Unveiling the "common soil" of cardiovascular disease and cancer

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ABSTRACT

The complex relationship between cardiovascular disease (CVD) and cancer has raised significant research interest, supported by growing evidence that these leading causes of morbidity and mortality share several pathogenetic aspects. The "common soil" hypothesis postulates that CVD and cancer emerge from the same piece of earth as distinct trees, but with intermingled roots, represented by modifiable risk factors and underlying molecular mechanisms. The integration of cardiovascular and cancer prevention through lifestyle and metabolic health improvements represents a necessity, for modern public health. This dual-benefit approach has the potential to reshape how we understand, approach, and ultimately reduce the burden of two of the world's most impactful groups of diseases.

Introduction

The complex relationship between cardiovascular disease (CVD) and cancer has raised significant research interest, supported by growing evidence that these leading causes of morbidity and mortality share several pathogenetic aspects. Indeed, in the last decades, more and more evidence has accumulated on the hypothesis of a "common soil" for such diseases.[1-3] This hypothesis postulates that CVD and cancer emerge from the same piece of earth as distinct trees, but with intermingled roots, represented by modifiable risk factors and underlying molecular mechanisms (Figure 1).

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Understanding the shared burden

Data from the Global Burden of Disease study show that CVD and cancer represent the two primary causes of mortality and global disability-adjusted life years (DALYs), with millions affected worldwide.[4] Intriguingly, these two groups of diseases share a number of modifiable risk factors such as smoking, physical inactivity, obesity, diabetes and unhealthy diet.

There is evidence that patients with coronary disease at multiple level have an increased risk of cancer (predominantly digestive and respiratory cancers) compared with patients with single vessel coronary disease[5] and reversely cancer survivors experience an increased risk of CVD morbidity and mortality in all age groups[6] and are more likely to have traditional cardiovascular risk factors compared with age-matched controls.[7]

Moreover, exposure to cardiovascular risk factors in apparently healthy subjects can increase the risk of both cardiovascular disease and cancer. Data from the Framingham Heart Study and PREVEND study[8] showed that traditional CVD risk factors including age, sex, and smoking status were independently associated with cancer ($p<0.001$ for all). Estimated 10-year atherosclerotic CVD risk was also associated with future cancer.

Life's Simple 7: a bridge between CVD and cancer prevention

The American Heart Association's Life's Simple 7 (LS7) metric, encompassing blood pressure, cholesterol, glucose control, body mass index (BMI), physical activity, diet, and smoking was conceived to assess and promote cardiovascular health, as a part of the AHA's 2020 strategic impact goal for reducing death from CVD and stroke by 20%.[8] These 7 metrics also cover the major modifiable risk factors shared between cancer and CVD.

The Moli-sani study, a large population-based cohort, has reinforced this connection by demonstrating that adherence to LS7 metrics is associated with a reduced risk of cancer and lower mortality rates among cancer survivors (unpublished data). Multivari-

able-adjusted survival analyses from this study reveal that higher LS7 scores are associated with significantly better outcomes. This finding underscores the broader implication that cardiovascular health optimization yields benefits that extended to cancer prevention, thus supporting a unified public health strategy.

Moreover, Kaneko *et al*.[9] showed that LS7 score could predict the incidence of major cardiovascular events also in patients with history of breast, colorectal, or stomach cancer.

The role of inflammation and coagulation pathways

Inflammation is a pivotal mechanism in the progression of both CVD and cancer. The inflammatory response contributes to conditions like obesity, diabetes, and metabolic syndrome, which are risk factors for both diseases.[10,11] Biomarkers such as C-reactive protein (CRP), fibrinogen, and D-dimers have emerged as crucial indicators of disease progression, reflecting a common pathophysiological thread.

The INFLA-score, derived from levels of CRP, platelet and leukocyte counts, and the granulocyte-to-lymphocyte ratio, highlights the role of chronic low-grade inflammation.[12] This scoring system, validated in studies including the Moli-sani cohort, shows that elevated inflammation markers are linked to increased risks of both cancer and cardiovascular mortality.[13] Additionally, findings from Ridker *et al.*[14] indicate that targeting inflammation through therapies such as anti-interleukin-1β antibodies not only reduces the incidence of cardiovascular events but also lowers cancer risk. This dual benefit underlines the profound connection among inflammation, thrombosis, and the shared pathogenetic mechanisms of CVD and cancer.

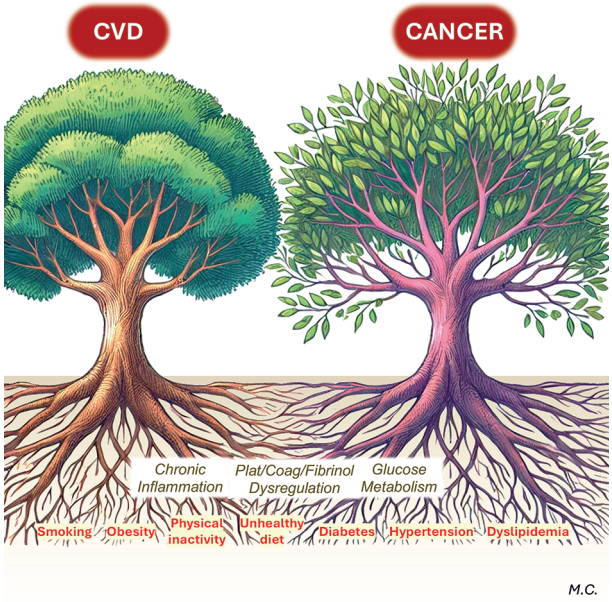

Figure 1. Graphical representation of the “common soil” hypothesis. Courtesy: Prof. Mario Colucci.

Glucose, fibrinolysis and coagulation as a shared pathway

Another critical intersection is glucose metabolism. Elevated glucose levels have been shown to drive the development of both cardiovascular disease (CVD) and cancer. Epidemiological studies provide evidence that excess sugar consumption can lead to cancer development and disease progression in cancer patients, independent of the association between sugar intake and obesity.[15] *In vitro* studies demonstrate that high glucose levels induce PAI-1 mRNA expression and PAI-1 protein secretion, as well as increased cell proliferation in vascular smooth muscle cells.[16] Moreover, PAI-1 exhibits pro-tumorigenic functions through its pro-angiogenic and anti-apoptotic activities, as well as by promoting the recruitment and polarization of monocytes/macrophages via distinct structural domains.[17] This shared pathway is highlighted in the EPICOR study, which underscores PAI-1's involvement in both ischemic vascular disease and cancer risk.[18]

Additional evidence links the activation of coagulation and fibrinolysis, which regulate vascular thrombus formation, to cancer pathogenesis. Findings from the Moli-sani study revealed that molecules involved in these pathways, such as tissue plasminogen activator (t-PA), fibrinogen, and antithrombin, are associated with the risk of breast cancer,[19] colorectal cancer,[20] and cancer mortality. [21,22] D-dimer, a degradation product of cross-linked fibrin, serves as a marker of both coagulation and fibrinolysis activation. Findings from the LIPID study demonstrated that elevated D-dimer levels predict mortality, cardiovascular events, and cancer in patients with stable coronary heart disease.[23]

A call for integrated prevention strategies

The possible overlapping nature of CVD and cancer pathogenetic mechanisms calls for an integrated approach to prevention. Public health strategies that emphasize lifestyle modifications based on LS7 principles can yield compounded benefits. Reducing inflammation, maintaining healthy glucose levels, and preventing coagulation abnormalities are all achievable through promoting ideal cardiovascular health. This multi-faceted approach could significantly lower the incidence and improve the prognosis of both diseases.

Moreover, the findings from the Moli-sani study and other large cohorts underscore the importance of cross-disciplinary research that links epidemiology, cardiology, oncology, and preventive medicine. By understanding the common soil from which CVD and cancer grow, healthcare providers can better tailor risk-reduction strategies that encompass the full spectrum of chronic disease prevention.

Conclusions

The evidence points to a clear convergence of cardiovascular and cancer disorders, rooted in shared modifiable risk factors and biological mechanisms. The concept of a “common soil” has moved from hypothesis to actionable insight, supported by robust cohort data and mechanistic studies. The integration of cardiovascular and cancer prevention through lifestyle and meta-

bolic health improvements represents not just an opportunity, but a necessity, for modern public health. This dual-benefit approach has the potential to reshape how we understand, approach, and ultimately reduce the burden of two of the world's most impactful group of diseases.

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