REVIEW

A systematic review of the association between circulating concentrations of C reactive protein and cancer

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The objective of this study was to review and summarise the published evidence for an association between circulating concentrations of C reactive protein (CRP) and cancer through a systematic review. 90 discrete studies were identified. 81 (90%) were prevalent case–control or cross-sectional studies, and only 9 studies had a prospective design. In most prevalent studies, CRP concentrations were found to be higher in patients with cancer than in healthy controls or controls with benign conditions. Of the nine large prospective studies identified in this review, four reported no relationship between circulating CRP levels and breast, prostate or colorectal cancers, and five studies found that CRP was associated with colorectal or lung cancers. Most of the studies evaluating CRP as a diagnostic marker of cancer did not present relevant statistical analyses. Furthermore, any association reported in the prevalent studies might reflect reverse causation, survival bias or confounding. The prospective studies provided no strong evidence for a causal role of CRP in cancer. Instead of further prevalent studies, more large prospective studies and CRP gene–cancer association studies would be valuable in investigating the role of CRP in cancer.

C reactive protein (CRP) is a marker of acute-phase inflammatory response. It is produced mainly by hepatocytes, and its production is regulated by interleukin 6 (IL6). Both genetic and environmental factors influence an individual's basal CRP concentration,[1 2] and thus circulating CRP levels in apparently healthy people can vary from 0.1 to 10 mg/l.[1] Increased CRP concentrations have been reported in many diseases, including cardiovascular diseases, type 2 diabetes, arthritis and many types of cancers.[1 3–7]

Several possible mechanisms have been proposed for the relationship between CRP and cancer. First, tumour growth can cause tissue inflammation and hence increase CRP levels.[8 9] Second, CRP could be an indicator of an immune response to tumour antigens.[10–12] Third, there is evidence that cancer cells can increase the production of inflammatory proteins, which could explain the high CRP concentrations in patients with cancer. Some cancerous cells have been shown to express CRP[2 6 13] and cancer cell lines have been shown to secrete IL6 and IL8, which in turn induce the production of CRP.[14 15] These mechanisms imply that increased CRP is a response to the neoplastic process and that CRP concentrations could thus provide a marker for identifying people with cancer at an early stage when treatment might be more effective. Finally, chronic inflammation, of which CRP is an important marker, might have an aetiological role in cancer. It has been suggested that inflammation creates a tissue microenvironment where the reactive oxygen and nitrogen species released by inflammatory cells could cause potentially malignant DNA alterations,[16] and that some inflammatory cytokines and proteins in chronic inflammation promote tumour growth.[17 18]

The prognostic use of CRP and other inflammatory markers has been demonstrated in many forms of cancer,[7] but the epidemiological evidence for a diagnostic or an aetiological role of circulating CRP in cancer has been inconsistent to date. Given the large and increasing body of research in this area, with different claims about the role of CRP in malignancy, we undertook a systematic review of the literature in order to summarise the currently available evidence for the role of circulating CRP in the diagnosis and aetiology of cancer, to assess the quality of studies and to discuss where further research resources in this area would be best placed.

MATERIALS AND METHODS

Electronic databases Medline, Embase and the Cochrane Library were searched systematically on 1 July 2006. The Web of Science database was searched for publications citing the articles identified from previous searches, and publications cited in the reviewed articles were included where relevant. Table 1 details the search terms used. Studies of any type of cancer in humans, written in any language and comparing patients with cancer with apparently healthy people or with people with benign conditions were included. Where more than one paper had been published using data from the same study, all publications were reviewed, but where duplication of the CRP data was apparent, the latest or the most conclusively reported study was included in the summary of studies. Any study including results of the relationship between CRP and any type of cancer was included in the review, irrespective of the primary focus of the study. As our aim in this review was to assess the role of circulating CRP in the diagnosis or aetiology of cancer, we did not specifically search for studies investigating CRP as a prognostic marker of cancer. However, as we extensively searched for studies comparing CRP concentrations in patients with cancer and in people free of

Abbreviation: CRP, C reactive protein; IL, interleukin

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Table 1 Search terms used in this study

MeSH terms	Text words
Neoplasms OR Neoplasms, second primary AND C-reactive protein AND epidemiologic studies/	cancer$ OR malign$ OR tumour$ OR tumor$ C-reactive protein OR CRP case control$ OR (cohort adj1 (study or studies)) OR cohort analy$ OR (follow up adj1 (study or studies)) OR (observational adj1 (study or studies)) OR longitudinal. tw. retrospective. OR cross sectional. tw. associat$ OR comparative study/

malignant diseases, we found studies evaluating CRP as a prognostic marker that also included a control group free of malignant diseases. These studies were included in the review if they presented relevant results.

If the title or abstract of the article seemed relevant, the abstract and, where necessary, the full text were reviewed to decide whether it should be included. Two reviewers (KH and DAL) independently extracted data from 50% of the publications using a standard data extraction sheet, and as the reviewers agreed on the extracted information over 95% of the time, KH extracted the data from the remaining papers and any uncertain issues were addressed by further joint inspection of the papers and discussion (with DAL). As the hypotheses, cancer types and designs of the identified studies were markedly different, it was deemed inappropriate to pool the results using meta-analysis.

RESULTS

The Medline search produced 1839 hits and the Embase search produced 1861 hits. No relevant publications were identified in the Cochrane Library. A total of 103 publications that fulfilled our inclusion criteria were identified; 40 publications did not contain relevant data and were excluded (fig 1). There were 13 duplicate publications among studies investigating CRP and other biochemical markers in patients with multiple myeloma, colorectal and lung cancer: of the 9 publications by the same group of investigators, CRP data from the same cancer cases seem to have been included in 7 publications[19–25] and the controls seem to have been the same in 5 of these.[19–21 23 25] Three publications on advanced lung cancer[26–28] and two publications on newly diagnosed lung cancer,[29 30] two on colorectal cancer,[31 32] two on multiple myeloma[33 34] and two on prostate cancer[35 36] also included the same participants. One publication drew together two sets of results previously published by the same authors[37] and was not treated as a discrete study. After excluding the duplicate publications, we were left with 90 discrete studies. Despite our efforts, we were unable to obtain a full-text copy of a study of bronchial carcinoma[38] and were unable to translate a Polish article on various cancers in children,[39] but we included the data that we were able to extract from the abstracts and tables only. Summaries of all the published papers are presented in two supplementary web tables (supplementary tables 1 and 2 are available at http://jech.bmj.com/supplemental). Examining the association between CRP and cancer was the primary aim in 54 discrete studies.[8 9 28 38–89] We also identified 36 studies in which CRP was not the main focus, but which contained relevant data.[10 12 23 29 32 34 36 90–117]

Table 2 lists the reviewed studies that examined various forms of cancer. The most commonly studied cancers in relation to circulating CRP were colorectal cancer, various types of lung cancer, multiple myeloma and gastrointestinal cancer. There were 81 studies of prevalent cancer cases and 9 prospective studies with incident cancer cases.[42 45 59 64 66 76 79 80 89] The studies comprised 78 case–control studies, 5 of which were nested in prospective cohorts and 2 in randomised controlled trials; 2 cohort studies, 1 of which was nested within a randomised controlled trial; 5 cross-sectional studies; and 5 interventional before-and-after studies (supplementary tables 1 and 2).

Limitations of studies

Design and selection of controls

As table 3 shows, most studies had a prevalent design and their results could not determine the temporal sequence of any observed association between CRP and cancer, and could be subject to survival bias, as cases of rapidly fatal cancer would be excluded. Only nine prospective studies investigated the possible aetiological role of circulating CRP in cancer.[42 45 59 64 66 76 79 80 89] Most studies had important limitations in the selection of participants. In all, 41 studies did not contain an adequate description of how the participants had been selected.[22 24 32 40 44 47 48 50 51 53 54 62 65 67–69 71 74 75 77 82 85–87 93 95–97 100 102–104 106 108–110 114–118] As only abstracts were available for two studies, we could not ascertain any details of the recruitment of controls for these.[38 39] Of the 78 case–control studies included in our review, 12 had selected controls from hospital staff, soldiers, or blood or organ donors, who might have been healthier than the general population from which the cancer cases were obtained.[8 23 27 28 40 46 52 60 78 88 90 113] In all, 22 case-control studies,[9 12 29 43 51 57 58 63 70 78 81 83 88 91 92 94 98 99 101 105 107 112] 2 before-and-after studies[49 73] and 4 cross-sectional studies[55 56 72 84] had recruited controls and participants free from cancer from hospital inpatients or outpatients who were likely to be less healthy than the general population. Only 10 case–control studies had used community controls,[36 42 45 59 61 66 76 79 80 107] and 2 cohort studies[64 89] and 1 cross-sectional study[34] had recruited community-living participants.

Adjustment for confounders

Few studies included adjustment for known potential confounders of the relationship between CRP and cancer, such as smoking,[119 120] body mass index[121] or socioeconomic position.[119] It would be unreasonable to expect the researchers to adjust for confounders in studies in which the relationship between CRP and cancer is not the main focus, but in the studies in which CRP is the primary aim, lack of adjustment is a major limitation. Of the 54 studies in which CRP was the main focus, 38 had adjusted for no confounders at all,[8 28 33 43 44 46–58 60–63 65 67–70 72–74 78 81–84 86–88] 1 had adjusted for age only [9] and 2 for age and sex only.[75 77] Only 11 studies included adjustment for age and sex as well as indicators of body mass, study site, race or other possible confounders.[40 42 45 59 64 66 71 76 79 80 89] Adjustment for any potential confounders was not clear from the abstracts of the two studies that we were unable to review in full.[38 39]

Circulating CRP in the diagnosis and aetiology of cancer

Most of the reviewed studies had compared CRP concentrations in patients with cancer and apparently healthy controls, and 49 prevalent studies[8 10 23 28 29 32 38–40 44 46 49–51 53 65 68 71 73–75 77 78 81 82 85 88 90 94–97 99 100 103 104 106–118] reported higher CRP concentrations in patients with cancer (table 3).

Forty-three prevalent studies compared CRP concentrations between patients with cancer and controls with other benign diseases (table 3). This is a useful design for determining whether increased CRP concentrations are specific to cancer, for specificity would provide evidence for their possible diagnostic or aetiological role.

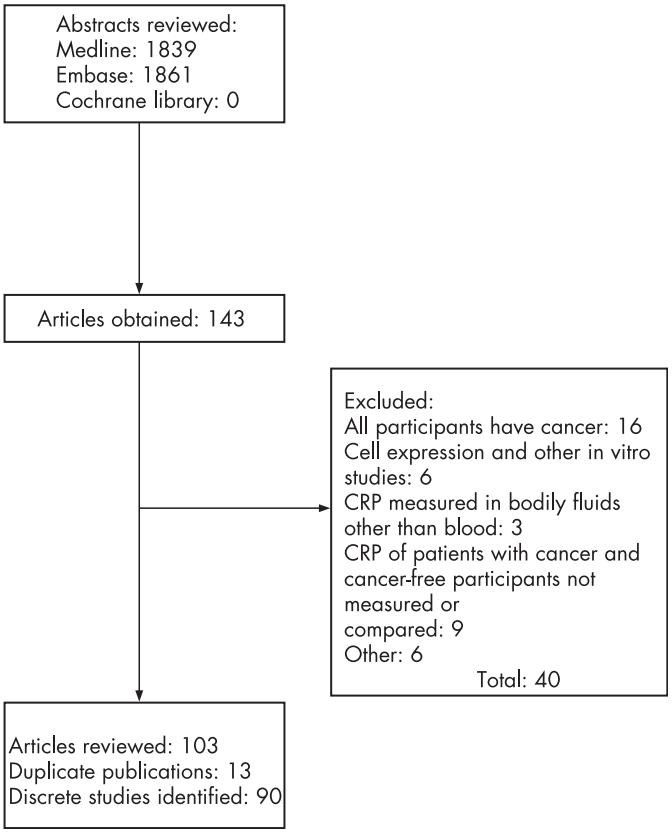

Figure 1 C reactive protein (CRP) systematic search results.

Of the 34 studies comparing patients with cancer with controls with benign diseases of the same organs or organ groups,[8 9 12 34 43 47 48 51 52 55–58 60–62 67 69 70 72 81 83 84 86 88 90 92 93 96 98 101 104 105 112] 14 (42%) reported higher CRP concentrations in patients with cancers of the lung,[56 90] pancreas,[8 98] breast,[12 81] ovary,[83 88] oesophagus,[62] liver,[60] the biliary tract,[48] stomach[43] and multiple myeloma.[34 61] However, the results of one of the breast cancer studies might have been influenced by the inclusion of healthy participants as well as those with benign diseases in the control group,[12] and the analysis in the study on ovarian cancer was based on data from a small subgroup for which serum samples were available.[83] In addition, three studies found higher CRP concentrations only in patients with advanced, but not with newly diagnosed, breast, gastrointestinal tract and prostate cancers when compared with controls with benign diseases.[9 69 105] Several studies reported contrasting findings: six studies of multiple myeloma and cervical, prostate or lung cancers reported no difference in CRP concentrations between patients with cancer and controls with benign diseases of these organs,[51 52 72 92 93 104] and a further four studies reported higher CRP concentrations in patients with benign prostate, lung, ovarian and myelogenous conditions than in patients with cancer.[55 57 58 88] In one study, no sufficient data was presented for the comparison between pancreatic cancer and benign pancreatic disease.[112]

Of the nine studies including a control group of people with non-cancerous conditions of different organs,[10 54 78 87 101 102 106 113 118] five studies only compared patients with malignant and benign diseases with healthy controls and reported no formal statistical comparison of CRP concentrations in patients with cancer and in people with other diseases. One study found higher CRP concentrations in patients with cancer-related thrombocytosis than in those with essential thrombocytosis[10] and one study found increased CRP in advanced gastrointestinal cancer in comparison with controls with hernia,[43] whereas two studies reported higher CRP concentrations in people with neurological conditions than in those with malignant brain tumours[101] and peritoneal sepsis.[87] In all, 19 studies (44% of all the studies including a control group with any benign disease) found that patients with cancer had higher CRP concentrations than participants with other non-malignant diseases (table 3).

Twenty-seven studies defined their aim as examining the value of serum CRP in the diagnosis of cancer, but only five of them presented analyses of the sensitivity and specificity of increased CRP concentrations in discriminating cancer cases from controls. In a study of hepatocellular carcinoma comparing cancer cases with patients with other liver conditions, sensitivity, specificity and diagnostic accuracy of CRP using a threshold of 5 mg/l were 78.9%, 56.0% and 34.9%,

Table 2 Number of discrete studies by type of cancer

Type of cancer	Studies with CRP as the main aim, n (%)	Studies with other main aim, n (%)
Lung cancer	5 (9.3)	6 (16.7)
Colorectal cancer	6 (11.1)	5 (13.9)
Multiple myeloma	3 (5.6)	4 (11.1)
Gastrointestinal cancer	4 (7.4)	2 (5.6)
Ovarian cancer	2 (3.7)	2 (5.6)
Prostate cancer	3 (5.6)	2 (5.6)
Pancreatic cancer	2 (3.7)	2 (5.6)
Hepatocellular carcinoma	4 (7.4)	—
Lymphatic cancers	3 (5.6)	1 (2.8)
Breast cancer	2 (3.7)	1 (2.8)
Cervical cancer	2 (3.7)	—
Testicular cancer	1 (1.9)	1 (2.8)
Head and neck squamous cell carcinoma	—	2 (5.6)
Glioma	1 (1.9)	—
Leukaemia	1 (1.9)	—
Bronchial carcinoma	1 (1.9)	—
Kaposi's sarcoma	—	1 (2.8)
Brain cancer	—	1 (2.8)
Renal cell carcinoma	—	1 (2.8)
Oesophageal cancer	1 (1.9)	––
Biliary tract	1 (1.9)	—
Various cancers grouped together in analysis	9 (16.7)	3 (8.3)
Various cancers analysed as separate types	3 (5.6)	2 (5.6)
Total	54 (100)	36 (100)

CRP, C reactive protein.

Table 3 Summary of results by study design

Study design	Number (%) of studies (n = 90)	Number (% of this design) reporting higher CRP in cases than the comparison group
Prevalent case–control/ cross sectional	81 (90.0)	55 (67.9)
Included healthy comparison group	55 (61.1)*	49 (89.1)
Included comparison group with any benign disease	43 (47.8)	19 (44.2)
Prospective	9 (10.0)	5 (55.6)
Included healthy comparison group	9 (10.0)	5 (55.6)
Included comparison group with any benign disease	0 (0)	0 (0)

CRP, C reactive protein.
*The number of studies cited here does not add up to the total number of prevalent studies, as some studies included several comparison groups.

respectively.[60] Another study comparing patients with hepatocellular carcinoma with healthy controls with a cut-off value of 12 μg/ml reported 82.4% sensitivity and 82.0% specificity.[70] Results from two other studies suggested that CRP is useful in distinguishing patients with pancreatic cancer from healthy controls[112] and people with malignant pleural effusions from those with non-malignant effusions,[56] but not in differentiating between malignant and non-malignant ascites.[91] A study of testicular cancer reported CRP to be highly sensitive and specific in differentiating epididymitis (in which the CRP concentrations were higher than in the malignant disease) from cancer.[57] Thus, the results from the studies that presented appropriate tests of diagnostic accuracy did not provide strong evidence to support the usefulness of increased CRP in early diagnosis of cancer. However, most studies claiming to examine the role of CRP in the diagnosis of cancer did not undertake appropriate analyses (sensitivity, specificity, receiver operator characteristics or other tests of calibration or discrimination) to determine the usefulness of CRP as a diagnostic tool in cancer.

As the only observational study design that assures the temporal relationship between exposure and outcome, prospective studies provide the best level of evidence for any potential role of circulating CRP in the diagnosis or aetiology of cancer. Table 4 summarises the nine prospective studies identified in this review. The findings in these studies were conflicting and provided no strong evidence of circulating CRP being causally related to cancer in general, but there was some evidence that it could be related specifically to certain types of cancer.

Two studies found increased circulating CRP concentrations to be associated with an increased risk of any incident cancer, even after excluding the first year of follow-up to avoid possible reverse causality,[45] although this association seemed stronger with deaths from cancer than non-fatal cancer events.[64] However, a prospective case–control study found no association between CRP and incident cancer in general or any specific form of incident cancer.[80] No association was reported in prospective studies between circulating CRP at baseline and the subsequent risk of prostate[64 79] or breast[64] cancers.

Evidence of an association between increased CRP and colorectal cancer is contradictory. In four prospective studies (nested in the Campaign Against Cancer and Heart Disease (CLUE II) cohort, α-Tocopherol, β-Carotene (ATBC) Trial, Health Aging and Body Composition Study and Japan Public Health Center-based Prospective study), the investigators found increased CRP concentrations to be associated with incident colorectal cancer, although the analysis in one of these was based on only 41 cancer events.[42 59 64 76] Results from two of these studies showed a more prominent association in colon cancer than in rectal cancer.[59 76] However, one prospective study, with 169 cancer cases, found a borderline statistically significant association between higher CRP concentrations and a reduced risk of colorectal cancer in age-adjusted multivariate models,[89] and in another study with 141 cases,[66] the researchers reported no association. Thus, overall, there is some evidence for a positive association between CRP and colorectal cancer.

A prospective cohort study and a prospective nested case–control study reported positive associations with incident cancer in general and incident lung cancer in particular.[45 64] However, the findings for lung cancer in both these studies were based on small numbers of cancer events, 42 cancer events in the cohort study and 72 events in the case–control study. In the cohort study, the positive association remained with adjustment for pack-years of cigarette smoking in multivariate analyses, but in the case–control study, stratified analysis showed little evidence for an association with any cancer among the participants who had never smoked.

DISCUSSION

In general, patients with cancer have been shown to have higher CRP concentrations than healthy controls and participants with some benign diseases. However, too few studies provided appropriate analyses to assess the diagnostic value of circulating CRP in cancer. Moreover, most studies to date measured CRP in prevalent cancer cases, and it is therefore possible that any association between CRP and cancer reported in these studies reflects reverse causation, survival bias or confounding. Of the nine large prospective studies identified in this review, four studies reported no association between circulating CRP and breast, prostate and colorectal cancers, but five studies provided some evidence that CRP could be related to colorectal and lung cancers.

Although the results of prospective studies are less likely to be influenced by reverse causation or bias, these associations can be explained by confounding. Associations between CRP concentrations and cancer are likely to be confounded by socioeconomic and lifestyle factors, particularly smoking and body mass index.[119 121] Although the prospective studies identified in this review did adjust for important confounding factors, residual confounding due to measurement error in these factors and poor modelling of their relationship with the outcome is possible.[122] In particular, the strong relationship between tobacco smoking and lung cancer will make adequate adjustment for its confounding effect difficult.

One way to overcome the problem of adequate adjustment would be to examine the association of functional CRP gene variants with cancer. This approach uses the principles of Mendelian randomisation to exploit the random allocation of genes at birth.[123 124] Therefore, the CRP gene variants will not be associated with socioeconomic or lifestyle factors, such as tobacco smoking, and examining the association of CRP gene polymorphisms with cancer would avoid any confounding from these factors. Although this approach has been used to determine the causal relationship of CRP with cardiovascular risk factors,[125 126] we are unaware of its use with cancer outcomes. This could be partly due to the large numbers of cancer cases required for such studies in order to reach reasonable precision with binary outcomes.[127]

What this paper adds

- Most prevalent studies have reported higher C reactive protein (CRP) concentrations in patients with cancer than in healthy controls and participants with some benign conditions, but this can be due to reverse causality, survival bias or confounding.
- The small number of prospective studies in this area provided no strong evidence for a causal role of CRP in cancer.

Policy implications

- Few studies published so far provided relevant analyses to assess the diagnostic value of circulating C reactive protein (CRP) in cancer, and the results from the small number of prospective studies are conflicting.
- Thus, currently, there is little evidence to support the use of CRP in the early diagnosis or aetiology of cancer.

Table 4 Summary of prospective studies of the association between circulating CRP and cancer

Study [author, year]	Study design	Number of cancer cases	Age	No. (%) female	Main aim of the study	Main results relating to CRP	Comments
Colorectal cancer							
CLUE II, US [Erlinger, 2004]	Case-control, nested in CLUE II cohort	Colorectal cancer: 172 Controls: 342	Mean (SD): Cases 63.6 (11) Controls 63.4 (11)	Cases: 95 (55.2) Controls: 189 (55.3)	**Aetiology** To assess the association between CRP and incident colorectal cancer.	OR for colorectal cancer across quartiles of CRP (mg/l) [95% CI]: 1st (<0.92): 1.00 2nd (0.92, 1.93): 1.16 [0.65, 2.09] 3rd (1.94, 3.69): 1.42 [0.82, 2.46] 4th (>3.69): 2.00 [1.16, 3.46] p for trend = 0.008	Up to 2 controls, matched for age, sex, race and date of blood sample, were selected from a community-based cohort for each case. Further adjustment for age, sex, smoking status, BMI and use of hormones or NSAIDs.
Women's Health Study, US [Zhang, 2005]	Cohort, nested in an RCT	Colorectal cancer: 169	45+ at baseline	27 913 (100)	**Aetiology** To evaluate whether plasma CRP concentrations predict colorectal cancer.	HR for colorectal cancer across categories of CRP, mg/l, [95% CI]: Crude <1 mg/l: 1.00 [ref.] 1–3 mg/l: 0.89[0.62, 1.29] >3 mg/l: 0.80 [0.55, 1.15] p = 0.24 Age-adjusted: <1 mg/l: 1.00 [ref.] 1–3 mg/l: 0.77 [0.53, 1.11] >3 mg/l: 0.67 [0.46, 0.97] p = 0.05 Multivariate adjusted: <1 mg/l: 1.00 [ref.] 1–3 mg/l: 0.79 [0.53, 1.17] >3 mg/l: 0.66 [0.43, 1.03] p = 0.09	Participants recruited from a community-based RCT. Adjusted for age, BMI, family history of colorectal cancer, physical activity, smoking, alcohol intake, menopausal status, use of aspirin, vitamin E, multivitamin, oral contraceptive or postmenopausal hormones.
Various locations, Japan [Ito, 2005]	Case-control nested in prospective cohort	Colorectal cancer: 141 Controls: 327	Range: 40–79	Cases: 78 (55.3) Controls: 179 (54.7)	**Aetiology** To investigate whether serum CRP is associated with colorectal cancer in the Japanese.	Crude OR [95% CI] for incident colorectal cancer, by tertiles of CRP: 1st: 1.0 (ref.) 2nd: 0.93 [0.52, 1.65] 3rd: 0.91 [0.50, 1.66] p for trend: 0.77 Multivariable-adjusted OR [95% CI] for incident colorectal cancer, by tertiles of CRP: 1st: 1.00 (ref.) 2nd: 1.05 [0.57, 1.94] 3rd: 0.97 [0.51, 1.83] p for trend: 0.98	Study nested in a large community-based multi-centre cohort. Controls matched for age, sex and site. Adjusted for BMI, smoking and alcohol consumption.
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Southwest Finland [Gunter, 2006]	Prospective case-control nested in an RCT	Colorectal cancer: 130 Controls: 260	Median (IQR): Colorectal cancer: 56 (53–61) Controls: 57 (53–59)	0 (0)	**Aetiology** To investigate the relationship between serum CRP and incident colorectal cancer and to examine whether any association differs by body size or cancer site.	Age-adjusted OR [95% CI] for incident colorectal cancer, by quartiles of CRP, mg/l: 1st: 1.0 (ref.) 2nd: 1.5 [0.8, 2.7] 3rd: 1.0 [0.5, 1.9] 4th: 2.0 [1.1, 3.7] p = 0.02 Multivariable-adjusted OR [95% CI] for incident colorectal cancer, by quartiles of CRP, mg/l: 1st: 1.0 (ref.) 2nd: 1.9 [1.0, 3.8] 3rd: 1.2 [0.6, 2.6] 4th: 2.9 [1.4, 6.0] p = 0.006	Study nested in an RCT where the participants were male smokers. Controls were matched on age, date of the baseline blood draw and intervention group (α-tocopherol, β-carotene, both or placebo). Further adjustment for age, BMI, aspirin use, smoking duration (years) and usual no. of cigarettes smoked per day.
Japan Public Health Center-based Prospective Study (JPHC), various locations, Japan [Otani *et al.*, 2006]	Prospective case-control nested in a cohort	Colorectal cancer: 375 Controls: 750	Mean: Colorectal cancer: 56.7 Controls: 56.6	Colorectal cancer: 179 (47.7) Controls: 358 (47.7)	**Aetiology** To assess the association of circulating CRP and colorectal cancer risk in relation to tumour location and invasion.	Multivariable-adjusted OR [95% CI] for incident colorectal cancer, by quartiles of CRP, mg/l: 1st: 1.0 (ref.) 2nd: 1.5 [0.99, 2.2] 3rd: 1.3 [0.85, 2.0] 4th: 1.6 [1.1, 2.5] p for trend = 0.053 By cancer type, highest vs. lowest quartile of CRP: Colon (n = 244): 1.6 [0.99, 2.7] p for trend = 0.041 Rectal (n = 111): 1.4 [0.63, 3.3] p for trend = 0.82 Colon, intramucosal (n = 94): 2.6 [1.1, 6.2] p for trend = 0.017 Colon, invasive (n = 146): 1.2 [0.64, 2.4] p for trend = 0.55	All participants selected from people with available blood samples, within a large community based cohort. Controls matched for age, sex, date of blood draw, time since last meal and study location. Further adjustment for smoking (pack-years), alcohol consumption, exercise, and family history of colorectal cancer.

Table 4 Continued

Study [author, year]	Study design	Number of cancer cases	Age	No. (%) female	Main aim of the study	Main results relating to CRP	Comments
Prostate cancer							
CLUE II, US [Platz, 2004]	Case-control study nested in CLUE II cohort	Prostate cancer: 264 Controls: 264	18+	0 (0)	**Aetiology** To examine the association of CRP with prostate cancer.	Geometric mean (SD) CRP (mg/l): Prostate cancer: 1.24 (2.94) Controls: 1.41 (2.97) p=0.16 Adjusted OR for prostate cancer across quartiles of CRP [95% CI]: 1st: 1 2nd: 1.29 [0.80, 2.08] 3rd: 0.98 [0.61, 1.58] 4th: 0.95 [0.57, 1.58] p for trend =0.66	Controls and cases selected from male participants of the CLUE II cohort who were Washington County residents. Controls matched on age, date of blood draw, race and time since last meal. Further adjustment for BMI, age at diagnosis and smoking history did not change the effect estimates.
Any cancer							
The Women's Health Study, US [Rifai, 2002]	Case-control, nested in an RCT	Any cancer: 513 Controls: 513	Mean: 56.7	1026 (100)	**Aetiology** To examine predictive value of CRP for cancer and coronary heart disease in women.	Crude RR for incident cancer across quartiles of baseline CRP (mg/l) [95% CI]: 1st (<1.0): 1.0 2nd [1.0, 2.3): 1.1 [0.8, 1.5] 3rd (2.5–5.6): 1.0 [0.7, 1.4] 4th (≥5.7): 1.2 [0.9, 1.6] p for trend >0.2 Baseline CRP was not associated with breast, ovarian or uterine, colon, lung, hematopoietic, thyroid, bladder, brain or pancreatic cancers, melanoma or other types of cancer (data not shown).	Community controls, matched on age and smoking status. Further adjustment for BMI, hypertension, diabetes, hyperlipidemia, exercise, parental history of heart disease and random assignment to vitamin E, aspirin or both. High baseline CRP in cancer patients may be a result of an already begun cancerous process.
Health Aging and Body Composition study, Memphis, TN and Pittsburgh, PA, US [Il'yasova, 2005]	Cohort	Total participants: 2438 Any incident cancers: 296	Median (IQR): Cases: 74 (71–76) Non-cases: 73 (71–76)	Cases: 55% Non-cases: 51% Numbers not cited	**Aetiology** To analyse the association between circulating inflammatory markers and incident cancer in elderly people.	HR [95% CI] for incident cancer events/log CRP (mg/l): Crude: 1.17 [1.02, 1.33] Adjusted: 1.25 [1.09, 1.43] HR [95% CI] for cancer events by type/log CRP (mg/l): Colorectal: 1.44 [1.03, 2.02] Lung: 1.64 [1.20, 2.24] Breast: 1.32 [0.91, 1.93] Prostate: 0.94 [0.70, 1.28] Estimates adjusted for age, gender, race and site.	Participants recruited from Medicare beneficiaries. Exclusion criteria were very poor physical condition, life-threatening disease or intent to leave the area in the subsequent 3 years. Adjustment for age, gender, race and site. Further adjustment for BMI, pack-years of cigarettes smoked, physical activity, education, baseline medical conditions and medication used did not change the effect estimates (data not shown). Colorectal and lung cancer analyses were based on subgroups of 41 and 42 events, respectively.
European Prospective Investigation into Cancer and Nutrition cohort, Greece [Trichopoulos, 2006]	Case-control, nested in EPIC cohort	Any cancer: 496 Controls: 996	No. (%) participants: <55 years: Cancer: 153 930.8) Controls: 289 (29.0) ≥55 years: Cancer: 215 (43.3) Controls: 707 (71.0)	Cancer cases: 253 (51.0) Controls: 512 (51.4)	**Diagnosis** To assess the association between CRP and subsequent risk of cancer and to determine whether CRP could be used to identify individuals at high risk at a sub-clinical stage of the disease.	Adjusted OR [95% CI] for incident cancer per 1 SD of log CRP: All cancers: 1.20 [1.10, 1.32] Cancers by site: Stomach: 1.10 [0.82, 1.47] Colon-rectum: 1.17 [0.93, 1.46] Liver cancer: 1.51 [1.20, 1.90] Pancreas: 1.29 [0.89, 1.87] Lung: 1.31 [1.11, 1.53] Skin: 1.24 [0.95, 1.62] Kidney: 1.48 [1.11, 1.53] Bladder: 1.21 [0.91, 1.61] Brain: 1.00 [0.54, 1.85] Leukemia/lymphoma: 1.26 [1.05, 1.51] Breast (women): 1.16 [0.95, 1.41] Cervix uteri: 1.31 [0.72, 2.35] Corpus uteri: 1.34 [1.03, 1.74] Ovary: 1.00 [0.67, 1.48] Prostate: 0.74 [0.37, 1.47] All cancers, stratified by smoking: Never-smokers: 1.17 [0.96, 1.42] Ever-smokers: 1.50 [1.22, 1.84]	Community controls matched for age, sex and date of cohort enrolment. Cases were participants free of cancer at baseline. Adjustment for age, sex, BMI, smoking, alcohol and NSAID use and duration of storage of plasma samples. Some site specific OR estimates were based on small subgroups. Effect estimates strengthened somewhat with removal of cases occurring in the first year of follow-up.

In conclusion, most of the studies attempting to evaluate the use of circulating CRP in the diagnosis of various cancers did not present relevant statistical analyses and most of the vast literature published on the association of circulating CRP with cancer has been based on studies of prevalent cancer cases, which cannot provide evidence for causality. The small number of prospective studies identified in this review did not provide strong evidence for a causal role of CRP in malignancy, although there was some evidence that CRP could be related to colorectal cancer in particular. Further prevalent studies in this area will not add to what is already known; more large prospective studies and studies examining the association of CRP functional genetic variants with cancer outcomes would be useful to determine the role of CRP in the aetiology of cancer.

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Supplementary tables are available at http://jech.bmj.com/supplemental

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REFERENCES

1 **Brull DJ**, Serrano N, Zito F, *et al.* Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. *Arterioscler Thromb Vasc Biol* 2003;**23**:2063–9.
2 **Greenfield JR**, Samaras K, Jenkins AB, *et al.* Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation* 2004;**109**:3022–8.
3 **Deichmann M**, Benner A, Waldmann V, *et al.* Interleukin-6 and its surrogate C-reactive protein are useful serum markers for monitoring metastasized malignant melanoma. *J Exp Clin Cancer Res* 2000;**19**:301–7.
4 **Kallio R**, Surcel HM, Bloigu A, *et al.* C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients. *Eur J Cancer* 2000;**36**:889–94.
5 **Kallio R**, Bloigu A, Surcel HM, *et al.* C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumours and lymphomas. *Support Care Cancer* 2001;**9**:124–8.
6 **Nozoe T**, Korenaga D, Futatsugi M, *et al.* Immunohistochemical expression of C-reactive protein in squamous cell carcinoma of the esophagus—significance as a tumor marker. *Cancer Lett* 2003;**192**:89–95.
7 **Wieland A**, Kerbl R, Berghold A, *et al.* C-reactive protein (CRP) as tumor marker in pediatric and adolescent patients with Hodgkin disease. *Med Pediatr Oncol* 2003;**41**:21–5.
8 **Basso D**, Fabris C, Meani A, *et al.* C reactive protein in pancreatic cancer and chronic pancreatitis. *Ann Clin Res* 1988;**20**:414–16.
9 **O'Hanlon DM**, Lynch J, Cormican M, Given HF. The acute phase response in breast carcinoma. *Anticancer Res* 2002;**22**:1289–93.
10 **Alexandrakis MG**, Passam FH, Moschandrea IA, *et al.* Levels of serum cytokines and acute phase proteins in patients with essential and cancer-related thrombocytosis. *Am J Clin Oncol* 2003;**26**:135–40.
11 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001;**357**:539–45.
12 **Blann AD**, Byrne GJ, Baildam AD. Increased soluble intercellular adhesion molecule-1, breast cancer and the acute phase response. *Blood Coagul Fibrinolysis* 2002;**13**:165–8.
13 **Jabs WJ**, Busse M, Kruger S, *et al.* Expression of C-reactive protein by renal cell carcinomas and unaffected surrounding renal tissue. *Kidney Int* 2005;**68**:2103–10.
14 **O'Riordain MG**, Falconer JS, Maingay J, *et al.* Peripheral blood cells from weight-losing cancer patients control the hepatic acute phase response by a primarily interleukin-6 dependent mechanism. *Int J Oncol* 1999;**15**:823–7.
15 **Wigmore SJ**, Fearon KC, Sangster K, *et al.* Cytokine regulation of constitutive production of interleukin-8 and -6 by human pancreatic cancer cell lines and serum cytokine concentrations in patients with pancreatic cancer. *Int J Oncol* 2002;**21**:881–6.
16 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002;**420**:860–7.
17 **Farrow B**, Evers BM. Inflammation and the development of pancreatic cancer. *Surg Oncol* 2002;**10**:153–69.
18 **Philip M**, Rowley DA, Schreiber H. Inflammation as a tumor promoter in cancer induction. *Semin Cancer Biol* 2004;**14**:433–9.
19 **Alexandrakis MG**, Passam FH, Boula A, *et al.* Relationship between circulating serum soluble interleukin-6 receptor and the angiogenic cytokines basic fibroblast growth factor and vascular endothelial growth factor in multiple myeloma. *Ann Hematol* 2003;**82**:19–23.
20 **Alexandrakis MG**, Passam FH, Sfiridaki A, *et al.* Elevated serum concentration of hepatocyte growth factor in patients with multiple myeloma: correlation with markers of disease activity. *Am J Hematol* 2003;**72**:229–33.
21 **Alexandrakis MG**, Passam FH, Ganotakis ES, *et al.* The clinical and prognostic significance of erythrocyte sedimentation rate (ESR), serum interleukin-6 (IL-6) and acute phase protein levels in multiple myeloma. *Clin Lab Haematol* 2003;**25**:41–6.
22 **Alexandrakis MG**, Passam FH, Sfiridaki A, *et al.* Serum levels of leptin in multiple myeloma patients and its relation to angiogenic and inflammatory cytokines. *Int J Biol Markers* 2004;**19**:52–7.
23 **Alexandrakis MG**, Passam FH, Sfiridaki K, *et al.* Interleukin-18 in multiple myeloma patients: serum levels in relation to response to treatment and survival. *Leuk Res* 2004;**28**:259–66.
24 **Alexandrakis MG**, Passam FH, Dambaki C, *et al.* The relation between bone marrow angiogenesis and the proliferation index Ki-67 in multiple myeloma. *J Clin Pathol* 2004;**57**:856–60.
25 **Alexandrakis MG**, Passam FH, Kyriakou DS, *et al.* Serum level of interleukin-16 in multiple myeloma patients and its relationship to disease activity. *Am J Hematol* 2004;**75**:101–6.
26 **Jamieson NB**, Brown DJ, Michael WA, *et al.* Adiponectin and the systemic inflammatory response in weight-losing patients with non-small cell lung cancer. *Cytokine* 2004;**27**:90–2.
27 **Brown DJ**, McMillan DC, Milroy R. The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. *Cancer* 2005;**103**:377–82.
28 **McKeown DJ**, Brown DJ, Kelly A, *et al.* The relationship between circulating concentrations of C-reactive protein, inflammatory cytokines and cytokine receptors in patients with non-small-cell lung cancer. *Br J Cancer* 2004;**91**:1993–5.
29 **Sattar N**, Scott HR, McMillan DC, *et al.* Acute-phase reactants and plasma trace element concentrations in non-small cell lung cancer patients and controls. *Nutr Cancer* 1997;**28**:308–12.
30 **Talwar D**, Ha TK, Scott HR, *et al.* Effect of inflammation on measures of antioxidant status in patients with non-small cell lung cancer. *Am J Clin Nutr* 1997;**66**:1283–5.
31 **Zaloudik J**, Lauerova L, Janakova L, *et al.* Immunological parameters in patients treated with regional chemo-immunotherapy for colorectal cancer metastases to the liver. *Klin Onkol* 1998;**11**:43–8.
32 **Zaloudik J**, Lauerova L, Janakova L, *et al.* Significance of pre-treatment immunological parameters in colorectal cancer patients with unresectable metastases to the liver. *Hepatogastroenterology* 1999;**46**:220–7.
33 **Ong F**, Kaiser U, Seelen PJ, *et al.* Serum neural cell adhesion molecule differentiates multiple myeloma from paraproteinemias due to other causes. *Blood* 1996;**87**:712–16.
34 **Schaar CG**, Kaiser U, Snijder S, *et al.* Serum interleukin-6 has no discriminatory role in paraproteinaemia nor a prognostic role in multiple myeloma. *Br J Haematol* 1999;**107**:132–8.
35 **Kuvibidila S**, Gauthier T, Warrier RP, *et al.* Increased levels of serum transferrin receptor and serum transferrin receptor/log ferritin ratios in men with prostate cancer and the implications for body-iron stores. *J Lab Clin Med* 2004;**144**:176–82.
36 **Kuvibidila S**, Rayford W. Correlation between serum prostate-specific antigen and alpha-1-antitrypsin in men without and with prostate cancer. *J Lab Clin Med* 2006;**147**:174–81.
37 **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.
38 **Sawa A**, Koziol-Montewka M, Gozdziuk K, *et al.* Indices of immune activation after bronchial carcinoma surgery. *Ann Univ Mariae Curie Sklodowska* (*Med*), 2003;**58**:161–6.
39 **Bien E**, Balcerska A. Clinical significance of erythrocyte sedimentation rate, C-reactive protein and serum lactate dehydrogenase levels in the diagnosis, prognosis and treatment monitoring of children suffering from cancer. *Med Wieku Rozwoj* 2004;**8**(Pt 2):1081–9.
40 **Aleman MR**, Santolaria F, Batista N, *et al.* Leptin role in advanced lung cancer. A mediator of the acute phase response or a marker of the status of nutrition? *Cytokine* 2002;**19**:21–6.
41 **Caruso C**, Lio D, Cavallone L, *et al.* Aging, longevity, inflammation, and cancer. *Ann NY Acad Sci* 2004;**1028**:1–13.
42 **Gunter MJ**, Stolzenberg-Solomon R, Cross AJ, *et al.* A prospective study of serum C-reactive protein and colorectal cancer risk in men. *Cancer Res* 2006;**66**:2483–7.
43 **Wu CW**, Lui WY, Peng FK, *et al.* Alterations of humoral immunity in patients with gastric cancer. *Asian Pac J Allergy Immunol* 1988;**6**:7–10.
44 **Tsavaris N**, Kosmas C, Kopterides P, *et al.* Retinol-binding protein, acute phase reactants and *Helicobacter pylori* infection in patients with gastric adenocarcinoma. *World J Gastroenterol* 2005;**11**:7174–8.
45 **Trichopoulos D**, Psaltopoulou T, Orfanos P, *et al.* Plasma C-reactive protein and risk of cancer: a prospective study from Greece. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:381–4.
46 **Tas F**, Duranyildiz D, Argon A, *et al.* Serum levels of leptin and proinflammatory cytokines in advanced-stage non-small cell lung cancer. *Med Oncol* 2005;**22**:353–8.
47 **Yanagawa H**, Sone S, Takahashi Y, *et al.* Serum levels of interleukin 6 in patients with lung cancer. *Br J Cancer* 1995;**71**:1095–8.
48 **Padillo FJ**, Muntane J, Montero JL, *et al.* Effect of internal biliary drainage on plasma levels of endotoxin, cytokines, and C-reactive protein in patients with obstructive jaundice. *World J Surg* 2002;**26**:1328–32.
49 **Lan AK**, Luk HN, Goto S, *et al.* Stress response to hepatectomy in patients with a healthy or a diseased liver. *World J Surg* 2003;**27**:761–4.
50 **Zaman K**, Driscoll R, Hahn D, *et al.* Monitoring multiple angiogenesis-related molecules in the blood of cancer patients shows a correlation between VEGF-A and MMP-9 levels before treatment and divergent changes after surgical vs. conservative therapy. *Int J Cancer* 2006;**118**:755–64.
51 **Åvall-Lundqvist E**, Blad E, Xiao L, *et al.* Pretreatment serum levels of C-reactive protein, alpha 1-antitrypsin, haptoglobin, alpha 1-acid glycoprotein and tissue polypeptide antigen in cervical carcinoma. *Eur J Gynaecol Oncol* 1991;**12**:375–83.
52 **Åvall-Lundqvist E**, Sjovall K, Hansson LO, *et al.* Peri- and postoperative changes in serum levels of four tumor markers and three acute phase reactants in benign and malignant gynecological diseases. *Arch Gynecol Obstet* 1992;**251**:69–78.

53 **Barber MD**, Fearon KC, Ross JA. Relationship of serum levels of interleukin-6, soluble interleukin-6 receptor and tumour necrosis factor receptors to the acute-phase protein response in advanced pancreatic cancer. *Clin Sci* (*Lond*), 1999;**96**:83–7.
54 **Bohn H**. Charakterisierung der schwangerschafts-assoziirten glykoproteine als akute phase-proteine. *Arch Gynakol* 1972;**213**:54–72.
55 **Castano Vidriales JL**, Amores AC. Use of pleural fluid C-reactive protein in laboratory diagnosis of pleural effusions. *Eur J Med* 1992;**1**:201–7.
56 **Chierakul N**, Kanitsap A, Chaiprasert A, *et al.* A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. *Respirology* 2004;**9**:66–9.
57 **Doehn C**, Fornara P, Kausch I, *et al.* Value of acute-phase proteins in the differential diagnosis of acute scrotum. *Eur Urol* 2001;**39**:215–21.
58 **Dubost JJ**, Ristori JM, Soubrier M, *et al.* Acute phase proteins in monoclonal gammapathies. *Pathol Biol* (*Paris*), 1991;**39**:769–73.
59 **Erlinger TP**, Platz EA, Rifai N, *et al.* C-reactive protein and the risk of incident colorectal cancer. *JAMA* 2004;**291**:585–90.
60 **Fabris C**, Pirisi M, Soardo G, *et al.* Value of serum C-reactive protein measurement in the detection of hepatocellular carcinoma superimposed on liver cirrhosis. *J Cancer Res Clin Oncol* 1994;**120**:229–32.
61 **Greco C**, Ameglio F, Alvino S, *et al.* Selection of patients with monoclonal gammopathy of undetermined significance is mandatory for a reliable use of interleukin-6 and other nonspecific multiple myeloma serum markers. *Acta Haematol* 1994;**92**:1–7.
62 **Guillem P**, Triboulet JP. Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. *Dis Esophagus* 2005;**18**:146–50.
63 **Hu RH**, Lee PH, Yu SC. Secretion of acute-phase proteins before and after hepatocellular carcinoma resection. *J Formos Med Assoc* 1999;**98**:85–91.
64 **Il'yasova D**, Colbert LH, Harris TB, *et al.* Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2413–18.
65 **Ilhan N**, Ilhan N, Ilhan Y, *et al.* C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. *World J Gastroenterol* 2004;**10**:1115–20.
66 **Ito Y**, Suzuki K, Tamakoshi K, *et al.* Colorectal cancer and serum C-reactive protein levels: a case-control study nested in the JACC Study. *J Epidemiol* 2005;**15**(Suppl 2):S185–9.
67 **Kreienberg R**, Koehler P, Kasemeyer R, *et al.* Clinical utility of different tumor markers in breast cancer and gynecological malignancies. *Cancer Detect Prev* 1983;**6**:221–5.
68 **Kuku I**, Bayraktar MR, Kaya E, *et al.* Serum proinflammatory mediators at different periods of therapy in patients with multiple myeloma. *Mediators Inflamm* 2005;**2005**:171–4.
69 **Lehrer S**, Diamond EJ, Mamkine B, *et al.* C-reactive protein is significantly associated with prostate-specific antigen and metastatic disease in prostate cancer. *BJU Int* 2005;**95**:961–2.
70 **Lin ZY**, Wang LY, Yu ML, *et al.* Role of serum C-reactive protein as a marker of hepatocellular carcinoma in patients with cirrhosis. *J Gastroenterol Hepatol* 2000;**15**:417–21.
71 **Mantovani G**, Maccio A, Madeddu C, *et al.* Antioxidant agents are effective in inducing lymphocyte progression through cell cycle in advanced cancer patients: assessment of the most important laboratory indexes of cachexia and oxidative stress. *J Mol Med* 2003;**81**:664–73.
72 **McArdle PA**, McMillan DC, Sattar N, *et al.* The relationship between interleukin-6 and C-reactive protein in patients with benign and malignant prostate disease. *Br J Cancer* 2004;**91**:1755–7.
73 **McMillan DC**, Sattar N, Talwar D, *et al.* Changes in micronutrient concentrations following anti-inflammatory treatment in patients with gastrointestinal cancer. *Nutrition* 2000;**16**:425–8.
74 **McMillan DC**, Talwar D, Sattar N, *et al.* The relationship between reduced vitamin antioxidant concentrations and the systemic inflammatory response in patients with common solid tumours. *Clin Nutr* 2002;**21**:161–4.
75 **Nikiteas NI**, Tzanakis N, Gazouli M, *et al.* Serum IL-6, TNF alpha and CRP levels in Greek colorectal cancer patients: prognostic implications. *World J Gastroenterol* 2005;**11**:1639–43.
76 **Otani T**, Iwasaki M, Sasazuki S, *et al.* 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* 2006;**15**:690–5.
77 **Pavlidis AN**, Kalef-Ezra J, Bourantas LC, *et al.* Serum tumor markers in non-Hodgkin's lymphomas and chronic lymphocytic leukemia. *Int J Biol Markers* 1993;**8**:14–20.
78 **Pepys MB**, Dash AC, Markham RE, *et al.* Comparative clinical study of protein SAP (amyloid P component) and C-reactive protein in serum. *Clin Exp Immunol* 1978;**32**:119–24.
79 **Platz EA**, De Marzo AM, Erlinger TP, *et al.* No association between pre-diagnostic plasma C-reactive protein concentration and subsequent prostate cancer. *Prostate* 2004;**59**:393–400.
80 **Rifai N**, Buring JE, Lee IM, *et al.* Is C-reactive protein specific for vascular disease in women? *Ann Intern Med* 2002;**136**:529–33.
81 **Robertson JF**, Pearson D, Price MR, *et al.* Prospective assessment of the role of five tumour markers in breast cancer. *Cancer Immunol Immunother* 1991;**33**:403–10.
82 **Timonen TT**, Koistinen P. C-reactive protein for detection and follow-up of bacterial and fungal infections in severely neutropenic patients with acute leukaemia. *Eur J Cancer Clin Oncol* 1985;**21**:557–62.
83 **van der Zee AG**, de Cuyper EM, Limburg PC, *et al.* Higher levels of interleukin-6 in cystic fluids from patients with malignant versus benign ovarian tumors correlate with decreased hemoglobin levels and increased platelet counts. *Cancer* 1995;**75**:1004–9.
84 **Wardman AG**, Bowen M, Struthers LP, *et al.* The diagnosis of pleural effusions—are cancer markers clinically helpful? *Med Pediatr Oncol* 1984;**12**:68–72.
85 **Weiss JF**, Morantz RA, Bradley WP, *et al.* Serum acute-phase proteins and immunoglobulins in patients with gliomas. *Cancer Res* 1979;**39**(Pt 1):542–4.
86 **Yamashita JI**, Shirakusa T, Fujine N, *et al.* Elevations of serum C-reactive protein occur independently of circulating interleukin 6 concentrations in patients with lung cancer. *Oncol Rep* 1995;**2**:215–19.
87 **Yildirim B**, Sari R, Isci N. Patients with spontaneous bacterial peritonitis, and malignant and cirrhotic ascites. *J Natl Med Assoc* 2005;**97**:276–80.
88 **Zbroja-Sontag W**. Defense proteins and immune complexes in the blood serum of women with inflammatory and neoplastic lesions of the ovary. *Am J Reprod Immunol* 1983;**4**:11–20.
89 **Zhang SM**, Buring JE, Lee IM, *et al.* C-reactive protein levels are not associated with increased risk for colorectal cancer in women. *Ann Intern Med* 2005;**142**:425–32.
90 **Alexandrakis MG**, Passam FH, Perisinakis K, *et al.* Serum proinflammatory cytokines and its relationship to clinical parameters in lung cancer patients with reactive thrombocytosis. *Respir Med* 2002;**96**:553–8.
91 **Alexandrakis MG**, Moschandrea JA, Koulocheri SA, *et al.* Discrimination between malignant and nonmalignant ascites using serum and ascitic fluid proteins in a multivariate analysis model. *Dig Dis Sci* 2000;**45**:500–8.
92 **Spicka I**, Cieslar P, Prochazka B, *et al.* Prognostic factors and markers of activity in multiple myeloma (results of the Cooperative Group for DIagnosis and Treatment of Multiple Myeloma). *Casopis Lekaru Ceskych* 2000;**139**:208–12.
93 **Almushatat AS**, Talwar D, McArdle PA, *et al.* Vitamin antioxidants, lipid peroxidation and the systemic inflammatory response in patients with prostate cancer. *Int J Cancer* 2006;**118**:1051–3.
94 **Staal-van den Brekel AJ**, Dentener MA, Drent M, *et al.* The enhanced inflammatory response in non-small cell lung carcinoma is not reflected in the alveolar compartment. *Respir Med* 1998;**92**:76–83.
95 **Brichory FM**, Misek DE, Yim AM, *et al.* An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer. *Proc Natl Acad Sci USA* 2001;**98**:9824–9.
96 **Chen Z**, Malhotra PS, Thomas GR, *et al.* Expression of proinflammatory and proangiogenic cytokines in patients with head and neck cancer. *Clin Cancer Res* 1999;**5**:1369–79.
97 **Chou PH**, Chen SH, Liao HK, *et al.* Nanoprobe-based affinity mass spectrometry for selected protein profiling in human plasma. *Anal Chem* 2005;**77**:5990–7.
98 **DeJong CH**, Busquets S, Moses AG, *et al.* Systemic inflammation correlates with increased expression of skeletal muscle ubiquitin but not uncoupling proteins in cancer cachexia. *Oncol Rep* 2005;**14**:257–63.
99 **Fearon KC**, McMillan DC, Preston T, *et al.* Elevated circulating interleukin-6 is associated with an acute-phase response but reduced fixed hepatic protein synthesis in patients with cancer. *Ann Surg* 1991;**213**:26–31.
100 **Crown AL**, Cottle K, Lightman SL, *et al.* What is the role of the insulin-like growth factor system in the pathophysiology of cancer cachexia, and how is it regulated? *Clin Endocrinol* (*Oxford*), 2002;**56**:723–33.
101 **Flaschka G**, Marth E, Desoye G, *et al.* Diagnostische wertigkeit biokemischer tumormarker bei hirntumoren literaturubersicht und eigene erfahrungen mit serumanalysen von sialinsaure (nana), carcinoembryonalem antigen (cea) und neuron-spezifischer enolase (NSE). *Zentralbl Neurochir* 1990;**51**:129–37.
102 **Fukuma H**, Morshed SA, Watanabe S, *et al.* Increased expression of cytokines in liver and serum in patients with extrahepatic diseases. *J Gastroenterol* 1996;**31**:538–45.
103 **Gallo O**, Gori AM, Attanasio M, *et al.* Interleukin-6 and acute-phase proteins in head and neck cancer. *Eur Arch Otorhinolaryngol* 1995;**252**:159–62.
104 **Gao WM**, Kuick R, Orchekowski RP, *et al.* Distinctive serum protein profiles involving abundant proteins in lung cancer patients based upon antibody microarray analysis. *BMC Cancer* 2005;**5**:110.
105 **Georgiannos SN**, Weston PM, Goode AW. Micronutrients in gastrointestinal cancer. *Br J Cancer* 1993;**68**:1195–8.
106 **Karter Y**, Uzun H, Tunckale A, *et al.* Interrelation of cytokines and their association with acute phase proteins in Hodgkin's disease and in rheumatoid arthritis. *Int Rev Allergol Clin Immunol* 2002;**8**:25–8.
107 **Kestens L**, Melbye M, Biggar RJ, *et al.* Endemic African Kaposi's sarcoma is not associated with immunodeficiency. *Int J Cancer* 1985;**36**:49–54.
108 **Lauerova L**, Dusek L, Simickova M, *et al.* Renal cell carcinoma-associated immune impairment that may interfere with the response to cytokine therapy. *Neoplasma* 1999;**46**:141–9.
109 **Maccio A**, Lai P, Santona MC, *et al.* High serum levels of soluble IL-2 receptor, cytokines, and C reactive protein correlate with impairment of T cell response in patients with advanced epithelial ovarian cancer. *Gynecol Oncol* 1998;**69**:248–52.
110 **Maccio A**, Madeddu C, Massa D, *et al.* Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: role of inflammation in cancer-related anemia. *Blood* 2005;**106**:362–7.
111 **Nuver J**, Smit AJ, Sleijfer DT, *et al.* Microalbuminuria, decreased fibrinolysis, and inflammation as early signs of atherosclerosis in long-term survivors of disseminated testicular cancer. *Eur J Cancer* 2004;**40**:701–6.
112 **Orchekowski R**, Hamelinck D, Li L, *et al.* Antibody microarray profiling reveals individual and combined serum proteins associated with pancreatic cancer. *Cancer Res* 2005;**65**:11193–202.

113 **Pidcock NB**, Cooper EH, el-Aaser AA, *et al.* Immunoglobulin A, G and E levels in Egyptians with cancer: influence of schistosomiasis. *Int J Cancer* 1984;**33**:771–5.
114 **Mantovani G**, Maccio A, Madeddu C, *et al.* Quantitative evaluation of oxidative stress, chronic inflammatory indices and leptin in cancer patients: correlation with stage and performance status. *Int J Cancer* 2002;**98**:84–91.
115 **Scott HR**, McMillan DC, Watson WS, *et al.* Longitudinal study of resting energy expenditure, body cell mass and the inflammatory response in male patients with non-small cell lung cancer. *Lung Cancer* 2001;**32**:307–12.
116 **Wallace AM**, Kelly A, Sattar N, *et al.* Circulating concentrations of ''free'' leptin in relation to fat mass and appetite in gastrointestinal cancer patients. *Nutr Cancer* 2002;**44**:157–60.
117 **Yagci M**, Sucak GT, Haznedar R. Fibrinolytic activity in multiple myeloma. *Am J Hematol* 2003;**74**:231–7.
118 **Drahovsky D**, Dunzendorfer U, Ziegenhagen G, *et al.* Reevaluation of C-reactive protein in cancer sera by radioimmunoassay and radial immunodiffusion. *Oncology* 1981;**38**:286–91.
119 **Lawlor DA**, Smith GD, Rumley A, *et al.* 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* 2005;**93**:955–63.
120 **Ohsawa M**, Okayama A, Nakamura M, *et al.* CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. *Prev Med* 2005;**41**:651–6.
121 **Ford ES**. Asthma, body mass index, and C-reactive protein among US adults. *J Asthma* 2003;**40**:733–9.
122 **Phillips AN**, Davey Smith G. Bias in relative odds estimation owing to imprecise measurement of correlated exposures. *Stat Med* 1992;**11**:953–61.
123 **Davey Smith G**, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;**32**:1–22.
124 **Davey Smith G**, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? *BMJ* 2005;**330**:1076–9.
125 **Timpson NJ**, Lawlor DA, Harbord RM, *et al.* C-reactive protein and its role in metabolic syndrome: mendelian randomisation study. *Lancet* 2005;**366**:1954–9.
126 **Davey Smith G**, Lawlor DA, Harbord R, *et al.* Association of C-reactive protein with blood pressure and hypertension: life course confounding and mendelian randomization tests of causality. *Arterioscler Thromb Vasc Biol* 2005;**25**:1051–6.
127 **Davey Smith G**, Harbord R, Ebrahim S. Fibrinogen, C-reactive protein and coronary heart disease: does Mendelian randomization suggest the associations are non-causal? *QJM* 2004;**97**:163–6.

SPEAKERS' CORNER

Bringing chronic disease epidemiology and infectious disease epidemiology back together

When modern epidemiology first took shape, there was only one kind of epidemiology – epidemiology, period. Over time has come specialisation into chronic and infectious disease epidemiology. Does this segregation into chronic and infectious disease epidemiologies benefit public health?

Dividing epidemiology into chronic disease and infectious disease ''camps'' is, in itself, problematic, in that each is based on an incompatible classification system. One classification is based on cause (infectious and non-infectious diseases) while the second is based on effect (chronic and acute diseases).[1] Many chronic diseases have an infectious origin, such as cervical cancer (human papillomavirus – HPV) and liver cancer (hepatitis B and C viruses). Many patients with infectious diseases require long-term care. Human immunodeficiency virus (HIV) infection has become a chronic disease in many countries.[1] Furthermore, some chronic diseases have a short duration. Pancreatic cancer is called a chronic disease despite the fact that very few sufferers survive even 1 year. Finally, some non-infectious diseases, such as diabetic ketoacidosis and myocardial infarction, require acute care.

More importantly, the ''infectiousness'' of chronic diseases needs to be understood. Many chronic diseases are associated with behavioural risk factors.[2] Although these diseases are not themselves communicable, their behavioural risk factors (e.g. smoking, excess alcohol consumption, poor nutrition and physical inactivity[2]) are readily transferable from one population to another, through international travel and modern communication. Unlike many infectious diseases, transmission of ''agents'' of chronic diseases does not even require physical contact. Ideas about smoking and physical inactivity can be transmitted globally and instantly, through satellite broadcasts and the internet.

Infectious and chronic diseases also interact with each other. Infectious diseases (such as seasonal influenza) can increase risk of hospital admission and death among people with pre-existing chronic diseases (such as circulatory and respiratory diseases).[3 4] Most of those who died in the severe acute respiratory syndrome (SARS) epidemic in Canada had pre-existing chronic conditions, such as diabetes.[5]

Although it is common to approach chronic and infectious diseases as having completely distinct aetiologies, there is an increasing appreciation for the common determinants of health that underlie both, such as housing and socioeconomic status.

Segregation of epidemiology into chronic and infectious diseases has led to a neglected area in public health – the interface between chronic disease and infectious disease. Indeed, this neglected area requires increased public health attention across a broad spectrum of activity, including research, surveillance, prevention and control. It is time to bring chronic disease epidemiology and infectious disease epidemiology back together.

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References

1 **Unwin N**, Epping Jordan J, *et al.* Rethinking the terms non-communicable disease and chronic disease (letter). *J Epidemiol Community Health* 2004;**58**:801.
2 **Choi BCK**. Modulated release of health risk information to the general public with the use of mnemonics. *J Epidemiol Community Health* 2004;**58**:809.
3 **Choi BCK**, Pak AWP. A simple approximate mathematical model to predict the number of severe acute respiratory syndrome cases and deaths. *J Epidemiol Community Health* 2003;**57**:831–5.
4 **Li CK**, Choi BCK, Wong TW. Influenza-related deaths and hospitalizations in Hong Kong: A subtropical area. *Public Health* 2006;**120**:517–24.
5 **Booth CM**, Matukas LM, Tomlinson G, *et al.* Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003;**289**:2801–9.