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EDITORIAL

Inflammation, cardiovascular disease, and cancer: a common link with far-reaching implications

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This editorial refers to 'The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease: a cohort study'†, by C.C. van't Klooster *et al.*, on page 3901.

The link between cardiovascular (CV) risk factors, inflammation, and cancer is probably well established (*Figure 1*). Chronic inflammation drives a lot of cancers by shaping the early tumour microenvironment and promoting cancer initiation and development.[1,2] This process involves complex tumour–immune cell interplay and it can be partly due to a deficit in the resolution of inflammation.[3] Notably, organs with high tumour incidence in inflammatory settings are often those that interact closely with microbial products or directly with microbiota, such as the intestine or lung.

In this issue of the *European Heart Journal*, van't Klooster *et al.* have prospectively evaluated the relationship between low-grade inflammation, as assessed by plasma levels of high sensitive C-reactive protein (hsCRP), and the risk of cancer in 7178 patients with stable CV disease (cerebrovascular, peripheral, or coronary artery disease) and plasma hsCRP levels ≤10 mg/L.[4] The incidence of cancer, especially lung cancer, was higher for patients with hsCRP levels within the last quintile as compared with those presenting first-quintile hsCRP levels. This relationship between inflammation and cancer was observed in current and former smokers, but not in patients who never smoked. This is the first clinical demonstration that low-grade inflammation in the context of atherosclerosis and smoking is associated with cancer development and recurrent CV events.

Worldwide, smoking causes 1.69 million deaths per year from lung cancer in men and women. A new analysis of the Framingham Heart Study went even further by showing that even 25 years after quitting, the risk of cancer remained three-fold higher compared with people who had never smoked. However, the risk dropped significantly 5 years after quitting, and continued to fall as time went on compared with continuing smoking.[5] It would have been interesting to analyse the association between the lifetime smoking history of the study patients of van't Klooster and hsCRP levels in order to further determine whether the relationship between low-grade inflammation and cancer incidence is likely to be promoted by smoking. Interestingly, in addition to direct effects on lung inflammation, smoking alters the gut microbiome, which may indirectly impact lung inflammatory responses and possibly cancer initiation.[6] Furthermore, local lung dysbiosis, elicited by lung infections, may also underlie cancer development. A study in mice indicates that local microbiota would activate lung-resident γδ T cells, which promotes tumour growth.[7] Notwithstanding, a pro-inflammatory gut microbiota has also been associated with accelerated atherosclerosis,[8] pointing to an interesting common link between cancer, CV disease, and low-grade inflammation.

In the continuum of liquid biopsies as emerging tools for cancer diagnosis, monitoring, and prognosis,[9] hsCRP measurements could help refine risk reduction strategies in selected patient populations. In addition, the findings of van't Klooster *et al.* might pave the way toward new inflammation-targeted therapies for cancer prevention and/or improved cancer outcomes in the context of CV disease. CRP is produced by the liver in response to elevation of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and transforming growth factor-β (TGF-β). In acute coronary syndrome (ACS) patients, several studies have been conducted with the aim of determining if targeting these cytokines with available drugs could reduce the inflammatory response at the time of ACS, and subsequent CV events. hsCRP levels relate to the occurrence of major CV events or death in patients who experienced a previous ACS. In a secondary analysis of the VISTA-16 study,[10] the initial and subsequent increases in hsCRP levels during 16 weeks after ACS were associated with a higher risk of the combined major CV event endpoint, CV death, and all-cause death despite optimized medical therapies. In the CANTOS

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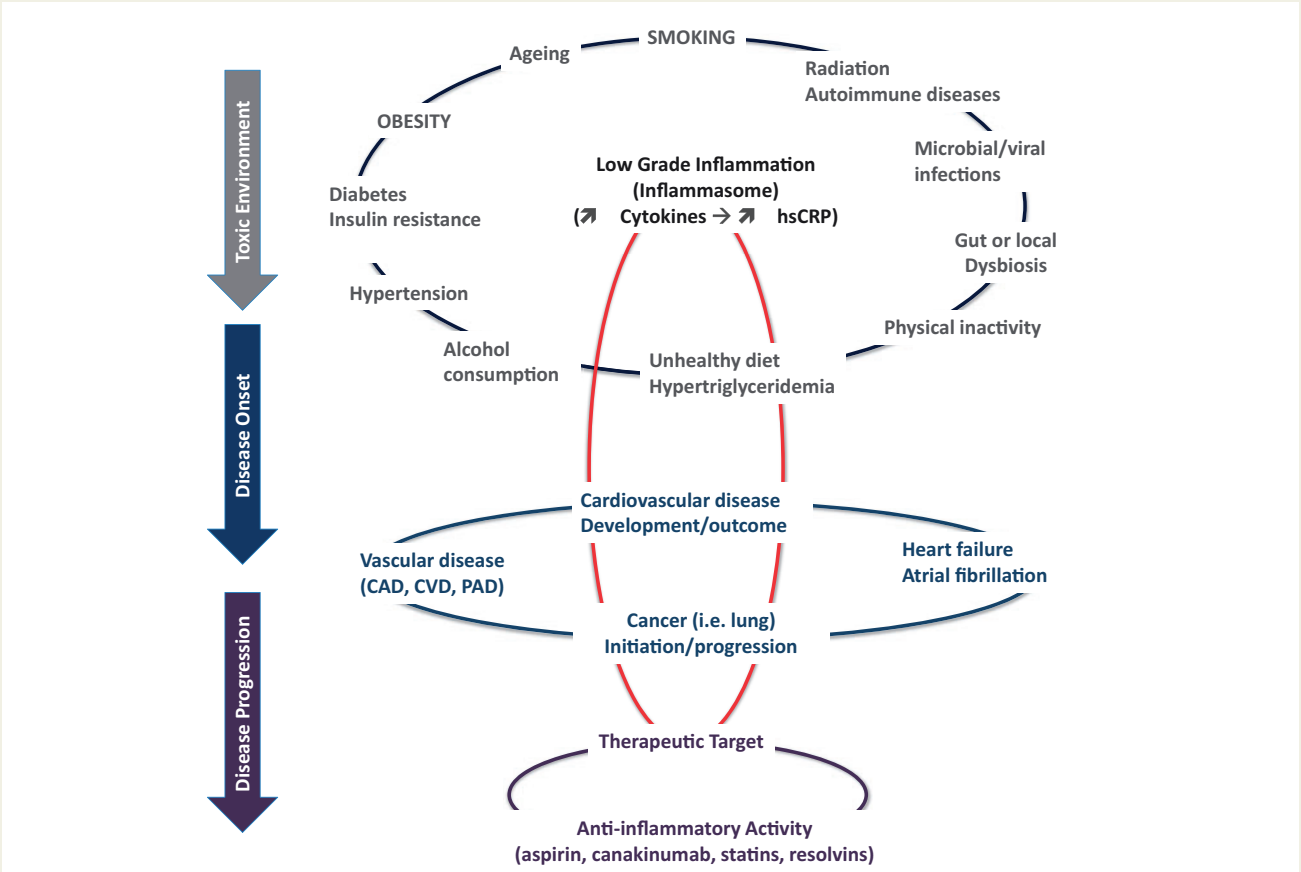

Figure 1 Relationship between cardiovascular risk factors, inflammation, cardiovascular disease, and cancer initiation/development. CVD, cerebrovascular disease; PAD, peripheral artery disease; CAD, coronary artery disease.

trial,[11] patients with previous myocardial infarction and CRP ≥2 mg/L who received canakinumab, a therapeutic monoclonal antibody targeting the inflammatory cytokine IL-1β, had a lower rate of recurrent CV events than placebo patients. In this trial, canakinumab also lowered lung cancer incidence, lung cancer death, and total cancer mortality. Now, the study by van't Klooster *et al.* strongly suggests that modulating inflammation could reduce not only the risk of major CV events but also the risk of cancer.

Certain anti-inflammatory therapies showed promising results in various malignancies.[12] Low-dose aspirin use in patients with CV disease is beneficial in reducing the risk of cancer in a duration-dependent manner.[13] More specifically, intake of low-dose aspirin for >5 years may reduce the risk of incident lung cancer in elderly patients without diabetes.[14] Statin use may also play a role in the prevention and treatment of cancer. The real breakthrough of the last years has been immune checkpoint blockade (ICB) targeting CTLA-4 or PD-1/PD-L1. However, while ICB is clinically very effective in a few tumour entities, most patients do not respond to checkpoint inhibitors.[12] The immune context of tumours, hot vs. cold tumours, appears critical in predicting tumour response to ICB. Today, it remains one of the biggest challenges to identify biomarkers that will allow predicting the ICB sensitivity of individual patients. Therefore, based on the study of van't Klooster *et al.*, we can speculate that hsCRP might facilitate the assessment of tumour immune characteristics by Immunoscore[15] or tumour circulome components.[9]

In the case of resectable cancers, a recent study in mice indicates that unleashing T cell immunity by pre-operative suppression of systemic inflammation or stimulation of inflammation resolution exhibits potent antitumour activity.[16] Interventions targeted to lower pre-operative CRP levels might thus be beneficial to improve cancer outcomes in combination with established therapies. Finally, it remains to be determined if IL-1β levels or levels of other cytokines that drive increases in CRP, such as IL-6 or TGF-β, are related to increased cancer incidence and CV risk or whether these cytokines may predict patient outcomes.

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