Research Article

Cancer Epidemiology, Biomarkers & Prevention

High-Sensitivity C-Reactive Protein Levels and Cancer Mortality

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Abstract

Background: High-sensitivity C-reactive protein (hs-CRP) is an important inflammatory marker, and inflammation is known to be involved in the initiation and progression of cancer. We investigated the association between serum hs-CRP levels and all-cause mortality, cancer mortality, and site-specific cancer mortality in apparently cancer-free Koreans.

Methods: A total of 33,567 participants who underwent routine check-ups at a single tertiary hospital health-screening center between May 1995 and December 2006, and whose serum hs-CRP level data were available, were included in the study. Baseline serum hs-CRP levels were obtained and subjects were followed up for mortality from baseline examination until December 31, 2008.

Results: During an average follow-up of 9.4 years, 1,054 deaths, including 506 cancer deaths, were recorded. The adjusted HRs (aHR; 95% confidence interval [CI]) of subjects with hs-CRP $\geq$3 mg/L for all-cause and cancer-related mortality were 1.38 (1.15–1.66) and 1.61 (1.25–2.07) in men, and 1.29 (0.94–1.77) and 1.24 (0.75–2.06) in women, respectively, compared with subjects with hs-CRP $\leq$1 mg/L. Elevated hs-CRP was also associated with an increased risk of site-specific mortality from lung cancer for sexes combined (2.53 [1.57–4.06]).

Conclusions: This study suggests that elevated levels of hs-CRP in apparently cancer-free individuals may be associated with increased mortality from all-causes and cancer, in particular, lung cancer in men, but not in women.

Impact: As a marker for chronic inflammation, hs-CRP assists in the identification of subjects with an increased risk of cancer death. *Cancer Epidemiol Biomarkers Prev; 21(11); 2076–86. ©2012 AACR.*

Introduction

Accumulating evidence suggests that there may be a link between inflammatory markers and cancer risk. High-sensitivity C-reactive protein (hs-CRP), which is one of the most important systemic inflammatory markers, is produced mainly by hepatocytes in response to inflammatory stimuli (1). Elevated hs-CRP levels have been documented in several conditions, such as inflammatory disease, bacterial infection, fatal and nonfatal myocardial infarction, trauma, and surgery (2).

Inflammation is also known to be involved in other causes of death, such as cancer and chronic obstructive lung disease. Elevated inflammatory biomarkers, including interleukin 6 (IL-6) and TNFα, have been associated with all-cause death and cancer death in several studies (3–7). Elevated hs-CRP levels are also shown to be associated with increased risks of all-cause death (8–10) and cancer death in several studies (9, 11). Some studies have suggested that hs-CRP acts as a survival predictor in cancer patients (6, 11, 12). Other studies in healthy and cancer-free populations also have shown a positive association between hs-CRP levels and cancer mortality (7, 9, 10).

Most of the studies on the influence of hs-CRP on cancer mortality have originated from western countries (7–12). The common causes of cancer mortality among Koreans, however, appear to differ from those of people in other countries. For example, the 4 main causes of cancer mortality in the United States in 2007 were lung, breast, colorectal, and prostate cancer (13), whereas those in Korea in 2009 were lung, liver, stomach, and colon cancer (14). Some evidence suggest that there is a relationship between hs-CRP and cancer in Asian populations. Recently, Lee and colleagues showed an association between hs-CRP concentrations and all-cancer risk and site-specific-cancer risks in 80,781 healthy Koreans (15). However, no study has yet examined the possible association of hs-CRP

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levels and cancer death or site-specific cancer death in an Asian population. Here, we sought to investigate the association between serum hs-CRP levels and mortality from all-causes, overall cancer, and site-specific cancer and we further examined the relationship of survival and cancer survival with inflammation-based prognostic scores including neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and prognostic nutrition index (PNI).

Materials and Methods

Study population

We retrospectively collected data representing individuals who had completed medical check-ups and had been screened for serum hs-CRP concentrations at the health screening center of Seoul National University Hospital between May 1995 and December 2006 ($n = 37{,}032$). We excluded 2,702 subjects based on missing data on anthropometric measures and behavioral factors (e.g., smoking status, alcohol consumption, regular exercise). We further excluded 774 subjects whose serum hs-CRP concentrations were >10 mg/L or who were treated or followed up because of cancer diagnosed before medical check-up. A total of 33,556 participants were included in the final analysis.

Demographic information on monthly income, smoking status, alcohol consumption, and regular exercise was assessed using a structured questionnaire. Smoking status was classified into 3 categories: current, former, and never-smokers. Regular drinker was defined as those who consume alcohol at least once a week. Regular exerciser referred to those who had light, moderate, or vigorous activities for more than 30 minutes at least 3 times a week.

Blood pressure was measured twice in a sitting position using an automated BP-measuring device (Jawon) after 20 minute-controlled rest period. Body mass index (BMI) was calculated using the following formula: weight (kg)/height $(m)^2$.

We defined hypertension as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg, or as having a self-reported medical history of hypertension or taking regular antihypertensive medications. Diabetes was determined by a fasting blood glucose level $\geq$126 mg/dL or a self-reported medical history of diabetes or taking antidiabetic medication.

After a 12-hour overnight fast, hs-CRP levels were measured with a highly sensitive latex-enhanced immunoassay run on an automated chemistry analyzer (Toshiba, Hitachi 760).

The NLR was calculated by dividing circulating neutrophil count into lymphocyte count and was scored as 0 or 1. The PLR was scored as 0, 1, or 2 according to the ratio of platelet count/lymphocyte count (<150:1, 150–300:1, and >300:1, respectively). The PNI was calculated by a combination of albumin and total lymphocyte count and scored as 0 or 1(16).

Mortality surveillance

The participants were followed up for mortality from baseline examination until December 31, 2008. Death was confirmed through a record link with the national death certificate files in Korea. The follow-up rate for deaths was 98% (17). Computerized searches of death certificate data from the National Statistical Office of Korea were conducted by personal identification numbers assigned at birth. The cause of death was classified according to the International Classification of Diseases, 10th revision. Death from cancer was coded as C00-C97.

Statistical methods

The participants were categorized into 3 groups according to their serum levels of hs-CRP, as follows: hs-CRP ≤ 1 mg/L, 1 mg/L < hs-CRP < 3 mg/L, and hs-CRP ≥ 3 mg/L. The baseline characteristics were expressed as means (*SD*) or absolute number (%) according to the hs-CRP categories. The χ^2 test and ANOVA were used to compare categorical variables and continuous variables, respectively, across sex-specific hs-CRP categories. The hs-CRP levels were log-transformed because of their skewed distribution.

The Kaplan–Meier method was used to describe the relationship between log-transformed hs-CRP and mortality from all causes and from cancer. The HRs for all-cause and cancer mortality (including site-specific cancers) were estimated according to the 3 hs-CRP categories. We used Cox-proportional hazard models after adjusting for potential confounders, such as age, sex, BMI, smoking status, hypertension, diabetes, total cholesterol level, high density lipoprotein (HDL)-cholesterol level, regular drinking (or not), regular exercise (or not), and monthly income. We also conducted the same analysis on subjects excluding those who died within 2 years after medical check-ups. Subgroup analyses were done to examine the relation between hs-CRP categories and all-cause mortality and cancer mortality according to smoking status (current, former, and nonsmoker) and obesity status (BMI $\geq$25 kg/m^2, and <25 kg/m^2). We examined the relationships between NLR, PLR, PNI, and overall survival and cancer survival using Cox-proportional hazard models.

The STATA software 11.0 (Stata Corp.) was used for statistical analysis, and *P* values <0.05 were considered to be statistically significant.

Results

During the mean follow-up of 9.42 years, 1,054 deaths from all causes and 506 deaths from cancer were identified. Table 1 shows the baseline characteristics of the study participants according to their hs-CRP categories and sex. The mean (*SD*) age was 48.75 (10.89) years in men, and 49.65 (15.25) years in women. The prevalence of hypertension and diabetes increased as the hs-CRP levels increased in both men and women. BMI, triglyceride, HDL-cholesterol, systolic blood pressure, and fasting blood glucose increased significantly as the hs-CRP levels

Table 1. Baseline characteristics according to sex-specific hs-CRP categories

	Serum level of hs-CRP (mg/L)									
	Men					Women				
	Hs-CRP ≤ 1	1 < Hs-CRP < 3	Hs-CRP ≥ 3	Total	*P* value	Hs-CRP ≤ 1	1 < Hs-CRP < 3	Hs-CRP ≥ 3	Total	*P* value
Number of subjects	11,973	3,133	2,385	17,491		11,647	2,716	1,702	16,065	
Median hs-CRP (mg/L)	1	2	4	1		1	2	4	1	
Age (years)	48.22 ± 10.81	49.39 ± 10.84	50.55 ± 11.13	48.75 ± 10.89	0.169	48.95 ± 16.74	50.82 ± 10.24	52.50 ± 9.81	49.65 ± 15.25	<0.001
Hypertension[a]	4,106 (34.29)	1,295 (41.33)	1,049 (43.98)	6,450 (36.77)	0.002	3,685 (31.64)	1,024 (37.70)	797 (46.83)	5,506 (34.27)	<0.001
Diabetes[b]	1,201 (10.01)	376 (12.00)	378 (15.85)	1,955 (11.18)	<0.001	665 (5.71)	217 (7.99)	211 (12.40)	1,093 (6.80)	<0.001
Smoking status										
Current smoker	5,758 (48.09)	1,583 (50.53)	1,244 (52.16)	8,585 (49.08)	0.032	643 (5.52)	136 (5.01)	103 (6.05)	882 (5.49)	<0.001
Nonsmoker	2,375 (19.84)	553 (17.65)	755 (31.66)	3,313 (18.94)		10,686 (91.75)	2,514 (92.56)	1,543 (90.66)	14,743 (91.77)	
Former smoker	3,835 (32.03)	994 (31.73)	385 (16.14)	5,584 (49.08)		317 (2.72)	65 (2.39)	55 (3.23)	437 (2.72)	
Regular drinker[c]	8,612 (71.93)	2,239 (71.47)	1,636 (68.60)	12,487 (71.39)	0.118	2,534 (21.76)	484 (17.82)	316 (18.57)	3,334 (20.75)	<0.001
Regular exerciser[d]	4,655 (38.88)	1,220 (38.94)	841 (35.22)	6,715 (38.39)	0.199	3,675 (31.55)	843 (31.04)	496 (29.14)	5,014 (31.21)	0.472
BMI (kg/m^2)	23.96 ± 2.79	24.54 ± 2.88	24.62 ± 2.98	24.15 ± 2.85	<0.001	23.34 ± 2.98	23.98 ± 93.19	25.04 ± 3.55	23.63 ± 3.13	<0.001
Total cholesterol (mg/dL)	198.41 ± 37.76	201.20 ± 36.86	201.52 ± 36.92	199.33 ± 37.51	0.128	200.95 ± 41.23	204.3 ± 40.05	206.81 ± 40.32	202.15 ± 40.99	0.100
Triglyceride (mg/dL)[e]	128.5 ± 0.5	143.7 ± 0.5	143.5 ± 0.5	133.1 ± 0.5	0.001	98.5 ± 0.5	111.6 ± 0.5	122.0 ± 0.5	103.0 ± 0.5	0.039
HDL-cholesterol (mg/dL)	49.24 ± 13.02	49.47 ± 12.37	46.94 ± 11.47	48.96 ± 12.73	<0.001	56.06 ± 14.61	56.27 ± 13.61	52.91 ± 12.43	55.76 ± 14.26	<0.001
Systolic BP[f] (mm Hg)	128.70 ± 19.83	131.90 ± 20.88	133.02 ± 20.73	129.86 ± 20.22	<0.001	127.68 ± 22.05	130.96 ± 22.44	135.84 ± 23.74	129.10 ± 22.45	<0.001
Diastolic BP[f] (mm Hg)	79.92 ± 12.10	81.94 ± 12.55	81.79 ± 12.16	80.54 ± 12.23	0.037	77.59 ± 12.12	79.46 ± 12.07	81.13 ± 12.58	78.28 ± 12.22	0.105
Glucose (mg/dL)	99.71 ± 26.76	102.28 ± 28.79	106.56 ± 35.28	101.10 ± 28.53	<0.001	94.63 ± 22.15	97.58 ± 24.77	101.77 ± 27.44	95.89 ± 23.33	<0.001
Monthly income (KRW)										
≤A million	880 (7.35)	244 (7.79)	241 (10.10)	1,365 (7.80)	<0.001	1,632 (14.01)	400 (14.73)	278 (16.33)	2,310 (14.38)	0.065
1–2 million	3,304 (27.60)	786 (25.09)	650 (27.25)	4,740 (27.10)		3,456 (29.67)	810 (29.82)	550 (32.31)	4,816 (29.98)	
2–4 million	4,433 (37.02)	1,099 (35.08)	875 (36.69)	6,407 (26.63)		3,565 (30.61)	810 (29.82)	481 (28.26)	4,856 (30.23)	
≥4 million	3,103 (25.92)	898 (28.66)	556 (23.31)	4,557 (26.05)		2,391 (20.53)	536 (19.73)	274 (16.10)	3,201 (19.93)	
Don't know	253 (2.11)	106 (3.38)	63 (2.64)	422 (2.42)		603 (5.18)	160 (5.89)	119 (6.99)	882 (5.49)	

NOTE: Data are expressed as mean ± *SD* or number (%).

[a]Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a self-reported medical history of hypertension or regularly taking antihypertensive medication.

[b]Diabetes was defined as fasting blood glucose ≥126 mg/dL, or a self-reported medical history of diabetes or taking antidiabetic medication.

[c]Regular drinker (%) was defined as subjects who consume alcohol at least once a week.

[d]Regular exerciser (%) means light moderate, or vigorous activities for more than 30 minutes at least 3 times a week.

[e]Triglyceride levels are expressed as geometric means after log transformation, due to their skewed distribution.

[f]blood pressure

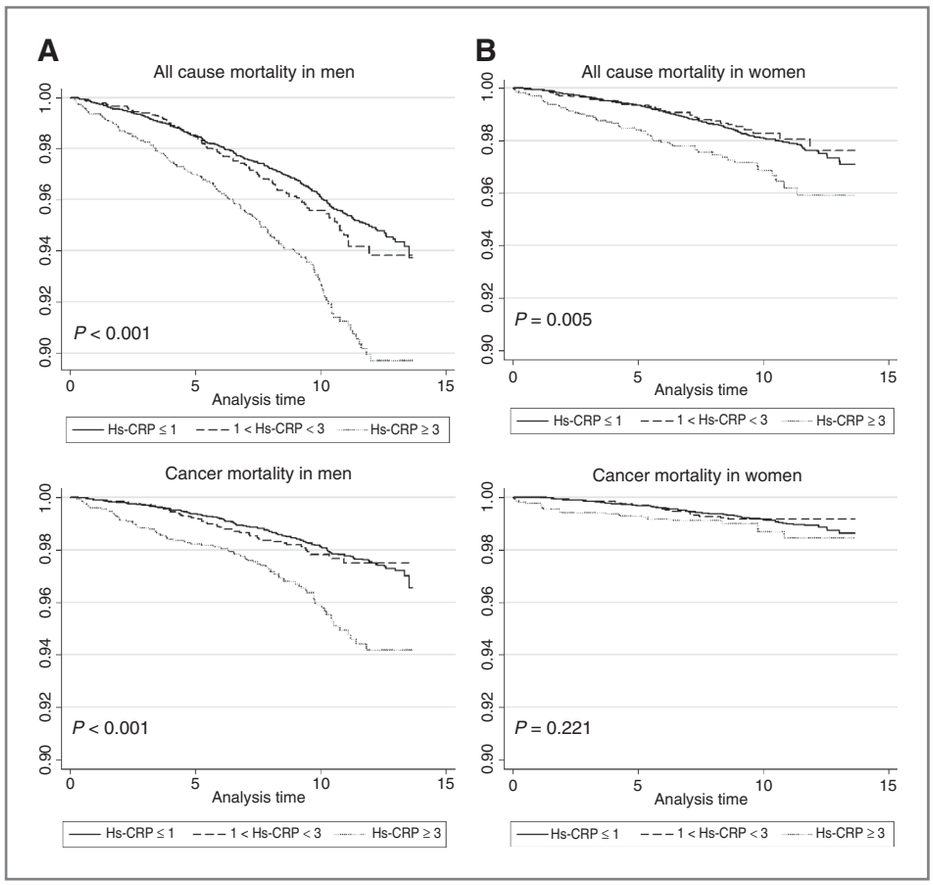

Figure 1. A, all-cause mortality and cancer mortality in men. A1, all-cause mortality. A2, cancer mortality. B, all-cause mortality and cancer mortality in Women. B1, All-cause mortality. B2, cancer mortality.

increased in both sexes. The subjects in the highest hs-CRP group were more likely to be current smokers in both sexes, and less likely to be regular drinkers among women.

Figure 1 shows the Kaplan–Meier curves for total mortality-free survival and cancer mortality-free survival according to the 3 hs-CRP categories, separated by sex. Total mortality-free survival and cancer mortality-free survival decreased with increasing levels of serum hs-CRP in both men and women.

As shown in Table 2, the age-adjusted HRs (95% CI) of all-cause mortality and cancer mortality for the men with hs-CRP $\geq$3 mg/L were significantly higher at 1.54 (1.29–1.85) and 1.77 (1.38–2.28), respectively, compared with men with hs-CRP $\leq$1 mg/L. When we adjusted for age, diabetes, hypertension, regular drinking, smoking status, BMI, regular exercise, monthly income, total cholesterol, and HDL-cholesterol, the adjusted HRs (aHR; 95% CI) of the men in the highest hs-CRP group were 1.38 (1.15–1.66) for all-cause mortality and 1.61 (1.25–2.07) for cancer mortality (P_{trend} = 0.001 for both), compared with the men in the lowest hs-CRP group. The association remained similar after excluding those who died within 2 years of medical check-ups.

For women, the age-adjusted HRs (95% CI) of all-cause mortality and cancer mortality were 1.73 (95% CI = 1.27–2.36) and 1.43 (95% CI = 0.87–2.34), respectively, in the highest hs-CRP group compared with the lowest hs-CRP group (P_{trend} = 0.005 and 0.223, respectively). When we adjusted for the above-listed confounders, however, this positive relationship was disappeared: the multivariate-adjusted HRs (95% CI) of the hs-CRP $\geq$3 mg/L versus hs-CRP $\leq$1 mg/L groups were 1.29 (0.94–1.77) for all-cause mortality and 1.24 (0.75–2.06) for cancer mortality (P_{trend} = 0.326 and 0.517, respectively).

Table 3 presents the aHRs of site-specific cancer mortality by the hs-CRP categories for both sexes combined. Of the 506 cancer deaths, 60 was from stomach cancer, 108 from lung cancer, 96 from liver cancer, 51 from colorectal cancer, and 8 from prostate cancer, which altogether accounted for 63.83% of deaths from all cancers. The age-adjusted HRs (95% CI) in the highest hs-CRP group versus the lowest hs-CRP group were 2.92 (1.84–4.65) for lung cancer, 1.76 (1.03–3.02) for liver cancer, and 2.56 (1.35–4.88) for colorectal cancer. After we adjusted for the identified confounders, the aHRs (95% CI) in the highest hs-CRP group versus the lowest hs-CRP group were 2.53 (1.57–4.06) for lung cancer, 1.58 (0.97–2.74) for liver cancer, and 1.96 (1.01–3.78) for colorectal cancer. The age-adjusted HR (95% CI) for prostate cancer mortality was 10.64 (2.12–53.29) and the multivariate aHR was 13.53 (2.59–70.71; P_{trend} = 0.002). The multivariate aHR (95% CI) for stomach

Table 2. Cox-regression analysis of hs-CRP on all-cause and cancer mortality

	All						Exclusion of those who died within 2 years after check-up					
	N	Number of deaths/ 1,000 person-years	Age-adjusted[a] HR (95% CI)	P_{trend}	Multivariate-adjusted[b] HR (95% CI)	P_{trend}	*N*	Number of deaths/ 1,000 person-years	Age-adjusted[a] HR (95% CI)	P_{trend}	Multivariate-adjusted[b] HR (95% CI)	P_{trend}
Men												
All-cause mortality												
Hs-CRP ≤1 mg/L	11,647	467/11,5931.44 (4.03)	1		1		11,622	411/115,769.55 (3.55)	1		1	
1 mg/L < hs-CRP < 3 mg/L	2,716	122/27,373.76 (4.45)	1.05 (0.86–1.28)		1.02 (0.83–1.25)		2,708	111/27,363.21 (4.05)	1.11 (0.90–1.37)		1.07 (0.87–1.33)	
Hs-CRP ≥ 3 mg/L	1,702	160/21,352.26 (6.41)	1.54 (1.29–1.85)	<0.001	1.38 (1.15–1.66)	0.001	1,689	129/21,319.45 (6.05)	1.44 (1.18–1.75)	<0.001	1.28 (1.04–1.57)	0.018
Cancer mortality												
Hs-CRP ≤ 1mg/L	11647	224/115931.44 (1.93)	1		1		11622	200/115769.55 (1.72)	1		1	
1 mg/L < hs-CRP < 3 mg/L	2,716	57/27,373.76 (2.08)	1.03 (0.77–1.38)		1.01 (0.75–1.35)		2,708	52/27,363.21 (1.90)	1.07 (0.79–1.46)		1.04 (0.76–1.41)	
Hs-CRP ≥ 3 mg/L	1,702	87/21,352.26 (4.07)	1.77 (1.38–2.28)	<0.001	1.61 (1.25–2.07)	0.001	1,689	66/21,319.45 (3.09)	1.53 (1.16–2.03)	0.005	1.37 (1.03–1.82)	0.039
Women												
All-cause mortality												
Hs-CRP ≤ 1 mg/L	11,973	215/112,488.13 (1.91)	1		1		11,917	190/112,457.11 (1.68)	1		1	
1 mg/L < hs-CRP < 3 mg/L	3,133	40/23,907.54 (1.67)	0.90 (0.64–1.27)		0.80 (0.56–1.13)		3,122	32/23,897.01 (1.33)	0.83 (0.57–1.22)		0.74 (0.50–1.08)	
Hs-CRP ≥ 3 mg/L	2,385	50/15,332.15 (3.26)	1.73 (1.27–2.36)	0.005	1.29 (0.94–1.77)	0.326	2,354	37/15,319.47 (2.41)	1.47 (1.03–2.10)	0.132	1.09 (0.76–1.57)	0.912
Cancer mortality												
Hs-CRP ≤ 1mg/L	11,973	99/112,488.13 (0.88)	1		1		11,917	88/112,457.11 (0.78)	1		1	
1 mg/L < hs-CRP < 3 mg/L	3,133	20/23,907.54 (0.83)	0.99 (0.61–1.60)		0.93 (0.57–1.52)		3,122	18/23,897.01 (0.75)	1.02 (0.61–1.71)		0.96 (0.58–1.61)	
Hs-CRP ≥ 3 mg/L	2,385	19/15,332.15 (1.23)	1.43 (0.87–2.34)	0.223	1.24 (0.75–2.06)	0.517	2,354	9/15,319.47 (0.58)	0.77 (0.39–1.54)	0.576	0.67 (0.33–1.36)	0.324

[a]Adjusted for age.

[b]Adjusted for age, diabetes (yes or no), hypertension (yes or no), regular drinker (yes or no), smoker (never, former, current), BMI, regular exerciser (yes or no), monthly income, total cholesterol, and HDL-cholesterol.

Table 3. HRs and 95% CI for site-specific cancer mortality by hs-CRP category

	All						Exclusion of those who died within 2 years after check-up					
Site-specific cancer	*N*	Number of deaths/ 1,000 person-years	Age-adjusted[a] HR (95% CI)	P_{trend}	Multivariate-adjusted[b] HR (95% CI)	P_{trend}	*N*	Number of deaths/ 1,000 person-years	Age-adjusted[a] HR (95% CI)	P_{trend}	Multivariate-adjusted[b] HR (95% CI)	P_{trend}
Stomach cancer												
Hs-CRP ≤ 1 mg/L	23,620	44/228,319.57 (0.192)	1		1		23,539	37/228,226.67 (0.16)	1		1	
1 mg/L < hs-CRP < 3 mg/L	5,849	6/51,281.30 (0.117)	0.63 (0.27–1.49)		0.61 (0.26–1.44)		5,830	5/51,260.23 (0.09)	0.64 (0.25–1.65)		0.60 (0.23–1.54)	
Hs-CRP ≥ 3 mg/L	4,087	10/36,684.42 (0.272)	1.44 (0.72–2.88)	0.583	1.33 (0.66–2.67)	0.754	4,043	7/36,638.92 (0.19)	1.23 (0.54–2.77)	0.919	1.12 (0.49–2.54)	0.883
Colorectal cancer												
Hs-CRP ≤ 1 mg/L	23,620	34/228,319.57 (0.148)	1		1		23,539	31/228,226.67 (0.13)	1		1	
1 mg/L < hs-CRP < 3 mg/L	5,849	4/51,281.30 (0.078)	0.59 (0.21–1.68)		0.55 (0.19–1.58)		5,830	4/51,260.23 (0.07)	0.67 (0.23–1.93)		0.61 (0.21–1.77)	
Hs-CRP ≥ 3 mg/L	4,087	13/36,684.42 (0.354)	2.56 (1.35–4.88)	0.021	1.96 (1.01–3.78)	0.120	4,043	9/36,638.92 (0.24)	1.99 (0.94–4.20)	0.168	1.47 (0.68–3.14)	0.520
Lung cancer												
Hs-CRP ≤ 1 mg/L	23,620	59/228,319.57 (0.258)	1		1		23,539	54/228,226.67 (0.23)	1		1	
1 mg/L < hs-CRP < 3 mg/L	5,849	23/51,281.30 (0.448)	1.92 (1.18–3.13)		1.85 (1.13–3.02)		5,830	22/51,260.23 (0.42)	2.05 (1.24–3.39)		1.96 (1.18–3.24)	
Hs-CRP ≥ 3 mg/L	4,087	26/36,684.42 (0.708)	2.92 (1.84–4.65)	<0.001	2.53 (1.57–4.06)	<0.001	4,043	21/36,638.92 (0.57)	2.62 (1.58–4.35)	<0.001	2.27 (1.35–3.80)	<0.001
Liver cancer												
Hs-CRP ≤ 1 mg/L	23,620	63/228,319.57 (0.275)	1		1		23,539	60/228,226.67 (0.26)	1		1	
1 mg/L < hs-CRP < 3 mg/L	5,849	16/51,281.30 (0.312)	1.23 (0.70–2.13)		1.19 (0.68–2.09)		5,830	14/51,260.23 (0.27)	1.15 (0.64–2.07)		1.10 (0.61–1.99)	
Hs-CRP ≥ 3 mg/L	4,087	17/36,684.42 (0.463)	1.76 (1.03–3.02)	0.040	1.58 (0.97–2.74)	0.097	4,043	11/36,638.92 (0.30)	1.21 (0.63–2.31)	0.488	1.07 (0.55–2.06)	0.762
Prostate cancer[c]												
Hs-CRP ≤ 1 mg/L	11,647	2/115,931.44 (0.017)	1		1		11,622	2/115,769.55 (0.01)	1		1	
1 mg/L < hs-CRP < 3 mg/L	2,716	0/27,373.76	NA		NA		2,708	0/27,363.21	NA		NA	
Hs-CRP ≥ 3 mg/L	1,702	6/21,352.26 (0.281)	10.64 (2.12–53.29)	0.004	13.53 (2.59–70.71)	0.002	1,689	5/21,319.45 (0.23)	9.06 (1.74–47.23)	0.010	11.20 (2.06–60.87)	0.006
Cervical cancer[d]												
Hs-CRP ≤ 1 mg/L	11,973	3/112,488.13 (0.026)	1		1		11,917	2/112,457.11 (0.01)	NA		NA	
1 mg/L < hs-CRP < 3 mg/L	3,133	0/23,907.54	NA		NA		3,122	0/23,897.01	NA		NA	
Hs-CRP ≥ 3 mg/L	2,385	2/15,332.15 (0.130)	4.68 (0.78–28.14)	0.175	5.18 (0.82–32.58)	0.139	2,354	0/15,319.47	NA	NA	NA	NA

Abbrevation: NA, non-applicable.

[a]Adjusted for age.

[b]Adjusted for age, diabetes (yes or no), hypertension (yes or no), regular drinker (yes or no), smoker (never, former, current), BMI, regular exerciser (yes or no), monthly income, total cholesterol, and HDL-cholesterol.

[c]Calculated only for men.

[d]Calculated only for women.

Table 4. Cox-regression analysis of hs-CRP on all-cause and cancer mortality according to smoking and obesity status

		All-cause mortality				Cancer mortality			
		No. of death/1,000 person-year	Multivariate-adjusted[a] HR (95% CI)	P_{trend}	*P* for interaction	No. of death/1,000 person-year	Multivariate-adjusted[a] HR (95% CI)	P_{trend}	*P* for interaction
Smoking status									
Nonsmoker	Hs-CRP $\leq$ 1 mg/L	264/126,092.92 (2.09)	1			117/126,092.92 (0.92)	1		
	1 mg/L < hs-CRP < 3 mg/L	52/26,932.86 (1.93)	0.88 (0.65, 1.19)			25/26,932.86 (0.92)	1.02 (0.66, 1.58)		
	Hs-CRP $\geq$ 3 mg/L	58/17,336.71 (3.34)	1.31 (0.98, 1.76)	0.179		27/17,336.71 (1.55)	1.56 (1.02, 2.39)	0.069	
Former smoker	Hs-CRP $\leq$ 1 mg/L	154/38,709.40 (3.97)	1			72/38,709.40 (1.86)	1		
	1 mg/L < hs-CRP < 3 mg/L	42/9,033.76 (4.64)	1.07 (0.76, 1.52)			20/9,033.76 (2.21)	1.10 (0.67, 1.82)		
	Hs-CRP $\geq$ 3 mg/L	57/7,092.83 (8.03)	1.52 (1.11, 2.07)	0.012		39/7,092.83 (5.49)	2.33 (1.56, 3.47)	<0.001	
Current smoker	Hs-CRP $\leq$ 1 mg/L	264/63,457.56 (4.16)	1			134/63,457.56 (2.11)	1		
	1 mg/L < hs-CRP < 3 mg/L	68/15,275.44 (4.45)	1.10 (0.84, 1.44)			32/15,275.44 (2.09)	1.03 (0.70, 1.52)		
	Hs-CRP $\geq$ 3 mg/L	95/12,238.66 (7.76)	1.66 (1.30, 2.11)	<0.001	0.418	40/12,238.66 (3.26)	1.40 (0.97, 2.01)	0.089	0.574
Obesity status									
BMI[b] < 25 kg/m^2	Hs-CRP $\leq$ 1 mg/L	446/155,816.07 (2.86)	1			215/155,816.07 (1.03)	1		
	1 mg/L < hs-CRP < 3 mg/L	102/31,466.16 (3.24)	1.10 (0.88, 1.36)			46/31,466.16 (1.46)	1.04 (0.75, 1.44)		
	Hs-CRP $\geq$ 3 mg/L	136/20,115.50 (6.76)	1.82 (1.49, 2.21)	<0.001		71/20,115.50 (3.52)	2.06 (1.57, 2.71)	<0.001	
BMI[b] $\geq$ 25 kg/m^2	Hs-CRP $\leq$ 1 mg/L	236/72,503.49 (3.25)	1			108/72,503.49 (1.48)	1		
	1 mg/L < hs-CRP < 3 mg/L	60/19,815.14 (3.02)	0.94 (0.70, 1.25)			31/19,815.14 (1.56)	1.10 (0.73, 1.65)		
	Hs-CRP $\geq$ 3 mg/L	74/16,568.91 (4.46)	1.22 (0.93, 1.59)	0.215	0.057	35/16,568.91 (2.11)	1.35 (0.91, 1.99)	0.133	0.133

[a]Adjusted for age, diabetes (yes or no), hypertension (yes or no), regular drinker (yes or no), smoker (never, former, current), BMI, regular exerciser (yes or no), monthly income, total cholesterol, and HDL-cholesterol.

[b]Calculated using the following formula: weight (kg)/height (m)^2.

cancer mortality in the highest hs-CRP group was 1.33 (0.66–2.67) compared with that in the lowest hs-CRP group. After excluding the death within 2 years of medical check-ups, the relationship of hs-CRP concentrations with lung and prostate cancer death still remained. However, significance of association between level of hs-CRP and colorectal cancer death disappeared after exclusion [aHR (95% CI) = 1.47 (0.68–3.14)].

In Table 4, we conducted stratified analyses to check the effects of smoking and obesity on the association between hs-CRP concentrations and death for both sexes combined. The multivariate-adjusted HRs (95% CI) of all-cause and cancer mortality with hs-CRP ≥3 mg/L were significantly higher at 1.52 (1.11–2.07) and 2.33 (1.56–3.47) in former smokers and 1.66 (1.30–2.11) and 1.40 (0.97–2.01) in current smokers, respectively, compared with those with hs-CRP ≤1 mg/L. The positive associations between hs-CRP concentrations and all-cause and cancer mortality were statistically nonsignificant in nonsmokers. The association between levels of hs-CRP and all-cause and cancer mortality was not different across the smoking status (P for interaction = 0.418 for all-cause mortality, 0.574 for cancer mortality). The multivariate-adjusted HRs (95% CI) of the hs-CRP ≥3 mg/L versus hs-CRP ≤1 mg/L group in overweight subjects (BMI ≥ 25 kg/m^2) were 1.22 (0.93–1.59) for all-cause mortality and 1.35 (0.91–1.99) for cancer mortality ($P = 0.215$ and $P = 0.133$, respectively) whereas those in nonoverweight subjects (BMI < 25 kg/m^2) were 1.82 (1.49–2.21) for all-cause mortality and 2.06 (1.57–2.71) for cancer mortality ($P < 0.001$, both). The differential effect of adiposity on the association between levels of hs-CRP and all-cause mortality was marginally significant (P for interaction = 0.057).

Table 5 shows the aHRs of all-cause and cancer mortality according to the inflammation-based prognostic scores by sex. NLR and PLR were not significantly related with all-cause or cancer mortality in both sexes. PNI was an independent predictor of mortality from all-causes and cancer both in men [aHR (95% CI) = 6.85 (4.34–10.79) and 6.88 (3.49–13.56), respectively] and in women [aHR (95% CI) = 3.50 (2.48–4.96) and 3.96 (2.47–6.36)].

Discussion

In the present study, serum levels of hs-CRP were independently related to all-cause and cancer mortality in men, but not definitively in women. The subjects with hs-CRP ≥3 mg/L showed higher all-cause and cancer mortality than subjects with hs-CRP ≤1 mg/L. Elevated hs-CRP was also associated with an increased overall risk of cancer mortality from lung and prostate cancer, and possibly colorectal cancer as well. However, these results should be interpreted cautiously and are subjected to further investigation because there were relatively few deaths from prostate cancer.

Table 5. Cox-regression analysis of inflammation-based prognostic scores on all-cause and cancer mortality

			All-cause mortality			Cancer mortality		
		N	No. of death/1,000 person-year	Multivariate-adjusted[a] HR (95% CI)	*P* value	No. of death/1,000 person-year	Multivariate-adjusted[a] HR (95% CI)	*P* value
Men								
NLR[b]	0	15,975	301/150,926.05 (1.99)	1		137/150,926.05 (0.90)	1	
	1	90	4/801.77 (4.98)	2.81 (1.04, 7.54)	0.040	1/801.77 (1.24)	1.48 (0.20, 10.62)	0.694
PLR[c]	0	12,446	244/119,177.56 (2.04)	1		105/119,177.56 (0.88)	1	
	1	3,528	59/31,741.99 (1.85)	1.08 (0.81, 1.44)		32/31,741.99 (1.00)	1.26 (0.84, 1.88)	
	2	91	2/808.27 (2.47)	1.44 (0.35, 5.80)	0.495	1/808.27 (1.23)	1.53 (0.21, 11.00)	0.227
PNI[d]	0	15,886	285/150,159.92 (1.89)	1		129/150,159.92 (0.85)	1	
	1	179	20/1,567.90 (12.75)	6.85 (4.34, 10.79)	<0.001	9/1,567.90 (5.74)	6.88 (3.49, 13.56)	<0.001
Women								
NLR[b]	0	17,401	742/163,731.55 (4.53)	1		364/163,731.55 (2.22)	1	
	1	90	7/825.82 (8.47)	1.47 (0.69, 3.10)	0.312	4/825.82 (4.84)	1.91 (0.71, 5.15)	0.196
PLR[c]	0	15,820	673/149,588.48 (4.49)	1		332/149,588.48 (2.21)	1	
	1	1,621	73/14,506.36 (5.03)	0.96 (0.75, 1.23)		34/14,506.36 (2.34)	0.95 (0.67, 1.37)	
	2	50	3/462.63 (6.48)	0.89 (0.28, 2.80)	0.748	2/462.63 (4.32)	1.23 (0.30, 4.96)	0.925
PNI[d]	0	17,365	714/163,492 (4.36)	1		349/163,492 (2.13)	1	
	1	126	35/1,065.47 (32.84)	3.50 (2.48, 4.96)	<0.001	19/1,065.47 (17.83)	3.96 (2.47, 6.36)	<0.001

[a]Adjusted for age, diabetes (yes or no), hypertension (yes or no), regular drinker (yes or no), smoker (never, former, current), BMI, regular exerciser (yes or no), monthly income, total cholesterol, and HDL-cholesterol.

[b]Calculated as neutrophil count/lymphocyte count, scored as 1 (<5) or 1 (≥5).

[c]Calculated as platelet count/lymphocyte count, scored as 0 (<150), 1 (150–300), or 2 (>300).

[d]Calculated as "Albumin (g/L) + 5*total lymphocyte count*10^9/L," scored as 0 (≥45) or 1 (<45).

Our findings are consistent with previous studies showing an association between serum hs-CRP levels and cancer mortality in both healthy subjects and cancer patients (7, 9, 10). Elevated hs-CRP levels have been associated with disease progression and poor survival in patients with lung, breast, and colorectal cancer (11, 18–21). Il'yasova and colleagues (18) reported aHRs (95% CI) of 1.25 (1.09–1.43) for cancer incidence and 1.64 (1.20–2.24) for cancer death for a log unit increase in hs-CRP. They obtained similar results for deaths due to lung cancer [aHR = 1.64 (1.20–2.24)], colon cancer [aHR = 1.44 (1.03–2.02)], and breast cancer [1.32 (0.92–1.93)], but not prostate cancer [aHR = 0.94 (0.70–1.28)], in a cancer-free population aged 70 to 79 years (18).

However, it is difficult to directly compare present findings with those of prior studies in cancer-free populations, because previous studies were done in countries that do not routinely conduct national cancer screening (7, 9, 18). Korea has been providing a national cancer screening program since 1999, which is offered to individuals at an age of 40 or above. The program is offered every 2 years for an individual, and includes breast, cervical, colorectal, and stomach cancer screening for anyone, and an additional liver cancer screening for high-risk groups. The participation rate of national cancer screening in Korea was 32.7% in 2009. The rate of breast cancer screening was the highest (40.0%) followed by liver cancer (38.5%), and stomach cancer (34.3%) in 2009 (22). Any participant diagnosed as having cancer from the screening is referred to a specialized clinic for further evaluation and treatment. Therefore, those with a history of stomach, breast, colorectal, and cervical cancer were more likely to be excluded in our study than those in other previous studies.

Several hypotheses have been suggested to explain the apparent relationship between cancer risk and high hs-CRP levels. One possible mechanism might be that tumor growth could cause inflammation around the tumor, thereby increasing the serum level of hs-CRP (23). Alternatively, chronic inflammation, for which hs-CRP is a marker, could cause carcinogenesis (24). Inflammation-related oxidative damage might play a role in initiating carcinogenesis by causing inactivating mutations in tumor-suppressor genes, or by triggering posttranslational modifications in DNA repair- or apoptosis control-related proteins (24). In addition, inflammatory cytokines, enzymes, and transcription factors could facilitate cancer progression by promoting the growth and proliferation of tumor cells and interrupting apoptosis (24). Hs-CRP is known to be an independent predictor of cardiovascular disease and cardiovascular mortality (25). Our results here show that hs-CRP also seems to predict mortality from cancer, and we therefore speculate that the chronic low-grade inflammation represented by hs-CRP might be involved in common pathways of cancer and total mortality.

Previous reports observing the associations between hs-CRP and cancer risks also have failed to show the relationship in women. In particular, serum hs-CRP levels did not appear to be related to overall cancer (26), breast cancer (27), and colorectal cancer (28) risks in women. Similarly, present study also revealed a positive impact of hs-CRP on cancer mortality in men, but not definitively in women. This nonsignificant relationship between CRP and cancer deaths might suggest that the association between cancer and low-grade inflammation is not as important in women as in men (9). Another plausible explanation would be that the relationship between hs-CRP and cancer deaths in women might have been attenuated in postmenopausal hormone users, whose hs-CRP levels may be elevated but maintain relatively healthy lifestyles in terms of not smoking, doing regular exercises, and being more active in consuming health care resource, etc. (29). According to the 2007 Korean National Health and Nutrition Examination Survey data, 746 (5.8%) of women were hormone replacement therapy (HRT) users by self-reported questionnaires. However, there was no available information on hormone-replacement therapy among the women in the present study. We were therefore unable to investigate the influence of hormone-replacement therapy on the mortality from hormone-related cancers in women. Further studies might be needed to investigate the mechanism of nonsignificant relationship between hs-CRP and cancer deaths in women.

Recently, Lee and colleagues (15) showed a positive relationship between hs-CRP and colon cancer incidence, and a marginal significant relationship between hs-CRP and stomach cancer incidence in a Korean population. In our study, in contrast, hs-CRP was related to mortality from lung cancer and possibly from colorectal cancer. After excluding deaths within 2 years of medical check-ups, the relationship between hs-CRP and colorectal cancer disappeared. This apparent discrepancy might be because of the effect of the national cancer screening program, as previously mentioned. The possible early detection of cancer in Korea because of the national cancer screening program makes our study population more cancer-free than the western populations in previous studies. Also, the relationship between hs-CRP and common cancer deaths in Korea might have been attenuated owing to the national cancer screening program. Several reports have shown that population-based cancer screening can decrease mortality from cervical and breast cancers (30–33). In addition, the relationship between hs-CRP and mortality from lung cancer (which has no proven screening program and a relatively poor prognosis) appeared to be more prominent in our data set and showed tendencies similar to those observed in other countries (11).

We further conducted stratified analysis to contemplate whether the association between hs-CRP and total and cancer mortality, especially lung cancer and colorectal cancer might be originated from the effect of smoking and obesity. Smoking and obesity are known to be linked to high concentrations of hs-CRP. The well-known proatherogenic effects of smoking, including oxidative

stress, endothelial damage, and endothelial cell dysfunction, may play a major role in raising hs-CRP levels (34). In the present study, the association between serum levels of hs-CRP and all-cause and cancer mortality was not different across smoking status. Hs-CRP is synthesized and secreted mainly by hepatocytes in response to the stimuli from proinflammatory cytokine such as TNFα, IL-1, and IL-6 (35). Expanded adipose tissue in obese subjects might secrete such proinflammatory cytokines, which in turn stimulate the hepatocytes to synthesize hs-CRP (35). However, the association between hs-CRP and all cause and cancer mortality were more prominent in lean subjects than in overweight subjects in the present study. The possible explanation for this association might be that the main cancer death in this study was lung cancer in which nutritional status has been reported as a predictor of survival (36, 37). Nutritional decline represented by PNI in both sexes were also associated with survival in this study. In addition, inadequate nutrition was documented to be related to elevated hs-CRP level in the previous studies (38–40). Further investigation in other population is needed to examine the differential effect of adiposity on the relation between hs-CRP concentration and specific cancer mortality.

Inflammation-based prognostic scores are reported to be associated with cancer survival (16). In this study, we also examined the impact of inflammation-based prognostic scores (NLR, PLR, and PNI) on overall and cancer survival. Previously, NLR has been reported to predict survival in lung cancer patients (16). However, NLR did not significantly influence the mortality from all-cause or cancer among healthy individuals. In our study, Onodera's PNI, known as a possible predictor of survival in patients with pancreatic (41), esophageal (42), and gastric cancer (43), was significantly related to mortality from all-cause and cancer in healthy population. This result suggests that nutritional decline in both sexes and low-grade inflammation in men are possible predictors of all-cause and cancer mortality in apparently cancer-free Koreans.

To our knowledge, this is the first study to examine the possible association of hs-CRP levels with mortality from all-cause-, cancer-, and site-specific cancer mortality in Koreans. We studied the use of elevated hs-CRP levels as a prognostic marker for overall mortality and cancer survival in apparently healthy adults. We compared the predictive value of inflammation-based prognostic scores on total and cancer deaths in apparently cancer-free individuals in addition to cancer patients.

Our study has several potential limitations. First, the data were obtained from a single health screening center in a single university hospital, which may limit the generalization of our results. Second, the number of cancer deaths was not large enough to show the exact relationship in cancer-specific mortality, especially in women. Third, the use of a single assessment of hs-CRP at baseline, rather than repeated measurements, restricted our ability to adjust for regression dilution bias, allowing for possible underestimation of the association (11). Fourth, detailed information on lifestyle factors including diet, alcohol intake, and exercise status, which might influence on both serum level of hs-CRP and mortality were lacking. In addition, there was no available information on hormone-replacement therapy among the women or on the use of aspirin. Finally, the national cancer screening program of Korea, which is conducted every 2 years among subjects older than 40 years, might have attenuated our ability to assess the exact relationship between hs-CRP and common cancers in Korea, including stomach, breast, and cervical cancer.

In conclusion, we found that increased hs-CRP levels in apparently cancer-free individuals were significantly associated with all-cause mortality and cancer mortality in men, but not definitively in women. In addition, elevated levels of hs-CRP were related to an increased risk of mortality from lung cancer and possibly colorectal cancer. In the future, assessment of the level of serum hs-CRP, a marker of chronic low-grade inflammation, might help identify subjects at increased risk of cancer death.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: YJ. Ko, B. Cho, M. Park
Development of methodology: YJ. Ko, B. Cho, M. Park
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): YJ. Ko, B. Cho, M. Park
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): YJ. Ko, Y. Kwon, K.H. Kim, H.-J. Yoon, B. Cho, M. Park
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