JACC: CARDIOONCOLOGY VOL. 7, NO. 5, 2025
© 2025 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

BIDIRECTIONAL CARDIO-ONCOLOGY FOCUS ISSUE

Cancer Development in Atherosclerotic Cardiovascular Disease

JACC: CardioOncology Short-Form Primer

Jessie M. Dalman, BA,[a,b] Kathryn J. Moore, PhD[a,c]

Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide. Recent studies suggesting that CVD independently influences cancer development and progression have prompted the emergence of a new discipline often referred to as "reverse cardio-oncology" or "bidirectional cardio-oncology." While studies within the field have encompassed various CVD diagnoses, this short-form primer explores evidence for the relationship between atherosclerotic CVD and oncogenesis.

OBSERVATIONAL EVIDENCE

A prospective cohort study published by Hasin et al in 2016[1] established the first association between atherosclerotic CVD and cancer. The authors found that more than 1,000 patients diagnosed with myocardial infarction (MI) and subsequent cardiac sequelae between 2002 and 2010 were more susceptible to the development of cancer than the general population.[1] A nationwide cohort study conducted by Malmborg et al[2] later observed that among more than 2 million patients, those diagnosed with MI had a greater chance of developing malignancies. Additionally, Berton et al[3] prospectively evaluated 589 individuals with acute coronary syndrome, discovering that 99 of these patients were diagnosed with cancer during follow-up, a rate 3 times that which would be otherwise expected in the general population. Those patients who did develop malignancies following an acute coronary event also had worse prognoses.[3] The adverse impact of atherosclerotic CVD on oncogenesis was further supported by the finding that patients with peripheral artery disease, another common sequela of atherosclerosis, are more susceptible to developing cancer.[4] Interestingly, Bell et al[5] showed higher rates of brain, colon, bladder, liver, hematologic, and lung cancers and lower rates of uterine, breast, and ovarian cancers in patients with atherosclerotic CVD, suggesting that the protumorigenic effects of CVD may vary by tumor type. Finally, an analysis of more than 21,000 patients demonstrated that atherosclerotic CVD is independently associated with increased likelihood of metastatic disease at time of cancer diagnosis, even after adjusting for age, sex, smoking status, obesity, and other shared risk factors.[6]

MECHANISTIC EVIDENCE

The first mechanistic study into the connection between CVD and cancer was published in 2018 by Meijers et al,[7] who induced MI leading to heart failure in APC^{min} mice predisposed to developing intestinal tumors. At 6 weeks, mice in the experimental cohort were found to have a >2-fold increase in tumor burden compared with mice in the sham cohort, with an association between tumor growth and degree of left ventricular dysfunction. Using a heterotopic transplantation model, the authors demonstrated that the protumorigenic effects of heart failure are independent of hemodynamic impairment, thereby implicating cardiac secreted factors. Screening of

From the [a]Cardiovascular Research Center, Department of Medicine, NYU Grossman School of Medicine, New York, New York, USA; [b]University of Michigan Medical School, Ann Arbor, Michigan, USA; and the [c]Department of Cell Biology, NYU Grossman School of Medicine, New York, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 24, 2025; revised manuscript received May 16, 2025, accepted May 26, 2025.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2025.05.016

HIGHLIGHTS

- CVD impacts cancer onset and progression, yet the underlying mechanisms remain unclear.
- Cardiac-secreted factors, altered hematopoiesis, and innate immune changes link atherosclerotic CVD to cancer promotion.
- Addressing common risk factors, enhancing surveillance, and targeting inflammation in CVD patients may improve cancer outcomes.

candidate proteins in the plasma of patients with heart failure and mice post-MI identified elevated levels of serpinA3, also known as α-1-antichymotrypsin, as a factor that increased proliferation and AKT signaling of human colon cancer (HT-29) cells in vitro. This translational study provided the first direct evidence that post-MI heart failure can stimulate tumor formation.

Koelwyn et al[8] advanced the field in 2020 by showing that coronary artery ligation leading to acute MI accelerates breast cancer outgrowth and cancer-specific mortality by altering antitumor immunity. Using both E0771 syngeneic and MMTV-PyMT genetically engineered mouse models of breast cancer, they demonstrated that MI caused a doubling of tumor growth compared with sham surgery control animals. MI-accelerated tumor growth was accompanied by sustained increases in Ly6C^{high} monocytes in the circulation, and depletion of these cells reduced tumor development.[8] Multiomic analysis of Ly6C^{high} monocyte reservoirs in the bone marrow showed that MI induced epigenetic reprogramming of these monocytes to an immunosuppressive phenotype that persisted at the transcriptional level after exit to the circulation and recruitment to tumors. This was associated with an altered tumor immune microenvironment characterized by increases in myeloid-derived suppressor cells and regulatory T cells, both of which contribute to immunosuppression. Interestingly, the protumorigenic phenotype after MI could be transferred to naïve mice through bone marrow transplantation, implicating MI-induced changes to hematopoietic progenitor cells in the process of altering the immune response to cancer. A retrospective analysis of more than 1,700 patients from 2 prospective cohort studies complemented these mechanistic evaluations by demonstrating that cardiovascular events increased risk of cancer-specific death and recurrence in individuals with early-stage breast cancer.[8]

Dysfunctional myelopoiesis is also implicated in cancer growth in the setting of peripheral atherosclerotic disease. Newman et al[9] demonstrated that mice that underwent femoral artery ligation, a model of peripheral artery disease, exhibited accelerated growth of E0771 mammary tumors, as well as increased circulatory monocytes and neutrophils at the expense of lymphocytes. These changes were correlated with increased accumulation of immunosuppressive monocytes and regulatory T cells within tumors. Single-cell RNA sequencing and assay for transposase-accessible chromatin with sequencing of the bone marrow compartment showed that femoral artery ligation induced transcriptional and epigenetic changes in myeloid progenitors consistent with inflammaging. Notably, bone marrow transplantation demonstrated transmissibility of the accelerated tumor growth and myeloid bias after peripheral ischemia, indicating long-lasting alterations to antitumoral immunity. In concert with the study by Koelwyn et al,[8] these findings implicate dysfunctional reprogramming of hematopoietic reservoirs following ischemic injury in promoting cancer growth.

Transcriptomic analyses of tumoral gene expression following MI have further illuminated oncogenic signaling mechanisms. Utilizing a mouse model in which 4T1 mammary cancer cells were implanted 2 weeks post-MI, Tani et al[10] noted that gene pathways related to tumor progression, particularly the PI3K-AKT pathway, were enriched in tumors of mice 5 weeks post-MI. Increased phosphorylation of tropomyosin receptor kinase A (TRKA), an upstream regulator of the PI3K-AKT pathway, was detected in tumors post-MI, and administration of the TRKA inhibitor GW441756 decreased tumor volume without affecting cardiac function. Last, nerve growth factor (NGF), a known ligand of TRKA that was upregulated within the myocardium and in the peripheral circulation after MI, increased tumor cell proliferation and AKT signaling in vitro. Though NGF serves a cardioprotective function at the infarct border zone in the immediate aftermath of a cardiac ischemic event by protecting against reactive oxygen species, these findings suggest that signaling via NGF also augments mammary tumor growth.[10]

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

MI = myocardial infarction

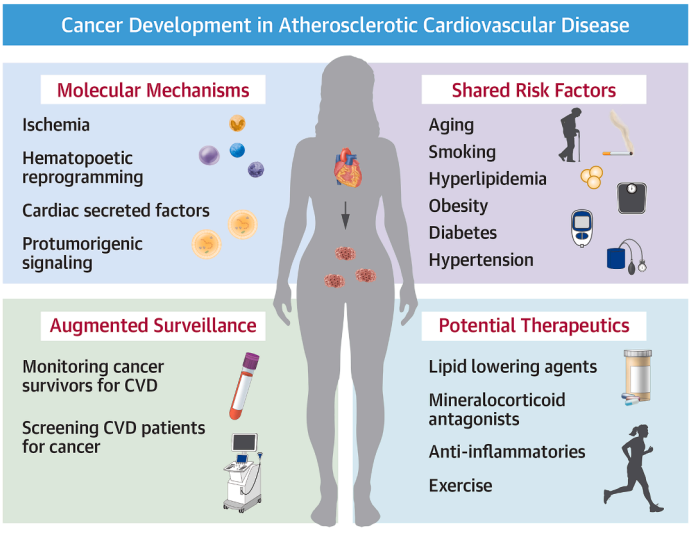
NGF = nerve growth factor

TRKA = tropomyosin receptor kinase A

CURRENT THERAPEUTICS AND FUTURE PERSPECTIVES

Though CVD and cancer have traditionally been treated as distinct clinical diagnoses, evidence

FIGURE 1 Cancer Development in Atherosclerotic CVD



Cancer development in the context of cardiovascular disease (CVD) is driven by shared risk factors (top right) and molecular mechanisms identified in in human cohorts and preclinical animal models (top left). There may be a role for augmented surveillance protocols (bottom left) to monitor cancer survivors for the development of CVD, as well as to screen CVD patients for new cancer diagnoses. While no therapies have been specifically approved for these bidirectional cardio-oncologic treatment paradigms, existing therapies (bottom right) may target the mechanistic pathways contributing to cancer progression in the setting of CVD.

increasingly suggests that these pathologies are driven by shared risk factors including aging, smoking, hyperlipidemia, obesity, diabetes, and hypertension, as well as common pathophysiologic mechanisms (**Figure 1**).[11] Thus, appropriate guideline-directed management of these determinants could combat the influence of CVD on oncogenesis.

Current scope of practice encompasses several existing pharmacologic therapies that, while not explicitly approved for oncologic therapy, have demonstrated some promise in the treatment of cancer in the setting of CVD. As cancerous cells may rely on cholesterol for accelerated growth, cholesterol-lowering medications including statins and inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) may provide antitumorigenic benefits, with early investigations suggesting some efficacy in hepatic, pancreatic, esophageal, hematologic, and colorectal malignancies (reviewed in Newman et al[11]). Exercise has also been associated with decreased rates of breast, kidney, endometrial, bladder, and prostate cancers (reviewed in Newman et al[11]).

Anti-inflammatory therapies may also represent a promising pathway for intervention. Chronic inflammation has been hypothesized to mediate cross-disease communication between atherosclerotic CVD and tumors, a connection that may be driven by clonal hematopoiesis, which has been connected to the development of atherosclerosis and cancers.[12] Indeed, administration of canakinumab, an anti-interleukin-1β monoclonal antibody, induced a 67% decrease in total incidence of cancer and a 77% decrease in fatal incidence of cancer in patients with prior MI but without prior cancer diagnosis.[13] Even so, the use of targeted anti-inflammatories to decrease oncogenesis remains speculative. A recent evaluation of transcriptomic datasets in both atherosclerosis and cancer identified pathways regulating inflammation, hypoxia, and epithelial to mesenchymal transition as shared pathogenic mechanisms.[14] Subsequent application of the OCTAD (Open Cancer TherApeutic Discovery) drug repurposing software identified approved and preclinical therapeutic compounds able to reverse gene expression signatures for both pathologies. While such an approach has yet to be evaluated in clinical trials, these results indicate that certain antitumor therapies may concurrently combat atherosclerotic CVD.[14]

Augmented clinical care guidelines may also improve patient outcomes. Consider, for instance, the implementation of robust cancer screening guidelines for patients who have experienced at least 1 cardiac event. Just as all men between 65 and 75 years of age who have ever smoked are recommended to undergo abdominal ultrasound to evaluate for abdominal aortic aneurysm, patients who have a diagnosis of MI, heart failure, or peripheral artery disease could be recommended to get imaging or laboratory testing on a specified cadence.

Cancer and CVD impact billions of people worldwide. As the general population lives longer and consequently shoulders increased risk of developing either or both of these diseases, it becomes increasingly necessary to understand the pathologic symbioses between these diagnoses. The field of bidirectional cardio-oncology holds immense potential to illuminate crucial findings for the benefit of patients and all those who support them.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors were supported by grants from the Sarnoff Cardiovascular Research Foundation (to Ms Dalman) and the National Institutes of Health (R01HL172335, R01HL172365, and P01HL131481 to Dr Moore). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Kathryn J. Moore, New York University Langone Health, 435 East 30th Street, Science Building 706, New York, New York 10016, USA. E-mail: kathryn.moore@nyulangone.org. X handle: @KathrynMooreLab.

REFERENCES

1. Hasin T, Gerber Y, Weston SA, et al. Heart failure after myocardial infarction is associated with increased risk of cancer. *J Am Coll Cardiol*. 2016;68:265–271.

2. Malmborg M, Christiansen CB, Schmiegelow MD, Torp-Pedersen C, Gislason G, Schou M. Incidence of new onset cancer in patients with a myocardial infarction - a nationwide cohort study. *BMC Cardiovasc Disord*. 2018;18:198.

3. Berton G, Cordiano R, Cavuto F, Bagato F, Segafredo B, Pasquinucci M. Neoplastic disease after acute coronary syndrome: incidence, duration, and features: the ABC-4* Study on Heart Disease. *J Cardiovasc Med (Hagerstown)*. 2018;19:546–553.

4. Nohara S, Mok Y, Van't Hof JR, et al. Subsequent risk of cancer among adults with peripheral artery disease in the community: the Atherosclerosis Risk in Communities (ARIC) study. *Int J Cardiol*. 2025;418:132577.

5. Bell CF, Lei X, Haas A, et al. Risk of cancer after diagnosis of cardiovascular disease. *JACC CardioOncol*. 2023;5:431–440.

6. Caller T, Fardman A, Gerber Y, et al. Atherosclerotic cardiovascular diseases are associated with incident metastatic and non-metastatic cancer. *JACC CardioOncol*. 2024;6:949–961.

7. Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. *Circulation*. 2018;138:678–691.

8. Koelwyn GJ, Newman AAC, Afonso MS, et al. Myocardial infarction accelerates breast cancer via innate immune reprogramming. *Nat Med*. 2020;26:1452–1458.

9. Newman AAC, Barcia Durán JG, Von Itter R, et al. Ischemic injury drives tumor growth via accelerated hematopoietic aging. *JACC CardioOncol*. 2025;7(5):587–605.

10. Tani T, Oikawa M, Misaka T, Ishida T, Takeishi Y. Heart failure post-myocardial infarction promotes mammary tumor growth through the NGF-TRKA pathway. *JACC CardioOncol*. 2024;6:55–66.

11. Newman AAC, Dalman JM, Moore KJ. Cardiovascular disease and cancer: a dangerous liaison. *Arterioscler Thromb Vasc Biol*. 2025;45:359–371.

12. Libby P, Kobold S. Inflammation: a common contributor to cancer, aging, and cardiovascular diseases-expanding the concept of cardio-oncology. *Cardiovasc Res*. 2019;115:824–829.

13. Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390:1833–1842.

14. Baylis RA, Gao H, Wang F, et al. Identifying shared transcriptional risk patterns between atherosclerosis and cancer. *iScience*. 2023;26:107513.

KEY WORDS **atherosclerosis, cardiovascular disease, coronary artery disease, epigenetics, heart failure, myocardial infarction, neoplasm, reverse cardio-oncology, tumor**