JACC: CARDIOONCOLOGY VOL. 5, NO. 4, 2023

EDITORIAL COMMENT

Tracing the Pathways From Cardiovascular Disease to Cancer

The Unseen Link*

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Cardiovascular disease (CVD) and cancer persist as the primary contributors to global mortality. Knowledge of cancer and cancer-related therapies leading to CVD has laid the foundation for the field of cardio-oncology as we know it today. Cancer therapeutics, including systemic antineoplastic therapies and radiation, have been linked with increased short- and long-term risk for adverse cardiovascular outcomes in patients with cancer. Recent studies have unraveled a more complex and bidirectional relationship between cancer and CVD, suggesting a reverse association of CVD with cancer incidence, progression, and mortality.

In clinical practice, cancer and CVD often coexist. For example, a large electronic health records-based study showed high pre-existing CVD prevalence in patients with newly diagnosed cancers (ranging between 17% and 43%, depending on the cancer type).[1] These conditions coexist because of shared risk factors such as age, smoking, diabetes, obesity, environmental exposures, and others (**Figure 1**).[2] Accordingly, shared risk factor management and diligent cardiac surveillance are recommended in high-risk individuals.[3]

The premise of shared biology remains an active area of investigation. Pathophysiological mechanisms such as inflammation and oxidative stress underlie the common links between the 2 diseases. For example, a proinflammatory milieu driven by adipokines (eg, interleukin-6) in patients with obesity can result in increased CVD risk while also inhibiting cancer cell apoptosis. Other biological mediators linking obesity, cancer, and CVD include insulin-like growth factor-1, leptin, and adiponectin.[2] The deleterious effects of insulin-like growth factor-1, which is elevated in patients with metabolic syndrome, on cancer cell proliferation and metastasis have been shown in colon and prostate cancer.[2]

In animal models with precancerous colon adenomas, ischemic heart failure has shown enhanced tumor growth, suggesting a role of cardiac-derived circulating factors that exert exocrine effects on tumor cells.[4] Evidence of therapeutic modulation of inflammation (eg, targeting interleukin-1β with canakinumab) has shown concomitant reduction in CVD events and lung cancer and related mortality.[5] Other potential shared risk factors and biologic intermediates include clonal hematopoiesis of indeterminate potential, which is associated with 11-fold higher relative risk for developing hematological malignancies and a 2- to 4-fold increased risk for developing CVD.[6] Additionally, cancer therapeutics may induce CVD risk factors, and interact with CVD medications, resulting in polypharmacy and worsened financial toxicity.

In this issue of *JACC: CardioOncology*, Bell et al[7] report a study in which they stratified 27 million cancer-free individuals identified from the IBM MarketScan database obtained from multiple sources (large employers, managed care organizations, hospitals, electronic health record providers, federal

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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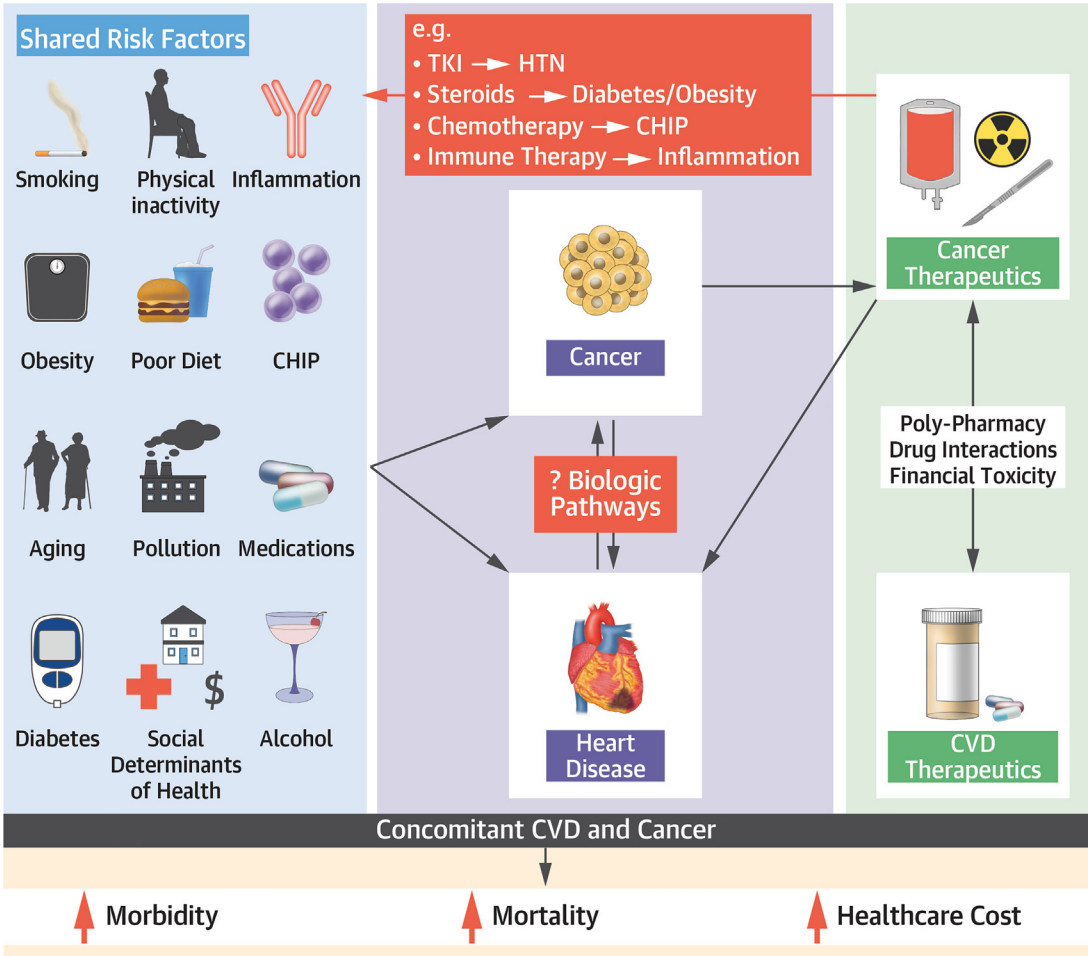
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.07.002

FIGURE 1 Shared Risk Factors, Bidirectional Relationship, and Therapeutic Interactions Between Cancer and CVD



Shared risk factors contribute to the bidirectional relationship between cancer and cardiovascular disease (CVD). Comorbid CVD and cancer are associated with increased morbidity, mortality, and health care costs. CHIP = clonal hematopoiesis of indeterminate potential; HTN = hypertension; TKI = tyrosine kinase inhibitor.

insurance programs) by the presence or absence of CVD (atherosclerotic CVD [aCVD] vs non-atherosclerotic CVD [naCVD]) and compared the incidence of cancer in both groups. At a median follow-up of 33 months, patients with CVD had 12% higher hazard of cancer than those without CVD (HR: 1.12; 95% CI: 1.11-1.13). The findings revealed stronger effects for the association between aCVD and cancer (HR: 1.20; 95% CI: 1.19-1.21) than between naCVD and cancer (HR: 1.11; 95% CI: 1.11-1.12). When analyzing cancer subtypes, aCVD was linked to lung, bladder, liver, colon, and other hematologic cancers but had a lower risk for breast, uterine, and ovarian cancers. The strength of the study lies in the large sample size and the ability to stratify individual cancer subtypes and adjust for common risk factors. The results of this study build upon prior literature suggesting that CVD is linked with future cancer risk and underscore the complexity of the interaction between CVD and cancer. For example, Suzuki et al[8] showed a 3% greater incidence of cancer and 2-fold higher mortality in patients with aCVD compared with naCVD. Roderburg et al[9] elucidated a similar association between heart failure and incident cancer diagnosis.

The strong association of lung and colon cancer with pre-existing CVD observed in the present study, particularly for aCVD, suggests an opportunity for more aggressive screening strategies in this patient

population. Current guidelines recommend lung cancer screening for adults aged 50 to 80 years with 20-pack-year smoking histories and current or former smokers within 15 years.[10,11] Considering that the greater incidence of lung cancer in patients with CVD in this study is independent of tobacco exposure, there may be a role for screening earlier in those with premature CVD and those without smoking histories. Recent guidelines recommend initiating colon cancer screening at 45 years of age.[10,11] Bell et al[7] showed that CVD predisposes to colon cancer, thus establishing the need for further studies to investigate the potential association of premature CVD and CVD risk factors with the development of colon cancer before the age of 45 years. In fact, the current literature identifies obesity, dyslipidemia, and physical inactivity as risk factors for early-onset colon cancer.[12]

In population-based studies, achievement of ideal cardiovascular health is associated with significant reduction in cancer risk.[13] The American Cancer Society guidelines on nutrition for cancer prevention align with the American Heart Association guidelines for prevention of CVD, both having an emphasis on a plant-based diet, whole grains, and fruits and vegetables and avoidance of processed meat.[14] Primordial prevention strategies focusing on the same health behavioral principles may help prevent premature CVD as well as early cancer. Cardiometabolic interventions, such as the use of sodium-glucose cotransporter-2 inhibitors, which have proved beneficial in myriad of cardiovascular conditions, may be useful in cancer prevention and treatment in the future because of the anticancer effects noted in preliminary studies.[15]

Although this study shed light on an important issue, there are a few notable limitations inherent to the data source. For example, physical activity, environmental, and socioeconomic variables were not taken into consideration. We have previously shown that area-based social determinants of health are associated with increased risk for both CVD and cancer.[16] Studies also suggest that environmental exposures affect both CVD and cancer.[17] In the United States, we have recently identified multiple geographic risk factors associated with CVD and cancer mortality, including exposure to particulate matter air pollution and other environmental hazards.[18] Accordingly, it is essential to design future studies to understand the comprehensive impact of environmental exposure and social determinants on concomitant CVD and cancer and account for these differences. An additional limitation of this study, as correctly noted by the investigators, is that it did not account for competing risk, which may have biased the results. The lower risk for breast, ovarian, and uterine cancers requires additional study to investigate confounding effects.

In conclusion, shared risk factors, pathophysiological mechanisms, and epidemiologic observations underscore the interplay of CVD and cancer. Recognizing this relationship is imperative for using preventive strategies and developing therapeutic targets. Future research into biological pathways driving the interaction will provide further insight into optimizing care for this unique patient population.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cancer, cardiovascular disease, environmental exposures, prevention