

Inflammatory Plasma Markers and Pancreatic Cancer Risk: A Prospective Study of Five U.S. Cohorts

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Abstract

Chronic inflammation may play a role in the development of pancreatic cancer. However, few prospective studies have examined the association between plasma inflammatory markers and pancreatic cancer risk. Therefore, we investigated the association of prediagnostic circulating C-reactive protein (CRP), interleukin-6 (IL-6), and TNF- α receptor II (TNF- α R2) with subsequent pancreatic cancer risk in a prospective, nested case-control study of 470 cases and 1,094 controls from Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, Women's Health Initiative, and Women's Health Study. The median follow-up time of cases was 7.2 years (range 1–26 years). No association was observed between plasma CRP, IL-6, and TNF- α R2 and the risk of pancreatic cancer. Comparing extreme quintiles, the multivariate ORs were 1.10 [95% confidence interval (CI), 0.74–1.63; $P_{\text{trend}} = 0.81$] for CRP, 1.19 (95% CI, 0.81–1.76; $P_{\text{trend}} = 0.08$) for IL-6, and 0.88 (95% CI, 0.58–1.33; $P_{\text{trend}} = 0.57$) for TNF- α R2. In conclusion, prediagnostic levels of circulating CRP, IL-6, and TNF- α R2 were not associated with the risk of pancreatic cancer, suggesting that systemic inflammation as measured by circulating inflammatory factors is unlikely to play a major role in the development of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*; 22(5); 855–61. ©2013 AACR.

Introduction

Chronic inflammation may promote cancer development through several mechanisms, including enhanced cellular proliferation and mutagenesis, poor adaptability to oxidative stress, promotion of angiogenesis, and inhibition of apoptosis (1, 2). Certain chronic inflammatory conditions, such as chronic pancreatitis, obesity, and type-

II diabetes, predispose to pancreatic cancer (3–5). In addition, pancreatic cancer induces a strong desmoplastic reaction that provides inflammatory mediators and growth factors to support tumor growth and metastases (6–8). However, the inflammatory mediators that promote pancreatic cancer development remain poorly defined.

Several inflammatory markers may play a direct pathogenic role in the development of pancreatic cancer or act as surrogate biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and TNF- α (TNF- α). CRP is a biomarker increasingly used in cardiovascular screening (9, 10), and plasma CRP levels are increased in obesity, impaired glucose tolerance, and metabolic syndrome (11). IL-6 and TNF- α are cytokines that play important roles in triggering the inflammatory response, and are associated with risk factors for pancreatic cancer, such as obesity, insulin resistance, and diabetes mellitus (12–15). Interestingly, these inflammatory cytokines are expressed by pancreatic cancer cells and surrounding stroma, and have been noted to facilitate tumor cell growth and metastases (6–8, 16–18). Prospective studies have shown that elevated levels of CRP, IL-6, and TNF- α may be linked to higher risk of cancer (19–21).

Several small, hospital-based case-control studies showed that pancreatic cancer cases had higher levels of CRP, IL-6, and TNF- α /receptors than controls (22–25). Although a strong rationale exists to suspect a role for inflammatory cytokines in pancreatic cancer

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pathogenesis, few prospective epidemiologic studies have examined the association of pancreatic cancer risk with CRP (21, 26, 27), IL-6 (27), or TNF- α receptors (27). We therefore examined the association between pre-diagnostic plasma CRP, IL-6, and TNF- α receptor 2 (TNF- α R2, TNFRSF1B) and subsequent risk of pancreatic cancer in 5 U.S. prospective cohorts with up to 26 years of follow-up.

Materials and Methods

Study participants

We pooled the primary data from five U.S. prospective cohorts. The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals aged 40–75 years in 1986. The Nurses' Health Study (NHS) enrolled 121,700 female nurses aged 30–55 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 40–84 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 50–79 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 more 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 (28–32). The current study was approved by the Human Research Committee at the Brigham and Women's Hospital (Boston, MA) and participants provided informed consent.

Blood collection and plasma assays

Blood samples were collected from 18,225 men in HPFS from 1993–1995, 32,826 women in NHS from 1989–1990, 14,916 men in PHS from 1982–1984, 93,676 women in WHI from 1994–1998, and 28,345 women in WHS from 1992–1995. Details on blood draw, transportation, and storage of plasma samples have been described previously (33–37).

Plasma CRP, IL-6, and TNF- α R2 were measured in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA), using reagents from Roche Diagnostics. Of note, we measured TNF- α R2 because TNF- α R2 has greater stability in plasma than TNF- α and acts as a comprehensive measure of TNF- α pathway activation (38). In previous studies, we showed that TNF- α R2 levels were

correlated with adiposity (39) and predicted the risk of diabetes (40) and coronary heart disease (41).

All samples for CRP, IL-6, and TNF- α R2 were handled identically in a single batch. Laboratory personnel were blinded to case, control, or quality control status. The mean intra-assay coefficients of variance for each assay were $\leq 10\%$ for blinded, replicate, and quality control samples.

Pancreatic cancer cases and matched controls

We included cases of pancreatic adenocarcinoma diagnosed through 2008 among participants who had provided blood samples and no prior history of cancer, except non-melanoma skin cancer. Incident cases were identified by self-report or during follow-up of a participant's death. Deaths were ascertained from next-of-kin or the U.S. postal service and by searching the National Death Index. This method has been shown to capture more than 98% of deaths (42). Medical records of the cases were requested and reviewed by study physicians blinded to exposure data. More than 99% of cases in this study were confirmed by review of medical records, tumor registry data, or death certificates.

Eligible controls 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 3 controls for each case, matching on year of birth, prospective cohort (which concurrently matched on sex), smoking status (never, past, current), fasting status (fasting, non-fasting), and month of blood draw.

For the present analysis, 491 pancreatic cancer cases and 1,137 matched controls were available. For the analyses of CRP and TNF- α R2, 2 cases and 1 control were removed due to failure of the assay, and for those 2 cases, we also removed their matched controls ($n = 4$). For the analysis of IL-6, 10 cases and 23 controls were removed because of failure of the assay, and for those 10 cases, we removed their matched controls ($n = 17$). Because of concern regarding the possible influence of subclinical malignancy on body mass index, lifestyle choices, and plasma markers levels, we further excluded pancreatic cancer cases diagnosed within 1 year of blood draw ($n = 19$) and their matched controls ($n = 38$). Therefore, for the analyses of CRP and TNF- α R2, we had a total of 470 cases (HPFS: 74; NHS: 103; PHS: 70; WHI: 194; WHS: 29) and 1,094 controls (HPFS, 180; NHS, 307; PHS I, 173; WHI, 380; WHS, 54); for the analysis of IL-6, we had a total of 462 cases (HPFS: 74; NHS: 95; PHS: 70; WHI: 194; WHS: 29) and 1,059 controls (HPFS, 180; NHS, 275; PHS I, 170; WHI, 380; WHS, 54). The median follow-up time of cases was 7.2 years (range 1–26 years).

Statistical analysis

We pooled the primary data from five cohorts. Participants were categorized into quintiles based on the distributions among all controls. We additionally conducted separate analyses in men and women using gender-specific quintiles. For analysis of CRP and pancreatic cancer

risk, we also used the cut-off points proposed in clinical guidelines for cardiovascular disease and categorized participants into CRP levels of less than 1, 1 to 3, and more than 3 mg/L (43).

To compute ORs and 95% confidence intervals (CI), we used conditional logistic regression conditioned on the matching factors including year of birth, prospective cohort (HPFS, NHS, PHS I, WHI, WHS, which concurrently matched on sex), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw. In multivariate models, we adjusted for established or suspected risk factors of pancreatic cancer including race (White, Black, other), history of diabetes mellitus (yes, no), body mass index (BMI, <18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m²), physical activity (quartiles), current multivitamin use (yes, no), plasma 25(OH)D levels (quartiles), and plasma C-peptide levels (quartiles). In no instance did including any of these covariates change the estimate by more than 10%. P_{trend} were calculated by the Wald test of a score variable that contained median values of quintiles.

To evaluate whether the associations between inflammatory markers and pancreatic cancer risk were linear, we compared the model fit including linear and cubic spline terms selected by a stepwise regression procedure with the model fit with only the linear term using the likelihood ratio test (44). Additional analyses in which plasma markers were modeled as a continuous variable were conducted if the nonparametric regression curves showed that the associations of pancreatic cancer risk with plasma markers were consistent with linear associations.

We also conducted a meta-analysis of individual study data. We calculated ORs for each cohort and then pooled these cohort-specific ORs to compute a summary OR using the DerSimonian and Laird random effects model (45). Heterogeneity across studies was tested using the Q statistic (45).

To examine whether the associations between inflammatory markers and risk of pancreatic cancer were 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 cases, smoking status, BMI, and physical activity. Tests for interaction were carried out by the Wald test of cross-product terms. To test the robustness of our results, we conducted a sensitivity analysis excluding individuals with diabetes. To further mitigate any effect of subclinical pancreatic cancer on plasma biomarker levels, we did additional analyses excluding pancreatic cancer cases diagnosed within 2 or 4 years from the date of blood draw. Finally, we repeated the analyses after inflammatory biomarkers were log-transformed to improve normality. All statistical analyses were conducted with the SAS 9.1 statistical package (SAS Institute, Cary, North Carolina) and all P values are two sided.

Results

Median plasma level was higher in cases versus controls for IL-6 (1.5 vs. 1.2 pg/mL, $P = 0.002$) and not as apparent for CRP (1.8 vs. 1.6 mg/L, $P = 0.15$) and TNF- α R2 (2.7 vs. 2.6 mg/mL, $P = 0.23$). Among controls, CRP levels and IL-6 levels were highly correlated (Spearman rank correlation coefficient $r = 0.47$); we observed moderate correlations between CRP levels and TNF- α R2 levels ($r = 0.24$) and between IL-6 levels and TNF- α R2 levels ($r = 0.26$). Individuals in the upper quintiles of these inflammatory markers were older, more likely to be female, current smokers, or have diabetes, less likely to exercise, and had higher BMI and C-peptide levels (Table 1).

No association was observed between plasma CRP, IL-6, and TNF- α R2 and risk of pancreatic cancer. Comparing extreme quintiles, the multivariate ORs were 1.10 (95% CI, 0.74–1.63; $P_{\text{trend}} = 0.81$) for CRP, 1.19 (95% CI, 0.81–1.76; $P_{\text{trend}} = 0.08$) for IL-6, and 0.88 (95% CI, 0.58–1.33; $P_{\text{trend}} = 0.57$) for TNF- α R2 (Table 2). There was no statistically significant heterogeneity due to sex (for the multivariate ORs of quintile 5, men vs. women, $P_{\text{heterogeneity}} = 0.40$ for CRP, 0.09 for IL-6, and 0.49 for TNF- α R2) and no association was observed between any of these inflammatory markers and pancreatic cancer risk among men and among women (Supplementary Table S1). The results were virtually unchanged when we excluded cases diagnosed within 2 or 4 years from the date of blood draw, or limited to nondiabetics (Supplementary Table S2).

Spline analyses showed that the associations of pancreatic cancer risk with CRP, IL-6, and TNF- α R2 were consistent with linear associations ($P_{\text{nonlinear}} = 0.28$ for CRP, 0.19 for IL-6, and 0.57 for TNF- α R2). In additional analyses with plasma markers modeled as continuous variables, the multivariate ORs for an increment of one unit was 0.99 (95% CI, 0.98–1.01) for CRP, 1.01 (95% CI, 0.99–1.04) for IL-6, and 0.92 (95% CI, 0.82–1.04) for TNF- α R2 (Table 2).

We observed similar ORs when analyzing each cohort separately (Supplementary Table S3), with no statistically significant heterogeneity across studies ($P = 0.42$ for CRP, 0.23 for IL-6, and 0.40 for TNF- α R2). In a meta-analysis pooling the cohort-specific ORs, an increment of one unit for CRP had an OR of 0.99 (95% CI, 0.97–1.02); for IL-6, 1.00 (95% CI, 0.96–1.04); and for TNF- α R2, 0.95 (95% CI, 0.82–1.09).

For analysis of CRP, we further categorized participants using the cut-off points proposed in clinical guidelines for cardiovascular disease (43). Comparing with CRP level less than 1 mg/L, the multivariate ORs of pancreatic cancer were 0.92 (95% CI, 0.69–1.23) for CRP level of 1 to 3 mg/L, and 1.07 (95% CI, 0.78–1.45) for CRP level of more than 3 mg/L. We also found no statistically significant interactions by sex, age at blood draw, follow-up time of cases, smoking status, BMI, and physical activity (Supplementary Table S4). We repeated all the analyses after inflammatory biomarkers were log-transformed and observed similar results.

Table 1. Age/study-standardized baseline characteristics according to quintiles of inflammatory plasma markers among controls

Characteristic	CRP, mg/L			IL-6, pg/mL			TNF- α R2, mg/mL		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Age at blood draw, y	60.9	62.6	63.3	59.0	63.0	64.6	59.8	62.4	65.5
Men, %	49.6	32.5	17.0	40.3	31.1	32.7	48.8	29.0	11.8
Race, %									
White	88.5	94.0	94.7	89.9	93.5	91.6	83.3	93.7	96.1
Black	3.4	1.8	3.0	3.6	2.7	2.2	4.2	2.0	1.9
Other	8.2	4.2	2.3	6.5	3.8	6.2	12.5	4.3	2.1
BMI, kg/m ²	23.7	25.9	27.6	23.7	25.8	27.5	25.1	26.2	26.8
Physical activity, MET-hour/week	20.6	22.1	17.5	20.4	19.0	17.2	24.1	18.3	17.0
Cigarette smoking, %									
Never	47.4	42.3	42.9	45.7	45.4	40.4	43.4	44.1	46.8
Past	41.5	44.8	42.2	46.0	43.3	38.6	45.7	43.4	35.8
Current	10.0	12.5	14.3	6.4	10.7	20.7	11.0	11.1	16.8
Missing	1.1	0.4	0.6	1.8	0.6	0.3	0.0	1.5	0.6
History of diabetes mellitus, %	0.9	3.6	5.6	1.1	2.5	5.1	1.7	3.3	3.2
Regular multivitamin use, %	38.3	42.2	35.4	37.6	42.2	33.9	35.9	37.9	41.5
Fasting time, hours	10.5	10.4	10.1	10.2	10.6	10.3	10.2	10.5	10.7
Plasma 25(OH)D, nmol/L	63.6	66.6	60.7	66.2	66.4	60.9	66.4	65.4	62.8
Plasma C-peptide, ng/mL	1.7	2.2	2.4	1.8	2.2	2.7	1.8	2.0	2.6

Discussion

In this large prospective study of five U.S. cohorts, prediagnostic plasma CRP, IL-6, and TNF- α R2 were not associated with risk of pancreatic cancer. Furthermore, there were no associations between these biomarkers and pancreatic cancer risk in any of the subgroups evaluated.

The prospective design and high follow-up rates in this study minimize the possibility that our null findings are due to selection bias or differential case ascertainment. Because we excluded cases diagnosed within 1 year of blood draw, it is unlikely that disease status or treatment may influence the biomarker levels (reverse causation). This concern was further minimized by analyses that excluded cases diagnosed within 2 and 4 years after blood collection. Our results are also unlikely to be explained by the cut-off points chosen because we consistently found no associations by using quintile distribution of biomarkers among controls, by using the cut-off points in clinical guidelines (for CRP), or by using biomarkers as a continuous variable.

Confounding might be of minor importance in the present study as we matched cases and controls on important risk factors of pancreatic cancer such as age and smoking, and then adjusted for risk factors such as BMI, physical activity, and diabetes for a more complete control for confounding.

Measurement error could potentially explain the lack of associations in this study. Inflammatory markers were measured only once at baseline, therefore may not represent long-term levels. However, CRP, IL-6, and TNF-

α R2 levels have been shown to be stable over time (46). Subgroup analyses also showed that the results for less than 7.2 years of follow-up (median follow-up time of cases) were similar to those for 7.2 or more years of follow-up. In addition, the single measurement of baseline CRP, IL-6, and TNF- α R2 has strongly predicted the risk for many diseases including diabetes (36, 40). Furthermore, we attempted to reduce the measurement error by measuring CRP, IL-6, and TNF- α R2 in a single laboratory as a single batch, and the coefficients of variance were low for blinded, replicate quality control samples.

Our findings are consistent with previous studies examining plasma inflammatory markers and pancreatic cancer risk. Three prospective studies examined prediagnostic CRP levels in relation to pancreatic cancer risk (21, 26, 27). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of male Finnish smokers (26), a weak inverse association was observed (OR, 0.94; 95% CI, 0.89–0.99), whereas no association was observed in a small Greek prospective study (21), the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (26), or the European Prospective Investigation into Cancer and Nutrition study (27). Only one prospective study has examined prediagnostic IL-6 and TNF- α receptors in relation to pancreatic cancer risk, and neither biomarker was significantly associated with overall risk of pancreatic cancer (27), although an inverse association was observed for TNF- α R1 among women.

In conclusion, our findings do not seem to support a positive association of pancreatic cancer risk with prediagnostic plasma CRP, IL-6, and TNF- α R2. Although

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Table 2. ORs and 95% CIs for pancreatic cancer according to inflammatory plasma markers

	Quintiles of inflammatory plasma markers					<i>P</i> _{trend} ^a	One-unit increase
	1	2	3	4	5		
CRP							
Levels, mg/L	<0.5	0.5–1.1	1.2–2.1	2.2–4.2	≥4.3		
No. of cases	79	101	86	95	109		470
No. of controls	215	219	220	220	220		1094
Base model ^b	1.0	1.23 (0.85–1.76)	1.00 (0.69–1.45)	1.16 (0.80–1.68)	1.27 (0.88–1.83)	0.31	1.00 (0.98–1.02)
Multivariate ^c	1.0	1.18 (0.81–1.71)	0.97 (0.65–1.42)	1.09 (0.73–1.62)	1.10 (0.74–1.63)	0.81	0.99 (0.98–1.01)
IL-6							
Levels, pg/mL	<0.7	0.7–1.0	1.1–1.4	1.5–2.1	≥2.2		
No. of cases	83	68	77	109	125		462
No. of controls	212	211	211	212	213		1059
Base model ^b	1.0	0.81 (0.56–1.19)	0.88 (0.60–1.28)	1.24 (0.85–1.80)	1.38 (0.96–1.98)	0.01	1.02 (1.00–1.05)
Multivariate ^c	1.0	0.82 (0.56–1.21)	0.81 (0.55–1.21)	1.14 (0.77–1.69)	1.19 (0.81–1.76)	0.08	1.01 (0.99–1.04)
TNF-αR2							
Levels, mg/mL	<2.1	2.1–2.4	2.5–2.8	2.9–3.4	≥3.5		
No. of cases	89	95	82	101	103		470
No. of controls	218	219	219	219	219		1094
Base model ^b	1.0	1.05 (0.74–1.49)	0.89 (0.61–1.29)	1.03 (0.72–1.48)	1.02 (0.69–1.49)	0.93	0.98 (0.88–1.10)
Multivariate ^c	1.0	0.96 (0.67–1.39)	0.79 (0.54–1.17)	0.92 (0.63–1.34)	0.88 (0.58–1.33)	0.57	0.92 (0.82–1.04)

^a*P* values were calculated by the Wald test of a score variable that contained median values of quintiles.

^bORs and 95% CI were estimated by conditional logistic regression conditioned on the matching factors including year of birth, prospective cohort (HPFS, NHS, PHS I, WHI, WHS, which concurrently matched on sex), smoking status (never, past, current), fasting status (fasting, nonfasting), and month of blood draw.

^cBase model further adjusted for race (White, Black, other), history of diabetes mellitus (yes, no), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), physical activity (quartiles), current multivitamin use (yes, no), plasma 25(OH)D levels (quartiles), and plasma C-peptide levels (quartiles).

local inflammatory pathway activation seems to play an important role in pancreatic carcinogenesis (6–8), systemic inflammation as measured by circulating inflammatory factors does not seem to represent a material predictor of risk.

Disclosure of Potential Conflicts of Interest

N. Rifai is employed (other than primary affiliation; e.g., consulting) as an Editor in Clinical Chemistry. L.S. Lessin is a consultant/advisory board member of Celgene and has expert testimony in Quintiles International. No potential conflicts of interest were disclosed by the other authors.

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