Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Association between Levels of C-Reactive Protein and Leukocytes and Cancer: Three Repeated Measurements in the Swedish AMORIS Study

Mieke Van Hemelrijck[1], Lars Holmberg[1,2], Hans Garmo[1,2], Niklas Hammar[3,4], Göran Walldius[4,6], Elisa Binda[5], Mats Lambe[2,7], and Ingmar Jungner[8]

## Abstract

**Objective:** To study levels of C-reactive protein (CRP) and leukocytes, as inflammatory markers, in the context of cancer risk.

**Methods:** From the Apolipoprotein MOrtality RISk (AMORIS) study, we selected 102,749 persons with one measurement and 9,273 persons with three repeated measurements of CRP and leukocytes. Multivariate Cox proportional hazards regression was applied to categories of CRP (<10, 10–15, 15–25, 25–50, >50 g/L) and quartiles of leukocytes. An inflammation-based predictive score (IPS) indicated whether someone had CRP levels of more than 10 mg/L combined with leukocytes of more than $10 \times 10^9$/L. Reverse causality was assessed by excluding those with less than 3, 5, or 7 years of follow-up. To analyze repeated measurements of CRP and leukocytes, the repeated IPS ($IPS_r$) was calculated by adding the IPS of each measurement.

**Results:** In the cohort with one measurement, there was a positive trend between CRP and risk of developing cancer, with the lowest category being the 0.99 (0.92–1.06), 1.28 (1.11–1.47), 1.27 (1.09–1.49), and 1.22 (1.01–1.48) for the second to fifth categories, respectively. This association disappeared when excluding those with follow-up of less than 3, 5, or 7 years. The association between leukocytes and cancer was slightly stronger. In the cohort with repeated measurements, the $IPS_r$ was strongly associated with cancer risk: 1.87 (1.33–2.63), 1.51 (0.56–4.06), and 4.46 (1.43–13.87) for $IPS_r = 1$, 2, and 3 compared with $IPS_r = 0$. The association remained after excluding those with follow-up of less than 1 year.

**Conclusions and Impact:** Our large, prospective cohort study adds evidence for a link between inflammatory markers and cancer risk by using repeated measurements and ascertaining reverse causality. *Cancer Epidemiol Biomarkers Prev; 20(3); 428–37. ©2011 AACR.*

## Introduction

C-reactive protein (CRP), a marker of acute-phase inflammatory response, has been suggested to be useful for early detection of cancer. A recent meta-analysis using 14 prospective studies of circulating CRP and any incident cancer, comprising 3,957 cancer cases, showed that a log unit increase in CRP was associated with a 1.1-unit increase in overall cancer risk (1). Inflammation-associated oxidative damage could initiate carcinogenesis, which causes inactivating mutations in tumor suppressor genes or posttranslational modifications in proteins involved in DNA repair or apoptotic control. Tumor progression can also be facilitated by inflammatory cytokines, enzymes, and transcription factors inhibiting apoptosis and promoting the growth and proliferation of cancer cells (1). However, it is also possible that the immune response of the host is a consequence of the tumor growth itself (2). Nevertheless, the evidence for whether there is an association between CRP and cancer risk remains inconclusive, mainly due to a lack of large-scale studies in which CRP is measured prospectively (3). The largest prospective study today is based on a total of 10,408 individuals from the Danish general population, of whom 1,624 developed cancer. In this study, an increased risk of developing both overall cancer and lung cancer was associated with elevated levels of CRP in cancer-free individuals (4).

**Authors' Affiliations:** [1]Cancer Epidemiology Group, Division of Cancer Studies, School of Medicine, King's College London, London, United Kingdom; [2]Regional Oncologic Centre, Uppsala University, Uppsala; [3]AstraZeneca Sverige, Södertalje; [4]Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [5]Peter Gorer Department of Immunobiology, Division of Immunology, Infection and Inflammatory Disease, School of Medicine, King's College London; [6]Department of Medicine, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; [7]Department of Medical Epidemiology and Biostatistics and [8]Clinical Epidemiological Unit, Department of Medicine, Karolinska Institutet and CALAB Research, Stockholm, Sweden

**Corresponding Author:** Mieke Van Hemelrijck, Research Oncology, Cancer Epidemiology Group, Division of Cancer Studies, School of Medicine, King's College London, 3rd Floor, Bermondsey Wing, Guy's Hospital, London SE1 9RT, United Kingdom. Phone: 44(0)20-3287-9815; Fax: 44(0) 20-7188-9986. E-mail: mieke.vanhemelrijck@kcl.ac.uk

**doi:** 10.1158/1055-9965.EPI-10-1190

Because CRP is an acute-phase protein, repeated measurements and other markers of inflammation could potentially be more informative in predicting cancer risk in the context of inflammation. To our knowledge no prospective study has yet conducted an analysis of more than 2 repeated measurements of CRP and only 1 study assessed CRP in parallel with leukocytes (5). Infiltration of leukocytes is part of the inflammatory process associated with cancer (6), as it has been shown that lymphocytes naturally acquire the ability to recognize cancer cells; however, they cannot control cancer growth (7). Moreover, congenital and acquired immunodeficiencies have been associated with cancer development, indicating that lymphocytes also have an active protective role in surveillance against cancer (8). Leukocytes appear at sites of infection, chronic irritation, and inflammation at different times after tissue injury and they are involved both in the control of infection and in tissue remodeling (9, 10). In a prospective cohort study including 143,748 women aged 50 to 79 years, a statistically significant positive association was found between leukocytes and bladder, colorectal, endometrial, and lung cancer risk when comparing the fourth quartile with the first quartile (11). Another prospective cohort study including 4,831 subjects aged 43 to 86 years found a 2.8-fold increased risk for developing lung cancer when comparing the upper tertile with the lowest tertile of leukocyte counts (12).

We examined possible associations between CRP, leukocytes, and cancer risk in a prospective cohort study of 102,749 persons in whom 6,913 were diagnosed with cancer. In a subgroup of 9,273 persons, we analyzed the association between CRP and leukocytes in 3 repeated measurements and cancer risk.

## Methods

### Study population and data collection

The Central Automation Laboratory (CALAB) database (1985–1996) includes laboratory measurements obtained from 351,487 men and 338,101 women, mainly from the greater Stockholm area (Sweden). All individuals were either healthy individuals referred for clinical laboratory testing as part of a general health checkup or outpatients referred for laboratory testing. No individuals were inpatients at the time their blood samples were taken and none were excluded because of disease symptoms or because of treatment. Apart from the information on blood testing, no personal data were included in the CALAB database (13). This database was linked to several Swedish national registries such as the National Cancer Register, the Hospital Discharge Register, the Cause of Death Register, the consecutive Swedish Censuses during 1970–1990, and the National Register of Emigration by using the Swedish 10-digit personal identity number to provide information on socioeconomic status (SES), vital status, cancer diagnosis, and emigration. This linkage of national registers to the CALAB database is called the Apolipoprotein MOrtality RISk (AMORIS) study and it has been described in detail elsewhere (13–19). This study complied with the Declaration of Helsinki, and the Ethics Review Board of the Karolinska Institutet approved the study.

For the analysis of 1 measurement of CRP and cancer risk, we used all 102,749 persons aged 20 years or older whose levels of CRP and leukocytes were measured at baseline and who did not die or were not diagnosed with cancer within 3 months after their measurement. Follow-up started at time of measurement. For the repeated measurement analysis, we used a subcohort of all 9,273 persons aged 20 years or older whose levels of CRP and leukocytes were measured 3 times within a time frame of 5 years and with a minimum of 9 months between each measurement. These restrictions were set to avoid confounding by indication (e.g., if an infection was found at the first measurement, people might have had repeated measurements taken within the next few months). Follow-up started at time of the third measurement. Nobody in either cohort was diagnosed with benign neoplasms or cancer before the last measurement. In each cohort, follow-up time ended at time of event (i.e., cancer diagnosis), death from any cause, emigration, or end of follow-up (December 31, 2002), whichever occurred first.

The following information was obtained from the CALAB database: CRP (mg/L), leukocytes ($10^9$/L), age at measurement, and gender. All other information was retrieved from the national registries. SES was obtained from the censuses and is based on occupational groups and allows classification of gainfully employed subjects into manual workers and nonmanual employees, designated as blue-collar and white-collar workers in the following text (20). The quantitative determination of CRP was done with an established turbidimetric assay (reagents from Orion Diagnostics), using fully automated multichannel analyzers (an AutoChemist-PRISMA and DAX 96; Technicon Instruments Corporation). High sensitive CRP was not available at any time of the period of blood sampling collection (1985–1996; ref. 21). Leukocytes were counted with routinely used hematology analyzers (Coulter STKS Hematology System; Coulter Corporation). Total imprecision calculated by the coefficient of variation was less than 2.7% at leukocytes level $10 \times 10^9$/L and 12% at CRP level 40 mg/L. All methods were fully automated with automatic calibration and accredited laboratory facilities (14).

### Data analysis for the cohort with 1 measurement of CRP and leukocytes

Multivariate Cox proportional hazards regression was used to investigate the log transformation of leukocytes and quartiles of leukocytes (<5.27, 5.25–6.30, 6.30–7.60, >7.60) and 5 categories of CRP (<10, 10–15, 15–25, 25–50, >50 g/L) in relation to cancer risk. Because of the nonhsCRP measurements, this biomarker was not analyzed

as a continuous variable. All models took into account age, SES, gender, and history of circulatory disease [International Classification of Diseases, Revision 10 (ICD-10): I00-I99] prior to measurement. A test for trend was conducted by using assignment to categories as an ordinal scale. The analysis was also repeated for CRP and leukocytes categorized according to their clinical cutoff of 10 mg/L and $10 \times 10^9$/L (22). Moreover, an inflammation-based predictive score (IPS) was devised on the basis of levels of CRP and leukocytes to take into account the variability of the acute-phase protein CRP. Study subjects were given a score of 1 when they had abnormal values of both CRP and leukocytes according to their clinical cutoffs (CRP > 10 mg/L and leukocytes $>10 \times 10^9$/L; refs. 22, 23) and a score of zero otherwise. A stratified analysis was conducted by gender and history of circulatory disease. The 5 most common cancers among Swedish men (prostate, lung, colon, bladder, and other skin cancers) and women (breast, colon, cervix, lung, and melanoma) were studied separately (24). To assess the effect of reverse causation, 3 sensitivity analyses were conducted in which all persons with follow-up time less than 3, 5, and 7 years were excluded ($n = 3{,}459$, 6,173, and 20,398, respectively). Because no information on smoking (a possible confounder for the association between inflammation and cancer) was available in the current study, another sensitivity analysis was conducted in which all smoking-related cancers (lung, bladder, and head and neck: ICD-7, 162, 163, 181, 140–149) were excluded ($n = 939$).

### Data analysis for the cohort with 3 measurements of CRP and leukocytes

To take into account the 3 repeated measurements and the variability of the acute-phase protein CRP, we developed a repeated score for CRP and leukocytes, according to their clinical cutoff, and IPS ($CRP_r$, $leukocytes_r$, and $IPS_r$, respectively). The 3 repeated scores ranged from 0 to 3 and were calculated by adding the score of each repeated measurement. The same multivariate Cox proportional hazards regression analysis as conducted for single measurements was used to investigate $CRP_r$, $leukocytes_r$, and $IPS_r$ in relation to cancer risk. The adjustment for age was based on age at time of the third measurement. To assess the effect of reverse causation, a sensitivity analysis was conducted in which all persons with follow-up time of less than 1 year were excluded ($n = 219$). Because of the smaller sample size of this cohort, a shorter exclusion time than that for the cohort with 1 measurement was chosen. Moreover, at time of the third measurement, everyone had been free of cancer for at least 18 months since the first measurement. A similar sensitivity analysis excluding smoking-related cancers was conducted to assess the possible effects of smoking.

All analyses were conducted with Statistical Analysis Systems (SAS) release 9.1.3 (SAS Institute).

## Results

### Results for the cohort with 1 measurement of CRP and leukocytes

A total of 13,631 persons (14.22%) had high levels of CRP (>10 mg/L) in the group free of cancer compared with 1,368 persons (19.79%) in the group who developed cancer during follow-up, whereas a total of 5,452 persons (5.69%) had high levels of leukocytes ($>10 \times 10^9$/L) in the group free of cancer compared with 519 persons (7.51%) in the group who developed cancer during follow-up. Participant characteristics are shown in Table 1.

Multivariate adjusted HRs for incident cancer showed an increased incidence by CRP categories of more than 15 mg/L, with the lowest category being the reference: 1.28 (1.11–1.47), 1.27 (1.09–1.49), and 1.22 (1.01–1.48) for the third to fifth categories, respectively ($P_{trend} < 0.001$). Excluding those with follow-up time of less than 3, 5, or 7 years resulted in null findings. Compared with the overall results, excluding smoking-related cancers resulted in slightly attenuated HR for the association between CRP and cancer risk. The association between leukocytes and cancer turned out to be slightly stronger and showed statistically significant findings for the log transformation and the quartiles and the clinical cutoff of leukocytes [e.g., HR for log unit increase in leukocytes: 1.47 (95% CI: 1.34–1.61)]. Sensitivity analyses did not alter the association between leukocytes and cancer; however, the strength of the associations attenuated [e.g., HR for log unit increase in leukocytes when excluding smoking-related cancers: 1.29 (1.18–1.42)]. The IPS score was statistically significantly associated with risk of developing cancer for the main analysis and the sensitivity analyses (Table 2).

A stratified analysis showed no clear differences in HRs by gender or history of circulatory disease (results not shown). A cancer site–specific analysis for the 5 most common Swedish male and female cancers showed only statistically significant findings for CRP and incident male lung cancer: 1.20 (1.00–1.44), 2.02 (1.48–2.77), 2.09 (1.47–2.99), and 1.58 (0.96–2.99) for the second to fifth categories, respectively ($P_{trend} < 0.001$; Table 3). The same observation was made when the clinical cutoff of CRP was used (HR: 1.75; 95% CI: 1.43–2.14). Adjustment for respiratory disease (ICD-10: J00-J99), as a proxy for smoking, did not alter these findings (results not shown). Leukocytes and IPS were also positively associated with male lung cancer risk; moreover, the association was also observed for female lung cancer (e.g., HR: 2.82; 95% CI: 1.39–5.71 for IPS = 1; Table 3). Finally, a difference in risk for developing colon cancer was observed between men and women. When further investigating this risk by gender in stratified analyses of inflammatory markers, we did not find any significant differences (results not shown).

### Results for the cohort with 3 measurements of CRP and leukocytes

A total of 875 persons developed cancer during follow-up. A larger proportion of persons with a diagnosis of

**Table 1.** Descriptive characteristics by cancer status for the cohort with 1 measurement of CRP and leukocytes

| | *n* (%) | |
|---|---|---|
| | **No cancer (*N* = 95,836; 93.27%)** | **Cancer (*N* = 6,913; 6.73%)** |
| Age, mean (SD), y | 47.31 (16.31) | 61.00 (13.01) |
| Gender | | |
| Men | 4,0347 (42.10) | 3,182 (46.03) |
| Women | 55,489 (57.90) | 3,731 (53.97) |
| SES | | |
| White collar | 31,818 (33.20) | 2,530 (64.66) |
| Blue collar | 40,099 (41.48) | 2,512 (36.34) |
| Not gainfully employed/missing | 23,919 (24.96) | 1,871 (27.06) |
| Circulatory disease before CRP measurement | | |
| Yes | 8,327 (8.69) | 1,089 (15.75) |
| Follow-up time, mean (SD), y | 9.74 (2.96) | 5.90 (3.69) |
| CRP, mg/L | | |
| Mean (SD) | 6.21 (13.24) | 7.19 (13.20) |
| <10 | 82,205 (85.78) | 5,545 (80.21) |
| 10–15 | 8,900 (9.29) | 908 (13.13) |
| 15–25 | 2,060 (2.15) | 194 (2.81) |
| 25–50 | 1,587 (1.66) | 159 (2.30) |
| >50 | 1,084 (1.13) | 107 (1.55) |
| Leukocytes ($10^9$/L) | | |
| Mean (SD) | 6.62 (2.03) | 6.90 (2.64) |
| Q1: <5.27 | 24,146 (25.20) | 1,531 (22.15) |
| Q2: 5.25–6.30 | 22,970 (23.97) | 1,569 (22.70) |
| Q3: 6.30–7.60 | 23,934 (24.97) | 1,712 (24.76) |
| Q4: ≥7.60 | 24,786 (25.86) | 2,101 (30.39) |
| IPS | | |
| 0 | 94,669 (98.78) | 6,798 (98.34) |
| 1 | 1,167 (1.22) | 115 (1.66) |

cancer had values of CRP and leukocytes above the clinical cutoff at all 3 measurements than among those who did not develop cancer (e.g., at the third measurement, 8.00% of persons diagnosed with cancer had leukocytes >$10^9$/L vs. 5.11% of those without cancer). All participant characteristics are shown in Table 4. The multivariate adjusted HRs for different values of $CRP_r$, $leukocytes_r$, and $IPS_r$ showed a positive trend [e.g., HR: 1.87 (1.33–2.63), 1.51 (0.56–4.06), and 4.46 (1.43–13.87) for $IPS_r = 1$, 2, and 3 compared with $IPS_r = 0$]. The sensitivity analyses in which those with short follow-up or with smoking-related cancer were excluded slightly attenuated these findings (Table 5).

## Discussion

In the present study, we found evidence for an association between elevated levels of CRP and leukocytes and risk of developing cancer overall. Specifically, a single measurement of CRP or leukocytes was associated with an increased risk for developing lung cancer. Combining CRP with leukocytes or using repeated measurements of CRP and leukocytes strengthened the association with overall cancer risk, even after excluding those with a smoking-related cancer or those with a short follow-up.

### Inflammation and cancer

The hypothesis that a causal link between chronic inflammation and cancer exists has been studied for several decades, but the precise underlying molecular and cellular mechanisms causing cancer and stimulating tumor growth remain unresolved (9, 25). Experimental studies have shown that tumor cells produce various cytokines and attract a diverse leukocyte population that is capable of producing different mediators of cell killing such as TNF-α, interleukins (IL), and interferons (9). This is, for instance, shown in mouse models in which growing intestinal tumor burden coincided with significantly increased levels of inflammatory cytokines IL-9, IL-6, and IL-17 (25). IL-6 is a strong inducer of acute-phase response, which can result in elevation of acute-phase

**Table 2.** HR and 95% CI for categories of CRP, leukocytes, IPS, and risk of cancer diagnosis

| | HR (95% CI) | HR (95% CI)[a] | HR (95% CI)[b] | HR (95% CI)[c] | HR (95% CI)[d] |
|---|---|---|---|---|---|
| CRP, mg/L | | | | | |
| Categories of CRP | | | | | |
| <10 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 10–15 | 0.99 (0.92–1.06) | 0.94 (0.87–1.03) | 0.95 (0.87–1.04) | 0.92 (0.83–1.03) | 0.96 (0.89–1.04) |
| 15–25 | 1.28 (1.11–1.47) | 1.30 (1.09–1.54) | 1.27 (1.04–1.56) | 1.15 (0.88–1.51) | 1.22 (1.04–1.43) |
| 25–50 | 1.27 (1.09–1.49) | 1.08 (0.88–1.32) | 0.95 (0.74–1.23) | 0.84 (0.60–1.18) | 1.27 (1.07–1.51) |
| >50 | 1.22 (1.01–1.48) | 0.91 (0.70–1.19) | 0.79 (0.57–1.11) | 0.79 (0.52–1.21) | 1.13 (0.91–1.40) |
| $P_{trend}$ | <0.001 | 0.623 | 0.521 | 0.142 | 0.009 |
| Clinical cutoff of CRP (>10) | 1.20 (1.10–1.30) | 1.10 (0.99–1.22) | 1.05 (0.92–1.19) | 0.96 (0.81–1.14) | 1.05 (1.01–1.08) |
| Leukocytes ($10^9$/L) | | | | | |
| log (leukocytes) | 1.48 (1.36–1.61) | 1.31 (1.18–1.44) | 1.29 (1.15–1.45) | 1.42 (1.24–1.63) | 1.29 (1.18–1.42) |
| Quartiles of leukocytes | | | | | |
| <5.27 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 5.27–6.30 | 1.02 (0.95–1.09) | 1.02 (0.94–1.10) | 1.06 (0.96–1.16) | 1.11 (0.99–1.24) | 1.00 (0.93–1.07) |
| 6.30–7.60 | 1.04 (0.97–1.11) | 1.01 (0.93–1.09) | 1.02 (0.93–1.12) | 1.02 (0.91–1.15) | 0.99 (0.92–1.06) |
| >7.60 | 1.27 (1.19–1.36) | 1.19 (1.10–1.28) | 1.21 (1.11–1.32) | 1.31 (1.17–1.46) | 1.16 (1.08–1.24) |
| $P_{trend}$ | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Clinical cutoff of leukocytes (>10) | 1.47 (1.34–1.61) | 1.32 (1.18–1.47) | 1.24 (1.08–1.41) | 1.35 (1.15–1.58) | 1.34 (1.21–1.48) |
| IPS | | | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 1.37 (1.14–1.64) | 1.32 (1.05–1.66) | 1.23 (0.92–1.63) | 1.25 (0.87–1.80) | 1.22 (0.99–1.50) |

NOTE: The models are adjusted for gender, age, SES, and history of circulatory disease.

[a]Sensitivity analysis in which all persons with follow-up of less than 3 years were deleted ($n = 3,459$).

[b]Sensitivity analysis in which all persons with follow-up of less than 5 years were deleted ($n = 6,173$).

[c]Sensitivity analysis in which all persons with follow-up of less than 7 years were deleted ($n = 20,398$).

[d]Sensitivity analysis in which all persons with smoking-related cancer were deleted ($n = 939$).

proteins such as CRP. It has been speculated that CRP may have significant proinflammatory effects because of its capacity to activate the complement in order to exacerbate tissue infection. However, an occasional high CRP value can also relate to minor and subclinical infections, inflammation, or trauma whereas a moderately increased CRP value may reflect subclinical pathologies (10). The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease so that circulating CRP concentration directly reflects the intensity of the pathologic process stimulating CRP production. When the stimulus for increased production ceases, the circulating CRP concentration also decreases rapidly (10). Leukocytes, on the other hand, have often been studied as markers of systematic inflammation in the context of cancer survival (22).

Following an increasing number of experimental studies suggesting a link between inflammation and cancer, more observational studies have been conducted to look at a link between markers of inflammation, such as CRP and leukocytes, and risk of developing cancer. The most recent observational study on CRP and cancer risk focused on lung cancer in a nested case–control study of 592 lung cancer patients and 670 controls matched on age, sex, entry year, follow-up time, and smoking. Comparing the fourth quartile (≥5.6 mg/L) with the first quartile (<1.0 mg/L) resulted in a significant positive association between elevated CRP levels and risk of developing lung cancer (26). This association between CRP and lung cancer was also observed in the largest published observational study on CRP and incident cancer. In this Danish prospective cohort of 10,408 individuals, baseline CRP level of greater than 3 mg/L versus less than 1 mg/L was associated with multivariate smoking adjusted HRs of 1.3 for overall cancer and 2.2 for lung cancer (4). In another prospective cohort study of 4,831 participants, it was found that those with leukocyte counts in the upper tertile were 2.81 times more likely to develop lung cancer than those with counts in the lowest tertile (12). Despite these findings, a meta-analysis carried out by Heikillä and colleagues showed that several studies did not find any association between elevated CRP levels and incident cancer and suggested that reverse causation might bias the observed associations (1). Our study in AMORIS is probably the first study that is large enough to exclude a sufficiently long period of early follow-up without losing statistical power.

**Table 3.** HR and 95% CI for categories of CRP and risk of cancer diagnosis, by cancer type in men and women

| **Men** | **Prostate ($N_{events}$ = 1,047)** | **Lung ($N_{events}$ = 265)** | **Colon ($N_{events}$ = 219)** | **Bladder ($N_{events}$ = 210)** | **Other skin ($N_{events}$ = 189)** |
|---|---|---|---|---|---|
| *CRP* | | | | | |
| Categories of CRP | | | | | |
| <10 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 10–15 | 0.91 (0.76–1.10) | 1.34 (0.96–1.88) | 0.63 (0.39–1.02) | 1.03 (0.69–1.55) | 0.92 (0.60–1.41) |
| 15–25 | 1.03 (0.70–1.52) | 2.48 (1.46–4.19) | 1.54 (0.88–3.10) | 0.37 (0.09–1.51) | 1.20 (0.53–2.72) |
| 25–50 | 1.18 (0.81–1.73) | 2.02 (1.10–3.72) | 0.94 (0.39–2.29) | 1.25 (0.55–2.81) | 0.62 (0.20–1.95) |
| >50 | 1.24 (0.80–1.94) | 1.38 (0.57–3.36) | 0.57 (0.14–2.29) | 1.25 (0.46–3.38) | 0.33 (0.05–2.33) |
| $P_{trend}$ | 0.461 | 0.001 | 0.454 | 0.922 | 0.254 |
| Clinical cutoff (>10 mg/L) | 1.08 (0.87–1.34) | 1.83 (1.30–2.58) | 0.94 (0.58–1.52) | 1.05 (0.66–1.69) | 0.81 (0.47–1.40) |
| *Leukocytes* | | | | | |
| log (leukocytes) | 0.83 (0.66–1.04) | 6.13 (4.33–8.69) | 1.86 (1.17–2.96) | 1.18 (0.72–1.93) | 0.84 (0.50–1.44) |
| Quartiles of leukocytes | | | | | |
| <5.27 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 5.27–6.30 | 1.11 (0.93–1.32) | 1.67 (0.99–2.80) | 1.73 (1.09–2.76) | 1.35 (0.90–2.03) | 0.90 (0.60–1.36) |
| 6.30–7.60 | 0.99 (0.83–1.18) | 2.53 (1.57–4.09) | 1.93 (1.23–3.02) | 1.20 (0.79–1.80) | 0.81 (0.54–1.22) |
| >7.60 | 0.92 (0.77–1.10) | 4.69 (2.99–7.38) | 2.06 (1.32–3.21) | 1.16 (0.78–1.76) | 0.84 (0.56–1.27) |
| $P_{trend}$ | 0.173 | 0.05 | 0.002 | 0.152 | 0.351 |
| Clinical cutoff of CRP (>10 $10^9$/L) | 0.96 (0.73–1.27) | 3.11 (2.24–4.33) | 1.07 (0.61–1.87) | 1.24 (0.72–2.13) | 1.13 (0.62–2.08) |
| IPS | | | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 0.88 (0.51–1.53) | 2.35 (1.21–4.57) | 0.60 (0.15–2.43) | 0.98 (0.31–3.08) | 1.09 (0.35–3.40) |
| **Women** | **Breast ($N_{events}$ = 1,241)** | **Colon ($N_{events}$ = 261)** | **Cervix ($N_{events}$ = 64)** | **Lung ($N_{events}$ = 251)** | **Melanoma ($N_{events}$ = 129)** |
| *CRP* | | | | | |
| Categories of CRP | | | | | |
| <10 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 10–15 | 1.00 (0.84–1.18) | 0.88 (0.61–1.29) | 1.04 (0.49–2.21) | 1.10 (0.76–1.60) | 0.60 (0.32–1.11) |
| 15–25 | 1.14 (0.78–1.66) | 0.87 (0.36–2.12) | 2.43 (0.76–7.78) | 1.99 (1.06–3.77) | 1.06 (0.33–3.32) |
| 25–50 | 0.98 (0.62–1.55) | 1.30 (0.58–2.93) | NA | 0.76 (0.24–2.38) | NaN |
| >50 | 0.76 (0.41–1.43) | 1.82 (0.81–4.10) | NA | 1.84 (0.76–4.48) | 1.95 (0.62–6.17) |
| $P_{trend}$ | 0.774 | 0.400 | 0.749 | 0.122 | 0.469 |
| Clinical cutoff (>10 mg/L) | 0.95 (0.75–1.20) | 1.29 (0.84–1.98) | 1.02 (0.37–2.82) | 1.43 (0.93–2.20) | 0.82 (0.38–1.77) |
| *Leukocytes* | | | | | |
| log (leukocytes) | 1.05 (0.86–1.28) | 1.49 (0.97–2.29) | 1.29 (0.55–3.02) | 5.13 (3.48–7.55) | 1.28 (0.70–2.35) |
| Quartiles of leukocytes | | | | | |
| <5.27 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 5.27–6.30 | 0.94 (0.82–1.07) | 1.08 (0.75–1.55) | 1.06 (0.49–2.29) | 1.09 (0.67–1.78) | 0.87 (0.53–1.44) |
| 6.30–7.60 | 0.93 (0.80–1.09) | 1.11 (0.78–1.58) | 1.31 (0.64–2.69) | 2.13 (1.40–3.25) | 0.89 (0.54–1.45) |
| >7.60 | 1.01 (0.86–1.17) | 1.33 (0.95–1.87) | 1.49 (0.74–2.97) | 3.58 (2.42–5.29) | 1.04 (0.65–1.66) |
| $P_{trend}$ | 0.477 | 0.106 | 0.206 | <0.001 | 0.857 |
| Clinical cutoff of CRP (>10 $10^9$/L) | 0.97 (0.76–1.25) | 1.27 (0.78–2.11) | 0.53 (0.13–2.16) | 2.62 (1.81–3.80) | 1.78 (0.98–3.23) |
| IPS | | | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 0.73 (0.39–1.35) | 1.63 (0.67–3.95) | NA | 2.82 (1.39–5.71) | 0.70 (0.10–4.98) |

NOTE: The models were adjusted for age, SES, and history of circulatory disease.

**Table 4.** Descriptive characteristics by cancer status for the cohort with 3 repeated measurements of CRP and leukocytes

| | *n* (%) | |
|---|---|---|
| | **No cancer (*N* = 8,398; 90.56%)** | **Cancer (*N* = 875; 9.44%)** |
| *Age at third measurement, mean (SD), y* | 59.19 (14.96) | 66.48 (11.06) |
| *Gender* | | |
| Men | 3,186 (37.94) | 416 (47.54) |
| Women | 5,212 (62.06) | 459 (52.46) |
| *SES* | | |
| White collar | 3,091 (36.81) | 344 (39.31) |
| Blue collar | 3,115 (37.09) | 256 (29.26) |
| Not gainfully employed/missing | 2,192 (26.10) | 275 (31.43) |
| *Circulatory disease before CRP measurement* | | |
| Yes | 2,916 (34.72) | 372 (42.51) |
| Follow-up time, mean (SD), y | 7.91 (2.24) | 4.36 (2.82) |
| *First measurement* | | |
| CRP, mg/L | | |
| Mean (SD) | 5.39 (10.55) | 5.54 (9.09) |
| >10 | 529 (6.30) | 63 (7.20) |
| Leukocytes ($10^9$/L) | | |
| Mean (SD) | 0.24 (0.43) | 0.23 (0.42) |
| >10 | 436 (5.19) | 61 (6.97) |
| *Second measurement* | | |
| CRP, mg/L | | |
| Mean (SD) | 5.15 (8.07) | 5.46 (10.21) |
| >10 | 453 (5.39) | 63 (7.20) |
| Leukocytes ($10^9$/L) | | |
| Mean (SD) | 0.25 (0.43) | 0.23 (0.42) |
| >10 | 452 (5.38) | 61 (6.97) |
| *Third measurement* | | |
| CRP, mg/L | | |
| Mean (SD) | 5.93 (9.26) | 6.78 (13.11) |
| >10 | 673 (8.01) | 94 (10.74) |
| Leukocytes ($10^9$/L) | | |
| Mean (SD) | 0.24 (0.43) | 0.23 (0.42) |
| >10 | 429 (5.11) | 70 (8.00) |
| *Repeated CRP using clinical cutoff* | | |
| 0 | 7,056 (84.02) | 709 (81.03) |
| 1 | 1,095 (13.04) | 123 (14.06) |
| 2 | 181 (2.16) | 32 (3.66) |
| 3 | 66 (0.79) | 11 (1.26) |
| *Repeated leukocytes using clinical cutoff* | | |
| 0 | 7,488 (98.16) | 752 (85.94) |
| 1 | 613 (7.30) | 76 (8.69) |
| 2 | 187 (2.23) | 25 (2.86) |
| 3 | 110 (1.31) | 22 (2.51) |
| *Repeated IPS using clinical cutoff* | | |
| 0 | 8,165 (97.23) | 833 (95.20) |
| 1 | 200 (2.38) | 35 (4.00) |
| 2 | 28 (0.33) | 4 (0.46) |
| 3 | 5 (0.06) | 3 (0.34) |

**Table 5.** HR and 95% CI for values of the repeated IPS and risk of cancer diagnosis

| | HR (95% CI) | HR (95% CI)[a] | HR (95% CI)[b] |
|---|---|---|---|
| Repeated CRP with clinical cutoff | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 1.15 (0.95–1.39) | 1.07 (0.87–1.33) | 1.01 (0.81–1.25) |
| 2 | 1.83 (1.29–2.61) | 2.04 (1.41–2.95) | 1.82 (1.25–2.66) |
| 3 | 2.05 (1.13–3.73) | 2.44 (1.34–4.34) | 1.49 (0.71–3.14) |
| $P_{trend}$ | <0.001 | <0.001 | 0.025 |
| Repeated leukocytes with clinical cutoff | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 1.42 (1.12–1.79) | 1.45 (1.13–1.87) | 1.24 (0.95–1.62) |
| 2 | 1.61 (1.08–2.40) | 1.50 (0.96–2.35) | 1.48 (0.95–2.31) |
| 3 | 2.18 (1.43–3.34) | 2.38 (1.52–3.71) | 1.87 (1.14–3.07) |
| $P_{trend}$ | <0.001 | 0.002 | 0.001 |
| Repeated IPS | | | |
| 0 | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| 1 | 1.87 (1.33–2.63) | 2.16 (1.53–3.05) | 1.43 (0.94–2.17) |
| 2 | 1.51 (0.56–4.03) | 1.77 (0.66–4.74) | 1.31 (0.42–4.06) |
| 3 | 4.46 (1.43–13.87) | 5.29 (1.70–16.50) | 3.68 (0.92–14.79) |
| $P_{trend}$ | <0.001 | <0.001 | 0.03 |

NOTE: The models are adjusted for age, SES, gender, and history of circulatory disease.
[a]Sensitivity analysis in which all persons with follow-up of less than 1 year were deleted ($n = 219$).
[b]Sensitivity analysis in which all persons with smoking-related cancer were deleted ($n = 114$).

### One measurement of CRP and leukocytes

Our study results confirm that reverse causation can affect the association between CRP and incident cancer: excluding those with less than 3 years of follow-up resulted in null findings. However, a weak association was still apparent when using the clinical cutoff of CRP, suggesting that those with CRP level of more than 10 mg/L are indeed at increased risk for developing cancer. As we used non-hsCRP, we could not specify strata of less than 10 mg/L. Despite the association between dichotomized CRP and cancer, male lung cancer was the only neoplasm for which we could observe a strong association with increasing levels of CRP. These findings are consistent with what has been shown previously in Dutch and Danish prospective cohort studies (2, 4). In contrast to these studies, we did not use hsCRP measurements. Smoking may drive the association with male lung cancer. However, adjustment for lung disease (ICD-10: J00-J99), as a proxy for smoking, did not alter the findings. Our sensitivity analysis in which we excluded smoking-related cancer attenuated the associations, but despite the strong link observed with lung cancer, as shown in Table 3, a weak association remained between inflammatory markers and overall cancer risk. This suggests an association between inflammation and cancer over and above the influence of smoking habits. Despite the positive findings in several other studies for elevated levels of CRP and risk of developing colon and stomach cancer, our findings in the AMORIS study found only an association between log(leukocytes) and male and female colon cancer risk (2, 3, 27). Combining men and women or combining stomach and colon cancer did not alter the findings.

Even though the association between CRP and incident cancer was rather weak, a combination with leukocytes resulted in a statistically significant positive finding that remained in the sensitivity analyses. By using leukocytes as another marker to indicate systemic inflammation, we tried to exclude elevated CRP levels due to acute infections. From our findings, it can be seen that defining those with elevated CRP and elevated leukocyte levels as the risk group is more predictive for cancer risk than for only CRP levels. Nevertheless, the small increase in HRs suggests that levels of CRP and leukocytes are more interesting in the context of cancer etiology rather than for clinical use in cancer risk prediction.

### Three measurements of CRP and leukocytes

The HR for IPS of 1.37, when using 1 measurement, became much stronger when using 3 repeated measurements of IPS (HR: 4.46). It can be observed from our findings that the association with cancer became stronger for both $CRP_r$ and $leukocytes_r$ and also for $IPS_r$. By choosing a minimum interval time of 9 months between measurements, we excluded those who had a strong indication of infection at the time of their first measurement and likely oversampled those who are more health conscious and go for annual checkups. Because we do not know how the association between markers of

inflammation and cancer risk differs between those who are healthy and those who are burdened with more comorbidities, we cannot know how the oversampling is affecting our results. From the sensitivity analyses, one can see that part of the association between CRP, leukocytes, and cancer risk is driven by smoking-related cancers. Nevertheless, after excluding these smoking-related cancers, the statistically significant trends remained for repeated CRP, leukocytes, and IPS.

### Strengths and limitations

The major strength of this analysis lies in the large number of persons with prospective measurements of CRP and leukocytes in AMORIS, all measured at the same clinical laboratory. Use of national health registers provided complete follow-up for each person and detailed information on cancer diagnosis, time of death, and emigration. Furthermore, assessment of both exposures (CRP and leukocytes measurement) and outcome (cancer) were conducted in an accurate manner. In addition, we were able to take into account within-person variation because CRP was measured 3 times in a cohort of 9,273 persons. The AMORIS population was selected by analyzing blood samples from health checkups in nonhospitalized individuals. During the study period, the all-cause mortality was about 14% lower in the AMORIS population than in the general population of Stockholm County when taking age, gender, and calendar year into account (28). This healthy cohort effect does not affect the internal validity of our study and it is also likely to be minor because it has been shown that the AMORIS cohort is similar to the general working population of Stockholm County in terms of SES and ethnicity. A limitation of this study is that information on other commonly measured markers for inflammation such as hsCRP or IL-6 was not available; moreover, CRP and leukocytes are nonspecific markers of inflammation. In the AMORIS study, it was not possible to study hsCRP because at the time of blood sampling and analysis (1985–1996), assay methods for plasma proteins had limited sensitivity so that CRP concentrations of less than 10 mg/L could not be measured precisely [i.e., non–high sensitivity CRP (non-hsCRP)] and the cutoff of 10 mg/L was widely accepted as the upper limit of the health-associated reference range (29). To our knowledge, no study has investigated the effect of using hsCRP instead of non-hsCRP in the context of inflammation and cancer risk, but it is likely that low-grade inflammation is not captured by using this cutoff, resulting in an underestimation of the association between CRP and cancer. However, the cutoff value of 10 mg/L is thought to be satisfactory for the purpose of medical events such as ischemic necrosis (29) and has been used in several other studies looking into the association between CRP and cancer diagnosis and prognosis (30, 31). Furthermore, we did not have information on other possible confounders such as smoking habits or obesity. By excluding smoking-related cancers, our sensitivity analysis addressed this limitation and showed that there was still an association between inflammation and cancer. Obesity is associated with a state of low-grade chronic inflammation, characterized by infiltrating macrophages within adipose tissue and elevated concentrations of proinflammatory molecules (32, 33). To date, it is unclear whether inflammation is an intermediate on the pathway between obesity and cancer or whether obesity is confounding the association between inflammation and cancer. As our study focused on the association between inflammation as a marker of any disease or abnormality, we believe that residual confounding due to lack of information on body mass index is minor. Finally, no information was available on tumor stage and CRP genotypes (34).

### Conclusions

By replicating our findings for 1 measurement of CRP and leukocytes in a cohort with 3 repeated measurements of CRP and leukocytes and by assessing reverse causality in a very large prospective cohort study, our findings provide additional evidence for a link between markers of inflammation and cancer risk. As this link is not yet well understood, the current observations call for experimental studies assessing the association between markers of inflammation and the processes they are reflecting in the context of cancer development.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Grant Support

The study was supported by grants from the Gunnar and Ingmar Jungner Foundation for Laboratory Medicine (Stockholm) and Cancer Research UK.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 11, 2010; revised January 11, 2011; accepted January 11, 2011; published OnlineFirst February 4, 2011.

## References

1. Heikkilä K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.

2. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, et al. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006;24:5216–22.

3. Boffetta P. Exploring a cancer biomarker: the example of C-reactive protein. J Natl Cancer Inst 2010;102:142–3.
4. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009;27:2217–24.
5. dos Santos Silva I, De Stavola BL, Pizzi C, Meade TW. Circulating levels of coagulation and inflammation markers and cancer risks: individual participant analysis of data from three long-term cohorts. Int J Epidemiol 2010;39:699–709.
6. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 2002;23:549–55.
7. Ganss R, Hanahan D. Tumor microenvironment can restrict the effectiveness of activated antitumor lymphocytes. Cancer Res 1998;58:4673–81.
8. Ippoliti G, Rinaldi M, Pellegrini C, Vigano M. Incidence of cancer after immunosuppressive treatment for heart transplantation. Crit Rev Oncol Hematol 2005;56:101–13.
9. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420:860–7.
10. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12.
11. Margolis KL, Rodabough RJ, Thomson CA, Lopez AM, McTiernan A. Prospective study of leukocyte count as a predictor of incident breast, colorectal, endometrial, and lung cancer and mortality in postmenopausal women. Arch Intern Med 2007;167:1837–44.
12. Sprague BL, Trentham-Dietz A, Klein BE, Klein R, Cruickshanks KJ, Lee KE, et al. Physical activity, white blood cell count, and lung cancer risk in a prospective cohort study. Cancer Epidemiol Biomarkers Prev 2008;17:2714–22.
13. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026–33.
14. Jungner I, Marcovina SM, Walldius G, Holme I, Kolar W, Steiner E. Apolipoprotein B and A-I values in 147576 Swedish males and females, standardized according to the World Health Organization-International Federation of Clinical Chemistry First International Reference Materials. Clin Chem 1998;44:1641–9.
15. Holme I, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2008;264:30–8.
16. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Relationships between lipoprotein components and risk of ischaemic and haemorrhagic stroke in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2009;265:275–87.
17. Walldius G, Jungner I, Kolar W, Holme I, Steiner E. High cholesterol and triglyceride values in Swedish males and females: increased risk of fatal myocardial infarction. First report from the AMORIS (Apolipoprotein related MOrtality RISk) study. Blood Press Suppl 1992;4:35–42.
18. Van Hemelrijck M, Garmo H, Binda E, Hayday A, Karagiannis SN, Hammar N, et al. Immunoglobulin E and cancer: a meta-analysis and a large Swedish cohort study. Cancer Causes Control 2010;21:1657–67.
19. Van Hemelrijck M, Garmo H, Holmberg L, Walldius G, Jungner I, Hammar N, et al. Prostate cancer risk in the Swedish AMORIS study: the interplay between triglycerides, total cholesterol, and glucose. Cancer 2010 Nov 29. [Epub ahead of print].
20. Central Bureau for Statistics. Statistics Sweden. Stockholm, Sweden: Central Bureau for Statistics; 2008. Available from:http://www.scb.se/.
21. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Inflammatory markers, lipoprotein components and risk of major cardiovascular events in 65,005 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). Atherosclerosis 2010;213:299–305.
22. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12:223–6.
23. World Health Organization. Manual of Basic Techniques for a Health Laboratory. 2nd ed. Geneva, Switzerland: World Health Organization; 2003.
24. Curado M, Edwards B, Shin H, Storm H, Ferlay J, Heanue M, , et al. Cancer Incidence in Five Continents. Vol IX. Lyon, France: IARC Scientific Publications; 2007. IARC Scientific Publication No. 160.
25. Erdman SE, Poutahidis T. Cancer inflammation and regulatory T cells. Int J Cancer 2010;127:768–79.
26. Chaturvedi AK, Caporaso NE, Katki HA, Wong HL, Chatterjee N, Pine SR, et al. C-reactive protein and risk of lung cancer. J Clin Oncol 2010;28:2719–26.
27. Helzlsouer KJ, Erlinger TP, Platz EA. C-reactive protein levels and subsequent cancer outcomes: results from a prospective cohort study. Eur J Cancer 2006;42:704–7.
28. Holzmann M, Jungner I, Walldius G, Ivert I, Nordqvist T, stergren J. Apolipoproteins B and A-I, standard lipid measures and incidence of myocardial infarction in men and women, with or without chronic kidney disease. Study IV in Thesis for doctorial degree (PhD). In: Holzmann M, editor. Renal Insufficiency, Mortality and Myocardial Infarction. Stockholm, Sweden: Karolinska Institutet; 2008.
29. Wilkins J, Gallimore JR, Moore EG, Pepys MB. Rapid automated high sensitivity enzyme immunoassay of C-reactive protein. Clin Chem 1998;44:1358–61.
30. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dagg K, Scott HR. A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer 2005;92:1834–6.
31. Proctor MJ, Talwar D, Balmar SM, O'Reilly DS, Foulis AK, Horgan PG, et al. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. Br J Cancer 2010;103:870–6.
32. Navab M, Gharavi N, Watson AD. Inflammation and metabolic disorders. Curr Opin Clin Nutr Metab Care 2008;11:459–64.
33. Hsing AW, Sakoda LC, Chua S Jr. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr 2007;86:S843–57.
34. Heikkilä K, Silander K, Salomaa V, Jousilahti P, Koskinen S, Pukkala E, et al. C-reactive protein-associated genetic variants and cancer risk: Findings from FINRISK 1992, FINRISK 1997 and Health 2000 studies. Eur J Cancer 2011;47:404–12.