Circulating Levels of Inflammatory Markers and Cancer Risk in the Health Aging and Body Composition Cohort

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Abstract

Background: **Chronic inflammation is associated with processes that contribute to the onset or progression of cancer. This study examined the relationships between circulating levels of the inflammatory markers interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) and total as well as site-specific cancer incidence.**

Methods: **Study subjects (n = 2,438) were older adults (ages 70-79 years) participating in the Health Aging and Body Composition study, who did not report a previous cancer diagnosis (except for nonmelanoma skin cancer) at baseline. Incident cancer events (n = 296) were ascertained during an average follow-up of 5.5 years. Inflammatory markers were measured in stored baseline fasting blood samples.**

Results: **The adjusted hazard ratios (95% confidence intervals) for incident cancer associated with a 1-unit increase on the natural log-scale were 1.13 (0.94-1.37), 1.25 (1.09-1.43), and 1.28 (0.96-1.70) for IL-6, CRP, and TNF-α, respectively. Markers were more strongly associated with cancer death: hazard ratios were 1.63 (1.19-2.23) for IL-6, 1.64 (1.20-2.24) for CRP, and 1.82 (1.14-2.92) for TNF-α. Although precision was low for site-specific analyses, our results suggest that all three markers were associated with lung cancer, that IL-6 and CRP were associated with colorectal cancer, and that CRP was associated with breast cancer. Prostate cancer was not associated with any of these markers.**

Conclusions: **These findings suggest that (*a*) the associations between IL-6, CRP, and TNF-α and the risk of cancer may be site specific and (*b*) increased levels of inflammatory markers are more strongly associated with the risk of cancer death than cancer incidence.** (Cancer Epidemiol Biomarkers Prev 2005;14(10):2413–8)

Introduction

Chronic inflammation is thought to promote carcinogenesis and may predispose an individual to cancer (1-3). Chronic activation of the immune system by parasitic, viral, and bacterial infections is associated with tumors at several sites, including bladder (4), liver (5), and stomach (6). Noninfectious chronic inflammation is also associated with several types of cancer, including colorectal (7, 8), lung (9, 10), and cancer of the esophagogastric junction (11). Organ transplantation increases both local and systemic levels of inflammation (12) and is associated with increased rates of malignancies (13, 14), although the association may be confounded by immunosuppressive therapy.

Inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), increase manifold in response to infection and tissue damage and in active diseases states. However, variations within the reference range predict the onset of health events, such as cardiovascular disease and disability (15-17), in individuals without an obvious inflammatory stimulus. Both cancer risk and plasma levels of inflammatory markers increase with age (18-20), but it is unclear whether variations in the levels of circulating inflammatory markers are associated with increased risk of cancer. We present a prospective analysis of the association between circulating levels of three inflammatory markers (IL-6, TNF-α, and CRP) measured at baseline and cancer incidence in the Health Aging and Body Composition study. In the site-specific analysis, we focused on common cancers: lung, colorectal, breast, and prostate. Because of the possibility of a preclinical cancer effect (i.e., cancer present but clinically undetected at baseline), we also examined the relationship by the duration from baseline to cancer diagnosis.

Materials and Methods

Study Population. The Health Aging and Body Composition study is an ongoing prospective cohort study designed to investigate the effect of changes in body composition and weight-related health conditions on incident functional limitation. Three thousand seventy-five participants, Black and White men and women, ages 70 to 79 years, were recruited from April 1997 to June 1998 from a list of Medicare beneficiaries residing in the areas surrounding Pittsburgh, PA, and Memphis, TN. Eligibility criteria included (*a*) no difficulty walking one-fourth mile, climbing 10 steps, or doing basic activities of daily living, (*b*) no life-threatening illness, and (*c*) no plans to leave the area for 3 years. Participants under active cancer treatment were not eligible. Although subjects with a cancer history were eligible for recruitment into the Health Aging and Body Composition cohort, they were excluded from the present analysis (121 cases and 461 noncases). All participants provided an informed consent; the protocol was approved by the institutional review boards of the clinical sites.

Follow-up and Cancer Ascertainment. Participants were contacted every 6 months either by telephone or in person and interviewed about health status, interim hospitalizations, major outpatient procedures, and new cancer diagnoses. Other

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Table 1. Baseline characteristics of the study population

	Noncases 25%-median-75% or % (n = 2,169)	Cancer cases 25%-median-75% or % (n = 296)	P*
Follow-up time (mean years)	5.92	2.85	
Age	71-73-76	71-74-76	0.09
Gender (females; %)	55	38	<0.001
Race (Caucasian; %)†	55	51	0.16
Site (Memphis; %)†	50	48	0.49
Education (%)			
Less than high school	27	25	0.30
High school	33	31	
Postsecondary	40	44	
Smoking status (%)			
Never	46	33	<0.001
Former	44	52	
Current	10	16	
Pack-years (continuous)	0-2-27	0-15-43	
Comorbid conditions (%)			
Cardiovascular disease	23	23	0.98
Diabetes	16	16	0.91
Chronic obstructive pulmonary disease and other pulmonary diseases	12	12	0.73
BMI	24.1-27.0-30.2	24.2-27.1-30.7‡	0.71
Abdominal visceral fat area (cm^2)	93-129-178	99-138-183†	0.08
Physical activity, kcal/wk (%)			
0-499.9	37	40	0.15
500-999.9	34	35	
≥1,000	29	25	
Medication use (%)			
NSAIDs	23	18	0.04
Corticosteroids	4	3	0.38
ACE inhibitors	15	17	0.43
Statins	12	14	0.34

*For continuous variables: P for Wilcoxon rank test (two-group comparison). For categorical variables: P for χ^2 test.
†Other categories are as follows: race, African American; site, Pittsburgh.
‡Only 185 cases ascertained 2 years after baseline examination (see Materials and Methods).

sources of information about incident cancer cases included reports of hospitalization from proxy reports and hospital records. The study period includes events reported and adjudicated through August 2004. For cancer cases, follow-up time was the interval from baseline to date of diagnosis (based on the confirming pathology report). For noncases, follow-up time was the interval from the baseline visit until the last contact date or death (for those who died of noncancer causes). Underlying cause of death was determined by a study adjudication committee after reviewing all available medical information. Incident nonmelanoma skin cancer is not included. Fatal cancer cases are those incident cases resulting in death.

We identified a total of 435 cancer events during the follow-up period (median follow-up time was 2.7 years for cases and 6.4 years for noncases) and excluded 12 cases because of unconfirmed cancer diagnosis, 121 cases because of previous cancer diagnoses, and 6 cases with missing data on previous cancer diagnoses. Exclusions from 2,640 noncases were the following: 461 subjects with previous cancer diagnosis and 10 with missing data. Thus, 296 incident cancer cases and 2,169 noncases were included in the analysis.

Inflammatory Markers. Baseline levels of IL-6, TNF-α, and CRP were measured in frozen stored serum (IL-6 and CRP) or plasma (TNF-α) collected by venipuncture after an overnight fast. Blood samples were obtained in the morning, and after processing, the specimens were aliquoted into cryovials, frozen at −70°C, and shipped to the Health Aging and Body Composition Core Laboratory at the University of Vermont. Cytokines were measured in duplicate using an ELISA kit from R&D Systems (Minneapolis, MN). The detectable limit was 0.10 pg/mL for IL-6 (by HS600 Quantikine kit) and 0.18 pg/mL for TNF-α (by HSTA50 kit). Serum levels of CRP were also measured in duplicate by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay was standardized according to WHO First International Reference Standard with a sensitivity of 0.08 mg/L. The lower limit of detection for CRP was 0.007 mg/L. Blind duplicate analyses (n = 150) for IL-6, CRP, and TNF-α showed interassay coefficients of variation of 10.3%, 8.0%, and 15.8%, respectively.

Statistical Analysis. We estimated the associations between the baseline inflammatory markers and the risk of cancer events by calculating hazard ratios (HR) and their 95% confidence intervals (95% CI) using separate Cox proportional hazards models. The distributions of inflammatory markers were strongly skewed to the right. We used log-transformed (natural log) continuous variables for inflammatory markers in most models to reduce the influence of extreme values at the high end. In the dose-response analysis, we used four-level index variables with cut points at equal intervals on original scale, the lowest level serving as the reference; the P for a corresponding ordinal variable was presented in the trend test. The final models included age (years), gender, race (African American/Caucasian), and site (Memphis/Pittsburgh) as covariates. Additional adjustments for continuous measures of body mass index (BMI; kg/m^2), computed tomography–measured visceral adiposity (cm^2), smoking (pack-years), questionnaire-measured physical activity (kcal/wk), categorically defined education (less than high school/high school/postsecondary), medical conditions at baseline (diabetes, chronic obstructive pulmonary disease, and cardiovascular diseases), and medication use [nonsteroidal anti-inflammatory drugs (NSAID), systemic corticosteroids, ACE inhibitors, and statins] did not materially change the estimates of the associations between cancer events and each inflammatory marker. We examined the interactions between each inflammatory marker and the following covariates: smoking (as pack-years and as smoking status ever/never), visceral adiposity, BMI, and physical activity. Interaction terms between each inflammatory marker and a covariate were included into the model (one at a time); $P > 0.3$ for the β coefficient was considered as an indicator of no interaction. None of the examined interactions were significant, so no results are reported.

We examined differences in the distributions of the variables listed in Table 1 by case status using Wilcoxon rank test for continuous variable and using χ^2 test for categorical variables. With respect to BMI and visceral adiposity, we excluded early diagnosed cases (<2 years after baseline), because clinically undetected cancer could influence these variables measured at baseline. Similar analysis examined the

Table 2. Distribution of inflammatory markers in the study population

Inflammatory marker	Range	Mean (SD)	5%	25%	50%	75%	95%
IL-6, pg/mL (n = 2,339)	0.21-15.96	2.42 (1.99)	0.72	1.26	1.83	2.82	6.39
CRP, mg/L (n = 2,432)	0.15-85.18	3.07 (4.99)	0.64	1.01	1.69	3.17	9.99
TNF-α, pg/mL (n = 2,298)	0.57-29.55	3.44 (1.70)	1.59	2.14	3.14	4.06	6.21

Table 3. Association between incident cancer events and inflammatory markers

Inflammatory markers	HR* (95% CI) Number of events					
	All cancer events			Nonfatal cancer events	Cancer death	
	Unadjusted	Adjusted†	NSAIDs users excluded†	Adjusted†	Adjusted†	NSAIDs users excluded†
log(IL-6), pg/mL	1.18 (0.98-1.41) 273	1.13 (0.94-1.37) 273	1.10 (0.90-1.35) 229	0.95 (0.75-1.19) 189	1.63 (1.19-2.23) 84	1.65 (1.19-2.29) 80
log(CRP), mg/L	1.17 (1.02-1.33) 291	1.25 (1.09-1.43) 291	1.23 (1.06-1.43) 243	1.17 (1.00-1.38) 201	1.41 (1.13-1.77) 90	1.51 (1.19-1.92) 85
log(TNF-α), pg/mL	1.32 (1.00-1.76) 275	1.28 (0.96-1.70) 275	1.39 (1.02-1.90) 229	1.07 (0.76-1.52) 188	1.82 (1.14-2.92) 87	1.95 (1.20-3.15) 82

*Log-transformed variables: the HR present the associations with the inflammatory markers related to a unit change on the log scale.
†HR adjusted for age, gender, race, and site.

difference in the distributions of inflammatory markers by study characteristics. Pearson correlation coefficients were used to evaluate the amount of correlation among the levels of inflammatory markers (log-transformed).

Results

Cases included a lower proportion of women, nonsmokers, and users of NSAIDs compared with noncases (Table 1). The distributions of other characteristics were similar in cases and noncases. The distribution of the inflammatory markers in the study population is presented in Table 2. The median level of CRP in the entire study population was higher than the established median reference level in healthy individuals [1.69 versus 0.64-0.80 mg/L (21)]. However, the CRP and IL-6 levels (Table 2) are similar to other studies of elderly populations (18, 22). A formal comparison of the time to diagnosis in the three groups of cases (baseline CRP <5, 5-10, and >10 mg/L) indicated that this variable did not differ between the groups ($P = 0.6$, Kruskal-Wallis test). In addition, time to diagnosis did not correlate with baseline levels of inflammatory markers among cases; Pearson correlation coefficients were −0.020 for ln(IL-6), 0.006 for ln(CRP), and −0.024 for ln(TNF-α); Ps for all three coefficients were ≥0.7.

Use of NSAIDs was associated with lower levels of IL-6 ($P < 0.01$) and higher levels of TNF-α ($P = 0.005$) but was not associated with CRP levels ($P = 0.77$). The participants treated with systemic corticosteroids had higher levels of IL-6 ($P < 0.01$) and CRP ($P < 0.01$). Higher levels of inflammatory markers were seen in smokers, those with higher BMI, and participants with diabetes (Ps < 0.01). Physical activity was associated with lower levels of IL-6 and CRP (Ps < 0.001; ref. 23) but not with TNF-α. Levels of inflammatory markers were correlated: Pearson correlation coefficients were 0.47 for ln(IL-6) and ln(CRP), 0.28 for ln(IL-6) and ln(TNF-α), and 0.14 for ln(CRP) and ln(TNF-α); Ps < 0.01.

Four common cancers comprised 63% of incident cancer events: breast cancer 11.1%, colorectal cancer 14.5%, lung cancer 14.5%, and prostate cancer 22.9%. Gastrointestinal (specifically colon and stomach) and lung cancers accounted for 23% and 27% of fatal cancers ($n = 93$), respectively.

All three inflammatory markers showed weak unadjusted associations with increased risk of cancer events, and the magnitude of increase in risk ranged from 18% to 33% per unit increase of the respective inflammatory marker on the log scale (Table 3). Adjustments for age, gender, race, and site did not markedly influence the magnitude of these associations, nor did adjustment for several other potential confounders (data not shown; Table 3). Exclusion of the NSAIDs users did not change these estimates materially (Table 3). We conducted stratified analysis of all cancer events by CRP levels (CRP <5 and ≥5 mg/L) to examine whether the association with CRP is limited to the highest levels. We did not find a stronger association with CRP at levels ≥5 mg/L (HR, 1.04; 95% CI, 0.63-1.72) compared with the association at levels <5 mg/L (HR, 1.12; 95% CI, 0.91-1.39). The dose-response analysis showed a monotonic increase in the HR associated with each increment of CRP (1 mg/L), whereas TNF-α (increment, 2 pg/mL) and IL-6 (increment, 1 pg/mL) did not exhibit a linear pattern (Fig. 1). CRP was more strongly associated with cancer death than with nonfatal cancer (Table 3). The associations with IL-6 and TNF-α were limited to cancer deaths (Table 3).

Because clinically undetected malignancies may lead to an increase in circulating levels of inflammatory markers, we examined the association by time of diagnosis (i.e., in Fig. 2, we presented the associations with all incident cancer cases and with cases diagnosed later than 1, 2, and 3 years of follow-up). Exclusion of earlier diagnosed cancer cases did not decrease

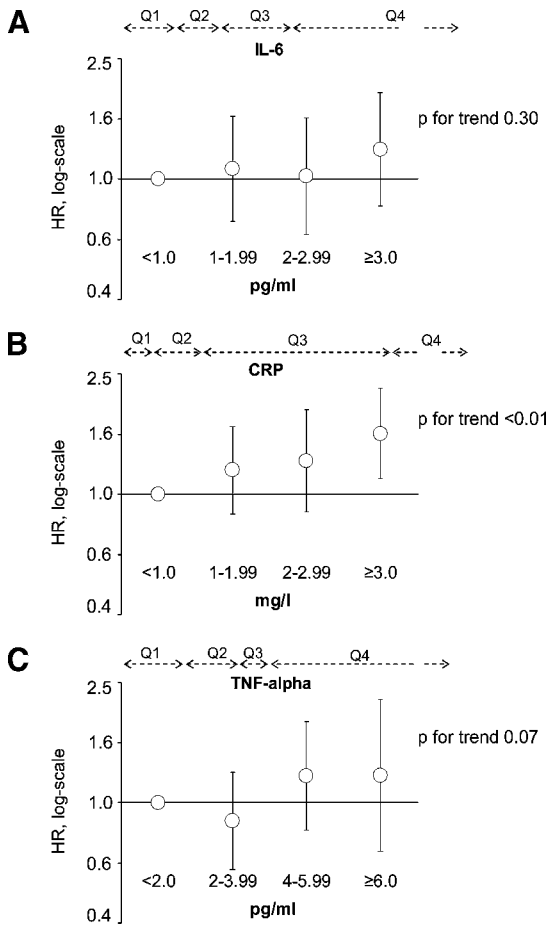

Figure 1. Dose-response relationships between circulating levels of inflammatory markers and the risk of cancer events: IL-6 (**A**), CRP (**B**), and TNF-α (**C**).

Table 4. Associations between inflammatory markers and common cancers

Inflammatory markers*	HR*,† (95% CI) Number of events			
	Breast	Colorectal	Lung	Prostate
log(IL-6), pg/mL	0.95 (0.54-1.65) 30	1.44 (0.90-2.31) 40	1.43 (0.91-2.26) 42	0.88 (0.59-1.30) 63
log(CRP), mg/L	1.32 (0.91-1.93) 33	1.44 (1.03-2.02) 41	1.64 (1.20-2.24) 42	0.94 (0.70-1.28) 59
log(TNF-α), pg/mL	0.70 (0.29-1.72) 31	0.90 (0.42-1.94) 39	1.67 (0.79-3.55) 39	1.10 (0.61-1.98) 64

*Log-transformed variables: the HR present the associations with the inflammatory markers related to a unit change on the log scale.
†HR adjusted for age, gender, race, and site.

the magnitude of the associations with the inflammatory markers. In addition, a formal test for proportional hazards assumption showed no indication of an interaction with time: *P*s were 0.4 for IL-6, 0.9 for CRP, and 0.5 for TNF-α. There did not seem to be a stronger association for those cancers diagnosed earlier during the follow-up. A similar analysis for the fatal cancer events showed comparable results (data not shown).

The analysis by cancer site yielded imprecise estimates probably due to the limited number of cases. However, several trends in this analysis were evident. Prostate cancer was not associated with any of the examined inflammatory markers (Table 4). Lung cancer showed an association with CRP and a tendency for positive association with IL-6 and TNF-α; additional adjustment for smoking reduced the magnitude of these estimates: the HRs were 1.22 (0.75-1.97), 1.54 (1.12-2.12), and 1.19 (0.55-2.59) for IL-6, CRP, and TNF-α, respectively. Colorectal cancer showed an association with CRP and a tendency for positive association with IL-6 levels; additional adjustments for BMI and use of NSAIDs did not influence these results.

Discussion

This analysis examined the associations between baseline levels of three inflammatory markers and the risk of cancer in the Health Aging and Body Composition cohort. In this cohort, proportions of subjects with the CRP levels indicative of an underlying pathologic process or an acute inflammatory response were similar to previous studies in elderly populations (24, 25). All three markers were weakly associated with the risk of cancer events, and the estimates of the associations with CRP were more precise than for the other two markers (i.e., the 95% CIs for the CRP estimates were consistently narrower compared with other inflammatory markers in this analysis). There was no evidence of a preclinical cancer effect: none of the inflammatory markers significantly correlated with the time to cancer diagnosis, and the strength of the associations with all markers did not decrease with exclusion of the earlier cancer events. However, these results do not exclude a possibility that the levels of markers are influenced by a preclinical disease, especially in case of cancers with a long latency. A longer follow-up time is required to rule out the preclinical cancer effect.

The association between inflammatory markers and cancer may be site specific. Taking into account that the estimates in the site-specific analysis are imprecise, we point to the following tendencies. The results were most consistent for lung cancer, with associations noted for all three markers. To our knowledge, there are no similar data in the literature with which to compare this finding. Colorectal cancer was associated with IL-6 and CRP. The association with CRP is consistent with the report from a large case-control study of colon cancer (172 cases, 342 controls) nested in a prospective cohort (26), although no association was found between CRP and colorectal cancer in the prospective Women's Health Study (27). Breast cancer was weakly associated only with CRP, but the other two markers were unrelated. Although inflammation in prostate often accompanies prostate tumors (28), none of the examined inflammatory markers was associated with the risk of prostate cancer, which is consistent with a previous report from a prospective study (29).

The most intriguing findings of this analysis are stronger associations with fatal cancers. We offer two possible explanations (nonmutually exclusive) for the associations between inflammatory markers and fatal cancer events. First, this association may be driven by the large contribution of colorectal and lung cancers to this pool, as those cancer types showed associations in site-specific analysis. Second, these findings may reflect a role of the inflammatory mediators in the tumor-host interaction. Tumor-host interaction is related to the development of metastases and of paraneoplastic syndromes, such as cachexia (30-32). Elevated levels of inflammatory markers have been linked to the presence of metastases and to the development of cachexia (31-35). It has

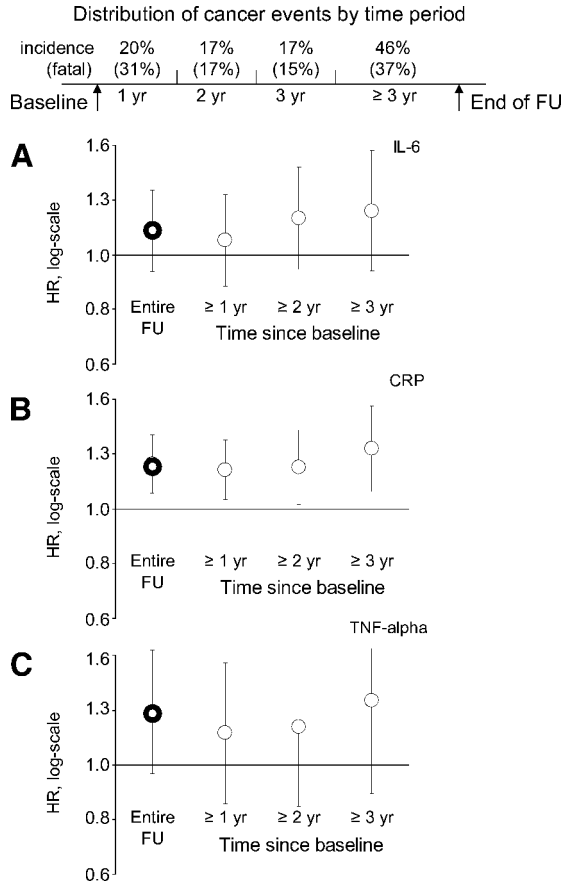

Figure 2. Time trends in the relationships between circulating levels of inflammatory markers and the risk of cancer events: IL-6 (**A**), CRP (**B**), and TNF-α (**C**). *FU,* follow-up.

been shown that increased levels of CRP and IL-6 are associated with poor prognosis and/or survival in patients with different cancer types, including lung (36), colorectal (33), metastatic mammary (37), pancreatic (38, 39), renal cell (40, 41), and multiple myeloma (42). Thus, elevation of inflammatory markers above the normal cut point is a prognostic factor for cancer patients. We hypothesize that the levels of inflammatory markers before cancer diagnosis indicate predisposition to a strong systemic inflammatory response of the host to the tumor. If proven to be true, this hypothesis could explain a link seen between the baseline levels of inflammatory markers and the risk of cancer death. In accord with this hypothesis, anti-inflammatory treatment (steroids and NSAIDs) prolonged survival among cancer patients. However, it remains unclear whether despite the use of anti-inflammatory agents at baseline the higher levels of inflammatory markers are associated with fatal cancer. We could not address this question because of the limited sample size: only approximately a quarter the study population used NSAIDs or systemic corticosteroids (Table 1).

One could expect that use of NSAIDs and corticosteroids is associated with the lower levels of the inflammatory markers. However, our findings for the three markers were discordant. The associations with NSAIDs use were negative for IL-6, positive for TNF-α, and absent for CRP. Systemic corticosteroids were positively associated with IL-6 and CRP and were not associated with TNF-α. These crude cross-sectional associations may be confounded by the presence an inflammatory illness or other factors, including the dose of the medicine; we did not examine these associations in detail, because they were not the focus of this analysis. Alternatively, these results suggest that anti-inflammatory agents unequally affect systemic levels of the examined inflammatory markers.

The present study has several strengths. It is a prospective study with multiple markers of inflammatory status as opposed to the earlier studies that used only CRP levels (26, 27, 29). In addition, the study population includes a larger number of African Americans and people with different educational backgrounds (Table 1). In this study, all participants are in a relatively narrow age range (70-79 years at baseline). This decreases (although does not eliminate) a possibility of unaccounted confounding by age, which is the strongest predictor of cancer incidence, and by unmeasured comorbidities, the prevalence of which increases with age. The major limitation of this study is a small number of site-specific cancer cases. Because the relationship between inflammatory markers and cancer incidence may be site specific, it will be important to determine whether our results can be replicated in larger samples. The use of a single assessment of inflammatory markers at baseline is also a limitation of the study. In case of relatively large intraindividual variability, a single measurement may result in a significant exposure misclassification. However, previous studies showed that the repeated measurements of CRP in serum clustered around a typical characteristic value for each subject (43) and that the within-subject variability was ~2-fold lower than the between-subject variability (21). The reported correlation coefficient for the repeated measures of CRP was 0.6 (44, 45); the intraclass correlation coefficients for IL-6 ranged between 0.48 in young women (46) and 0.86 in elderly subjects (47) and was 0.73 (46) for TNF-α. These correlations between the repeated measures of the inflammatory markers are close to the observed value for systolic blood pressure (0.6; ref. 48), which is the established risk factor for cardiovascular disease.

In summary, our results suggest that (*a*) CRP levels are a more consistent indicator of cancer risk than IL-6 and TNF-α, (*b*) the association between cancer incidence and inflammatory markers may be site specific, and (*c*) increased levels of inflammatory markers show stronger associations with the risk of cancer death compared with the risk of cancer incidence. Further studies are needed to refine estimates of the association between inflammatory markers and site-specific cancers.

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