Associations of Circulating C-Reactive Protein and Interleukin-6 with Survival in Women with and without Cancer: Findings from the British Women's Heart and Health Study

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Abstract

Background: **Inflammation is associated with worse prognosis and survival in many cancers. Our aim was to investigate the associations of circulating C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations with all-cause mortality in cancer patients and to determine whether any associations were specific to malignancy.**

Method: **We used data from the British Women's Heart and Health Study, a cohort of 4,286 women aged 60 to 79 years. We investigated the associations between CRP, IL-6, and survival in women with and without cancer using Cox regression and assessed the interaction between cancer status and these inflammatory markers to determine whether these associations differed according to cancer status.**

Results: **Elevated CRP and IL-6 were associated with decreased survival in women with cancer [unadjusted hazard ratio per doubling of CRP, 1.22, 95% confidence interval (95% CI), 1.03, 1.46; and per doubling of IL-6, 1.52, 95% CI, 1.25, 1.86] and in women without cancer [CRP: 1.24 (1.12, 1.37); IL-6: 1.53 (1.35, 1.75)]. Adjustment for age, body mass index, physical activity level, socioeconomic position, HRT use, and tobacco smoking did not change these associations. After mutual adjustment, IL-6 but not CRP was independently associated with survival. We found no strong evidence that these associations differed between cancer patients and cancer-free women.**

Conclusions: **Elevated CRP and IL-6 concentrations were similarly associated with an increased risk of death in elderly women with and without cancer. Thus, in this group, these markers are likely to be indicators of non-cancer comorbidities rather than related to the malignancy itself.** (Cancer Epidemiol Biomarkers Prev 2007; 16(6):1155–9)

Introduction

Inflammation is associated with poor prognosis and decreased survival in many types of cancer. As a marker of persistent inflammation, elevated concentrations of the inflammatory cytokine interleukin-6 (IL-6) have been shown to be associated with shorter survival period in patients with various cancers, including colorectal (1, 2) and pancreatic cancers (3), melanoma (4), head and neck squamous cell carcinoma (5), soft tissue sarcoma (6), and diffuse large-cell lymphoma (7). Elevated concentrations of the acute phase reactant C-reactive protein (CRP) have been reported to be associated with shorter survival in, among others, prostate (8), breast (9), upper digestive tract (10), pancreatic (11), and colorectal, gastric, breast, and bronchogenic cancers (12).

IL-6 and CRP have related roles in the inflammatory response: IL-6 induces CRP production in the liver by activating Janus kinases. Signal transducers and activators of transcription subsequently switch on the CRP gene expression, leading to the production of CRP. However, few studies have examined both CRP and IL-6 together in the same study population, which would be important to determine whether measuring both markers provides better prognostic information or whether one marker alone is better than the other. A study reported shorter disease-free survival in colorectal cancer patients with IL-6 concentrations higher than 8 pg/mL ($P < 0.05$) and CRP concentrations higher than 7 mg/L (<0.05; ref. 2). However, in another study, elevated circulating CRP but not IL-6 was reported to be associated with overall survival in multiple myeloma (13).

An important limitation of previous studies in this area is that as far as we are aware, none have compared the associations of inflammatory markers with survival in cancer patients and individuals who are cancer free. This is important to assess the specificity and the use of these markers in prognosis and in evaluating the effect of any treatment on survival. The association of IL-6 or CRP with survival in cancer patients may either be due to cancer pathology or other comorbidities. It is possible that elevated concentrations of inflammatory markers in people with cancer reflect a more advanced cancer stage at diagnosis or a more aggressive tumor, hence leading to worse prognosis (14). Alternatively, elevated IL-6 or CRP concentrations may indicate other non-cancer comorbidities (15, 16) or a cumulative effect of a lifetime of adverse health events (17, 18) and may thus be associated with decreased survival irrespective of the presence of cancer or the course of any malignant disease.

Our aim was to investigate the independent associations of circulating IL-6 and CRP concentrations with all-cause mortality in cancer patients and to determine whether any associations were specific to individuals with cancer. To explore this, we compared the associations of these biomarkers

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Table 1. Main cancer types in women with cancer at baseline (n = 353)

Type of primary cancer	Number (%)
Breast	141 (39.9)
Melanoma	25 (7.1)
Cervical	23 (6.5)
Colon	20 (5.7)
Other	144 (40.8)
Total	353 (100)*

*Each cancer type included in this category contributed <5% to the total number (353) of women with cancer.

with survival in two groups of women: those who had established cancer at the time when IL-6 and CRP were measured and women who were free of cancer at the time of CRP and IL-6 measurement and remained cancer-free throughout the follow-up.

Materials and Methods

Participants. Data from the British Women's Heart and Health Study (BWHHS) were used. This ongoing cohort study comprises 4,286 women aged 60 to 79 years at the baseline assessment undertaken between 1999 and 2001, who were randomly selected from 23 towns in Britain. Full details of the data collection have been published previously (17, 18). The participants were flagged with the National Health Service Cancer Register for information on cancer registrations and deaths, and all deaths registered up to 31 January 2006 were included in the analysis. Cancer cases were obtained from either the participants' self-report, medical records review, or the National Health Service Cancer Registry data and coded using the International Classification of Diseases–10 coding system. Cancer date was defined as the earliest date when a participant had a record of cancer from any of the three sources. After excluding women who did not have complete data on IL-6, CRP, and all potential confounders (n = 659), women whose first record of a cancer event was in their death certificate (n = 26; these women were excluded because we could not be certain of the real date of their cancer diagnosis) and women who were cancer free at study baseline but developed cancer during the follow-up (n = 174; these women were excluded because we could not see the clinical value for estimating the prognostic role of CRP or IL-6 concentrations in women who have not been diagnosed with cancer), we were left with 3,427 women. Eleven women were recorded as cancer cases in at least one of the sources, but we had insufficient information of the type or site of their cancer. These women were included in the study as cancer cases. We conducted sensitivity analyses in which these women were included in the cancer-free group or excluded altogether, but the results from these analyses did not differ from the results presented here. Participants with nonmelanoma skin cancer (n = 156) were treated as noncancer cases in the main analyses because nonmelanoma skin cancer is a relatively benign condition. A sensitivity analysis in which they were included in the number of cancer cases produced results similar to those presented here. A total of 3,074 women were free of cancer throughout the study, and 353 had cancer at study baseline when the inflammatory markers were measured. Baseline cancer cases were women who had a record of cancer before or up to 60 days after their date of entry to the study.

Exposure Measurement. CRP was measured at study baseline using an ultrasensitive nephelometric assay (Dade Behring). Concentrations lower than 0.162 mg/L could not be detected by this method, and the 55 participants, whose CRP concentration was measured as 0.162 mg/L, were treated as having this value. IL-6 was measured using high-sensitivity ELISA (R&D Systems), and because concentrations higher than 30 pg/mL could not be quantified, the 73 women with higher IL-6 concentrations were analyzed as having this value. Intra- and interassay coefficients of variation were 4.7% and 8.3% for CRP and 7.5% and 8.9% for IL-6.

Potential Confounders. Age, body mass index (BMI), physical activity level, use of hormone replacement therapy (HRT), tobacco smoking, and childhood and adult socioeconomic position were considered to be potential confounders. Age was calculated from the date of birth and the date of entry to study. BMI was calculated from the height and weight measured by a nurse at the baseline medical examination (18). Data on physical activity levels (hours of physical activity in a typical week) and smoking (never, past, current 1-9, current 10-19 cigarettes/day, current 20-29 and current >29 cigarettes) were obtained from the self-completed baseline questionnaire. At the baseline examination, the women were asked to bring along all medications they were taking at the time. Details of these were recorded and coded according to the British National Formulary. In addition, the baseline questionnaire included questions about the use of HRT. HRT use (never, past, current at the time of CRP and IL-6 measurement) was ascertained from the responses to the questionnaire and assessment of the medication brought to the baseline examination. Childhood socioeconomic position was obtained from the responses to questions about the participant's father's longest held occupation and adult socioeconomic position from questions on the longest held occupation of the participant's husband and the participant herself. Both were classified into six categories according to the Registrar

Table 2. Participant characteristics

Mean (SD) for continuous variables and number (%) for binary variables	Cancer status		Mean difference for continuous variables or odds ratio for binary variables (95% CI), P
Inflammatory markers	Never had cancer (n = 3,074)	Cancer at baseline (n = 353)	
Geometric mean CRP, mg/L	1.75 (3.13)	1.85 (3.28)	1.06 (0.93, 1.20), 0.4
Geometric mean IL-6, pg/mL	2.31 (1.97)	2.50 (2.13)	1.08 (1.00, 1.17), 0.04
Potential confounders			
Age (y)	69.2 (5.5)	69.6 (5.3)	−0.47 (−1.08, 0.12), 0.1
BMI (kg/m^2)	27.6 (5.0)	27.7 (5.1)	−0.13 (−0.68, 0.42), 0.6
Smoker at baseline	311 (10.1)	39 (11.1)	1.10 (0.78, 1.57), 0.6
Childhood manual SEP	643 (20.9)	83 (23.5)	1.16 (0.90, 1.51), 0.3
Adult manual SEP	1,396 (45.4)	165 (46.7)	1.06 (0.85, 1.320), 0.6
HRT user at baseline	292 (9.5)	18 (5.1)	0.51 (0.31, 0.84), 0.007

Abbreviation: SEP: socioeconomic position.

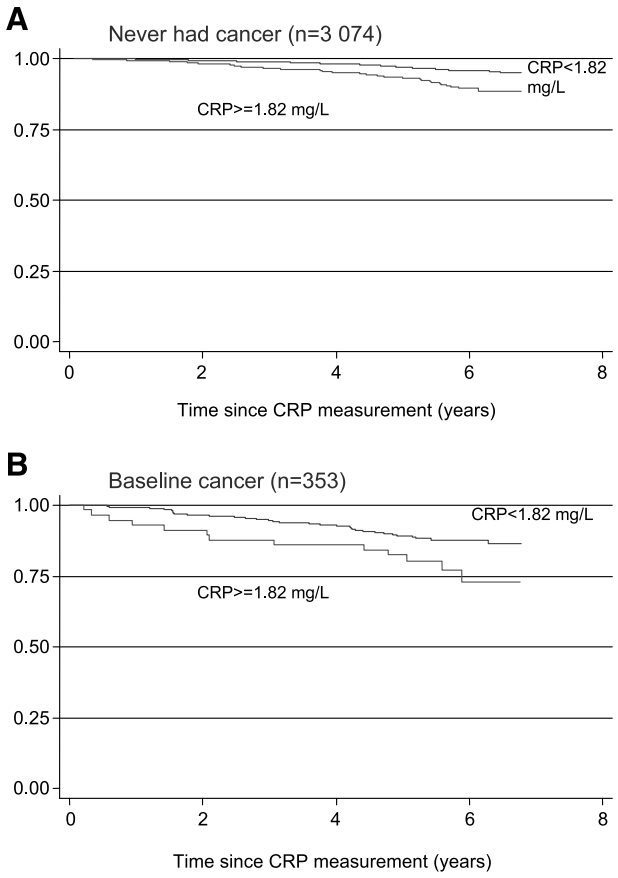

Figure 1. A. Survival in women who had never had cancer according to circulating CRP concentrations. **B.** Survival in women with cancer at baseline according to circulating CRP concentrations.

General's classification (Office of Population Censuses and Surveys). Details of the classification have been published previously (17, 18).

Statistical Analysis. Mean (SD) and number (%) for each inflammatory marker and all potential confounding factors are presented for women with and without cancer, and generalized linear regression models were used to estimate mean differences and odds ratios with 95% confidence intervals (95% CI) for a comparison between these groups. We used Cox proportional hazards regression models to investigate the association between circulating IL-6 and CRP and survival. Because the participants entered the study at different times, time at risk was defined as time since birth and survival time was defined as the period between the date of entry to the study, when IL-6 and CRP were measured, and death of any cause or the end of follow-up, January 31, 2006. We fitted unadjusted, confounder-adjusted, and mutually (CRP and IL-6) adjusted models separately for women who were free of cancer throughout the study and women who had established cancer at the time of IL-6 and CRP measurement. An interaction term (cancer status × inflammatory marker) was fitted into the models, and a likelihood ratio test was computed to assess whether there was evidence that the association of IL-6 and CRP with survival differed according to cancer status. We plotted Kaplan-Meyer graphs to illustrate the difference in survival after the date of entry to the study between those with high and low concentrations of CRP and IL-6, according to cancer status, using median values as cutoff points to dichotomize women into high and low CRP or IL-6 groups. All statistical analyses were conducted using Stata 9.2 (Stata Corporation).

Results

The most common primary cancer was breast cancer (n = 141), followed by melanoma and cervical and colon cancers (Table 1). The CRP and IL-6 concentrations and the distributions of potential confounders in all women included in this study are shown in Table 2. Geometric mean CRP concentrations were similar in women with and without cancer; geometric mean IL-6 concentration was slightly higher in women with cancer. The proportions of individuals with an IL-6 measurement exceeding the assay quantification limit, 30 pg/mL, were slightly higher among women with cancer (n = 13, 3.7%) than in those without malignant disease (n = 60, 2%), P = 0.03. To ensure that including the 73 women with IL-6 concentrations at or above 30 pg/mL did not influence our findings, we repeated our analyses without these women. The results did not differ from those presented here. Women with cancer were slightly older and less likely to be HRT users at study baseline, but other characteristics did not vary between the two groups of women. There were 263 deaths among the 3,601 women included in the study, 143 among the group of women who were free of cancer throughout the study, and 49 among those with cancer at baseline.

Figures 1 and 2 illustrate the proportion of women surviving over the follow-up period according to whether their CRP (Fig. 1A and B) and IL-6 concentrations (Fig. 2A and B) were above or below the median in the sample.

Elevated CRP and IL-6 concentrations were associated with decreased survival time in women who had an established cancer at study baseline as well as in women who were free of cancer throughout the study. Table 3 shows the results from

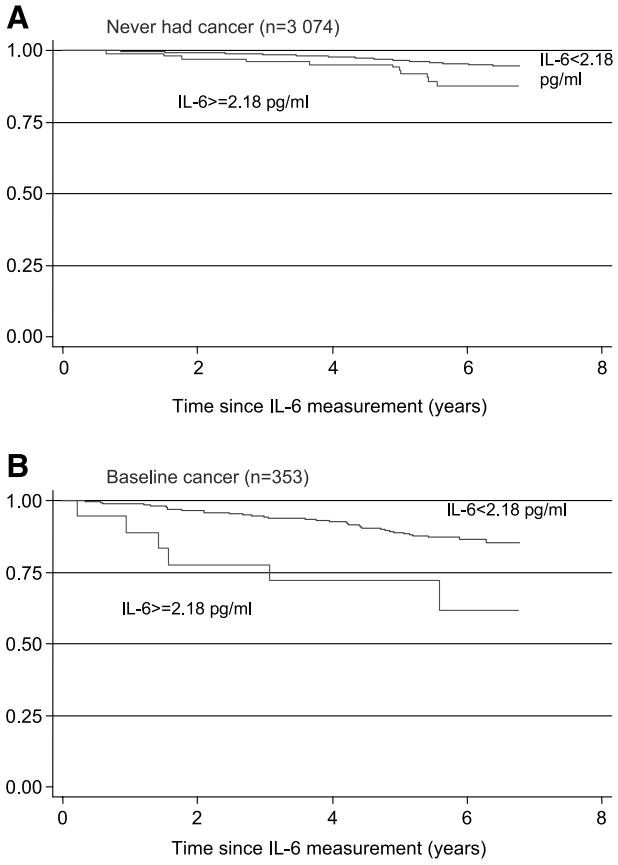

Figure 2. A. Survival in women who had never had cancer according to circulating IL-6 concentrations. **B.** Survival in women who had cancer at baseline according to circulating CRP concentrations.

Table 3. Hazard ratios for death (per doubling of the exposure) in relation to CRP and IL-6 according to cancer status

CRP	Hazard ratio (95% CI) per doubling of inflammatory marker					
	Model 1: unadjusted	*P*	Model 2: adjusted for confounders*	*P*	Model 3: Adjusted for one another and confounders	*P*
Never had cancer (n = 3,074)	1.24 (1.12, 1.37)	<0.001	1.19 (1.07, 1.33)	0.001	1.07 (0.96, 1.19)	0.2
Cancer at baseline (n = 353)	1.22 (1.03, 1.46)	0.03	1.23 (1.03, 1.28)	0.02	1.12 (0.93, 1.34)	0.2
P for interaction between cancer status and CRP	0.9		0.9		0.9	
IL-6						
Never had cancer (n = 3,074)	1.53 (1.35, 1.75)	<0.001	1.47 (1.28, 1.68)	<0.001	1.41 (1.21, 1.64)	<0.001
Cancer at baseline (n = 353)	1.52 (1.25, 1.86)	<0.001	1.44 (1.17, 1.78)	0.001	1.37 (1.09, 1.73)	0.007
P for interaction between cancer status and IL-6	0.8		0.7		0.8	

*Adjusted for smoking, BMI, physical activity, use of hormone replacement therapy, and childhood and adult socioeconomic position.

the multivariable survival analyses in women with cancer and cancer-free women. The associations of both CRP and IL-6 with survival in women with cancer at baseline and in those free of cancer were not markedly attenuated by adjustment for potential confounders (model 2; Table 3).

CRP and IL-6 concentrations were modestly correlated with each other in women who remained cancer free throughout the study (Pearson's correlation coefficient, $r = 0.44$, $P < 0.001$) and were similarly correlated with each other in those who had cancer at baseline ($r = 0.40$, $P < 0.001$). There was little evidence for an independent association of CRP with the risk of death once IL-6 had been adjusted for, but IL-6 was associated with an increased risk of death even with adjustment for CRP (model 3, Table 3). There was no strong statistical evidence that the associations between each marker of inflammation and survival differed between cancer patients and cancer-free women (Table 3).

Discussion

Our results show that high circulating concentrations of IL-6 and CRP are similarly associated with decreased survival in women with established cancer and those without cancer. The similar association in women with and without cancer suggests that any association with survival time observed in cancer patients is related to comorbidities, lifestyle, and socioeconomic factors rather than any specific aspect of cancer pathology. IL-6 remained associated with survival in both women with and without cancer even with adjustment for CRP, whereas CRP was not associated with survival independently of IL-6. We found no difference in mean CRP concentrations between women with prevalent cancer and those who were cancer free at baseline: these findings differ from the results of some, although not all, prevalent studies examining this association (19).

Limitations and Strengths of the Study. To our knowledge, no previous study examining the prognostic role of markers of inflammation in cancer patients has compared the effects in individuals with cancer to those without any malignant disease, and an important strength of our study is that we have assessed the specificity of this association. Although the number of women with cancer in our study was similar to numbers in previous prognostic studies, we did not have sufficient power to examine the possible prognostic role of these biomarkers in different cancer types. Because all our participants were elderly women, our results may not necessarily be generalizable to men or younger people. It is possible that in cancers that occur only or more commonly in men, such as prostate, testicular, lung, and liver cancers, or that are more common at younger ages, such as neurologic cancers, inflammatory markers are stronger indicators of survival than they are for the predominant cancer in this cohort (breast cancer), and that these effects are stronger when compared with cancer-free individuals. It is also possible that as a hormone-related disease, breast cancer is less strongly associated with systemic inflammation (19). We do not have detailed information on tumor stage or grade for our participants and were thus unable to determine whether the association between circulating CRP and IL-6 and survival depends on the extent of the disease. Thus, we would suggest that future studies compared the prognostic value of inflammatory biomarkers in men and women with a range of cancer types and those who are cancer free and investigated whether these associations differ according to the type and stage of the malignancy.

Conclusion

We found that as markers of survival, IL-6 and CRP are not specific to cancers that occur commonly in elderly women. Thus, it is likely that these markers are indicators of non-cancer comorbidities or cumulative effects of a lifetime of adverse health events rather than related to malignancy itself in this group.

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