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Article

Prediagnostic Inflammation and Pancreatic Cancer Survival

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Abstract

Background: Chronic inflammation may promote initiation and progression of pancreatic cancer, but no studies have examined the association between inflammation in the period before diagnosis and pancreatic cancer survival. **Methods:** We prospectively examined the association of prediagnostic plasma levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α receptor 2 with survival among 492 participants from 5 large US prospective cohort studies who developed pancreatic cancer. Using an empirical dietary inflammatory pattern (EDIP) score, we evaluated whether long-term proinflammatory diets were associated with survival among 1153 patients from 2 of the 5 cohorts. Cox proportional hazards regression was used to estimate hazard ratios for death with adjustment for potential confounders. All statistical tests were 2-sided. **Results:** Higher prediagnostic levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α receptor 2 were individually associated with reduced survival ($P_{trend} = .03$, .01, and .04, respectively). Compared with patients with a combined inflammatory biomarker score of 0 (all 3 marker levels below medians), those with a score of 3 (all 3 marker levels above medians) had a hazard ratio for death of 1.57 (95% confidence interval = 1.16 to 2.12; $P_{trend} = .003$), corresponding to median overall survival times of 8 vs 5 months. Patients consuming the most proinflammatory diets (EDIP quartile 4) in the prediagnostic period had a hazard ratio for death of 1.34 (95% confidence interval = 1.13 to 1.59; $P_{trend} = .01$), compared with those consuming the least proinflammatory diets (EDIP quartile 1). **Conclusion:** Prediagnostic levels of inflammatory biomarkers and long-term proinflammatory diets were inversely associated with pancreatic cancer survival.

Pancreatic cancer is the third-leading cause of cancer-related death in the United States, with a 5-year survival rate of only 10% (1). Most patients are diagnosed at an advanced stage when the cancer can no longer be cured. A better understanding of the factors that promote pancreatic cancer progression would help in the development of novel preventive and therapeutic strategies for this highly lethal malignancy.

Data from preclinical models have suggested that chronic inflammation promotes the initiation and progression of pancreatic cancer (2-6). We have previously shown that several

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proinflammatory conditions, including obesity, diabetes, and tobacco use, in the years prior to diagnosis are associated with reduced survival of patients with pancreatic cancer (7–9). These studies suggest that chronic inflammation may modulate pancreatic tumor behavior in the period preceding diagnosis. However, it is not known whether chronic inflammation in the prediagnostic period leads to impaired survival times in patients who develop pancreatic cancer.

In this pooled study of patients diagnosed with pancreatic cancer from 5 large US cohorts, we analyzed patient survival by prediagnostic inflammation prospectively assessed in 2 ways: 1) by examining prediagnostic plasma levels of inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α receptor 2 (TNF-αR2); and 2) by evaluating long-term diets with high inflammatory potential (10) in 2 of the 5 cohorts.

Methods

Study Population

This study included participants from 5 US prospective cohort studies: the Health Professionals Follow-Up Study (HPFS), the Nurses' Health Study (NHS), the Physicians' Health Study I (PHS I), the Women's Health Initiative (WHI) observational study, and the Women's Health Study (WHS). HPFS enrolled 51 529 male health professionals aged 40-75 years in 1986 (11). NHS enrolled 121 700 female registered nurses aged 30-55 years in 1976 (12). PHS I is a randomized clinical trial of aspirin and β-carotene that enrolled 22 071 male physicians aged 40-84 years in 1982 (13). After the trial was completed in 1995, study participants have been followed as an observational cohort. The WHI observational study enrolled 93 676 postmenopausal women aged 50-79 years between 1993 and 1998 (14). WHS is a randomized clinical trial of low-dose aspirin and vitamin E that enrolled 39 876 female health professionals aged 45 years or older between 1992 and 1995 (15). After the trial was completed in 2004, 33 682 study participants have been followed as an observational cohort.

The analysis of prediagnostic inflammatory biomarkers included 492 patients with pancreatic cancer from the 5 cohorts (76 from HPFS, 101 from NHS, 70 from PHS I, 208 from WHI, and 37 from WHS) with a single measurement of these markers. To evaluate the long-term impact of dietary inflammatory potential in a larger number of patients, we calculated an empirical dietary inflammatory pattern (EDIP) score among 1153 patients with pancreatic cancer from HPFS and NHS (n = 480 and 673, respectively). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health and those of participating registries as required.

Identification of Cases of Pancreatic Cancer

Follow-up for clinical outcomes including pancreatic cancer was performed annually in PHS I, WHI, and WHS and biennially in HPFS and NHS by mailing participants a self-administered questionnaire. Cases of pancreatic cancer could also be identified during follow-up of participant deaths, using the International Classification of Diseases code of 157 to ascertain deaths from pancreatic cancer. Physicians blinded to exposure status confirmed the diagnosis of pancreatic cancer by review of medical records, death certificates, or cancer registry data. Patients with pancreatic tumor types other than adenocarcinoma were excluded.

Mortality Assessment

In all cohorts, deaths were reported by proxy (eg, next of kin, the US Postal Service) or ascertained from the National Death Index that has been shown to capture approximately 98% of deaths (16). Because pancreatic cancer is a highly lethal malignancy and most patients die from the disease, we used overall mortality data in our analyses, as opposed to pancreatic cancer-specific mortality.

Assessment of Plasma Inflammatory Biomarkers

Collection and storage of prediagnostic plasma samples were described in the Supplementary Methods (available online). In the laboratory of Dr Nader Rifai (Children's Hospital, Boston, MA), CRP was measured by a highly sensitive immunoturbidimetric assay; IL-6 and soluble TNF-αR2 were measured by an enzyme-linked immunosorbent assay. We measured TNF-αR2, a validated surrogate for the TNF-α pathway activation, because of its greater stability in frozen plasma and lower diurnal variability (17). All samples were handled identically in a single batch. In 22 sets of blinded duplicate samples from quality control plasma pools (mean concentrations: 3.2 mg/L for CRP, 1.7 pg/mL for IL-6, and 1.8 ng/mL for TNF-αR2), the mean coefficients of variation across all sets were 1.6% for CRP, 7.7% for IL-6, and 5.7% for TNF-αR2. In the analysis of IL-6 and the combined inflammatory biomarker score, 8 patients were removed because of failure of the assay.

Assessment of Dietary Inflammatory Potential

Dietary intake was obtained from NHS participants via validated semiquantitative food frequency questionnaires (FFQs) in 1984, 1986, and every 4 years thereafter and from HPFS participants every 4 years starting in 1986. Participants were asked to report their average frequency of intake during the preceding year for a specified serving size of each food. An EDIP score that measures dietary inflammatory potential was calculated as detailed elsewhere (10). Briefly, researchers identified a dietary pattern most predictive of IL-6, CRP, and TNF-αR2, using 39 predefined food groups by reduced rank regression followed by stepwise linear regression. The EDIP score is the weighted sum of 18 component food groups: 9 anti-inflammatory (beer, wine, tea, coffee, dark yellow vegetables, green leafy vegetables, snacks, fruit juice, pizza) and 9 proinflammatory (processed meat, red meat, organ meat, fish, vegetables other than dark yellow vegetables and green leafy vegetables, refined grains, high-energy beverages, low-energy beverages, tomatoes); a higher score indicates greater dietary inflammatory potential. The score was validated in several independent cohorts (10,18).

Assessment of Covariates

In HPFS and NHS, date of birth and race and ethnicity were asked at enrollment, and data on body mass index (BMI), physical activity, smoking status, alcohol intake, and history of diabetes were obtained from the questionnaire near blood collection for the biomarker analysis and from the questionnaire near cancer diagnosis for the EDIP analysis. In PHS I, WHI, and WHS,

data on the aforementioned covariates were collected at the time of blood collection. In WHI consisting of participants with diverse career backgrounds, income and education level were ascertained as indicators of socioeconomic status. In all cohorts, date of pancreatic cancer diagnosis and stage at diagnosis were determined through physician review of medical records.

Statistical Analyses

We pooled the data from the 5 cohorts and examined the association between inflammatory biomarker levels and overall survival, using Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Survival time was calculated from the date of diagnosis to the date of death or the end of follow-up (June 2014), whichever came first. Proportional hazards assumption was satisfied by evaluating a time-dependent variable, which was the product of the biomarker and time (all $P \geq .47$). Spearman rank correlation coefficient was used to measure correlations between inflammatory biomarkers.

Each biomarker was categorized into quartiles and evaluated for a linear trend across quartiles using an ordinal variable. To investigate the additive effect of these biomarkers on survival, we created a combined inflammatory biomarker score by summing the number of biomarkers with levels above the study population medians. The score thus ranged from 0 (all 3 marker levels below medians) to 3 (all 3 marker levels above medians).

In the primary model, we adjusted for age at diagnosis, cohort (which also adjusted for sex), race and ethnicity, smoking status, month of blood collection, fasting time at blood collection, diagnosis period, and cancer stage. Survival curves were investigated using direct adjusted survival estimation (19,20). Because obesity and diabetes are both associated with elevated systemic inflammation, we additionally adjusted for BMI and history of diabetes in a secondary model. We performed stratified analyses by sex, BMI, smoking status, time from blood collection to cancer diagnosis, and cancer stage and assessed interaction by entering cross-product terms of the combined score and the stratification variable into the model, evaluated by the likelihood ratio test. Heterogeneity across the cohort study populations was tested by Cochran Q statistic (21).

We next evaluated the association between the EDIP score and overall survival by pooling the data from HPFS and NHS. To reflect long-term dietary inflammatory potential, we calculated the average EDIP score for each participant using FFQs returned within 20 years before diagnosis except those with aberrant caloric intake (<800 or >4200 kcal/day for males; <600 or >3500 kcal/day for females). The score was categorized into quartiles and evaluated for a linear trend across quartiles using an ordinal variable. In the primary model, we adjusted for age at diagnosis, cohort, race and ethnicity, smoking status, diagnosis period, cancer stage, and total energy intake. BMI and diabetes status were additionally adjusted for in a secondary model. Statistical analyses were performed using SAS 9.4, and all P values are 2-sided. A P value of less than .05 was considered statistically significant.

Results

Prediagnostic Inflammatory Biomarkers and Pancreatic Cancer Survival

Among 492 patients with pancreatic cancer from the 5 cohorts (Supplementary Table 1, available online), blood samples were collected at a median of 6.7 (range = 0.1-24.5) years before diagnosis. Among those with known disease stage (n = 404), 16.1% had localized disease, 29.7% had locally advanced disease, and 54.2% had metastatic disease. At the end of follow-up, 465 patients (94.5%) were deceased.

We observed modest correlations between the 3 inflammatory biomarkers. The correlation coefficient ranged from 0.23 for CRP and TNF-αR2 levels to 0.50 for CRP and IL-6 levels (all $P < .05$; Supplementary Table 2, available online). Baseline characteristics by the combined inflammatory biomarker score are listed in Table 1. Patients with a higher score were older and more likely to be female and have a history of diabetes, had higher BMI, and were less physically active.

Higher prediagnostic levels of CRP, IL-6, and TNF-αR2 were associated with reduced survival (P_{trend} = .03, .01, and .04, respectively; Table 2). Comparing extreme quartiles, the multivariable hazard ratio for death was 1.44 (95% CI = 1.09 to 1.91) for CRP, 1.37 (95% CI = 1.04 to 1.81) for IL-6, and 1.25 (95% CI = 0.92 to 1.70) for TNF-αR2. Adjusting for BMI and history of diabetes slightly attenuated the associations, with hazard ratios of 1.39 (95% CI = 1.03 to 1.86; P_{trend} = .07) for CRP, 1.33 (95% CI = 1.00 to 1.77; P_{trend} = .03) for IL-6, and 1.21 (95% CI = 0.88 to 1.65; P_{trend} = .09) for TNF-αR2. In sensitivity analyses, we further adjusted for time from blood collection to diagnosis, and the results remained unchanged (data not shown).

The combined inflammatory biomarker score was more strongly associated with survival than individual biomarkers (P_{trend} = .003; Table 3). Compared with patients with a score of 0 (all 3 marker levels below medians), those with a score of 3 (all 3 marker levels above medians) had a multivariable hazard ratio for death of 1.57 (95% CI = 1.16 to 2.12), corresponding to median overall survival times of 8 vs 5 months (Table 3; Supplementary Figure 1, available online); the association remained statistically significant after adjustment for BMI and history of diabetes (HR = 1.53, 95% CI = 1.11 to 2.11; P_{trend} = .01; Table 3). Models with and without adjustment for cancer stage had similar results, and among WHI participants, adjusting for income and education level did not alter the results (data not shown). To address the possible influence of occult cancer on inflammatory biomarkers, we performed sensitivity analyses by excluding patients who developed pancreatic cancer within 1, 2, and 3 years after blood collection, respectively, and the association remained largely unchanged, with respective hazard ratios of 1.56 (95% CI = 1.14 to 2.12; P_{trend} = .007), 1.46 (95% CI = 1.06 to 2.01; P_{trend} = .02), and 1.45 (95% CI = 1.03 to 2.05; P_{trend} = .05). To investigate the contribution of individual biomarkers to the combined score, we performed sensitivity analyses by individually excluding each marker from the score. All modified scores were associated with survival (data not shown), indicating that the association was not predominantly driven by any one of the markers. No statistically significant interactions were observed by sex, BMI, smoking status, time from blood collection to diagnosis, or cancer stage (all $P_{interaction} \geq .41$; Supplementary Table 3, available online). Furthermore, no heterogeneity was noted across the cohort study populations ($P_{heterogeneity}$ = .97).

Long-Term Dietary Inflammatory Potential and Pancreatic Cancer Survival

We calculated the EDIP score in the prediagnostic period among 1153 patients with pancreatic cancer from HPFS and NHS (Supplementary Table 4, available online). At the end of follow-up, 1118 (97.0%) patients were deceased. Patients consuming

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Table 1. Characteristics at blood collection among patients with pancreatic cancer from 5 prospective cohorts by prediagnostic inflammatory biomarker score

Characteristic	Inflammatory biomarker score[a]				Overall
	0	1	2	3	
No. of patients	111	134	124	115	484
Age at blood collection, mean (SD), y	60.2 (8.8)	62.6 (7.7)	64.7 (8.7)	66.5 (7.6)	63.5 (8.5)
Age at diagnosis, mean (SD), y	69.8 (9.1)	70.6 (7.6)	71.6 (8.3)	72.6 (7.8)	71.2 (8.2)
Female sex, No. (%)	52 (46.8)	88 (65.7)	97 (78.2)	102 (88.7)	339 (70.0)
Cohort					
HPFS	26 (23.4)	25 (18.7)	15 (12.1)	9 (7.8)	75 (15.5)
NHS	21 (18.9)	26 (19.4)	23 (18.5)	24 (20.9)	94 (19.4)
PHS I	33 (29.7)	21 (15.7)	12 (9.7)	4 (3.5)	70 (14.5)
WHI	22 (19.8)	53 (39.6)	64 (51.6)	69 (60.0)	208 (43.0)
WHS	9 (8.1)	9 (6.7)	10 (8.1)	9 (7.8)	37 (7.6)
Race/ethnicity, No. (%)					
White	96 (86.5)	112 (83.6)	109 (87.9)	110 (95.7)	427 (88.2)
Black	1 (0.9)	6 (4.5)	9 (7.3)	2 (1.7)	18 (3.7)
Other	4 (3.6)	8 (6.0)	1 (0.8)	2 (1.7)	15 (3.1)
Missing	10 (9.0)	8 (6.0)	5 (4.0)	1 (0.9)	24 (5.0)
Body mass index, mean (SD), kg/m^2	24.4 (2.9)	25.0 (3.5)	27.3 (4.1)	29.3 (7.1)	26.5 (5.0)
Physical activity, mean (SD), MET h/wk	21.3 (23.9)	20.7 (24.9)	14.2 (17.3)	12.9 (20.9)	17.3 (22.2)
Tobacco use, No. (%)					
Never	51 (45.9)	51 (38.1)	57 (46.0)	43 (37.4)	202 (41.7)
Past	50 (45.0)	62 (46.3)	49 (39.5)	55 (47.8)	216 (44.6)
Current	10 (9.0)	21 (15.7)	17 (13.7)	15 (13.0)	63 (13.0)
Missing	0 (0)	0 (0)	1 (0.8)	2 (1.7)	3 (0.6)
Alcohol (≥1 drink/day), No. (%)	31 (27.9)	43 (32.1)	30 (24.2)	16 (13.9)	120 (24.8)
History of diabetes, No. (%)	4 (3.6)	7 (5.2)	8 (6.5)	10 (8.7)	29 (6.0)
Fasting status at blood collection, No. (%)					
<8 h	50 (45.0)	23 (17.2)	19 (15.3)	14 (12.2)	106 (21.9)
≥8 h	55 (49.5)	109 (81.3)	100 (80.6)	97 (84.3)	361 (74.6)
Missing	6 (5.4)	2 (1.5)	5 (4.0)	4 (3.5)	17 (3.5)
Time from blood collection to diagnosis, median (range), y	9.3 (0.5-24.5)	7.5 (0.1-23.6)	5.9 (0.5-24.4)	5.6 (0.5-18.6)	6.7 (0.1-24.5)
Diagnosis period, No. (%)					
1984-1989	4 (3.6)	2 (1.5)	3 (2.4)	0 (0)	9 (1.9)
1990-1994	7 (6.3)	9 (6.7)	9 (7.3)	9 (7.8)	34 (7.0)
1995-1999	43 (38.7)	44 (32.8)	50 (40.3)	47 (40.9)	184 (38.0)
2000-2004	43 (38.7)	58 (43.3)	46 (37.1)	49 (42.6)	196 (40.5)
2005-2009	14 (12.6)	21 (15.7)	16 (12.9)	10 (8.7)	61 (12.6)
Cancer stage, No. (%)					
Localized	23 (20.7)	20 (14.9)	10 (8.1)	11 (9.6)	64 (13.2)
Locally advanced	21 (18.9)	31 (23.1)	33 (26.6)	35 (30.4)	120 (24.8)
Metastatic	51 (45.9)	59 (44.0)	60 (48.4)	47 (40.9)	217 (44.8)
Unknown	16 (14.4)	24 (17.9)	21 (16.9)	22 (19.1)	83 (17.1)

[a]Calculated by summing the number of inflammatory biomarkers (C-reactive protein, interleukin-6, and tumor necrosis factor-α receptor 2) with levels above the study population medians. HPFS = Health Professionals Follow-Up Study; MET = metabolic equivalent; NHS = Nurses' Health Study; PHS = Physicians' Health Study; WHI = Women's Health Initiative; WHS = Women's Health Study.

the most proinflammatory diets (EDIP quartile 4) had higher BMI, consumed less alcohol, and were more likely to have long-term diabetes, compared with those consuming the least proinflammatory diets (EDIP quartile 1) (Table 4).

Higher EDIP score was associated with reduced survival (P_{trend} = .01; Table 5). Comparing patients in the highest vs lowest quartile of EDIP, the multivariable hazard ratio for death was 1.34 (95% CI = 1.13 to 1.59), corresponding to median overall survival times of 4 vs 6 months (Table 5; Supplementary Figure 1, available online). Further adjustment for BMI and diabetes status did not materially alter the association (HR = 1.30, 95% CI = 1.09 to 1.56; P_{trend} = .03; Table 5). In sensitivity analyses excluding FFQs returned within 3 years before diagnosis, the EDIP score was similarly associated with survival (HR = 1.30, 95% CI = 1.09 to 1.56; P_{trend} = .03). No statistically significant interactions were observed by sex, BMI, smoking status, or cancer stage (all $P_{interaction} \geq .28$; Supplementary Table 5, available online).

Discussion

Among 492 patients with pancreatic cancer from 5 large US prospective cohort studies, prediagnostic plasma levels of CRP, IL-6, and TNF-αR2 were inversely associated with survival. Furthermore, patients with elevations in all 3 markers had the shortest survival times. In a partially overlapping population of 1153 patients with pancreatic cancer, long-term diets with higher inflammatory potential were associated with reduced survival. Taken together, these data suggest that chronic

Table 2. Hazard ratios for death among patients with pancreatic cancer from 5 prospective cohorts by quartile of prediagnostic plasma inflammatory biomarkers

Biomarker	Quartile of plasma inflammatory biomarker				Per IQR increase	P_{trend}[a]
	1	2	3	4		
C-reactive protein						
Median (range), mg/L	0.38 (≤0.69)	1.10 (0.70-1.77)	2.68 (1.79-4.03)	6.34 (≥4.07)		
Person-months	1786	1465	1423	1298		
Patients/deaths	122/116	124/118	123/115	123/116		
Median overall survival, mo	8	6	7	5		
Age-adjusted, HR (95% CI)	Referent	1.12 (0.87 to 1.45)	1.11 (0.85 to 1.43)	1.24 (0.95 to 1.60)	1.13 (0.96 to 1.33)	.14
Multivariable HR (95% CI)[b]	Referent	1.27 (0.97 to 1.65)	1.12 (0.85 to 1.48)	1.44 (1.09 to 1.91)	1.22 (1.02 to 1.46)	.03
Multivariable HR (95% CI)[c]	Referent	1.27 (0.97 to 1.66)	1.10 (0.83 to 1.46)	1.39 (1.03 to 1.86)	1.19 (0.98 to 1.44)	.07
Interleukin-6						
Median (range), pg/mL	0.665 (≤0.916)	1.157 (0.918-1.493)	1.842 (1.494-2.366)	3.655 (≥2.419)		
Person-months	1629	1819	1218	1104		
Patients/deaths	121/113	121/113	121/117	121/115		
Median overall survival, mo	8	8	6	5		
Age-adjusted HR (95% CI)	Referent	0.88 (0.68 to 1.15)	1.15 (0.89 to 1.50)	1.17 (0.90 to 1.52)	1.16 (0.98 to 1.38)	.08
Multivariable HR (95% CI)[b]	Referent	0.99 (0.75 to 1.30)	1.17 (0.89 to 1.55)	1.37 (1.04 to 1.81)	1.26 (1.05 to 1.50)	.01
Multivariable HR (95% CI)[c]	Referent	0.97 (0.74 to 1.28)	1.15 (0.87 to 1.52)	1.33 (1.00 to 1.77)	1.23 (1.02 to 1.48)	.03
Tumor necrosis factor-α receptor 2						
Median (range), ng/mL	2.012 (≤2.218)	2.427 (2.247-2.672)	2.963 (2.683-3.292)	3.865 (≥3.296)		
Person-months	1592	2156	1153	1071		
Patients/deaths	123/118	123/116	123/112	123/119		
Median overall survival, mo	7	8	5	5		
Age-adjusted HR (95% CI)	Referent	0.84 (0.65 to 1.08)	1.06 (0.81 to 1.38)	1.08 (0.83 to 1.41)	1.10 (0.93 to 1.31)	.27
Multivariable HR (95% CI)[b]	Referent	0.87 (0.66 to 1.14)	1.28 (0.95 to 1.72)	1.25 (0.92 to 1.70)	1.23 (1.01 to 1.50)	.04
Multivariable HR (95% CI)[c]	Referent	0.87 (0.66 to 1.15)	1.27 (0.94 to 1.71)	1.21 (0.88 to 1.65)	1.20 (0.97 to 1.47)	.09

[a]Two-sided test for trend performed by entering the quartile of the biomarker as an ordinal variable in Cox proportional hazards regression. CI = confidence interval; HR = hazard ratio; IQR = interquartile range.
[b]Hazard ratios from Cox proportional hazards regression adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-Up Study, Nurses' Health Study, Physicians' Health Study I, Women's Health Initiative, Women's Health Study; also adjusted for sex), race and ethnicity (White, Black, other, missing), smoking status (never, past, current, missing), month of blood collection (2-month intervals), fasting time at blood collection in hours (<4, 4 to <8, 8 to <12, ≥12, missing), diagnosis period (1984-1999, 2000-2009), and cancer stage (localized, locally advanced, metastatic, unknown).
[c]Further adjusted for body mass index (continuous) and history of diabetes (yes, no).

Table 3. Hazard ratios for death among patients with pancreatic cancer from 5 prospective cohorts by prediagnostic inflammatory biomarker score

Outcome	Inflammatory biomarker score[a]				P_{trend}[b]
	0	1	2	3	
Person-months	1835	1671	1222	1042	
Patients/deaths	111/104	134/129	124/117	115/108	
Median overall survival, mo	8	7	6	5	
Age-adjusted HR (95% CI)	Referent	1.21 (0.93 to 1.57)	1.25 (0.96 to 1.64)	1.35 (1.03 to 1.78)	.03
Multivariable HR (95% CI)[c]	Referent	1.10 (0.84 to 1.45)	1.22 (0.92 to 1.64)	1.57 (1.16 to 2.12)	.003
Multivariable HR (95% CI)[d]	Referent	1.10 (0.83 to 1.45)	1.21 (0.90 to 1.62)	1.53 (1.11 to 2.11)	.01

[a]Calculated by summing the number of inflammatory biomarkers (C-reactive protein, interleukin-6, and tumor necrosis factor-α receptor 2) with levels above the study population medians. CI = confidence interval; HR = hazard ratio.
[b]Two-sided test for trend performed by entering the score in Cox proportional hazards regression.
[c]Hazard ratios from Cox proportional hazards regression adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-Up Study, Nurses' Health Study, Physicians' Health Study I, Women's Health Initiative, Women's Health Study; also adjusted for sex), race and ethnicity (White, Black, other, missing), smoking status (never, past, current, missing), month of blood collection (2-month intervals), fasting time at blood collection in hours (<4, 4 to <8, 8 to <12, ≥12, missing), diagnosis period (1984-1999, 2000-2009), and cancer stage (localized, locally advanced, metastatic, unknown).
[d]Further adjusted for body mass index (continuous) and history of diabetes (yes, no).

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inflammation induced by dietary and other factors may influence pancreatic cancer progression.

Multiple studies have examined circulating levels of CRP, IL-6, and TNF-α at diagnosis of pancreatic cancer and reported shorter survival in patients with elevations in these markers of inflammation (22-40). However, it is not possible to determine if increased inflammation at diagnosis is a cause or consequence of more rapid cancer progression. To evaluate the impact of systemic inflammation on cancer progression, we assessed circulating markers of inflammation and proinflammatory diets in the years before diagnosis. This approach lessens the impact of reverse causation and allows for exploration of chronic

Table 4. Characteristics at diagnosis among patients with pancreatic cancer from 2 prospective cohorts by quartile of the empirical dietary inflammatory pattern score in the prediagnostic period[a]

Characteristic	Quartile of the empirical dietary inflammatory pattern score				Overall
	1	2	3	4	
No. of patients	288	288	289	288	1153
Age at diagnosis, mean (SD), y	71.8 (8.8)	73.9 (8.4)	73.4 (8.3)	72.2 (8.8)	72.8 (8.6)
Female sex, No. (%)	151 (52.4)	188 (65.3)	172 (59.5)	162 (56.3)	673 (58.4)
Race/ethnicity, No. (%)					
White	276 (95.8)	275 (95.5)	274 (94.8)	268 (93.1)	1093 (94.8)
Black	1 (0.3)	4 (1.4)	6 (2.1)	5 (1.7)	16 (1.4)
Other	2 (0.7)	5 (1.7)	5 (1.7)	10 (3.5)	22 (1.9)
Missing	9 (3.1)	4 (1.4)	4 (1.4)	5 (1.7)	22 (1.9)
Body mass index, mean (SD), kg/m^2	25.0 (4.1)	25.5 (4.5)	26.7 (4.8)	27.1 (5.1)	26.1 (4.7)
Physical activity, mean (SD), MET h/wk	29.9 (34.1)	21.6 (29.2)	17.7 (23.3)	20.1 (27.5)	22.3 (29.1)
Tobacco use, No. (%)					
Never	84 (29.2)	107 (37.2)	122 (42.2)	115 (39.9)	428 (37.1)
Past	153 (53.1)	125 (43.4)	125 (43.3)	123 (42.7)	526 (45.6)
Current	39 (13.5)	34 (11.8)	22 (7.6)	32 (11.1)	127 (11.0)
Missing	12 (4.2)	22 (7.6)	20 (6.9)	18 (6.3)	72 (6.2)
Alcohol (≥1 drink/day), No. (%)	139 (48.3)	67 (23.3)	48 (16.6)	34 (11.8)	288 (25.0)
Diabetes status, No. (%)					
No or unreported	251 (87.2)	235 (81.6)	228 (78.9)	192 (66.7)	906 (78.6)
Short-term diabetes (≤4 y)	19 (6.6)	6 (2.1)	17 (5.9)	28 (9.7)	70 (6.1)
Long-term diabetes (>4 y)	18 (6.3)	47 (16.3)	44 (15.2)	68 (23.6)	177 (15.4)
Diagnosis period, No. (%)					
1986-1989	18 (6.3)	16 (5.6)	17 (5.9)	17 (5.9)	68 (5.9)
1990-1994	31 (10.8)	32 (11.1)	34 (11.8)	38 (13.2)	135 (11.7)
1995-1999	57 (19.8)	40 (13.9)	46 (15.9)	63 (21.9)	206 (17.9)
2000-2004	62 (21.5)	87 (30.2)	75 (26.0)	55 (19.1)	279 (24.2)
2005-2009	77 (26.7)	73 (25.3)	70 (24.2)	72 (25.0)	292 (25.3)
2010-2014	43 (14.9)	40 (13.9)	47 (16.3)	43 (14.9)	173 (15.0)
Cancer stage, No. (%)					
Localized	49 (17.0)	34 (11.8)	36 (12.5)	41 (14.2)	160 (13.9)
Locally advanced	33 (11.5)	26 (9.0)	32 (11.1)	38 (13.2)	129 (11.2)
Metastatic	144 (50.0)	141 (49.0)	144 (49.8)	123 (42.7)	552 (47.9)
Unknown	62 (21.5)	87 (30.2)	77 (26.6)	86 (29.9)	312 (27.1)

[a]MET = metabolic equivalent.

Table 5. Hazard ratios for death among patients with pancreatic cancer from 2 prospective cohorts by quartile of the empirical dietary inflammatory pattern score in the prediagnostic period

Outcome	Quartile of the empirical dietary inflammatory pattern score				P_{trend}[a]
	1	2	3	4	
Person-months	3649	2773	3134	2457	
Patients/deaths	288/278	288/282	289/278	288/280	
Median overall survival, mo	6	5	6	4	
Age-adjusted HR (95% CI)	Referent	1.09 (0.93 to 1.29)	0.98 (0.83 to 1.16)	1.19 (1.01 to 1.41)	.14
Multivariable HR (95% CI)[b]	Referent	1.11 (0.94 to 1.31)	0.99 (0.84 to 1.18)	1.34 (1.13 to 1.59)	.01
Multivariable HR (95% CI)[c]	Referent	1.09 (0.92 to 1.30)	0.98 (0.83 to 1.17)	1.30 (1.09 to 1.56)	.03

[a]Two-sided test for trend performed by entering the quartile of the score as an ordinal variable in Cox proportional hazards regression.
[b]Hazard ratios from Cox proportional hazards regression adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-Up Study, Nurses' Health Study; also adjusted for sex), race and ethnicity (White, Black, other, missing), smoking status (never, past, current, missing), diagnosis period (1986-1999, 2000-2014), cancer stage (localized, locally advanced, metastatic, unknown), and total energy intake (continuous).
[c]Further adjusted for body mass index (continuous) and diabetes status (no or unreported, short-term diabetes [≤4 y], long-term diabetes [>4 y]).

inflammatory states because of other factors, such as lifestyle choices and comorbidities. To our knowledge, this is the first study to examine systemic inflammation in the prediagnostic period in relation to pancreatic cancer survival.

Several potential mechanisms may explain the association between higher prediagnostic systemic inflammation and shorter patient survival times. Higher systemic measures of inflammation in the years preceding diagnosis may be due to the occult disease and reflect more aggressive tumor biology. In this circumstance, the growing cancer causes elevated levels of systemic inflammation, which is reflected in the higher prediagnostic levels of circulating CRP, IL-6, and TNF-αR2. Although the

growing malignancy may contribute to levels of inflammation prior to diagnosis, this explanation would not account for the association between long-term proinflammatory diets and worse survival outcomes. Thus, increased systemic inflammation may also promote tumor progression by acting on tumor cells and modifying the tumor microenvironment (41). Notably, in genetically engineered mouse models of pancreatic cancer, inflammation cooperates with *KRAS* to initiate and accelerate tumor progression (6,42), whereas anti-inflammatory treatment delays tumor initiation (5). In terms of the circulating markers directly measured in the current study, IL-6 signaling is known to activate pathways involved in pancreatic cancer pathogenesis, such as JAK-STAT3, Ras-MAPK, and PI3K-PkB/Akt (43), and suppresses T-cell mediated antitumor immune response (44,45). TNF-α stimulates collagen synthesis in pancreatic stellate cells (46), which forms the desmoplastic stroma that acts as a physical barrier for drug delivery.

Several important strengths of this study are notable. Prediagnostic chronic inflammation was assessed in a comprehensive manner by evaluating diets leading to systemic inflammation, as well as levels of circulating markers that are surrogates of ongoing systemic inflammation. The study included a large patient population from 5 US prospective cohorts, which collected detailed information on demographic and lifestyle factors allowing rigorous control for potential confounding. The prospective cohort design also allowed for the investigation of reverse causation, as blood samples were collected before cancer diagnosis. Exclusion of patients who developed pancreatic cancer up to 3 years after blood collection did not materially alter our results.

This study has several limitations. CRP, IL-6, and TNF-αR2 were measured at a single time point, so we were unable to assess the influence of the dynamic changes of these markers. Dietary intake was self-reported by participants and therefore subject to some measurement error, but the EDIP score to measure dietary inflammatory potential has been shown to predict inflammatory biomarker levels in large population studies (10,18). Information on cancer treatments including chemotherapy and radiotherapy was not available. Nonetheless, these strategies were unlikely to have varied by inflammatory biomarker levels or dietary inflammatory potential that were measured years before diagnosis. Although covariate data were rigorously collected within the prospective cohorts, residual confounding remains a possibility as in any observational study. Finally, our patient population consisted primarily of White participants, and further studies in a more racially diverse population are warranted.

In conclusion, chronic inflammation in the prediagnostic period was inversely associated with pancreatic cancer survival. Reduced survival was observed for patients with higher prediagnostic levels of inflammatory biomarkers, as well as for patients consuming long-term proinflammatory diets. Improved understanding of the influence of the chronic inflammation on tumor initiation and progression may allow for new approaches to disease prevention and treatment.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding authors.

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