The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease: a cohort study

Cilie C. van’t Klooster, Paul M. Ridker, Jesper Hjortnaes, Yolanda van der Graaf, Folkert W. Asselbergs, Jan Westerink, Joachim G.J.V. Aerts, and Frank L.J. Visseren; On behalf of the UCC-SMART study group

Aims

Low-grade inflammation, measured by elevated plasma concentrations of high-sensitive C-reactive protein (CRP), is a risk factor for cardiovascular disease (CVD). There is evidence that low-grade inflammation is also related to a higher risk of cancer. The present prospective cohort study evaluates the relation between low-grade systemic inflammation and risk of cancer in patients with stable CVD.

Methods and results

In total, 7178 patients with stable CVD and plasma CRP levels < 10 mg/L were included. Data were linked to the Dutch national cancer registry. Cox regression models were fitted to study the relation between CRP and incident CVD and cancer. After a median follow-up time of 8.3 years (interquartile range 4.6–12.3) 1072 incident cancer diagnoses were observed. C-reactive protein concentration was related to total cancer [hazard ratio (HR) 1.35; 95% confidence interval (CI) 1.10–1.65] comparing last quintile to first quintile of CRP. Especially lung cancer, independent of histopathological subtype, was related to CRP (HR 3.39; 95% CI 2.02–5.69 comparing last to first quintile of CRP). Incidence of epithelial neoplasms and especially squamous cell neoplasms were related to CRP concentration, irrespective of anatomical location. Sensitivity analyses after excluding patients with a cancer diagnosis within 1, 2, and 5 years of follow-up showed similar results. No effect modification was observed by smoking status or time since smoking cessation (P-values for interaction > 0.05).

Conclusion

Chronic systemic low-grade inflammation, measured by CRP levels ≤10 mg/L, is a risk factor for incident cancer, markedely lung cancer, in patients with stable CVD. The relation between inflammation and incident cancer is seen in former and current smokers and is uncertain in never smokers.

Keywords

Chronic systemic low-grade inflammation • High-sensitive C-reactive protein • Risk factor • Incident cancer • Patients with vascular disease
Introduction

Chronic systemic low-grade inflammation plays an important role in the aetiology of atherosclerotic disease by initiating and accelerating arterial plaque formation and transformation to vulnerable plaques. Besides the role in atherosclerotic disease, there is evidence that low-grade inflammation is related to a higher risk of incident cancer: previous prospective cohort studies found an increased risk of incident cancer related to higher C-reactive protein (CRP) levels in population-based cohorts or cohorts of apparently healthy people. Especially a higher risk of lung cancer was observed, with hazard ratios (HRs) of 2.2; 95% confidence interval (CI) 1.0–4.6 and 2.8; 95% CI 1.6–4.9 for patients with plasma CRP concentrations >3 vs. <1 mg/L. In the CANTOS trial, which randomized patients in the stable phase after myocardial infarction to placebo or canakinumab, lowering CRP with an interleukin (IL) 1β antibody lowered the incidence of cardiovascular disease (CVD) as well as lung cancer, lung cancer death, and total cancer mortality.

C-reactive protein is part of the IL-1β, IL-6 inflammatory cascade, and can serve as a marker of systemic low-grade inflammation. It is unlikely that CRP itself is causally related to cancer development, as genetically elevated CRP is not related to risk of cancer in a Mendelian randomization study. Postulated mechanisms for the role of low-grade inflammation in the development of cancer are focused on the promotion phase, and include stimulation of tumour cell survival and proliferation, and promotion of metastatic spread. Chronic systemic low-grade inflammation, commonly defined as CRP levels ≤10 mg/L, is caused by various factors including smoking, abdominal obesity, atrial fibrillation, or heart failure. Shared risk factors for both CVD and cancer include smoking and (abdominal) obesity. In turn, these risk factors increase levels of systemic low-grade inflammation, further suggesting that low-grade inflammation could be a common pathway leading to CVD and cancer. Moreover, patients with stable CVD have a higher risk of cancer than the general population. These patients could benefit from therapy directed at lowering inflammation to reduce recurrent CVD risk and cancer risk. In the present study, the relation is evaluated between systemic low-grade inflammation and the risk of recurrent CVD and incident cancer in patients with stable CVD.

Methods

Study population

Patients originated from the Utrecht Cardiovascular Cohort - Second Manifestations of ARterial disease (UCC-SMART) cohort, an ongoing prospective cohort study since 1996, including 18–79-year-old patients referred to the University Medical Centre Utrecht (UMCU), the Netherlands. Central aim of the UCC-SMART cohort is to gain insight into arterial disease occurrence and risk factors for (recurrent) cardiovascular events. For the current study, patients with established CVD at baseline between September 1996 and March 2017 were included (N=8139). Inclusion in the UCC-SMART cohort occurs at least 2 months after the qualifying vascular event. The institutional review board of the UMCU approved the study and all patients gave written informed consent. Patients who did not give permission for data requests to other medical authorities were excluded (N=269). Study design and rationale have been described previously. In short, information on medical history and lifestyle was acquired and physical examination measurements were obtained according to a standardized protocol. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III definition. High-sensitive CRP level was determined by immunonephelometry (Nephelometer Analyzer BN II, Dade Behring). From 2013, high-sensitive CRP was determined in heparin plasma on an AUS811 routine chemistry analyzer (Beckman Coulter, Brea, CA, USA). Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Follow-up

During follow-up participants received questionnaires biannually, gathering information on occurrence of recurrent CVD, bleeding events, incident diabetes, and end-stage renal disease. Additional information was gained by collecting hospital or general practitioner’s data. Three physicians from the endpoint committee independently adjudicated all clinical events and conflicting classifications were discussed. The number of patients lost to follow-up was 412 (5.7%).

Data preparation

Missing data for high-sensitive C-reactive protein level [n=97 (1.2%)], smoking [n=28 (0.3%)], pack-years [n=32 (0.4%)], body mass index [BMI; n=18 (0.2%)], low-density lipoprotein cholesterol [LDL-c; n=138 (1.7%)], and systolic blood pressure [SBP; n=18 (0.2%)], were imputed. Single imputation was performed using bootstrapping and predictive mean matching based on multivariable regression including independent variables and outcome data (aregImpute-function in R, Hmisc-package). As CRP levels >10 mg/L are commonly associated with an acute inflammatory response, these patients (N=690) were excluded. Two patients had a recurrence of the same cancer diagnosed before entering the cohort and were therefore excluded.

Cox proportional hazard models were fitted to estimate HRs with 95% CIs describing the relation between CRP and recurrent CVD and incident cancer. With regard to the aetiologic nature of the study, there...
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Results

In total, 7178 patients with stable vascular disease and CRP levels ≤10 mg/L were included. Baseline characteristics stratified for CRP quintiles are shown in Table 1. Patients in the highest CRP stratum were more likely to be current smokers, generally had a higher number of pack-years, and fewer patients used lipid-lowering and antiplatelet medication. Other unfavourable trends with regard to cardiovascular risk profile in the highest CRP stratum included a slightly higher SBP, LDL-c, and higher prevalence of diabetes.

Relation between C-reactive protein and risk of recurrent cardiovascular events

During a median follow-up of 8.3 years [interquartile range (IQR) 4.6–12.3] and a total of 58 568 person-years of follow-up, 1289 patients experienced a recurrent cardiovascular event. Crude incidence rates were 1.53%, 1.55%, 2.07%, 2.64%, and 3.30% across CRP quintiles. Patients in the highest CRP quintile had a higher cardiovascular risk compared to patients in the lowest quintile of CRP (HR 1.58; 95% CI 1.31–1.91) (Figure 1A). The risk of cancer and/or CVD was 45% higher in the highest CRP quintile compared to the lowest (HR 1.45; 95% CI 1.26–1.68) (Figure 1B). CRP was significantly related to risk of myocardial infarction, vascular death, and all-cause mortality, but not to risk of stroke in categorical and continuous analyses (Supplementary material online, Figure S1).

Relation between C-reactive protein and risk of incident cancer according to anatomical location of origin

During follow-up 1072 incident malignancies were observed. Most frequently occurring diagnoses were cancer of the lung (n = 226), prostate (n = 188), and colon/rectum (n = 177). Crude incidence rates per person-year were 1.53%, 1.49%, 1.65%, 2.01%, and 2.50% across CRP quintiles. Patients with a higher CRP level had a higher risk of cancer, comparing patients in the highest CRP quintile to patients in the lowest quintile (HR 1.41; 95% CI 1.22–1.63) (Figures 1C and 2), and per 1 mg/L higher CRP (HR 1.07; 95% CI 1.04–1.10) (Figure 2). Risk of incident lung cancer was higher in the last CRP quintile compared to the first (HR 3.39; 95% CI 2.03–5.69) (Figures 1D and 2), and the risk increased 16% for each 1 mg/L higher CRP (HR 1.16; 95% CI 1.10–1.22) (Figure 2). Urinary tract cancer was possibly related to CRP concentration (HR 1.08; 95% CI 0.995–1.17 for every 1 mg/L higher CRP and HR 1.51; 95% CI 0.81–2.81 comparing last quintile with first CRP quintile) (Figure 2). Similarly, lymphoid/hematopoietic cancer was possibly related to CRP level, particularly in continuous analysis (HR 1.12; 95% CI 1.02–1.22 for every 1 mg/L higher CRP level, and HR 1.65; 95% CI 0.81–3.35 comparing fifth quintile with first CRP quintile; Figure 2). No relation was observed between CRP level and risk of breast or prostate cancer (in subgroups of women and men respectively), or incident colorectal cancer.

Relation between C-reactive protein and risk of incident cancer according to histopathology

The relation between plasma CRP and risk of lung cancer was similar for histopathological subtypes; small cell lung cancer and non-small-cell lung cancer, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Supplementary material online, Table S4). In secondary outcome analyses with cancer types according to histopathology irrespective of anatomical location of origin, CRP was significantly related to risk of epithelial neoplasms not further specified (hereinafter referred to as epithelial neoplasms) (HR 1.17; 95% CI 1.08–1.27), and squamous cell neoplasms (HR 1.11; 95% CI 1.02–1.20) (Supplementary material online, Figure S2).

was no need to take competing risks into account. Adjusted HRs from Cox regression analyses were added to the Kaplan–Meier plots. C-reactive protein was added to the model as a continuous and categorical variable. Subjects who were exempt from the outcome, were lost to follow-up or died of another cause were censored. Total cancer incidence was assessed, as well as cancer types separately, if a sufficient number of cases (>60) was present. Cancer types classified according to anatomical location of origin were taken as primary endpoint. Secondary outcome was cancer type classified according to histopathology. For the analyses of specific cancer types, the first diagnosis of that particular cancer was taken as the outcome, possibly being the second or third diagnosis of cancer during follow-up for a certain patient. Hazard ratios were adjusted for age and sex in Model 1. Additionally, smoking status, pack-years of smoking, BMI, LDL-c, diabetes mellitus, SBP, and kidney function were considered potential confounders in the relation between CRP and CVD or cancer and were added to Model 2. Estimates did not change in exploratory models with addition of year of inclusion in the cohort, the metabolic syndrome, or lipid-lowering or anti-platelet medication. To test potential effect modification by sex,²⁴ multiplicative interaction terms with CRP level were added to the models, showing no significant interactions (P > 0.05).

Linearity assumption was tested visually by adding continuous CRP level as a restricted cubic spline function to the model. No violations were observed. The proportional hazards assumption, examined graphically by plotting scaled Schoenfeld residuals against time, was not violated.

Influence of BMI and smoking on the relation between CRP and cancer was evaluated. Multiplicative interaction terms with BMI and smoking status were added to the models to assess effect modification, and additional stratified analyses were performed for smoking status. Adjustment for BMI and smoking specifically was performed to evaluate mediating effects. For the relation between CRP and lung cancer, a multiplicative interaction term with time since smoking cessation was assessed, as well as additional adjustment for time since smoking cessation. To examine influence of CRP additional to smoking effects on (lung) cancer risk, analyses were performed with a categorical determinant combining smoking status with CRP quintile, using never smokers in the lowest CRP quintile as a reference group for total cancer. For lung cancer, due to the low event number in never smokers, former smokers in the lowest CRP quintile were taken as reference group.

To evaluate effect modification by interim non-fatal cardiovascular events, multiplicative interaction terms were added to models of total and lung cancer. Reverse causality was evaluated by repeating analyses after excluding patients diagnosed with cancer within 1, 2, and 5 year(s) after inclusion. Also, analyses were stratified for location of vascular disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease) at baseline. Additional sensitivity analyses were performed after exclusion of patients with any type of cancer (except non-melanoma skin cancer) before inclusion in the cohort, and after excluding patients with CRP levels >5 mg/L. Stability of CRP levels during follow-up was assessed in a subset of SMART patients who revisited for second measurements (N = 1794).
Smoking and body mass index, and the relation between C-reactive protein and risk of incident (lung) cancer

No significant interaction terms with BMI were observed (P > 0.05). Adjustment for BMI or smoking did not mitigate the relation between CRP and cancer (Supplementary material online, Table S5). For the relation between CRP and lung cancer, no effect modification was observed by time since smoking cessation in former smokers (P-value for interaction 0.44) and additional adjustment for time since smoking cessation showed similar results (HR 1.16; 95% CI 1.10–1.22 of the original adjusted model).

Stratified analyses for smoking status showed similar HRs for lung cancer (HR 1.55; 95% CI 1.55–3.22 compared to never smokers in the lowest quintile) (P-value for trend <0.0001) (Figure 3A) and total cancer (HR 2.23; 95% CI 1.55–3.22 compared to never smokers in the lowest quintile) (P-value for trend <0.0001) (Figure 3B).
Discussion

The present study shows that in patients with stable vascular disease plasma CRP concentration is related to risk of recurrent cardiovascular events, as well as risk of cancer, especially lung cancer. No effect modification by smoking status was observed. A potential relation was observed between CRP and lymphoid/hematopoietic and urinary tract cancer. The relation between plasma CRP and incident cancer was seen for epithelial neoplasms, especially squamous cell neoplasms, irrespective of anatomical location of origin.

Results of the present study support the role of chronic systemic low-grade inflammation as a stimulating factor in cancer development in a cohort of patients with established vascular disease. The observed relation between CRP and cancer risk cannot be explained by reverse causality, meaning that an elevated CRP would simply be a sign of occult cancer, as similar results were observed after exclusion of patients with a diagnosis of cancer within 1, 2, and 5 year(s) after inclusion. Results of the present study correspond to results of the CANTOS trial and previous prospective cohort studies performed in population-based cohorts or cohorts of apparently healthy people. To our
knowledge, no previous studies investigated the relation between CRP and incident cancer in patients with established vascular disease specifically. Cancer incidence is higher in patients with established CVD compared to the general population, likely due to common risk factors, and the current study shows that systemic low-grade inflammation is a contributing factor in pathophysiology of CVD as well as cancer.

In accordance with previous observational studies and in line with the CANTOS trial results, lung cancer risk was especially related to CRP levels. Chronic low-grade inflammation is previously considered to be one of the causal pathways by which smoking leads to lung cancer. Epithelial neoplasms and squamous cell neoplasms, irrespective of anatomical location of origin, were mostly respiratory tract cancers; lung carcinomas and carcinomas of the lip, oral cavity, pharynx, and glottis. The elevated systemic inflammatory levels as a risk factor for respiratory tract cancer might reflect a local inflammatory microenvironment caused by smoking that contributes to cancer development. It is possible that low-grade inflammation initiated by smoking is not reversed when quitting smoking, emphasizing the importance of smoking abstinence. In the present study, the relation between CRP and total cancer risk in never smokers was uncertain (HR

Figure 2 Relation between CRP and incident cancer according to anatomical location of origin. Hazard ratios are adjusted for age, sex, smoking status, number of pack-years, body mass index, low-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, and kidney function. Analyses for breast cancer and prostate cancer were performed in subgroups of women and men respectively. The number of events per number of women or men in C-reactive protein quintiles are given. Continuous analyses represent hazard ratios per 1 mg/L higher C-reactive protein concentration.
1.05; 95% CI 0.98–1.13). However, no significant interaction was observed for smoking status (P > 0.05) and the point estimate was the same as in current smokers (HR 1.05; 95% CI 1.01–1.10). The incidence of lung cancer (n = 9) in never smokers was too low for reliable analysis. A previous case–control study nested in population-based cohorts showed no relation between CRP and lung cancer in never smokers. However, that higher inflammation levels as a risk factor for cancer are a direct result of smoking is unlikely based on the results of this study. Adjustment for smoking status and pack-years did not mitigate the relation between CRP level and cancer risk, suggesting that other pathophysiological pathway, and possibly other inflammatory pathways, play a role in mechanisms leading from smoking to cancer. Furthermore, the combination of a CRP level in the highest quintile with current smoking, conferred the highest cancer risk, suggesting an additive effect of inflammation and smoking on cancer risk. Potential relations between CRP and lymphoid/haematopoietic and urinary tract cancer should be interpreted with caution, as the relations were not statistically significant in all analyses, but suggest that inflammation could be involved in the pathogenesis of these neoplasms.

The relation between CRP and cancer risk is of great importance for clinical practice. As treatment for CVD has improved substantially over the last decades, more patients survive acute manifestations of CVD and survive long enough to develop cancer. C-reactive protein is a marker for CVD risk and could potentially also serves as a prognostic marker to identify those at high risk of (lung) cancer. Since patients from the third CRP quintile and higher had an increased risk

**Figure 3** Relation between CRP quintiles within categories of smoking status and risk of (A) lung cancer and (B) all cancers. Hazard ratios are adjusted for age, sex, body mass index, low-density lipoprotein cholesterol, diabetes mellitus, systolic blood pressure, and kidney function.
of lung cancer, CRP levels of ≥1.4 mg/L might be indicative of a higher risk of lung cancer. It could even be hypothesized that patients at high cardiovascular risk with high levels of inflammation are those that might benefit from anti-inflammatory treatment to reduce cardiovascular risk as well as risk of (lung) cancer. The CANTOS trial implicated that the IL-1β, IL-6, CRP inflammatory pathway is involved in cancer development. Results of trials studying other anti-inflammatory treatments could provide additional information on specific inflammatory pathways involved in cancer pathogenesis and the effectiveness of lowering inflammation on reduction of cancer risk, even though cancer was not the primary endpoint in these trials. However, the Cardiovascular Inflammation Reduction Trial (CIRT) was stopped due to ineffectiveness of methotrexate on CRP levels and CVD risk and no data are available yet on cancer incidence.27 The Low Dose Colchicine study (LoDoCo2, EudraCT Number: 2015-005568-40), trialling effect of colchicine on CVD risk is still ongoing and might provide additional information.

Strengths of the present study include the large patient population with established vascular disease and the prospective study design with long follow-up, large number of events, and histopathological cancer diagnoses. Potential limitations should be considered and include the single measurement of CRP level at baseline, as CRP levels might fluctuate during follow-up. However, patients were included in the cohort at least 2 months after the qualifying cardiovascular event, thus stable on medication that might influence CRP levels. Moreover, repeated CRP measurements over time are shown to be stable in a subset of UCC-SMART patients with repeated measurement as well as previous research.28 Data on other inflammatory markers, such as IL-6, was not available. Despite the large number of total cancer events, the number of certain specific cancer types was insufficient for reliable analyses. Additionally, subgroups of smaller size with limited number of events, for example, women, might be insufficient for reliable subgroup analyses. The number of lung cancer cases in never smokers was insufficient for reliable analysis, and the relation between CRP and lung cancer cannot be generalized to never smokers. Given the observational study design firm conclusions on causality should be made with caution as residual confounding cannot be ruled out.

Chronic systemic low-grade inflammation, measured by CRP levels <10 mg/L, is a risk factor for incident cancer, markedly lung cancer, in patients with stable CVD. The relation between inflammation and
incident cancer is seen in former and current smokers and is uncertain in never smokers.

Supplementary material
Supplementary material is available at European Heart Journal online.

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Ethics approval and participants’ informed consent
The authors do hereby declare that the current study complies with the Declaration of Helsinki. The institutional review board of the University Medical Centre approved the study and all patients gave written informed consent.

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References
The list of references is available on the online version of this paper.