RESEARCH ARTICLE

High-Sensitivity C-Reactive Protein and Risks of All-Cause and Cause-Specific Mortality in a Japanese Population

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Abstract

Background: High-sensitivity C-reactive protein (hsCRP) levels are lower in Japanese compared with Western subjects. Since it is uncertain whether hsCRP is a potent predictor of mortality at low CRP concentrations, the present study examined associations with all-cause and cause-specific mortality in a large population of Japanese. Materials and Methods: Subjects were 4,737 men and 6,343 women aged 49-76 years participating in the baseline survey of an ongoing cohort study of lifestyle-related diseases between February 2004 and July 2006. Hazard ratios for all-cause and cause-specific mortality associated with hsCRP levels were estimated using Cox proportional hazards regression. Results: A total of 436 all-cause deaths occurred during a median follow-up of 8 years. The main cause of death was cancer. In men, hsCRP levels were positively associated with the risk of all-cause mortality as well as deaths from cancer and cardiovascular disease (CVD). All-cause mortality hazards for the 2nd (0.34-0.84 mg/L) and the 3rd (≥ 0.85 mg/L) tertiles of hsCRP were 1.27 (95% confidence interval [CI], 0.93-1.73) and 1.75 (1.30-2.37), respectively (p for trend=0.001). In women, increased risk of all-cause and cause-specific mortality associated with elevated hsCRP levels was observed, but the associations were not statistically significant. Conclusions: HsCRP may be an independent predictor of all-cause, cancer and CVD mortality in apparently healthy Japanese men, but not women. The differential effect of hsCRP in predicting mortality risk by sex warrants further investigation.

Keywords: C-reactive protein - mortality - cancer - cardiovascular disease - inflammation

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Introduction

Chronic low-grade inflammation can lead to the development of chronic diseases and increased mortality risk (De Martinis et al., 2006; Hotamisligil, 2006). C-reactive protein (CRP) is an acute phase protein synthesized by the liver that increases in response to systemic inflammation and is one of the most important inflammatory markers (Pepys and Hirschfield, 2003). CRP is acknowledged to be an established risk factor for cardiovascular disease (CVD) (Ridker, 2016), and has been associated with the risk of cancer development (Guo et al., 2013). Several prospective studies have demonstrated that elevated CRP levels were associated with increased risks of all-cause and CVD mortality in combined men and women (Arima et al., 2008; Zacho et al., 2010; Swede et al., 2014; Zuo et al., 2016), and some studies have suggested that the association of CRP with CVD mortality differed by sex (Ko et al., 2012; Ahmadi-Abhari et al., 2013; Doran et al., 2013). The findings on the relationship between CRP and cancer mortality are inconsistent. For example, multiple studies suggested a modest increase in the risk of overall cancer mortality associated with elevated CRP levels (Il'yasova et al., 2005; Allin and Nordestgaard, 2011), but a recent study failed to find an association (Zuo et al., 2016).

The information on the importance of CRP as a predictor of mortality is derived mainly from studies performed in Western populations (Kaptoge et al., 2010). Although Japanese had a lower hsCRP level compared with Western subjects (Kaptoge et al., 2010), a meta-analysis based on four Japanese studies showed that elevated hsCRP levels were significantly associated with an increased risk of ischemic stroke (Saito et al., 2014). However, the evidence on the associations of hsCRP with mortality risks from a large population-based studies is rare among Japanese subjects (Arima et al., 2008; Iso et al., 2009). The present study was to evaluate the associations between hsCRP and the risk of all-cause mortality as well as deaths from cancer, CVD, and other diseases in a large

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Japanese population. This is the first study regarding hsCRP and cancer mortality in middle-aged and elderly men and women in Japan.

Materials and Methods

Study subjects

Data were derived from the baseline survey of the Kyushu University Fukuoka Cohort Study on lifestyle-related diseases. The study was conducted with the approval of the Ethics Committee of Kyushu University Faculty of Medical Sciences, and written informed consent was obtained from all participants. Details of the survey have been described elsewhere (Nanri et al., 2008). The subjects were men and women aged 50-74 years living in the East Ward of Fukuoka City. A total of 12,948 subjects (5,817 men and 7,131 women) were recruited from February 2004 to August 2007, with participation rate of 24%. We excluded 1,862 subjects who had the following conditions: current medical care for cancer (n=498), ischemic heart disease (n=534), stroke (n=276), chronic liver disease (n=311), chronic renal failure (n=29), and alcohol addiction (n=4); prior history of ischemic heart disease (n=149) or stroke (n=158); and concentration of hsCRP >10 mg/L (n=212). Of the remaining 11,086 subjects, we further excluded 6 subjects with missing information on covariates. Our final sample for analyses included a total of 11,080 subjects (4,737 men and 6,343 women).

Laboratory measurements

Recorded information was obtained if the measurements had been done in the past year for eight types of serum biochemistry including total cholesterol and high density lipoprotein (HDL)-cholesterol. When recorded information was not available, 5 mL of venous blood was collected, and serum samples frozen in dry ice were shipped to an external laboratory (SRL, Hachioji, Japan). The limit of detection for hsCRP was 0.05 mg/L, and a value of 0.025 mg/L was assigned when the value was below the detection limit. HbA1c was measured using a latex agglutination turbidimetry, and serum concentrations of hsCRP were determined using a latex-enhanced immunonephelometric assay on aBNII analyzer (Dade Behring, Marburg, Germany). Both HbA1c and hsCRP were measured at an external laboratory (SRL, Hachioji, Japan).

Follow-up and ascertainment of mortality

We followed up the participant's vital status from the study entry to 31 December 2013. Information on death and causes of death was obtained from a record link with the national death certificate files in Japan. Main outcome of interest were all-cause mortality (defined as death from any cause) and mortality from cancers, CVD, and other diseases as underlying cause. Mortality from other diseases was death from diseases other than cancer and CVD. The cause of death was classified according to the International Classification of Diseases, 10th revision (ICD-10). Deaths were coded as C00-C97 for cancer and I00-I99 for CVD.

Baseline variables

Data on lifestyle measures were collected by self-administered questionnaires. The questionnaire inquired about smoking, alcohol consumption, physical activity, sleeping, stress, dietary intake, current or previous treatment of diseases, use of drugs and supplements, and family history of selected diseases. The returned questionnaire was confirmed by a nurse or a physician, and missing or inconsistent answers were clarified by in-person interview. Each subject undertook blood pressure measurement, anthropometric measurements (height in cm, body weight in kg, waist in cm, and hip in cm), and venous blood drawing.

Smokers were defined as those who had ever smoked one or more cigarettes daily for one year or longer, and categorized into never smokers, past smokers, and current smokers. Alcohol drinkers were defined as those who had drunk alcoholic beverages at least once per week over the period of 1 year or longer. The total ethanol intake per day was estimated on the basis of beverage-specific ethanol concentrations. Alcohol drinkers were classified as lifelong non-drinkers, past drinkers, and current drinkers. Questions on physical activity ascertained work-related and leisure-time physical activities over the previous year. With consideration to intensity in terms of metabolic equivalent (MET) and amount of time for each physical activity, MET-hours were calculated for work-related and leisure-time physical activity separately. Body mass index (BMI; in kg/m^2) was calculated. We slightly modified a 43-item food-frequency questionnaire for dietary assessment (Tokudome et al., 2004) and added five alcohol beverages, six-non alcohol beverages, and eight specific food items. A total of 49 food items were used to analyze a prudent dietary pattern characterized by higher intake of vegetables, fruits, and whole grains. A prudent dietary pattern was inversely associated with hsCRP in men and women of the present population (Nanri et al., 2008), and was considered as a covariate in the present study. Blood pressures were measured twice in a sitting position using an automated digital device (HEM-707, OMRON, Kyoto), and the second reading was used for the present study. Hypertension was systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or regular antihypertensive medication. Type 2 diabetes mellitus was determined by HbA1c of ≥6.5% or any anti-diabetic medication. Subjects with non-HDL cholesterol ≥170mg/dL were defined as having elevated non-HDL cholesterol (Shimano et al., 2008).

Statistical analysis

We calculated a follow-up time for each subject starting from the date of interview until the date of death or 31 December 2013, whichever came first. All analyses were sex-specific to explore potential differences in shape and magnitude of the associations in men and women. Vital status of men and women were compared using χ^2 test and Wilcoxon Mann-Whitney tests for categorical and continuous variables, respectively. Log transformation was applied to hsCRP to normalize the distribution. The hsCRP was analyzed as both continuous and sex-specific tertiles (0.03-0.33, 0.34-0.84, and 0.85-9.91 mg/L for men

and 0.03-0.25, 0.26-0.61, and 0.62-9.80 mg/L for women).

We used Cox proportional hazard regression models to calculate hazard ratios (HR) and 95% confidence interval (CI). The models were tested and plotted based on scaled Schoenfeld residuals to confirm that assumptions of proportional hazard by hsCRP tertiles were not violated. Multivariate models included adjustment for age (continuous), smoking (never, past, and current smoking), alcohol intake (never, past, and current drinking), BMI (<22.5, 22.5-24.9, and ≥25.0), hypertension, and type 2 diabetes mellitus. HR of mortality per 1-SD higher log hsCRP (SD=1.08) is equivalent to that for a threefold higher hsCRP on the original scale (mg/L). Trend of the association was assessed using tertiles ranked as a continuous variable in regression models. Interactions between hsCRP tertiles and sex were tested for by computing a likelihood ratio test comparing the statistical fit of models with and without a two-factor interaction term. A two-sided p-value <0.05 was considered significant. Statistical analyses were calculated using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Behavioral and clinical characteristics by geometric mean hsCRP concentration in men and women have been previously reported (Hirata et al., 2012). A total of 436 deaths (292 men and 144 women) occurred among the 11,080 participants during a median follow-up of 8 years (range, 0.1-9.9 years). Over half (53%) of all deaths (N=436) was attributable to cancer, and CVD deaths accounted for 15% of all deaths. A higher proportion of those who died during follow-up was male (67%). Baseline characteristics of men and women by vital status are summarized in Table 1. Deceased men and women were older at baseline. In men, decedents were more likely to be past smoker and current drinker, and had a lower baseline BMI than men who were alive. Work-related physical activity and prudent dietary pattern were not different between the 2 groups in men. Deceased women were less likely to physically active at work and more likely to have prudent dietary pattern than women who were alive, but BMI, smoking, and alcohol intake were

Table 1. Baseline Characteristics of Men and Women According to Vital Status

Variable	Men, n=4,737			Women n=6,343		
	Alive, n=4,445 (%)	Deaths, n=292 (%)	p valuea	Alive, n=6,199 (%)	Deaths, n=144 (%)	p valuea
Age (year), mean±SD	62.2±6.7	66.6±6.1	<10-4	61.8±6.9	66.9±6.2	<10-4
Body mass index (kg/m^2)						
<22.5	34	41.4	0.01	52.7	45.8	0.11
22.5 - 24.9	37.8	29.8		28.1	28.5	
≥ 25.0	28	28.8		19.2	25.7	
Smoking (cigarettes/day)						
Never	26.4	18.1	0.003	88.6	87.5	0.15
Past	42.4	43.2		5.1	8.3	
Current	31.2	38.7		6.3	4.2	
Alcohol intake (mL/day)						
Never	21.3	19.5	0.001	70.5	75	0.5
Past	6	11.3		2.4	2.1	
Current	72.7	69.2		27.1	22.9	
Work-related activity (MET-hr/day)b						
Q1	30.6	30.5	0.79	21.6	29.8	0.02
Q2	13.7	11.6		31.3	35.4	
Q3	29	30.5		21.4	17.4	
Q4	26.7	27.4		25.7	17.4	
Leisure-time activity (MET-hr/week)b						
Q1	23.1	22.9	0.4	26.3	28.5	0.91
Q2	27.3	25.7		26.8	27.1	
Q3	24.8	22.3		21.5	19.4	
Q4	24.8	29.1		25.4	25	
Prudent dietary pattern (factor score)b						
Q1	39.6	36	0.44	13.8	7.64	0.02
Q2	26.3	26		23.8	21.5	
Q3	21.2	22.3		28.6	25.7	
Q4	12.9	15.7		33.8	45.1	
Hypertension	60.9	67.1	0.04	45.7	56.3	0.01
Type 2 diabetes mellitus	9.5	19.5	<10-4	4	9.7	0.001
Elevated non-HDL cholesterol	26.2	25	0.64	34.7	31.9	0.49
Statin use	6.5	6.2	0.83	13.9	18.8	0.1
hsCRP (mg/L)c						
T1	35.9	24.3	<10-4	34.5	28.5	0.001
T2	34	32.5		33.8	25.7	
T3	30.1	43.2		31.7	45.8	

[a]Difference between alive and death groups, [b]Quartile and ctertile categories

Table 2. Adjusted Hazard Ratios for All-Cause Mortality in Relation to hsCRP Levels in Men and Women

hsCRP (mg/L)	Na	Age-adjusted HR (95% CI)	Multivariate HRb (95% CI)
Men (n=4,737)			
Continuousc	292/4,445	1.30 (1.17-1.44)	1.26 (1.13-1.40)
Tertile 1 (0.03-0.33)	71/1,597	1.00 (referent)	1.00 (referent)
Tertile 2 (0.34-0.84)	95/1,512	1.32 (0.97-1.79)	1.27 (0.93-1.73)
Tertile 3 (0.85-9.91)	126/1,336	1.91 (1.43-2.56)	1.75 (1.30-2.37)
	P for trend	<10-4	0.001
Women (n=6,343)			
Continuousc	144/6,199	1.15 (0.98-1.34)	1.12 (0.95-1.32)
Tertile 1 (0.03-0.25)	41/2,139	1.00 (referent)	1.00 (referent)
Tertile 2 (0.26-0.61)	37/2,094	0.76 (0.49-1.18)	0.73 (0.47-1.15)
Tertile 3 (0.62-9.80)	66/1,966	1.28 (0.86-1.90)	1.19 (0.78-1.81)
	P for trend	0.04	0.07
P for interaction by gender		0.31	

[a]Number of deaths/alive. [b]Adjusted for age, smoking habits, alcohol intake, body mass index, hypertension, and type 2 diabetes mellitus. cGeometric means of hsCRP.

Table 3. Adjusted Hazard Ratios for Cause-Specific Mortality in Relation to hsCRP in Men and Women

	Cancer	CVD	Other diseases
	HRa (95%CI)	HRa (95%CI)	HRa (95%CI)
Men (n=4,737)			
Age-adjusted	1.31 (1.14-1.51)	1.44 (1.08-1.92)	1.22 (1.01-1.47)
Multivariate-adjusted[b]	1.28 (1.11-1.48)	1.40 (1.40-1.88)	1.21 (1.00-1.47)
N[c]	162	38	92
Women (n=6,343)			
Age-adjusted	1.02 (0.81-1.28)	1.43 (1.01-2.03)	1.20 (0.92-1.58)
Multivariate-adjusted[b]	1.00 (0.79-1.26)	1.43 (0.99-2.05)	1.17 (0.88-1.56)
N[c]	69	28	47
P for interaction by sex	0.15	0.23	0.54

[a]HR for 1-SD increment of log hsCRP. [b]Adjusted for age, smoking habits, alcohol intake, body mass index, hypertension, and type 2 diabetes mellitus. cNumber of deaths.

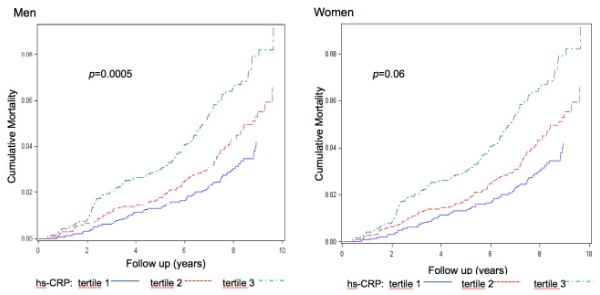

Figure 1. Cumulative Hazards of All-Cause Mortality According to Sex-Specific hsCRP Tertiles. After adjustment for age, smoking habits, alcohol intake, body mass index, hypertension, and type 2 diabetes mellitus

not different between alive and death group in women. Deceased men and women had higher proportions of hypertension and type 2 diabetes mellitus at baseline than survivors. Leisure-time physical activity, elevated non-HDL cholesterol, and statin use were not different between alive and death group in men and women, but hsCRP level was clearly different, with higher proportions of hsCRP 3rd tertile in those who died. Cumulative hazards (Figure 1) illustrates the higher hazards over time for all-cause death in men (p=0.0005) and women (p=0.06) with the higher hsCRP level. The proportionality assumptions of the hazard by hsCRP tertiles for these outcomes were satisfied.

In the multivariate Cox proportional hazard regression model (Table 2), HRs for all-cause mortality were progressively increased with higher hsCRP tertiles, especially in men. Significantly increased HRs for all-cause mortality was found in men with hsCRP 3rd tertile. The results in men did not change with additional adjustment for work-related activity (sex-specific quintiles), prudent dietary pattern (quintiles), and statin use; HRs (95%CI) for the 2nd and the 3rd hsCRP tertiles were 1.27 (0.93-1.74) and 1.75 (1.30-2.36), respectively (p for trend=0.001). Although women with hsCRP 3rd tertile had a somewhat increased in risk of all-cause mortality, the increase was not statistically significant. Results derived using geometric mean hsCRP in associations with risk of all-cause mortality in men and women were consistent with the results derived from hsCRP tertiles. Cause-specific mortality analyses (Table 3) showed that hsCRP concentrations were positively associated with risks of deaths from cancer and CVD in men, and the HRs for mortality from other diseases in men were marginally significant. Mortality risks from cancer, CVD, and other diseases increased with 1-SD increment in the log hsCRP in women, but the HRs were not statistically significant. There were no statistically significant interactions between hsCRP and sex in all models of mortality risk.

Discussion

In the large Japanese community-based study, elevated hsCRP levels were associated with the increased risk of all-cause mortality as well as deaths from cancer and CVD in apparently healthy Japanese men, but not women. Some studies have addressed the association between CRP level

and mortality risk by sex (Iso et al., 2009; Ko et al., 2012; Ahmadi-Abhari et al., 2013; Doran et al., 2013; Sung et al., 2014; Wulaningsih et al., 2016).The present findings are consistent with the results from previous studies showing no association of hsCRP levels with all-cause (Ko et al., 2012; Sung et al., 2014), cancer (Ko et al., 2012; Wulaningsih et al., 2016), or CVD (Ahmadi-Abhari et al., 2013; Doran et al., 2013; Sung et al., 2014) mortality in women.

Although different cut-off hsCRP levels were used, two prospective studies showed that hsCRP levels were associated with the increased risks of all-cause and CVD mortality in men (Doran et al., 2013; Sung et al., 2014). For example, CRP level of ≥3 mg/L was associated with an increased risk of all-cause mortality in men but not women participated in the National Health and Nutrition Examination Survey (NHANES) III study (Doran et al., 2013). In addition, a strong and consistent dose-response relationship between CRP levels and CVD mortality was observed in men, while CVD mortality in women were statistically significant only at CRP levels of 5.0, 8.0, and 9.0 mg/L in that study (Doran et al., 2013). Although a higher hsCRP quartile was associated with an increased risk of CVD mortality in Japanese men and women during 13-year follow-up, the CVD mortality risk was higher in men than women (Iso et al., 2009). On the other hand, a recent analysis within the European Prospective Investigation of Cancer (EPIC)-Norfolk study showed that CRP levels of 3-10 mg/L was associated with increased risks of all-cause and CVD mortality in both men and women (Ahmadi et al., 2013). These findings suggest that inconsistent results between men and women are derived from differences in definition of elevated and clinical cutoff hsCRP.

Likewise, sex differences have been reported in the association between hsCRP level and cancer mortality. In the British women population, the increased risks of cancer mortality associated with elevated CRP concentrations were found in those who had or never had cancer at baseline, but the associations were not statistically significant after adjustment for IL-6 (Heikkila et al., 2007). In contrast with the results of the present study, the EPIC-Norfolk study showed that women had a small increase in the risk of cancer mortality associated with 1 mg/L increase in CRP after 17 year follow-up, but an association between CRP levels and cancer mortality was not found in men (Ahmadi-Abhari et al., 2013). Geometric means of CRP concentrations were higher in women than men in this study (Ahmadi-Abhari et al., 2013).

In the present study, the median of hsCRP was higher in men than in women, at 0.49 mg/L and 0.38 mg/L, respectively. In addition, the proportions of men (7.2%) and women (4.3%) with hsCRP concentrations ≥ 3mg/L are very low in the present study, indicating that distribution of hsCRP concentration is clearly low in Japanese. Unlike findings from the present study and other Asian studies (Saito et al., 2007; Nanri et al., 2011; Sung et al., 2014), several studies among Western population found that CRP concentration was higher in women than in men (Ahmadi et al., 2013; Doran et al., 2013). The reason for the discrepancy in CRP levels with respect to sex is not clearly resolved, but genetic diversity has been reported to influence CRP levels (MacGregor et al., 2004). Furthermore, differences in lifestyle and metabolic risk factors between men and women have been suggested to affect CRP concentrations (Lee et al., 2009).

It remains unclear why elevated hsCRP is more highly associated with mortality risk in men, but not women. Higher hsCRP level may represent an ongoing inflammatory that impairs survival which warrant further investigation. In the present study, higher levels of hsCRP in men than women could be the reason of a greater number of deaths in men than women, which also reported in other studies of Asian subjects (Ko et al., 2012; Sung et al., 2014). In Western populations, women had higher CRP level at baseline than men, and not be at higher risk of mortality (Ahmadi-Abhari et al., 2013; Doran et al., 2013). A protective effect of endogenous female hormones may play a role in attenuating the effects of hsCRP (Gaskins et al., 2012). However, interpretation of the non-significant associations of hsCRP with mortality risks in women is rather difficult, particularly because sex hormone therapy is not commonly used (1.4%) among women in the present study. Another possible reason is that the effect of hsCRP is not the absolute value, but a somewhat increase in baseline hsCRP was associated with mortality (Parrinello et al., 2015).

The large size of the study population, sex-specific analysis, and control for important confounding factors were strengths of the present study. Several limitations need to be discussed, however. The hsCRP was measured only once which may have influenced the results due to within-person fluctuations, and thus tend to underestimate any associations. We excluded those subjects with life-limiting morbid conditions or acute inflammatory conditions to eliminate a random misclassification bias. Another limitation is that the self-reported on information of drug use, especially statin and HRT. However, this medication was rarely used in Japan, and this suggests that such a bias did not invalidate the present findings.

In conclusions, In the large Japanese community-based study, baseline hsCRP was an independent predictor of all-cause mortality as well as deaths from cancer and CVD in apparently healthy Japanese men, but not women. The present findings suggest that hsCRP may have a different effect on the risk of death in men and women, thus warrant further investigation.

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References

Ahmadi-Abhari S, Luben RN, Wareham NJ, et al (2013). Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *Eur J Epidemiol*, **28**, 541-50.

Allin KH, Nordestgaard BG (2011). Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci*, **48**, 155-70.

Arima H, Kubo M, Yonemoto K, et al (2008). High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol*, **28**, 1385-91.

De Martinis M, Franceschi C, Monti D, et al (2006). Inflammation markers predicting frailty and mortality in the elderly. *Exp Mol Pathol*, **80**, 219-27.

Doran B, Zhu W, Muennig P (2013). Gender differences in cardiovascular mortality by C-reactive protein level in the United States: evidence from the National Health and Nutrition Examination Survey III. *Am Heart J*, **166**, 45-51.

Gaskins AJ, Wilchesky M, Mumford SL, et al (2012). Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the Bio Cycle Study. *Am J Epidemiol*, **175**, 423-31.

Guo YZ, Pan L, Du CJ, et al (2013). Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. *Asian Pac J Cancer Prev*, **14**, 243-8.

Heikkila K, Ebrahim S, Rumley A, et al (2007). 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. *Cancer Epidemiol Biomarkers Prev*, **16**, 1155-9.

Hirata A, Ohnaka K, Morita M, et al (2012). Behavioral and clinical correlates of high-sensitivity C-reactive protein in Japanese men and women. *Clin Chem Lab Med*, **50**, 1469-76.

Hotamisligil GS (2006). Inflammation and metabolic disorders. *Nature*, **444**, 860-7.

Il'yasova D, Colbert LH, Harris TB, et al (2005). Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol Biomarkers Prev*, **14**, 2413-8.

Iso H, Cui R, Date C, et al (2009). C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. *Atherosclerosis*, **207**, 291-7.

Kaptoge S, Di Angelantonio E, Lowe G, et al (2010). C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*, **375**, 132-40.

Ko YJ, Kwon YM, Kim KH, et al (2012). High-sensitivity C-reactive protein levels and cancer mortality. *Cancer Epidemiol Biomarkers Prev*, **21**, 2076-86.

Lee YJ, Lee JH, Shin YH, et al (2009). Gender difference and determinants of C-reactive protein level in Korean adults. *Clin Chem Lab Med*, **47**, 863-9.

MacGregor AJ, Gallimore JR, Spector TD, et al (2004). Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clin Chem*, **50**, 130-4.

Nanri A, Yoshida D, Yamaji T, et al (2008). Dietary patterns and C-reactive protein in Japanese men and women. *Am J Clin Nutr*, **87**, 1488-96.

Nanri H, Nakamura K, Hara M, et al (2011). Association between dietary pattern and serum C-reactive protein in Japanese men and women. *J Epidemiol*, **21**, 122-31.

Parrinello CM, Lutsey PL, Ballantyne CM, et al (2015). Six-year change in high-sensitivity C-reactive protein and risk of diabetes, cardiovascular disease, and mortality. *Am Heart J*, **170**, 380-9.

Pepys MB, Hirschfield GM (2003). C-reactive protein: a critical update. *J Clin Invest*, **111**, 1805-12.

Ridker PM (2016). A Test in Context: High-Sensitivity C-Reactive Protein. *J Am Coll Cardiol*, **67**, 712-23.

Saito I, Maruyama K, Eguchi E (2014). C-reactive protein and cardiovascular disease in East asians: a systematic review. *Clin Med Insights Cardiol*, **8**, 35-42.

Saito I, Sato S, Nakamura M, et al (2007). A low level of C-reactive protein in Japanese adults and its association with cardiovascular risk factors: the Japan NCVC-collaborative inflammation cohort (JNIC) study. *Atherosclerosis*, **194**, 238-44.

Shimano H, Arai H, Harada-Shiba M, et al (2008). Proposed guidelines for hypertriglyceridemia in Japan with non-HDL cholesterol as the second target. *J Atheroscler Thromb*, **15**, 116-21.

Sung KC, Ryu S, Chang Y, et al (2014). C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. *Eur Heart J*, **35**, 1809-16.

Swede H, Hajduk AM, Sharma J, et al (2014). Baseline serum C-reactive protein and death from colorectal cancer in the NHANES III cohort. *Int J Cancer*, **134**, 1862-70.

Tokudome S, Goto C, Imaeda N, et al (2004). Development of a data-based short food frequency questionnaire for assessing nutrient intake by middle-aged Japanese. *Asian Pac J Cancer Prev*, **5**, 40-3.

Wulaningsih W, Holmberg L, Ng T, et al (2016). Serum leptin, C-reactive protein, and cancer mortality in the NHANES III. *Cancer Med*, **5**, 120-8.

Zacho J, Tybjaerg-Hansen A, Nordestgaard BG (2010). C-reactive protein and all-cause mortality--the Copenhagen city heart study. *Eur Heart J*, **31**, 1624-32.

Zuo H, Ueland PM, Ulvik A, et al (2016). Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality: the hordaland health study. *Am J Epidemiol*, **183**, 249-58.