Association of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis

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ORIGINAL PAPER

Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis

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Abstract
Objective We investigated the associations of circulating C-reactive protein (CRP) and interleukin-6 (IL-6) with cancer risk.
Methods We examined the associations of CRP and IL-6 with incident cancer in two prospective cohorts, the British Women's Heart and Health Study (4,286 women aged 60–80) and the Caerphilly Cohort (2,398 men aged 45–59) using Cox regression and pooled our findings with previous prospective studies' in fixed and random effects meta-analyses.
Results CRP and IL-6 were associated with some incident cancers in our cohorts, but the numbers of cancer cases were small. In our meta-analyses elevated CRP was associated with an increased overall risk of cancer (random effects estimate (RE): 1.10, 95% CI: 1.02, 1.18) and lung cancer (RE: 1.32, 95% CI: 1.08, 1.61). Its associations with colorectal (RE: 1.09, 95% CI: 0.98, 1.21) and breast cancer risks (RE: 1.10, 95% CI: 0.97, 1.26) were weaker. CRP appeared unrelated to prostate cancer risk (RE: 1.00 0.88, 1.13). IL-6 was associated with increased lung and breast cancer risks and decreased prostate cancer risk, and was unrelated to colorectal cancer risk.
Conclusions Our findings suggest an etiological role for CRP and IL-6 in some cancers. Further large prospective and genetic studies would help to better understand this role.

Keywords Cancer · Inflammation · C-reactive protein · Interleukin-6 · Meta-analysis

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Introduction

Inflammation is associated with the progression and severity of many cancers and may also have a causal role in malignancy [1]. Inflammation-associated oxidative damage could initiate carcinogenesis by causing inactivating mutations in tumor-suppressor genes or post-translational modifications in proteins involved in DNA repair or apoptotic control [2]. In addition, inflammatory cytokines, enzymes, and transcription factors inhibit apoptosis and promote the growth and proliferation of cancer cells [2, 3], and the activation of the inflammatory pathways promotes cell motility, vascular permeability, and angiogenesis, thus facilitating tumor progression [1, 4].

Our aim was to examine the etiological role of inflammation in cancer by investigating the associations of two

circulating biomarkers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6), with cancer risk. Dysregulated CRP and IL-6 pathways have been implicated in many diseases, including autoimmune and cardiovascular diseases and cancer [5–7]. IL-6 regulates the growth of multiple myeloma as well as lymphatic, lung, colorectal, breast, prostate, and other cancer cells [8], and CRP is produced in the liver in response to IL-6 signaling and is also expressed by esophageal and renal cancer cells [9, 10]. Our two recent comprehensive systematic reviews demonstrate that a large number of studies of the association of both CRP and IL-6 with prevalent cancer exist [11, 12]. However, it is unclear whether circulating CRP and IL-6 concentrations have causal roles in carcinogenesis or are indicators of a host response to the early neoplastic process [13, 14] because studies of prevalent cancer cases cannot distinguish between these possibilities.

As cancer is a relatively rare disease, small numbers of cancer cases and lack of power pose problems in all but the largest epidemiologic studies. Therefore, to add to the evidence base, we investigated the associations of circulating CRP and IL-6 with cancer risk in two prospective studies and pooled the results of our analyses and the previous prospective studies in a meta-analysis.

Materials and methods

British Women's Heart and Health Study (BWHHS) and Caerphilly Cohort

The BWHHS is ongoing prospective cohort study of 4,286 women aged 60–79 years at the study baseline 1999–2001, who were randomly selected from 23 towns in Britain. The Caerphilly Cohort is a prospective cohort of 2,398 men from Caerphilly and adjacent villages in South Wales, UK, who were aged 45–59 years at the first follow-up in 1984–1988, when the inflammatory biomarkers were measured. We took this time to be the baseline for the analyses presented here. Details of the data collection and participant characteristics for both studies have been published previously [15–17].

In both studies, the participants were followed up and flagged with the UK National Health Service Cancer Registry for information on cancer registrations and deaths. In the BWHHS the cancer cases were identified using data from the participants' self-report, review of their General Practice medical records or cancer registrations and in the Caerphilly Cohort on the basis of cancer and deaths registrations. All cancer events in both cohorts were coded using the ICD-10 system to indicate cancer type. We had insufficient information on cancer stage and grade in our two cohorts to be able to code disease severity at the time of diagnosis.

Exposure measurement

In both studies CRP and IL-6 were measured in the same laboratory (Division of Cardiovascular and Medical Sciences, University of Glasgow) using the same methods. CRP was measured using an ultrasensitive nephelometric assay (Dade Behring, Milton Keynes, UK) and IL-6 using high sensitivity ELISA (R & D Systems, Oxford, UK). The intra- and inter-assay coefficients of variation using these methods were 4.7% and 8.3%, respectively, for CRP and 7.5% and 8.9% for IL-6. They indicate that less than 10% of the variation in CRP or IL-6 concentrations between samples and batches was attributable to sampling variation.

Potential confounders

Age is a major confounder for any association between inflammation and cancer as older people are more likely to develop cancer and to suffer from low-level inflammation, indicated by elevated CRP and IL-6 concentrations [18–20]. Circulating CRP and IL-6 are also associated with many other cancer risk factors, including tobacco smoking [21–23], physical activity [24], socioeconomic position (SEP) [25, 26], over-weight and adiposity [20, 27, 28], the use of non-steroidal anti-inflammatory drugs (NSAIDs) [29–32], and postmenopausal hormone replacement therapy (HRT) [33–37]. Therefore, we adjusted our analyses for age, body mass index (BMI), tobacco smoking, childhood and adult SEP, physical activity, use of NSAIDs, and the use of HRT in the women in the BWHHS. Lung cancer analyses were additionally adjusted for years of smoking as a categorical indicator variable. Age was calculated from the participants' date of birth and the date of entry to the study and BMI from the height and weight measured by a nurse at the baseline medical examination [38, 39]. Data on SEP, smoking, and physical activity levels were obtained from the self-completed questionnaires in both studies. Childhood SEP was ascertained based on the participant's father's occupation, and adult SEP on the participant's own occupation or, in the BWHHS, their spouse's occupation. Both were classified in both studies into six categories according to the Registrar General's classification (Office of Population Censuses and Surveys). The use of NSAIDs and HRT were ascertained from the responses to the self-report questionnaire in both cohorts and additional assessment of the medication brought to the baseline examination in the BWHHS.

Statistical analysis

We used Cox proportional hazards regression to investigate the associations of circulating CRP and IL-6 with cancer risk. CRP and IL-6 concentrations were natural log

transformed to normalize their skewed distributions. We tested the proportional hazards assumption using Schoenfeld-test and found it to be valid for all exposure-outcome pairs. In our models, *origin* was defined as the date of birth and *entry* as the date of entry to the study. The participants were censored at the date of cancer diagnosis, date of death, or the end of follow-up, January 2006 for the BWHHS and April 2006 in the Caerphilly Cohort. We fitted age-adjusted (adjusted for age by the timescale in the model) and multivariable-adjusted models for any incident cancer and lung, colorectal, breast, and prostate cancers. All statistical analyses were conducted using Stata 9.2 (Stata Corporation, Texas).

Systematic reviews

Previous prospective studies of CRP, IL-6, and cancer risk were identified from our comprehensive systematic reviews [11, 12], which were updated to include any articles indexed in Embase or Medline by December 2007. We included articles of any cancer, published in any language, which reported results from studies in which the inflammatory biomarkers were measured at baseline and the participants followed up for cancer diagnoses. The systematic search terms are shown in the Web Supplement, Table W1.

Meta-analyses

We pooled the findings of our two prospective studies with the previously published prospective studies in meta-analyses. We considered odds ratios, hazard ratios, or risk ratios per natural logarithm increase in the inflammatory biomarker for each cancer outcome in each study to be an informative format that would allow us to combine the results. For most studies, we obtained the results in this format from the published articles or by contacting the authors. In four studies of CRP [40–43] and one study of IL-6 [44], however, the effect estimates were presented by quantile or category of the exposure, and we were unable to obtain results in the required format from the authors. For these studies we estimated the mean inflammatory biomarker in each quantile using a method outlined by Chêne and Thompson [45] and used the means and the reported effect estimates to estimate the log OR or RR per natural log unit increase in CRP by a method described by Greenland and Longnecker [46]. These methods are based on assuming a normal distribution of the log-transformed exposure and deal with the unbounded lowest and highest exposure categories and correlations between the effect estimates relating to the same reference group.

As any possible causal relationship between circulating CRP or IL-6 and cancer is a part of a network of biological, environmental, and lifestyle factors acting in concert in carcinogenesis, we did not want to make assumptions about whether the effect of these inflammatory biomarkers on different cancers varies in different populations. Therefore, we have presented both fixed and random effects meta-analyses. In addition, we used the Egger-test to examine small study bias and the I^2-test and stratified meta-analyses to examine heterogeneity among the studies.

Results

The BWHHS and the Caerphilly Cohort

The BWHHS participants excluded from our analyses are presented in Fig. 1. Of the 4,286 women in the BWHHS, 3,274 women had complete data available on the main exposures and all potential confounders. Of these women who were cancer-free at baseline, 200 women developed some form of cancer during the follow-up and 3,074 women remained cancer-free.

The Caerphilly Cohort participants excluded from our analyses are presented in Fig. 2. Of the 2,398 men in this cohort, 1,144 men had complete data on CRP and potential confounders and were cancer-free at baseline. Of these men, 897 remained cancer-free and 247 men developed cancer during follow-up. Of the 1,098 men who had complete data on IL-6 and all potential confounders and were cancer-free at baseline, 845 remained cancer-free and 247 men developed cancer during follow-up. Due to the small number of men who had complete data available for both biomarkers ($n = 1{,}084$) as well as all possible confounders ($n = 710$), we conducted all analyses separately for the men with data on CRP and IL-6. Summary of the

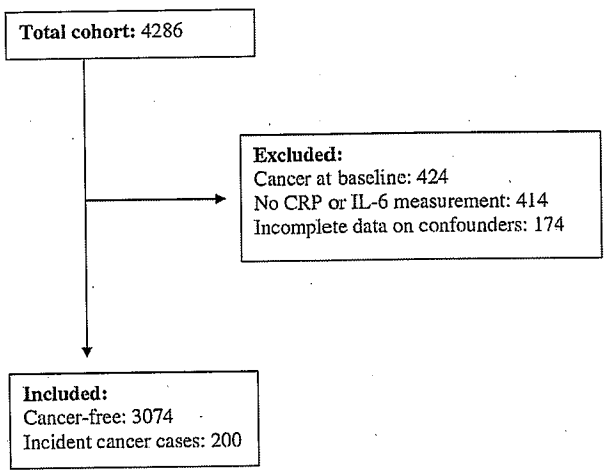

Fig. 1 BWHHS participants included in the analyses

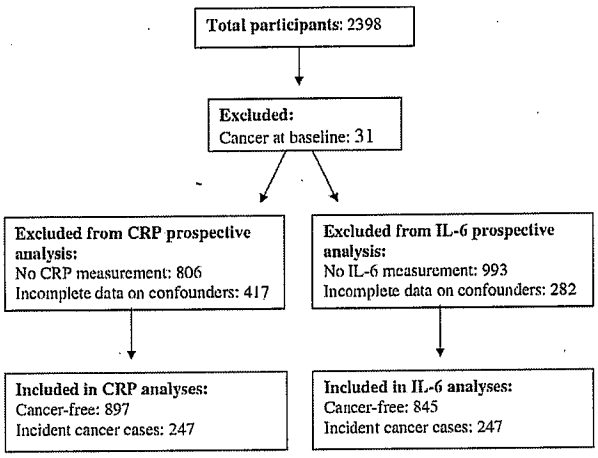

Fig. 2 Caerphilly Cohort participants included in the analyses

characteristics of the participants from both cohorts included in our analyses are presented in supplementary Web Tables W2 and W3.

A summary of the associations of circulating CRP and IL-6 with cancer risk in the BWHHS and the Caerphilly Cohort is presented in Table 1. Neither CRP nor IL-6 concentrations were associated with the overall cancer risk in either cohort, but the site-specific effect estimates varied in direction and magnitude. However, our findings were based on moderate numbers of cancer cases and thus imprecise.

Studies included in the meta-analyses

We identified 15 previous publications of prospective studies of circulating CRP [40–43, 47–57] and three studies of circulating IL-6 [44, 49, 58] and cancer. We excluded one publication that merely summarized two previously published analyses of CRP and cancer risk [48]. A study of any incident cancer in the Women's Health Study [53] was also excluded as it may have included same cancer cases as two subsequent analyses of colorectal and breast cancers in the same cohort [56, 57]. We also excluded two studies, which were conducted in individuals with inflammatory

Table 1 Association of circulating CRP and IL-6 with incident cancer in the BWHHS and the Caerphilly Cohort, by cancer type

Study and cancer type	HR for cancer per natural log increase in the inflammatory marker, by cancer type	
	Age-adjusted HR [95% CI], p	Multivariable-adjusted HR [95% CI], p
BWHHS[a]		
CRP		
Any cancer ($n = 200$)	1.06 [0.94, 1.20], $p = 0.3$	1.06 [0.93, 1.21], $p = 0.4$
Breast cancer ($n = 48$)	1.14 [0.89, 1.47], $p = 0.3$	1.00 [0.76, 1.31], $p = 0.9$
Lung cancer ($n = 23$)	1.16 [0.81, 1.67], $p = 0.4$	1.03 [0.71, 1.51], $p = 0.9$
Colorectal cancer ($n = 32$)	1.03 [0.75, 1.39], $p = 0.9$	0.97 [0.70, 1.34], $p = 0.8$
IL-6		
Any cancer ($n = 200$)	1.03 [0.84, 1.27], $p = 0.8$	0.99 [0.80, 1.23], $p = 0.9$
Breast cancer ($n = 48$)	1.33 [0.91, 1.95], $p = 0.1$	1.20 [0.79, 1.84], $p = 0.4$
Lung cancer ($n = 23$)	0.83 [0.43, 1.58], $p = 0.6$	0.61 [0.31, 1.22], $p = 0.2$
Colorectal cancer ($n = 32$)	1.00 [0.89, 1.68], $p = 0.9$	0.92 [0.53, 1.60], $p = 0.8$
Caerphilly Cohort[b]		
CRP		
Any ($n = 247$)	1.01 [0.90, 1.15], $p = 0.8$	1.02 [0.90, 1.16], $p = 0.7$
Lung ($n = 57$)	1.29 [1.01, 1.66], $p = 0.04$	1.17 [0.91, 1.50], $p = 0.2$
Colorectal ($n = 41$)	0.86 [0.63, 1.16], $p = 0.3$	0.89 [0.66, 1.22], $p = 0.5$
Prostate ($n = 36$)	1.11 [0.82, 1.52], $p = 0.5$	1.12 [0.81, 1.56], $p = 0.5$
IL-6		
Any ($n = 247$)	1.05 [0.90, 1.24], $p = 0.5$	1.03 [0.87, 1.21], $p = 0.8$
Lung ($n = 66$)	1.28 [0.99, 1.65], $p = 0.06$	1.07 [0.81, 1.43], $p = 0.6$
Colorectal ($n = 30$)	0.69 [0.42, 1.15], $p = 0.2$	0.71 [0.41, 1.23], $p = 0.2$
Prostate ($n = 40$)	0.61 [0.40, 0.93], $p = 0.02$	0.61 [0.40, 0.96], $p = 0.031$

[a] BWHHS: multivariable-adjusted models adjusted for age, BMI (continuous), smoking (ever versus never smoked) childhood and adult SEP (manual versus non-manual), physical activity (<2 h/typical week versus 2+ h/typical week) HRT use (ever versus never used), and NSAID use (Baseline user versus non-user). Lung cancer models were additionally adjusted for years smoked (5 categories). [b] Caerphilly: multivariable-adjusted models adjusted for age, BMI (continuous), and binary indicator variables smoking (ever versus never), work physical activity (score ≥11 vs. <11), leisure time physical activity level (≥300 kcl/day vs. <300 kcal/day), baseline NSAID use (yes/no), and childhood and adult SEP (manual versus non-manual). Lung cancer models were additionally adjusted for years smoked (four categories)

conditions—arthritis [50] and HIV [58]—and we could therefore not be certain about the generalizability of their results. These studies are, however, included in our summary tables of all prospective studies. After exclusions, we were left with 12 previously published studies of CRP and two studies of IL-6.

The main characteristics and findings of all the previously published prospective studies of CRP or IL-6 and cancer are detailed in the Supplementary Web Tables W4 and W5. Inflammatory biomarkers were measured from baseline blood samples in frozen storage in all studies included in our meta-analyses. In all but one of the studies incident cancer cases were ascertained from cancer registrations or medical or pathological records (Supplementary Web Tables W4 and W5). The details of cancer case ascertainment were unclear in one study [41].

Results of meta-analyses

Any incident cancer

In our meta-analysis of 14 prospective studies of circulating CRP and any incident cancer, comprising 3,957 cancer cases, a log unit increase in CRP was associated with an increase in the overall cancer risk (random effects estimate: 1.10, 95% CI: 1.02, 1.18). Figure 3 shows the main findings of each constituent study. In most studies the main outcome was all incident cancers combined, and in the remainder of the studies only one cancer type was included in the analysis. We observed considerable heterogeneity in this meta-analysis ($I^2 = 72.6\%$), which may be due to different cancer types studied.

Circulating IL-6 was not associated with the overall risk of incident cancer in a meta-analysis of four studies, consisting of 863 cancer cases (Fig. 4). The pooled fixed and random effect estimates were similar (pooled random effects estimate: 1.01, 95% CI: 0.91, 1.12) and there was little evidence of heterogeneity among the studies.

Lung cancer

In the random effects meta-analysis of six prospective studies of CRP and incident lung cancer, a natural log unit increase in CRP was associated with a 1.32-fold increase in lung cancer risk (95% CI: 1.08, 1.61) (Table 2). The fixed effects estimate was similar (1.27, 95% CI: 1.15, 1.40). All the studies had adjustment for smoking and other potential confounders. However, the notable heterogeneity ($I^2 = 73\%$) may relate to different effects of CRP on lung cancer risk in different populations as the only null-association estimated with precision was reported in an Asian population [43].

The pooled random effects estimate from the three studies of circulating IL-6 and incident lung cancer suggest that a log unit increase in IL-6 is associated with a 1.05-fold increase in lung cancer risk (95% CI: 0.72, 1.52) and the fixed effects estimate was very similar (Table 3). Although adjusted for smoking and other potential confounders, these estimates are based on only 131 cancer cases and thus lack precision.

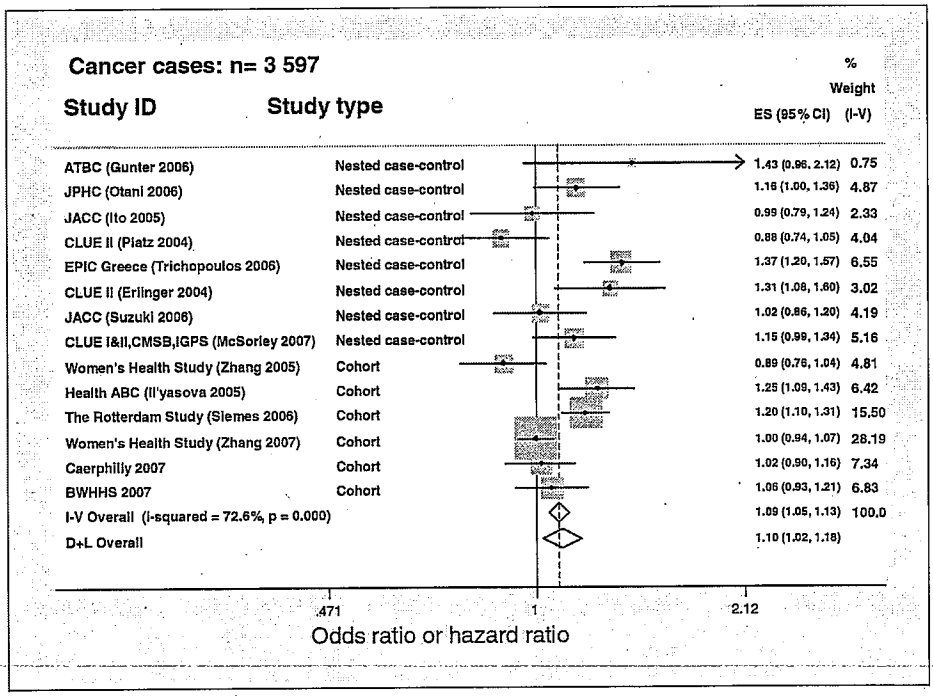

Fig. 3 Meta-analysis of CRP and any incident cancer. I–V overall: fixed effects estimate; D + L overall: random effects estimate. Case–control studies included here were nested in prospective cohorts or randomized controlled trials

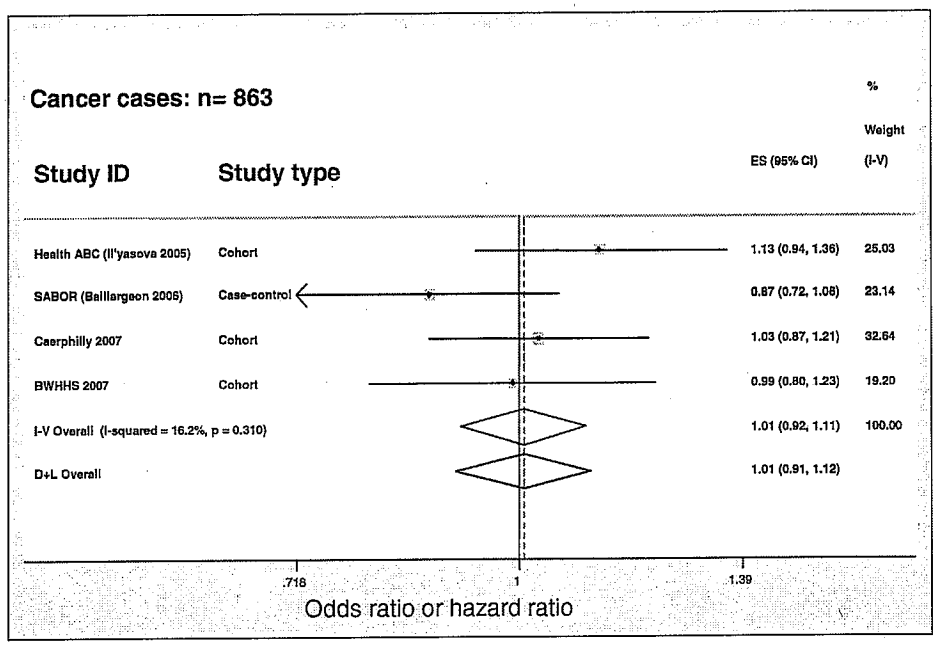

Fig. 4 Meta-analysis of IL-6 and any incident cancer. I–V overall: fixed effects estimate; D + L overall: random effects estimate

Colorectal cancer

When pooled together, the findings of the ten studies of CRP and incident colorectal cancer suggest that elevated CRP is associated with a slightly increased risk of colorectal cancer (random effects estimate: 1.09 (95% CI: 0.98, 1.21) (Table 2). All the analyses were adjusted for age, sex, smoking, BMI, and various lifestyle factors, but the results of some studies were inconsistent, with heterogeneity among the effect estimates ($I^2 = 50.2$).

The pooled effect estimates from three studies showed no association between IL-6 concentrations and colorectal cancer risk (random effects estimate: 1.00, 95% CI: 0.66, 1.52) (Table 3). However, even our pooled estimates were based on small numbers of cancer cases ($n = 102$) and thus imprecise.

Breast cancer

In the meta-analysis of five prospective studies, a log unit increase in CRP was associated with a 1.04-fold increase in breast cancer risk in the fixed effects meta-analysis and 1.10-fold increase in the random effects meta-analysis, but the 95% CIs of both pooled estimates crossed the null-value (Table 2). Also, there was heterogeneity among the studies ($I^2 = 51.0$) and the pooled effect estimates were heavily weighted on the findings of the largest investigations. These two studies (the Women's Health Study and the Rotterdam Cohort) did, nevertheless, provide the estimates that were best adjusted for the largest number of inflammation-related breast cancer risk factors.

The fixed and random effects combined estimates from two studies of IL-6 and breast cancer were identical (1.10,

Table 2 Meta-analyses of prospective studies of circulating CRP and cancer, by cancer type

Cancer type	*N* studies	*N* cases	HR [95% CI] per natural log increase in CRP	
			Fixed effects estimate	Random effects estimate
Lung cancer	6	551	1.27 [1.15, 1.40] $I^2 = 73\%$	1.32 [1.08, 1.61]
Colorectal cancer	10	1,301	1.07 [1.00, 1.15] $I^2 = 50.2\%$	1.09 [0.98, 1.21]
Breast cancer	5	1,240	1.04 [0.98, 1.10] $I^2 = 51.0\%$	1.10 [0.97, 1.26]
Prostate cancer	5	628	1.01 [0.91, 1.11] $I^2 = 26.0\%$	1.00 [0.88, 1.13]
Ovarian cancer	2	195	1.14 [0.99, 1.32] $I^2 = 0$	1.14 [0.99, 1.32]

Table 3 Meta-analyses of prospective studies of circulating IL-6 and cancer

Cancer type	*N* studies	*N* cases	HR [95% CI] per natural log increase in IL-6	
			Fixed effects estimate	Random effects estimate
Lung cancer	3	151	1.08 [0.86, 1.36] $I^2 = 51.7$	1.05 [0.72, 1.52]
Colorectal cancer	3	102	1.02 [0.78, 1.38] $I^2 = 48.2\%$	1.00 [0.66, 1.52]
Breast cancer	2	78	1.10 [0.79, 1.54] $I^2 = 0.0\%$	1.10 [0.79, 1.54]
Prostate cancer	3	228	0.80 [0.69, 0.93] $I^2 = 50.9\%$	0.78 [0.62, 0.99]

95% CI: 0.79, 1.54), and we observed no strong evidence for heterogeneity between these studies. However, based on only 78 cancer cases, the pooled effect estimates were imprecise, crossing the null-value (Table 3).

Prostate cancer

We observed no association of circulating CRP with prostate cancer risk in the meta-analysis of five studies including 628 cancer cases (random effects estimate: 1.00, 95% CI: 0.88, 1.13) (Table 2). Although the study-specific effect estimates ranged from a 20% reduction to 12% increase in prostate cancer risk per log unit increase in CRP, all study-specific 95% CIs crossed the null-value, even in the two studies with relatively large numbers of prostate cancer cases (Clue II: $n = 264$ and the Rotterdam Study: $n = 242$) (Table 4). Thus there is no evidence for an association between circulating CRP and prostate cancer risk.

Pooled findings of the three studies of IL-6 and prostate cancer suggested that elevated IL-6 concentrations were inversely associated with incident prostate cancer (Table 3). Random effects pooled estimate was 0.78 (95% C I: 0.62, 0.99) and the fixed effects estimate was very similar. Although these findings were based on small numbers of cancer cases ($n = 228$), all the study-specific effect estimates were consistent with each other, indicating a reduction in prostate cancer risk.

Ovarian cancer

We pooled the findings of the two prospective studies of circulating CRP and ovarian cancer risk, which together included 195 incident cancer cases. There was no evidence of heterogeneity between their findings ($I^2 = 0$), and the pooled fixed and random effects estimate were similar (1.14, 95% CI: 0.99, 1.32) (Table 2).

Table 4 Meta-analyses of prospective studies of circulating CRP and cancer, stratified by possible sources of heterogeneity

Possible source of heterogeneity	Stratified HR [95% CI] per natural log increase in CRP		
Study design	Nested case–control 1.14 [1.08, 1.22] $I^2 = 68.4\%$ *N* studies: 8	Cohort 1.06 [1.02, 1.11] $I^2 = 76.9\%$ *N* studies: 6	
Participants' sex	Men only 0.99 [0.90, 1.10] $I^2 = 61.3\%$ *N* studies: 3	Women only 1.01 [0.96, 1.07] $I^2 = 49.4\%$ *N* studies: 4	Both sexes 1.20 [1.14, 1.27] $I^2 = 47.8\%$ *N* studies: 7
Adjustment for	Yes	No	
NSAID use	1.16 [1.10, 1.21] $I^2 = 73.9\%$ *N* studies: 8	1.09 [1.05, 1.12] $I^2 = 39.6\%$ *N* studies: 6	
SEP	1.10 [1.02, 1.19] $I^2 = 60.6\%$ *N* studies: 3	1.08 [1.04, 1.13] $I^2 = 76.4\%$ *N* studies: 11	
Physical activity	1.07 [1.03, 1.11] $I^2 = 73.7\%$ *N* studies: 7	1.14 [1.07, 1.22] $I^2 = 72.8\%$ *N* studies: 7	

Exploring heterogeneity

All the studies analyzed here were well-conducted prospective studies, and we found no evidence of the effect estimates being related to the study size in the studies of CRP (Egger-test coefficient: 0.03, 95% CI: −0.17, 0.22, $p = 0.8$) or IL-6 (Egger-test coefficient: 0.30, 95% CI: −0.24, 3.03, $p = 0.7$). There was heterogeneity in all the meta-analyses of CRP and cancer risk (Fig. 3, Table 2). We explored participants' gender, study design, and adjustment for NSAID use, SEP, and physical activity as possible sources of heterogeneity by conducting meta-analyses stratified by these variables (Table 4). The differences in effect size between the studies of men or women reflect differences between cancer types, as studies of only men were investigations of prostate cancer and studies of women only focused on breast and ovarian cancers. Due to the small number of studies we were unable to investigate the heterogeneity among the effect estimates in the studies of IL-6 and cancer risk.

Discussion

CRP, IL-6, and cancer risk

Many cancer cells and other cells in the presence of cancer produce IL-6 and CRP, and IL-6 stimulates the growth and differentiation of many malignant cells [8–10]. Furthermore, population-based studies have shown that individuals with cancer tend to have higher circulating CRP and IL-6 concentrations than apparently healthy people or those with other benign diseases [11, 12]. In our meta-analyses, elevated CRP but not IL-6 concentrations were associated with an increased risk of cancer overall. However, as CRP is a non-specific marker of ill health implicated in many diseases, and the biological mechanisms involved in carcinogenesis in different organs can be very different, an association of CRP with overall cancer risk provides little information on specific processes involved in the malignant development.

The association of CRP and possibly IL-6 with lung cancer risk could reflect a role of these biomarkers in the pathology of lung cancer or lung diseases in general. Elevated CRP concentrations are commonly observed in benign lung diseases [59], although there is also evidence that inflammatory lung diseases predispose individuals to lung cancer [60]. Furthermore, in one, albeit small, prospective study elevated CRP concentrations were associated with the progression of airway dysplasia toward a more abnormal histological type, independently of age, sex, and smoking [61]. The authors of the latter study suggest that the poor lung function associated with inflammation may reduce the ability to clear carcinogenic substances from the lungs, thus increasing lung cancer risk. Smoking is also a strong confounder to an association of inflammatory biomarkers and lung cancer. Although the studies included in our meta-analyses were adjusted for tobacco smoking, it is possible that the associations of CRP and IL-6 with lung cancer risk are explained by residual confounding. This can occur, for instance, because of inaccurate self-report or failure to collect maximal data on smoking, such as pack-years.

The association of CRP with a slight increase in the risk of colorectal cancer may relate to the involvement of inflammation in general or the CRP-pathway in particular in the early stages of carcinogenesis. Our pooled estimates of CRP and colorectal cancer risk were similar to those of another recent meta-analysis, which did not include the BWHHS or the Caerphilly Cohort [62]. However, it is also possible that our findings were inflated by residual confounding from dietary colorectal cancer risk factors, which are difficult to adequately measure and adjust for. Furthermore, our meta-analysis showing no association of IL-6 with colorectal cancer did not support the strong evidence from laboratory-based studies that IL-6, an up-stream regulator of CRP, promotes colorectal cancer growth and progression [8]. Our findings suggest that IL-6 expression is not associated with the tumor initiation in colorectal carcinogenesis, yet further studies are required to confirm or reject these findings.

In our meta-analysis elevated CRP concentrations were associated with a slightly increased breast cancer risk, although due to the small number of cancer cases we were unable to determine whether IL-6 has a causal role in breast cancer. The association of CRP with an increased breast cancer risk may reflect the relationship of CRP and IL-6 with adiposity. Adipose tissue produces IL-6 [63, 64], which stimulates CRP synthesis. Adiposity is also associated with elevated concentrations of insulin-like growth factors [65], which can mediate cell proliferation and inhibit apoptosis in many cancers [66]. Although all the study-specific effect estimates included in the meta-analyses of CRP or IL-6 and breast cancer were adjusted for BMI, this measure may not have adequately captured the effect of adiposity on blood CRP and IL-6 concentrations and cancer.

Our pooled findings suggest that circulating CRP is not causally associated with prostate cancer. Elevated IL-6, on the other hand, was inversely associated with incident prostate cancer. These findings may reflect the pro- and anti-inflammatory roles of IL-6. As described in two recent reviews, IL-6 has the ability to promote the growth of some prostate cancer cell lines while inhibiting the growth of others [8, 67]. Also, research in mouse-models and histopathological studies has suggested that in monitoring tissues for potentially malignant changes, the immune

system can raise an inflammatory response against developing cancer cells [68, 69]. Our findings could therefore mean that the body's antitumor immune responses, indicated by elevated IL-6 concentrations, are successful in combating early stage prostate cancers.

The pooled findings of two prospective studies provided evidence that CRP may be implicated in ovarian cancer development. The two most popular hypotheses of ovarian carcinogenesis suggest that the cell-proliferative capacities of ovulation increase cancer risk, or that ovarian cancer is caused by pituitary gonadotropin and estrogen stimulating the growth of benign cysts into malignant tumors [70]. These ideas are supported by studies of cell-lines and animal models, which have shown that ovarian cancer cells aid their own growth and spread by producing tumor necrosis factor-α (TNF-α) [71] and positive associations between inflammatory exposures (including pelvic inflammatory disease, endometriosis, and ovulation) and ovarian cancer have been observed in epidemiologic studies [70].

Further research directions

Although all the analyses presented here were carefully adjusted for potential confounders, it is possible that the associations of circulating CRP or IL-6 with cancer risk have been inflated by residual confounding or reverse causality. Unless the confounders are measured with little or no error and appropriately modeled, residual confounding remains a possibility. Also, as cancer has a long latent period, elevated CRP or IL-6 concentrations observed in individuals who are subsequently diagnosed with cancer could be due to an early, yet undetected, malignant process. One way to try and overcome this problem is to exclude the cancer cases diagnosed during the early years of follow-up from any analysis, but to be able to exclude a sufficiently long period of early follow-up without losing statistical power, very large prospective studies would be needed. An alternative way to eliminate reverse causality and to minimize residual confounding would be to investigate the associations of cancer with genetic variants known to be associated with circulating CRP or IL-6. As genetic variants are randomly allocated at conception, such investigations would provide unconfounded and unbiased estimates of any associations of inflammatory markers and cancer outcomes [72, 73]. Thus far the evidence for associations of IL6 gene polymorphisms with cancer risk has been inconsistent [74–78] and we are aware of only one study of the CRP gene, which was reported to be related to an increased risk of lung cancer [54]. However, the findings of individual genetic association studies need to be replicated in other populations to provide robust evidence for a relationship between the genetic variants and the outcome.

Strengths and weaknesses of our analyses

We contributed to the existing evidence by investigating the associations of circulating CRP and IL-6 in two well-designed and carefully conducted prospective studies, the BWHHS and the Caerphilly Cohort. Although our analyses were based on small numbers of incident cancer cases, we pooled our findings with those from previously published studies in meta-analyses, thus producing more precise and reliable effect estimates. Our studies also add to the limited literature on IL-6 and cancer risk. However, even our meta-analyses are based on modest numbers of cancer cases and thus illustrate the need for further large prospective studies.

Conclusion

In our meta-analysis of prospective studies of circulating CRP and IL-6 and cancer risk, elevated CRP concentrations were associated with an increased risk of lung cancer and possibly colorectal, breast, and ovarian cancers but unrelated to prostate cancer risk. The evidence thus far, albeit limited, suggests that elevated IL-6 concentrations may be related to an increased risk of lung and breast cancers and a decreased risk of prostate cancer but unrelated to colorectal cancer risk. Future research should focus on further exploring the causal associations of biomarkers of inflammation with these cancer types as well as other cancers for which there is strong biological evidence for a causal relationship.

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References

1. Lu H, Ouyang W, Huang C (2006) Inflammation, a key event in cancer development. Mol Cancer Res 4(4):221–233. doi: 10.1158/1541-7786.MCR-05-0261

2. Perwez Hussain S, Harris CC (2007) Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 121(11):2373–2380. doi:10.1002/ijc.23173
3. Philip M, Rowley DA, Schreiber H (2004) Inflammation as a tumor promoter in cancer induction. Semin Cancer Biol 14(6): 433–439. doi:10.1016/j.semcancer.2004.06.006
4. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G (2006) Inflammation and cancer: how hot is the link? Biochem Pharmacol 72(11):1605–1621. doi:10.1016/j.bcp. 2006.06.029
5. Danesh J, Wheeler JG, Hirschfield GM et al (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350(14):1387–1397. doi:10.1056/NEJMoa032804
6. Hodge DR, Hurt EM, Farrar WL (2005) The role of IL-6 and STAT3 in inflammation and cancer. Eur J Cancer 41(16):2502–2512. doi:10.1016/j.ejca.2005.08.016
7. Ishihara K, Hirano T (2002) IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev 13(4–5):357–368. doi:10.1016/S1359-6101(02)00027-8
8. Hong DS, Angelo LS, Kurzrock R (2007) Interleukin-6 and its receptor in cancer: implications for translational therapeutics. Cancer 110(9):1911–1928. doi:10.1002/cncr.22999
9. Jabs WJ, Busse M, Kruger S, Jocham D, Steinhoff J, Doehn C (2005) Expression of C-reactive protein by renal cell carcinomas and unaffected surrounding renal tissue. Kidney Int 68(5):2103–2110. doi:10.1111/j.1523-1755.2005.00666.x
10. Nozoe T, Korenaga D, Futatsugi M, Saeki H, Maehara Y, Sugimachi K (2003) Immunohistochemical expression of C-reactive protein in squamous cell carcinoma of the esophagus—significance as a tumor marker. Cancer Lett 192(1):89–95. doi:10.1016/S0304-3835(02)00630-4
11. Heikkila K, Ebrahim S, Lawlor DA (2007) A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health 61(9): 824–833. doi:10.1136/jech.2006.051292
12. Heikkila K, Ebrahim S, Lawlor DA (2008) A systematic review of circulating concentrations of interleukin-6 (IL-6) and cancer. Eur J Cancer 44(7):937–945. doi:10.1016/j.ejca.2008.02.047
13. Basso D, Fabris C, Meani A et al (1988) C reactive protein in pancreatic cancer and chronic pancreatitis. Ann Clin Res 20(6): 414–416
14. O'Hanlon DM, Lynch J, Cormican M, Given HF (2002) The acute phase response in breast carcinoma. Anticancer Res 22(2B):1289–1293
15. Lawlor DA, Okasha M, Gunnell D, Davey Smith G, Ebrahim S (2003) Associations of adult measures of childhood growth with breast cancer: findings from the British Women's Heart and Health Study. Br J Cancer 89(1):81–87. doi:10.1038/sj.bjc.6600972
16. MRC Epidemiology Unit C (2007) Caerphilly prospective study. Department of Social Medicine, University of Bristol
17. Lawlor DA, Ebrahim S, Davey SG (2002) Socioeconomic position in childhood and adulthood and insulin resistance: cross sectional survey using data from British women's heart and health study. BMJ 325(7368):805–807. doi:10.1136/bmj.325.7368.805
18. Caruso C, Lio D, Cavallone L, Franceschi C (2004) Aging, longevity, inflammation, and cancer. Ann N Y Acad Sci 1028: 1–13. doi:10.1196/annals.1322.001
19. Bruunsgaard H, Pedersen M, Pedersen BK (2001) Aging and proinflammatory cytokines. Curr Opin Hematol 8(3):131–136. doi:10.1097/00062752-200105000-00001
20. Himmerich H, Fulda S, Linseisen J et al (2006) TNF-alpha, soluble TNF receptor and interleukin-6 plasma levels in the general population. Eur Cytokine Netw 17(3):196–201
21. Mendall MA, Patel P, Asante M et al (1997) Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart 78(3):273–277
22. Lowe GD (2005) Circulating inflammatory markers and risks of cardiovascular and non-cardiovascular disease. J Thromb Haemost 3(8):1618–1627. doi:10.1111/j.1538-7836.2005.01416.x
23. Fernandez-Real JM, Vayreda M, Richart C et al (2001) Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. J Clin Endocrinol Metab 86(3):1154–1159. doi:10.1210/jc.86.3.1154
24. Colbert LH, Visser M, Simonsick EM et al (2004) Physical activity, exercise, and inflammatory markers in older adults: findings from the health, aging and body composition study. J Am Geriatr Soc 52(7):1098–1104. doi:10.1111/j.1532-5415.2004.52307.x
25. Jousilahti P, Salomaa V, Rasi V, Vahtera E, Palosuo T (2003) Association of markers of systemic inflammation, C reactive protein, serum amyloid A, and fibrinogen, with socioeconomic status. J Epidemiol Community Health 57(9):730–733. doi:10.1136/jech.57.9.730
26. Lawlor DA, Davey Smith G, Rumley A, Lowe GD, Ebrahim S (2005) Associations of fibrinogen and C-reactive protein with prevalent and incident coronary heart disease are attenuated by adjustment for confounding factors. British Women's Heart and Health Study. Thromb Haemost 93(5):955–963
27. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM (2003) Relationship of total and abdominal adiposity with CRP and IL-6 in women. Ann Epidemiol 13(10):674–682. doi:10.1016/S1047-2797(03)00053-X
28. Ford ES (2003) Asthma, body mass index, and C-reactive protein among US adults. J Asthma 40(7):733–739. doi:10.1081/JAS-120023497
29. Harris RE, Beebe-Donk J, Doss H, Burr DD (2005) Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). Oncol Rep 13(4):559–583
30. Berg J, Fellier H, Christoph T, Grarup J, Stimmeder D (1999) The analgesic NSAID lornoxicam inhibits cyclooxygenase (COX)-1/-2, inducible nitric oxide synthase (iNOS), and the formation of interleukin (IL)-6 in vitro. Inflamm Res 48(7):369–379. doi:10.1007/s000110050474
31. Gonzalez E, de la Cruz CC, de Nicolas NR, Egido J, Herrero-Beaumont G (1994) Long-term effect of nonsteroidal anti-inflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis. Agents Actions 41(3–4):171–178. doi:10.1007/BF02001912
32. Prasad K (2006) C-reactive protein (CRP)-lowering agents. Cardiovasc Drug Rev 24(1):33–50. doi:10.1111/j.1527-3466.2006.00033.x
33. Cushman M, Meilahn EN, Psaty BM, Kuller LH, Dobs AS, Tracy RP (1999) Hormone replacement therapy, inflammation, and hemostasis in elderly women. Arterioscler Thromb Vasc Biol 19(4):893–899
34. Manns PJ, Williams DP, Snow CM, Wander RC (2003) Physical activity, body fat, and serum C-reactive protein in postmenopausal women with and without hormone replacement. Am J Hum Biol 15(1):91–100. doi:10.1002/ajhb.10117
35. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD (2002) Postmenopausal hormone replacement therapy: scientific review. JAMA 288(7):872–881. doi:10.1001/jama.288.7.872
36. Pradhan AD, Manson JE, Rossouw JE et al (2002) Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA 288(8):980–987. doi:10.1001/jama.288.8.980
37. Silvestri A, Gebara O, Vitale C et al (2003) Increased levels of C-reactive protein after oral hormone replacement therapy may not be related to an increased inflammatory response. Circulation 107(25):3165–3169. doi:10.1161/01.CIR.0000074208.02226.5E
38. Lawlor DA, Okasha M, Gunnell D, Davey Smith G, Ebrahim S (2003) Associations of adult measures of childhood growth with

breast cancer: findings from the British Women's Heart and Health Study. Br J Cancer 89(1):81–87. doi:10.1038/sj.bjc.6600972
39. MRC Unit (South Wales) (1985) The Caerphilly Collaborative Heart Disease Study Project Description and Manual of Operations. MRC Unit, South Wales
40. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ (2004) C-reactive protein and the risk of incident colorectal cancer. JAMA 291(5):585–590. doi:10.1001/jama.291.5.585
41. Ito Y, Suzuki K, Tamakoshi K et al (2005) Colorectal cancer and serum C-reactive protein levels: a case–control study nested in the JACC Study. J Epidemiol 15(Suppl 2):S185–S189. doi:10.2188/jea.15.S185
42. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S (2006) Plasma C-reactive protein and risk of colorectal cancer in a nested case–control study: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 15(4):690–695. doi:10.1158/1055-9965.EPI-05-0708
43. Suzuki K, Ito Y, Wakai K et al (2006) Serum heat shock protein 70 levels and lung cancer risk: a case–control study nested in a large cohort study. Cancer Epidemiol Biomarkers Prev 15(9): 1733–1737. doi:10.1158/1055-9965.EPI-06-0005
44. Baillargeon J, Platz EA, Rose DP et al (2006) Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiol Biomarkers Prev 15(7):1331–1335. doi: 10.1158/1055-9965.EPI-06-0082
45. Chene G, Thompson SG (1996) Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 144(6):610–621
46. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135(11):1301–1309
47. Gunter MJ, Stolzenberg-Solomon R, Cross AJ et al (2006) A prospective study of serum C-reactive protein and colorectal cancer risk in men. Cancer Res 66(4):2483–2487. doi: 10.1158/0008-5472.CAN-05-3631
48. Helzlsouer KJ, Erlinger TP, Platz EA (2006) C-reactive protein levels and subsequent cancer outcomes: results from a prospective cohort study. Eur J Cancer 42(6):704–707. doi:10.1016/j.ejca.2006.01.008
49. 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(10):2413–2418. doi:10.1158/1055-9965.EPI-05-0316
50. Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C, Ollier WE, Martin J, Gonzalez-Gay MA (2007) Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. Semin Arthritis Rheum 37(1):31–38. doi:10.1016/j.semarthrit.2007.01.002
51. McSorley MA, Alberg AJ, Allen DS et al (2007) C-reactive protein concentrations and subsequent ovarian cancer risk. Obstet Gynecol 109(4):933–941
52. Platz EA, De Marzo AM, Erlinger TP et al (2004) No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. Prostate 59(4):393–400. doi: 10.1002/pros.10368
53. Rifai N, Buring JE, Lee IM, Manson JE, Ridker PM (2002) Is C-reactive protein specific for vascular disease in women? Ann Intern Med 136(7):529–533
54. Siemes C, Visser LE, Coebergh JW et al (2006) C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 24(33):5216–5222. doi: 10.1200/JCO.2006.07.1381
55. Trichopoulos D, Psaltopoulou T, Orfanos P, Trichopoulou A, Boffetta P (2006) Plasma C-reactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol Biomarkers Prev 15(2):381–384. doi:10.1158/1055-9965.EPI-05-0626
56. Zhang SM, Buring JE, Lee IM, Cook NR, Ridker PM (2005) C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med 142(6):425–432
57. Zhang SM, Lin J, Cook NR et al (2007) C-reactive protein and risk of breast cancer. J Natl Cancer Inst 99(11):890–894. doi: 10.1093/jnci/djk202
58. Breen EC, MM van der, Cumberland W, Kishimoto T, Detels R, Martinez-Maza O (1999) The development of AIDS-associated Burkitt's/small noncleaved cell lymphoma is preceded by elevated serum levels of interleukin 6. Clin Immunol 92(3):293–299. doi:10.1006/clim.1999.4760
59. Gan WQ, Man SFP, Senthilselvan A, Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59(7):574–580. doi:10.1136/thx.2003.019588
60. Daniels CE, Jett JR (2005) Does interstitial lung disease predispose to lung cancer? Curr Opin Pulm Med 11(5):431–437. doi: 10.1097/01.mcp.0000170521.71497.ba
61. Sin DD, Man SFP, McWilliams A, Lam S (2006) Progression of airway dysplasia and C-reactive protein in smokers at high risk of lung cancer. Am J Respir Crit Care Med 173(5):535–539. doi: 10.1164/rccm.200508-1305OC
62. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA (2008) C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. Int J Cancer 123(5):1133–1140. doi:10.1002/ijc.23606
63. Fain JN (2006) Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Interleukins 74:443–477. doi: 10.1016/S0083-6729(06)74018-3
64. Mohamed-Ali V, Goodrick S, Rawesh A et al (1997) Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-{alpha}, in vivo. J Clin Endocrinol Metab 82(12):4196–4200. doi:10.1210/jc.82.12.4196
65. Bluher S, Kratzsch J, Kiess W (2005) Insulin-like growth factor I, growth hormone and insulin in white adipose tissue. Best Pract Res Clin Endocrinol Metab 19(4):577–587. doi:10.1016/j.beem.2005.07.011
66. Riedemann J, Macaulay VM (2006) IGF1R signalling and its inhibition. Endocr Relat Cancer 13(Supplement_1):S33–S43
67. Paule B, Terry S, Kheuang L, Soyeux P, Vacherot F, de la Taille A (2007) The NF-kappaB/IL-6 pathway in metastatic androgen-independent prostate cancer: new therapeutic approaches? World J Urol 25(5):477–489. doi:10.1007/s00345-007-0175-6
68. Weinberg RA (2007) Crowd control: tumour immunology and immunotherapy. In: The biology of cancer, 1st edn. Garland Science, Taylor and Francis Group, LLC
69. Dunn GP, Koebel CM, Schreiber RD (2006) Interferons, immunity and cancer immunoediting. Nat Rev Immunol 6(11):836–848. doi:10.1038/nri1961
70. Ness RB, Cottreau C (1999) Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 91(17):1459–1467. doi:10.1093/jnci/91.17.1459
71. Kulbe H, Thompson R, Wilson JL et al (2007) The inflammatory cytokine tumor necrosis factor-alpha generates an autocrine tumor-promoting network in epithelial ovarian cancer cells. Cancer Res 67(2):585–592. doi:10.1158/0008-5472.CAN-06-2941
72. Davey Smith G, Ebrahim S (2003) 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 32(1):1–22. doi: 10.1093/ije/dyg070
73. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey SG (2007) Mendelian randomization: Using genes as instruments for

making causal inferences in epidemiology. Stat Med 27(8):1133–1163. doi:10.1002/sim.3034
74. Theodoropoulos G, Papaconstantinou I, Felekouras E et al (2006) Relation between common polymorphisms in genes related to inflammatory response and colorectal cancer. World J Gastroenterol 12(31):5037–5043
75. Balasubramanian SP, Azmy IA, Higham SE et al (2006) Interleukin gene polymorphisms and breast cancer: a case control study and systematic literature review. BMC Cancer 6:188. doi:10.1186/1471-2407-6-188
76. Kamangar F, Abnet CC, Hutchinson AA et al (2006) Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). Cancer Causes Control 17(1):117–125. doi:10.1007/s10552-005-0439-7
77. Gunter MJ, Canzian F, Landi S, Chanock SJ, Sinha R, Rothman N (2006) Inflammation-related gene polymorphisms and colorectal adenoma. Cancer Epidemiol Biomarkers Prev 15(6):1126–1131. doi:10.1158/1055-9965.EPI-06-0042
78. Lan Q, Zheng T, Rothman N et al (2006) Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. Blood 107(10):4101–4108. doi:10.1182/blood-2005-10-4160