (157.7 or C25.4, histology type, 8150, 8151, 8153, 8155, 8240) were excluded because the etiology of these cancers is thought to be different. ATBC study cases were identified through the linkage to the Finnish Cancer Registry, which provides complete case ascertainment in Finland (23), whereas PLCO pancreatic cancer cases were identified by self-report in the annual mail-in survey, state cancer registries, death certificates, physician referrals, and reports of next of kin for deceased individuals. In the ATBC cohort, 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 9.4 years). For the PLCO cohort, we identified 182 exocrine pancreatic cancer cases between 1994 and 2006 (followed up to 11.7 years; median, 5.4 years). In total, 74.5% of the ATBC cases and 92.5% of the PLCO cases were confirmed through medical review. In sensitivity analyses, results were similar when the nonconfirmed cases were excluded; therefore, all cases were included to increase statistical power.

Controls were selected with a control to case ratio of 2:1 (ATBC, PLCO) and 1:1 for the ATBC cases identified during later follow-up (21). All controls were alive and free from pancreatic cancer on the date the matched case was diagnosed. Controls were matched to cases on age (±5 years), date of blood draw (± 30 days for ATBC and within 2 month blocks for PLCO), sex (PLCO), and race (PLCO).

Measurement of serum C-reactive protein

At the prerandomization visit, overnight fasting (ATBC) or nonfasting (PLCO) serum samples were obtained from study participants and stored at −70°C.

The ATBC and PLCO frozen serum samples were collected at different times (December 2006 and February 2009, respectively). CRP concentrations were measured by Dr. Michael Pollak's laboratory (The Lady Davis Institute for Medical Research in Montreal, Quebec, Canada) using ELISA with reagents from Beckman Coulter, Diagnostic Systems Laboratory in 2007 and 2009 for ATBC and PLCO, respectively. Case and control samples within their respective cohorts were handled in a similar manner and were laboratory blinded to case–control status. Matched samples were analyzed consecutively as triplets within batches and blinded replicate pooled quality control samples were placed in triplicate toward the beginning and end of each batch and comprised 10% of each batch. Using a variance components estimation procedure, with logarithmically transformed quality control measurements across all batches (24), the estimated overall (intrabatch and interbatch) coefficient of variation were 9.6% for ATBC and 7.9% for PLCO.

Statistical analysis

The distributions of selected characteristics of cases and controls for each cohort were compared using the Wilcoxon rank sum test for the continuous variables and χ^2 tests for categorical variables (Tables 1 and 2). Body mass index [BMI: weight (kg)/height $(m)^2$] was calculated from measured weight and height. Potential confounders were also identified by calculating means using generalized linear models and proportions using frequencies of baseline characteristics among the controls across CRP quintiles (Table 3). Potential confounders examined in the analyses were age; education; baseline height, weight, BMI; history of diabetes and family history of pancreatic cancer; dietary nutrients from foods (energy, carbohydrate, fat, saturated fat, protein); red meat; alcohol intake; and physical activity. BMI was categorized to be consistent with the WHO obesity classifications as less than 25 (normal), 25 to 30 (overweight), and 30 kg/m^2 or more (obese; ref. 25). Foods were energy adjusted using the residual method described by Willett and Stampfer (26). In ATBC, we examined cigarette smoking habits (number of years smoked and number of cigarettes smoked per day) and occupational and leisure activity. In PLCO, we investigated smoking status (never, former, current), history (number of cigarettes smoked per day, number of years smoked, pack-years, smoking cessation), and leisure physical activity.

Conditional logistic regression was used to estimate OR for pancreatic cancer, with the lowest quintile serving as the reference category. Linear tests for trend were based on a continuous variable, and the continuous CRP OR were standardized to the average size of the 3 central quintiles. Multivariable models were developed by individually entering potentially confounding variables into the model using both forward and backward methods. Confounders were defined as variables, which changed the risk estimates by more than 10%. No variables met these criteria; however, because smoking is the primary risk factor for pancreatic cancer (27), we adjusted for smoking (duration and intensity) for ATBC, and never, former quit 15 years or more ago, former quit less than 15 years ago, and current for PLCO. We present data separately for each cohort, and as there was no significant interaction by cohort ($P = 0.16$); we combined data from both cohorts by creating quintiles based on the controls from both studies. We also created cohort-specific cut-points based on the control cut-points from each study. For the cohort-specific cut-point analyses we used a score variable to calculate the trend.

Effect modification by age, BMI, and smoking intensity and duration was evaluated with cross-product terms composed of continuous CRP and dichotomized (median split) effect modifier variables in multivariable models, and in stratified analyses. We used unconditional logistic regression in stratified analyses adjusting for the matching variables and confounders. We also stratified our analyses *a priori* by follow-up year of case diagnosis (e.g., <5 years, ≥5 years, ≥10 years after baseline) to assess the potential impact of reverse causation.

All statistical analyses were performed using SAS software (SAS Institute Inc.), and statistical tests were 2-sided.

Results

Tables 1 and 2 show the baseline characteristics of the cases and controls for the ATBC and PLCO cohorts, respectively. Cases and controls tended to have similar baseline characteristics (Tables 1–2). In ATBC, compared to controls, cases had a significantly lower CRP concentrations ($P = 0.03$), and greater height ($P = 0.04$), total fat ($P = 0.04$), and red meat intake ($P = 0.01$); and tended to be more educated ($P = 0.02$). In PLCO, compared to controls, cases were more likely to be current smokers ($P < 0.0001$) and had lower carbohydrate ($P = 0.02$), energy ($P = 0.05$), and protein intake ($P = 0.05$).

Table 3 shows the mean or proportion of selected characteristics among control participants according to quintile of CRP concentration in the ATBC and PLCO studies, respectively. Higher CRP concentrations were directly associated with increasing BMI, obesity, and less vigorous (PLCO) or more sedentary (ATBC) leisure activity, and inversely associated with normal BMI and exercising to keep fit (ATBC) or more vigorous activity (PLCO). In the ATBC controls, higher CRP concentrations were positively associated with not working ($P = 0.04$). In PLCO, higher CRP concentrations were associated with current smoking ($P = 0.01$) and a medical history of diabetes ($P = 0.001$).

Table 4 shows the main effects for the association between CRP and pancreatic cancer in the ATBC, PLCO, and combined nested case–control set. In ATBC, higher concentrations of CRP tended to be inversely associated with pancreatic cancer [high compared to low quintile, OR = 0.71 (95% CI, 0.44–1.16), $P_{trend} = 0.03$; continuous OR = 0.94 (95% CI, 0.89–0.99)]. The inverse association

Table 1. Selected baseline characteristics of case and cohort control subjects (median and interdecile range or number and proportion) in the ATBC study, 1985–1988

Characteristics	Cases ($n = 311$)	Controls ($n = 510$)	P[a]
CRP, ng/mL	4.5 (2.1–8.9)	5.4 (2.4–12.3)	0.03
Age, y	58.0 (55.0–62.0)	58.0 (55.0–62.0)	0.73
Smoking history			
Total cigarettes per day	20.0 (15.0–25.0)	20.0 (15.0–25.0)	0.56
Years smoked, y	39.0 (32.0–43.0)	39.0 (34.0–43.0)	0.84
Height, cm	173 (166–182)	173 (165–180)	0.04
BMI, kg/m^2	25.8 (23.7–28.0)	26.1 (23.8–28.7)	0.25
BMI—WHO cut points, *n* (%)			
<25.0 (normal weight)	121 (38.9)	189 (37.1)	0.87
≥25.0 and <30.0 (overweight)	139 (44.7)	236 (46.3)	
≥30.0 (obese)	51 (16.4)	85 (16.6)	
Self-reported diabetes mellitus, *n* (%)	22 (7.1)	31 (6.1)	0.57
Education, *n* (%)			
Less than elementary school	12 (3.9)	31 (6.1)	0.02
Elementary school	228 (73.3)	385 (75.5)	
Some junior high school	15 (4.8)	27 (5.3)	
Junior high school graduate	19 (6.1)	40 (7.8)	
Some senior high school	9 (2.9)	6 (1.2)	
Senior high school graduate	28 (9.0)	21 (4.1)	
Living in city, *n* (%)	139 (44.7)	220 (43.1)	0.66
Dietary intake per day[b]			
Red meat, g	23.1 (7.3–49.5)	19.1 (6.0–46.0)	0.01
Alcohol, g	9.1 (2.1–24.2)	10.7 (2.8–26.2)	0.40
Energy, kcal	2,704 (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	50.5 (38.4–64.2)	49.4 (35.3–65.0)	0.34
Carbohydrate, g	287.6 (232.9–356.3)	299.3 (228.6–354.2)	0.51
Protein, g	102.1 (86.8–119.0)	103.2 (85.3–120.5)	0.11
Physical activity, *n* (%)			
Occupational			
Sedentary	50 (16.1)	50 (9.8)	0.10
Moderate	91 (29.3)	141 (27.7)	
Heavy	19 (6.1)	41 (8.0)	
Nonworking	151 (48.5)	278 (54.5)	
Leisure[c]			
Sedentary	128 (41.3)	231 (45.3)	0.66
Light, moderate	164 (52.9)	245 (48.0)	
Exercise to keep fit	18 (5.8)	34 (6.7)	

[a]*P* values for categorical variables based on χ^2 or Fisher's exact test and *P* values for continuous variables based on the Wilcoxon rank sum test.
[b]All foods and nutrients energy adjusted except alcohol and based on $n = 300$ cases and $n = 473$ controls.
[c]Leisure activity variables based on $n = 507$ controls and $n = 310$ cases.

remained when we excluded cases that occurred earlier during follow-up [i.e., high compared to low quintile CRP, cases occurring ≥ 5 years OR = 0.71 (95% CI, 0.41–1.23), $P_{trend} = 0.05$; continuous OR = 0.92 (95% CI, 0.86–0.99); and ≥ 10 years OR = 0.57 (95% CI, 0.26–1.22), $P_{trend} = 0.03$; continuous OR = 0.93 (95% CI, 0.85–1.01)]. In PLCO, higher concentrations of CRP were not significantly associated with pancreatic cancer risk [high compared to low quintile, OR = 0.84 (95% CI, 0.41–1.74), $P_{trend} = 0.79$; continuous OR = 0.99 (95% CI, 0.95–1.04)]. There was no association when early cases were excluded [high compared to low quintile, ≥5 years smoking-adjusted OR = 0.97 (95% CI, 0.90–1.05), $P_{trend} = 0.41$]. However, we observed a nonsignificant positive association for longer follow-up [high compared to low quintile, ≥8 years smoking-adjusted OR = 1.24 (95% CI, 0.92–1.66),

Table 2. Selected baseline characteristics of case and cohort control subjects (median and interdecile range or number and proportion) in PLCO, 1993–2001

Characteristics	Cases ($n = 182$)	Controls ($n = 364$)	P^a
CRP, ng/mL	9.3 (1.1–18.6)	8.8 (0.8–16.7)	0.11
Age, y	66.0 (61.0–69.0)	66.0 (61.0–69.0)	0.83
Sex, male, *n* (%)	121 (64.7)	242 (64.7)	1.00
Race, *n* (%)			
White	169 (90.4)	338 (90.4)	1.00
Black	6 (3.2)	12 (3.2)	
Hispanic	3 (1.6)	6 (1.6)	
Asian	9 (4.8)	18 (4.8)	
Smoking status, *n* (%)			
Never	72 (38.5)	174 (46.5)	<0.0001
Former quit ≥15 years	48 (25.7)	112 (30.0)	
Former quit <15 years	31 (16.6)	62 (16.6)	
Current	36 (19.2)	26 (6.9)	
Height, cm			
Male	177.1 (167.6–185.4)	177.1 (170.2–185.4)	0.74
Female	162.0 (152.4–170.2)	162.5 (154.9–170.2)	0.69
BMI, kg/m^2	26.7 (24.3–29.9)	26.5 (23.9–29.1)	0.18
BMI—WHO cut points, *n* (%)			
<25.0 (normal weight)	57 (30.5)	133 (35.6)	0.29
≥25.0 and <30 (overweight)	84 (44.9)	168 (44.9)	
≥30 (obese)	46 (24.6)	73 (19.5)	
Self-reported diabetes mellitus, *n* (%)	22 (12.2)	36 (9.9)	0.40
Family history of pancreatic cancer, *n* (%)	7 (3.8)	8 (2.2)	0.27
Education, *n* (%)			
Less than high school	14 (7.5)	39 (10.4)	0.50
High school graduate	48 (25.7)	86 (23.0)	
Post-high school, vocational training	22 (11.8)	41 (11.0)	
Some college	38 (20.2)	67 (17.9)	
College graduate	37 (19.8)	65 (17.4)	
Post-college graduate	28 (15.0)	76 (20.3)	
Dietary intake per day[b]			
Red meat, g	55.8 (31.7–96.5)	61.3 (33.1–102.9	0.38
Alcohol, g	1.4 (0.3–9.4)	0.9 (0.3–9.0)	0.60
Energy, kcal	1,819 (1,495–2,278)	1,976 (1,480–2,626)	0.05
Total fat, g	61.3 (41.0–77.9)	63.1 (45.2–90.8)	0.07
Saturated fat, g	20.4 (13.4–26.4)	21.0 (14.8–30.4)	0.07
Carbohydrate, g	247.5 (186.5–308.2)	265.8 (204.7–346.0)	0.02
Protein, g	72.9 (55.1–90.0)	77.3 (57.3–101.1)	0.05
Vigorous physical activity, hours per week,[c] *n* (%)			
None or <1 h	66 (38.1)	113 (32.1)	0.23
1–3 h	38 (22.0)	98 (27.8)	
>4 h	69 (39.9)	141 (40.1)	

[a] *P* values for categorical variables based on χ^2 or Fisher's exact test and *P* values for continuous variables based on the Wilcoxon rank sum test.

[b] All foods and nutrients energy adjusted, except alcohol, and based on $n = 181$ cases and $n = 358$ controls.

[c] Vigorous activity variables based on $n = 173$ cases and $n = 352$ controls.

$P_{trend} = 0.33$]. There was no association between CRP concentrations and pancreatic cancer in the combined analyses based on overall pooled cut-points [high compared to low quintile, OR = 1.00 (95% CI, 0.69–1.46), $P_{trend} = 0.12$; continuous OR = 0.98 (95% CI, 0.95–1.01)] and cohort-specific cut-points (OR = 1.01; 95% CI, 0.70–1.46; $P_{trend} = 0.76$). In the pooled analyses, we observed suggestive inverse associations among cases with longer

Table 3. Selected characteristics of control subjects (mean or proportion) by quintile of serum CRP concentration in ATBC and PLCO[a]

	ATBC			PLCO		
Characteristics	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
CRP, ng/mL	1.1	5.5	38.3	0.9	4.9	28.3
Age, y	58.7	58.1	58.6	64.7	65.8	64.9
Smoking history						
Total cigarettes per day	18.3	20.8	21.3	7.6	11.5	14.3
Years smoked, y	35.9	37.6	38.3	12.0	15.6	21.1
Smoking status, %						
Never	-	-	-	55.7	49.3	40.8
Former quit ≥15 years	-	-	-	30.4	22.7	29.6
Former quit <15 years	-	-	-	11.4	20.0	16.9
Current	100	100	100	2.5	8.0	12.7
Height, cm	172.0	173.4	172.3	173.1	172.8	170.5
BMI, kg/m^2	24.9	27.0	27.1	25.0	27.2	29.3
BMI—WHO cut points, %						
<25.0 (normal weight)	53.5	27.9	32.7	51.9	30.7	22.5
≥25.0 and <30 (overweight)	39.6	51.2	47.8	44.3	53.3	36.6
≥30 (obese)	6.9	20.9	19.5	3.8	16.0	40.9
Medical history, %						
Diabetes mellitus	5.0	6.0	6.2	3.9	13.5	18.6
Dietary intake per day[b]						
Red meat, g	25.6	22.8	26.1	67.5	78.8	81.6
Alcohol, g	18.2	19.0	21.7	12.0	15.8	15.1
Energy, kcal	2,781	2,696	2,893	2,000	2,139	2,117
Total fat, g	100.5	100.6	106.3	63.8	69.8	70.5
Saturated fat, g	48.6	51.9	54	21.1	23.3	24.4
Carbohydrate, g	313.6	300.3	296.8	271.4	280.2	273.1
Protein, g	104.1	103.0	102.9	77.0	82.7	83.4
Vigorous physical activity, hours per week (%)						
None or <1 h	-	-	-	21.1	28.8	41.8
1–3 h	-	-	-	36.6	30.1	26.9
>4 h	-	-	-	42.3	41.1	31.3
Physical activity, %						
Occupational						
Sedentary	12.9	15.8	7.1	-	-	-
Moderate	26.7	26.2	29.2	-	-	-
Heavy	8.9	7.1	6.2	-	-	-
Nonworking	51.5	50.8	57.5	-	-	-
Leisure						
Sedentary	35.6	45.4	59.3	-	-	-
Light, moderate	54.5	48.6	36.3	-	-	-
Exercise to keep fit	9.9	6.0	4.4	-	-	-

[a]Blank cells due to lack of available data.
[b]All dietary variables energy adjusted, except alcohol, based on controls with complete dietary data.

follow-up [≥5 years smoking-adjusted OR = 0.87 (95% CI, 0.55–1.37), $P_{trend} = 0.48$; continuous OR = 0.95 (95% CI, 0.86–1.05)].

Table 5 shows the association between CRP concentrations and pancreatic cancer stratified by age. Although no significant associations were observed in either the ATBC or PLCO datasets separately ($P_{interaction} = 0.91$ and 0.05, respectively), in the combined analyses we observed a significant interaction by age ($P_{interaction} = 0.02$) such that younger participants had a nonsignificant inverse association and trend [high compared to low quintile, OR = 0.81 (95% CI, 0.45–1.47), $P_{trend} = 0.17$], whereas older

Table 4. OR and 95% CI for pancreatic cancer by quintile of baseline serum CRP concentrations in ATBC, PLCO, and both cohorts combined

	Quintile of serum CRP concentration, ng/mL						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P_{trend}**	**Continuous**
ATBC							
CRP	≤1.97	>1.97 and ≤4.06	>4.06 and ≤7.42	>7.42 and ≤14.05	>14.05		
Cases/controls, *n*	64/102	71/102	81/102	50/103	45/101		
Crude OR (95% CI)[a]	1.00 (reference)	1.05 (0.67–1.64)	1.26 (0.82–1.93)	0.74 (0.47–1.18)	0.72 (0.44–1.17)	0.03	0.94 (0.89–0.99)
Smoking-adjusted OR (95% CI)[b]	1.00 (reference)	1.05 (0.67–1.65)	1.24 (0.81–1.91)	0.73 (0.46–1.16)	0.71 (0.44–1.16)	0.03	0.94 (0.89–0.99)
PLCO							
CRP	≤1.52	>1.52 and ≤2.96	>2.96 and ≤5.98	>5.98 and ≤10.48	>10.48		
Cases/controls, *n*	33/73	25/72	39/73	45/72	30/72		
Crude OR (95% CI)[c]	1.00 (reference)	0.70 (0.31–1.63)	1.27 (0.65–2.50)	1.55 (0.78–3.06)	1.12 (0.56–2.23)	0.88	1.00 (0.96–1.04)
Smoking-adjusted OR (95% CI)[d]	1.00 (reference)	0.53 (0.22–1.28)	1.34 (0.67–2.65)	1.46 (0.73–2.95)	0.84 (0.41–1.74)	0.79	0.99 (0.95–1.04)
Combined							
CRP	≤1.67	>1.67 and ≤3.64	>3.64 and ≤6.79	>6.79 and ≤12.59	>12.59		
Cases/controls, *n*	86/175	107/174	124/175	87/174	89/174		
Crude OR (95% CI)[c]	1.00 (reference)	1.12 (0.78–1.60)	1.25 (0.89–1.76)	1.00 (0.70–1.43)	0.88 (0.61–1.26)	0.06	0.97 (0.94–1.00)
Smoking-adjusted OR (95% CI)[d]	1.00 (reference)	1.18 (0.82–1.71)	1.32 (0.94–1.87)	1.05 (0.73–1.52)	1.00 (0.69–1.46)	0.12	0.98 (0.95–1.01)
Combined cohort-specific cut-points[e]							
CRP							
Cases/controls, *n*	97/175	96/174	120/175	95/175	85/173		
Crude OR (95% CI)[c]	1.00 (reference)	0.97 (0.68–1.38)	1.22 (0.87–1.69)	0.98 (0.70–1.38)	0.95 (0.67–1.37)	0.62	
Smoking-adjusted OR (95% CI)[d]	1.00 (reference)	1.02 (0.71–1.47)	1.24 (0.89–1.74)	0.99 (0.70–1.41)	1.01 (0.70–1.46)	0.76	

[a]Crude OR adjusted for matching variables (age, date of blood draw, follow-up time).
[b]Multivariable model additionally adjusted for smoking intensity and smoking duration.
[c]Crude OR adjusted for matching variables (age, race, sex, date of blood draw).
[d]Adjusted for smoking (never, former quit ≥15 years ago, former quit <15 years ago, current).
[e]Cohort-specific cut-points based on CRP concentrations observed separately in the ATBC and PLCO cohorts as defined above.

Table 5. Variable-adjusted OR and 95% CI of baseline serum CRP concentrations and pancreatic cancer stratified by median age in ATBC, PLCO, and both cohorts combined

	Quintile of serum CRP concentration, ng/mL[a]						
	Q1	Q2	Q3	Q4	Q5	P_{trend}	Continuous
ATBC							
<58 years old							
CRP	≤1.97	>1.97 and ≤4.06	>4.06 and ≤7.42	>7.42 and ≤14.05	>14.05		
Cases/controls, *n*	35/46	29/49	32/52	28/43	17/46		
Crude OR (95% CI)[b]	1.00 (reference)	0.77 (0.41–1.46)	0.80 (0.43–1.49)	0.85 (0.44–1.62)	0.49 (0.24–0.99)	0.04	0.90 (0.82–1.00)
Smoking-adjusted OR (95% CI)[c]	1.00 (reference)	0.76 (0.40–1.44)	0.76 (0.40–1.43)	0.82 (0.43–1.59)	0.48 (0.24–0.99)	0.05	0.90 (0.82–1.00)
≥58 years old							
Cases/Controls, *n*	29/56	42/53	49/50	22/60	28/55		
Crude OR (95% CI)[b]	1.00 (reference)	1.53 (0.83–2.79)	1.91 (1.05–3.48)	0.72 (0.37–1.41)	0.99 (0.52–1.87)	0.12	0.95 (0.90–1.01)
Smoking-adjusted OR (95% CI)[c]	1.00 (reference)	1.46 (0.79–2.68)	1.80 (0.98–3.30)	0.70 (0.36–1.36)	0.93 (0.49–1.78)	0.09	0.95 (0.89–1.01)
PLCO							
<66 years old							
CRP	≤1.52	>1.52 and ≤2.96	>2.96 and ≤5.98	>5.98 and ≤10.48	>10.48		
Cases/controls, *n*	24/38	13/40	16/30	17/31	20/35		
Crude OR (95% CI)[d]	1.00 (reference)	0.66 (0.21–2.11)	0.98 (0.36–2.68)	1.00 (0.35–2.85)	0.95 (0.37–2.45)	0.39	0.97 (0.90–1.04)
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	0.53 (0.15–1.80)	1.03 (0.34–3.17)	0.93 (0.31–2.80)	0.65 (0.23–1.84)	0.26	0.95 (0.86–1.04)
≥66 years old							
Cases/controls, *n*	9/35	12/32	23/43	28/41	20/37		
Crude OR (95% CI)[d]	1.00 (reference)	0.93 (0.25–3.49)	1.71 (0.62–4.69)	2.85 (1.01–8.05)	2.06 (0.68–6.24)	0.46	1.02 (0.97–1.08)
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	0.73 (0.18–3.01)	1.68 (0.60–4.67)	2.44 (0.81–7.33)	1.43 (0.43–4.78)	0.77	1.01 (0.95–1.08)
Combined							
Younger individuals[f]							
CRP	≤1.67	>1.67 and ≤3.64	>3.64 and ≤6.79	>6.79 and ≤12.59	>12.59		
Cases/controls, *n*	59/84	42/89	48/82	45/74	37/81		
Crude OR (95% CI)[d]	1.00 (reference)	0.67 (0.41–1.10)	0.82 (0.51–1.34)	0.86 (0.52–1.42)	0.65 (0.39–1.09)	0.13	0.96 (0.92–1.01)
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	0.66 (0.40–1.09)	0.83 (0.51–1.36)	0.81 (0.49–1.35)	0.60 (0.36–1.02)	0.08	0.95 (0.90–1.01)
Older individuals[g]							
Cases/controls, *n*	38/91	54/85	72/93	50/101	48/92		
Crude OR (95% CI)[d]	1.00 (reference)	1.51 (0.91–2.52)	1.91 (1.17–3.12)	1.25 (0.75–2.08)	1.29 (0.77–2.16)	0.82	0.98 (0.95–1.02)
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	1.49 (0.89–2.49)	1.89 (1.15–3.10)	1.19 (0.71–2.00)	1.19 (0.71–2.02)	0.24	0.98 (0.94–1.02)
Combined cohort-specific cut-points[h]							
Younger individuals[f]							
Cases/controls, *n*	59/84	42/89	48/82	45/74	37/81		
Crude OR (95% CI)[d]	1.00 (reference)	0.68 (0.38–1.22)	0.77 (0.45–1.31)	0.87 (0.51–1.49)	0.79 (0.44–1.40)	0.28	
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	0.72(0.40–1.31)	0.79 (0.46–1.37)	0.86 (0.50–1.48)	0.81 (0.45–1.47)	0.17	

(Continued on the following page)

Table 5. Variable-adjusted OR and 95 CI of baseline serum CRP concentrations and pancreatic cancer stratified by median age in ATBC, PLCO, and both cohorts combined (Cont'd)

	Quintile of serum CRP concentration, ng/mL[a]						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}	**Continuous**
Older individuals[g]							
Cases/controls, *n*	38/91	54/85	72/93	50/101	48/92		
Crude OR (95% CI)[d]	1.00 (reference)	1.32 (0.78–2.26)	1.98 (1.20–3.28)	1.32 (0.79–2.23)	1.25 (0.72–2.17)	0.68	
Smoking-adjusted OR (95% CI)[e]	1.00 (reference)	1.39 (0.80–2.41)	1.89 (1.13–3.15)	1.19 (0.69–2.04)	1.28 (0.73–2.27)	0.92	

[a]Interaction by age not significant for ATBC and PLCO, but significant in combined analyses ($P = 0.91$, $P = 0.05$, and $P = 0.02$, respectively).
[b]Crude OR adjusted for matching variables (age, date of blood draw, follow-up time).
[c]Multivariable model additionally adjusted for smoking intensity and smoking duration.
[d]Crude OR adjusted for matching variables (age, race, sex, date of blood draw).
[e]Adjusted for smoking (never, former quit $\geq$ 15 years ago, former quit < 15 years ago, current).
[f]Combined subjects <58 years old from ATBC and those <66 years old from PLCO.
[g]Combined subjects $\geq$58 years old from ATBC and those $\geq$66 years old from PLCO.

participants tended to have a pattern of nonsignificant elevated risk with increasing CRP concentrations. We did not observe a significant interaction of the CRP and pancreatic cancer association by BMI or smoking status in either the ATBC or PLCO studies.

Discussion

Overall, we observed inverse associations between CRP and risk of pancreatic cancer among men in the ATBC study cohort but not participants in the PLCO study. The association was significantly modified by age such that in analyses of both cohorts separately and in study combined analyses, nonsignificant inverse associations were most evident among younger individuals, whereas nonsignificant positive associations were observed among older cohort participants.

A number of studies have investigated CRP in relation to other cancers, particularly colorectal cancer with positive (3, 12) and inverse (10, 11) associations reported. Previous prospective studies conducted in Washington County, Maryland, and another in the ATBC study showed 2- to 3-fold elevated colorectal cancer risk with increasing CRP concentrations (3, 12). In contrast, similar to our results, others have reported inverse associations between CRP and adenoma and colorectal cancer (10, 11). One multiethnic trial from Honolulu examined whether IL-6 and CRP concentrations and single nucleotide polymorphisms (SNP) in the *IL-6* or *CRP* genes were associated with colorectal adenoma risk (10). In the main effects model, there was no association between CRP concentration and colorectal cancer. However, 2 different SNPs in the *CRP* gene (*rs1205* and *rs1130864*) showed that alleles that were associated with higher CRP concentrations were also associated with a reduced risk of adenoma. The Women's Health Study showed an inverse association between CRP and risk of proximal colon cancer (11), and no significant associations by tumor stage at diagnosis. Potential limitations of these and our study are that CRP is measured at only one point in time and it is possible that other factors correlated with higher CRP concentrations could explain the observed associations.

The inverse associations that we observe between CRP concentrations and pancreatic cancer are unexpected and mechanisms that may explain our association are speculative. Inflammation is important for tissue homeostasis and closely associates with immune response (10, 11, 28, 29). CRP recognizes damaged cells in the body and aids in their removal by binding to them and other viable apoptotic cells (10, 29). Therefore, higher CRP levels may augment phagocytosis of apoptotic cells and contribute to their removal. This, in turn, could prevent tumor development as high CRP levels are associated with tissue repair and exclusion of cells, which may be more apparent in smokers because they may have more inflammation. This could potentially explain the observed inverse association in ATBC but not PLCO, due to the ATBC population being composed of solely male smokers (30). The interaction of CRP and pancreatic cancer risk by age is also difficult to explain. There is evidence that the production of proinflammatory cytokines increase with age (31). Why younger individuals with high CRP would have lower pancreatic cancer risk than those with low levels is not clear, although it could possibly be due to chance.

Strengths of this study include the prospective design with CRP measured in blood samples collected several years before cancer diagnosis. The associations became stronger when cases occurring early during follow-up were excluded decreasing the likelihood of reverse causation, though there was some attenuation in ATBC during longer follow-up. The association between CRP and pancreatic cancer risk also switched from protective to positive after cases from the first 8 years were excluded in the PLCO study. By pooling data from 2 nested case–control studies, we increased the study size and our power to observe associations if they exist.

Our study also has limitations. A single measurement of CRP in peripheral blood may not represent lifetime inflammatory exposure or tissue-specific inflammation, such as that in the pancreas. CRP is known to be a nonspecific marker of inflammation, and it is also possible that other underlying diseases and cigarette smoking could influence CRP concentrations in the serum masking any contribution from pancreatic inflammation. There may be unknown correlates to serum CRP in our study that are not controlled and may explain the associations that we observe. All these factors could contribute to inaccurate risk estimates between CRP and pancreatic cancer.

In conclusion, we observed an inverse association between increasing CRP concentrations and risk of pancreatic cancer in the ATBC study; however, there was no significant association in the PLCO study or in cohort combined analyses. In combined analyses we observed a significant interaction such that inverse associations were apparent in younger but not older participants. Additional prospective studies are necessary to evaluate associations between CRP and perhaps more specific markers of pancreatic inflammation and risk of pancreatic cancer.

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