Commentary

Colorectal cancer and cardiovascular disease: A thrombo-inflammatory link?

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One of the few advantages of the Covid-19 pandemic is a renewed focus on the benefits of a healthy lifestyle, as a way to reduce both the risk of contracting SARS-CoV-2 infection and, in case of Covid-19, to improve the chance of survival [1]. In those not infected, living a healthy life is important anyway, in order to reduce the "corona" weight gain due to social deprivation, isolation and depression, leading to inactivity and increase in unhealthy eating habits. An associated response to this pandemic is a reorientation towards the way that we want to shape society, involving fundamental issues like durability, bioindustry, air pollution and the impact it all has on climate.

Interestingly, common diseases including malignancies and cardiovascular diseases (CVD), both leading causes of global morbidity and mortality, are for a substantial part driven by the same factors that threaten a healthy life, including lack of exercise/obesity/diabetes, smoking, poor food habits/diet and environmental pollution [2,3]. The interaction between CVD risk profile and cancer and *vice versa* is widely recognized and inspired calls for action to address this dangerous liaison [4]. In this issue of the Journal, Whelton and colleagues from Europe and the United States of America focus the attention to the specific interactions between colorectal cancer, a highly prevalent malignant disease, and CVD [5]. In a comprehensive narrative review paper, the authors address common pathophysiological risk factors and mechanisms as a basis for improvements in the therapeutic management of the patient with colorectal cancer, at risk of CVD.

In the list of common risk factors for colorectal cancer and CVD (figure 1 in [5]), "chronic inflammation" probably is the common denominator for most, if not all, other single risk factors as the pathways that link each risk factor to cancer or CVD, typically involve inflammation [6]. Additional mechanisms include hormonal challenges (eg hyperinsilunemia, hyperglycemia, IGF-1 in diabetes; angiotensin and vascular endothelial growth factor in hypertension), direct or indirectly connected through inflammatory pathways [6].

"Chronic inflammation" is a container concept for different inflammatory networks, combining cellular and humoral pathways, that are also intertwined with blood coagulation (thrombo-inflammation) and complement. "Inflammageing" is the name used to describe the age-related increase in chronic inflammation [7]. In real life, a combination of acute inflammatory stimuli (such as smoking, changes in air pollution status, noise, heavy caloric intake etc) superimposed on chronic inflammatory challenges, provide the biological determinants of many multifactorial diseases. The best way to manage these inflammatory challenges is to reduce the burden of triggers, accomplished by living healthier in general; however, this is not always feasible, as in particular the environment cannot be simply optimized for many people.

In epidemiological research as well as interventional studies in CVD, high sensitivity C reactive protein (hsCRP) is a key inflammation biomarker. Elevated levels of hsCRP (and also interleukin-6) are associated with increased risk of cardiovascular events independent of cholesterol and other traditional risk factors [8]. HsCRP, a marker of residual inflammatory risk, is also a useful tool to assess risk and direct medication including the use of statins and more recently anti-Il1beta therapy [8]. Chronic inflammation, characterized by detectable low levels of hsCRP, is a marker for severity of atherosclerosis, but also indicative of a higher risk of cancer, particularly lung cancer [9]. However, the association between elevated hsCRP and cancer is not consistent and absent for colorectal cancer [10], although colon cancer is considered a disease driven and aggravated by chronic inflammation [11].

A broader scope would also include markers for thrombo-inflammation; the links between inflammation and hypercoagulability are well established and of pivotal significance in both CVD [12] and cancer. A simple marker that reflects thrombo-inflammation is D-dimer, a fibrin cleavage fragment [13]. Elevated D-dimer levels are predictive of venous thromboembolism but also total mortality in a broader context [14]. D-dimer levels are associated with risk of atherothrombotic events in patients with systemic atherosclerosis [15]. Elevated D-dimer levels are predictive of poor outcome in patients with solid tumors [16]. Other biomarkers of thrombo-inflammation with potential not only to detect thrombosis but also recurrence of (breast) cancer, include thrombin generation analysis [17]. In the Vienna risk score for prediction of cancer associated thrombosis (CAT), D-dimer is an important element

and its time course in patients with different cancer types identifies highest risk for VTE patients [18]. One can imagine that a combination of different biomarkers reflecting thrombo-inflammation could be helpful for risk stratification in patients with cancer and increased risk of CVD, allowing individual optimization of preventive measures including pharmacotherapy.

As discussed by Whelton and colleagues, in addition to lifestyle changes aimed at reducing the burden of inflammatory challenges (including diet induced modifications of the microbiome), specific pharmacological interventions may be considered [5]. These include prescription of acetylsalicylic acid (aspirin) and other anti-inflammatory agents, like colchicine. These agents are prescribed to reduce the risk of CVD, but may also have some antitumor effects, although the evidence is still inconsistent. Other agents, like antihypertensive drugs and statins may similarly reduce the burden of chronic inflammation, but the evidence for anti-tumor effects is weak. Anti-Il 1 beta appeared to have some protective effects against lung cancer, but not against other malignancies [19]. Considering (thrombo) inflammation as a leading mechanism in CVD and cancer: can one imagine a single pharmacological approach to dampen its impact on these complex diseases? The simple answer is "no". The presented summary of data [5] does not reveal any major impact of agents that potentially target both atherosclerosis and cancer in *all subjects*. The same sobering conclusion was obtained regarding attempts to cure cancer with anticoagulant therapy. While animal studies provided strong evidence for antitumor effects of diverse anticoagulants, but in particular (low molecular weight) heparins, studies with these agents failed to reduce cancer burden in patients with solid tumors [20]. Newer strategies may include non-anticoagulant heparins, amongst other compounds, for their inhibitory potential against heparinase, a naturally occurring enzyme that degrades glycosaminoglycans and may thus facilitate tumor growth and metastasis [21]. Nonanticoagulant heparins are probably safer with regard to bleeding complications, a major side effect of all current antithrombotic agents. Theoretically, novel antithrombotic agents that target coagulation or platelets and lack substantial impact on hemostasis (ie bleeding risk; [22]) may be of interest both for preventing thrombosis in patients with cancer and perhaps by modifying the risks of atherosclerosis. A recently introduced combined antithrombotic regimen, comprising of the factor Xa inhibitor rivaroxaban and aspirin, successfully reduced cardiovascular mortality, albeit at a price of bleeding complications [23]. Combining anti-inflammatory and safer antithrombotic agents could become a feasible strategy to reduce thrombo-inflammatory burden in the future.

Whereas cancer used to be an ominous diagnosis, several decades ago, the chances of survival have substantially increased and fortunately, in many cases, cancer can be cured or reversed to a manageable, chronic condition. This brings along new challenges as cancer and its treatment put a burden on the cardiovascular system, with increased cardiovascular morbidity and mortality. Survivors of cancer therefore require extra attention for CV risk factors, even more so as cancer occurs more often in individuals with a suboptimal lifestyle, being exposed to risk factors like smoking, poor diet and overweight.

A way forward requires more precise individual characterization of patients, in order to find the best management of CVD; precision medicine will become important, like it is increasingly in cancer treatment. This strategy will ultimately need to make smart use of data from epigenetics, transcriptomics and proteomics analyses to characterize relevant pathways and networks for individual patient *endotyping,* in relation to outcomes.

Conflict of interest

HtC received research support from Bayer and Pfizer and is consultant for Aleveron and stockholder for Coagulation Profile.

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