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EDITORIAL COMMENT

Cancer Prevention and Early Detection in Patients With Cardiovascular Disease

A Goal of Bidirectional Cardio-Oncology

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The interplay between cardiovascular disease (CVD) and cancer is bidirectional.[1] On one side, cancer and particularly cancer treatment may cause or precipitate CVD, which has historically been the main focus of cardio-oncology.[2] On the other side, CVD shares risk factors with cancer and may facilitate tumorigenesis, hinder optimal onco-hematological care, and impact cancer prognosis.[3] This scenario is addressed by a subfield that has recently been established within cardio-oncology, sometimes referred to as reverse cardio-oncology.[4]

In this issue of *JACC: CardioOncology*, Caller et al[5] explore the interplay between CVD and cancer.[5] The investigators utilized data from a large cohort of adults, who participated in preventive health care programs in Israel between 2000 and 2018, and were free of atherosclerotic cardiovascular disease (ASCVD) and cancer at the time of enrollment. The absence of both conditions was ascertained by a complete medical evaluation including electrocardiogram and exercise stress test. They censored myocardial infarction (MI) and stroke, as main types of ASCVD, and cancer after the baseline visit, and assessed whether ASCVD would influence successive cancer diagnosis and death.

Of a total of 21,654 subjects, 1,333 (6.2%) were diagnosed with ASCVD and 1,793 (8.3%) with cancer over a median follow-up of 6 years. Incidence of cancer was higher in individuals with than without cardiovascular risk factors (CVRF), namely chronic kidney disease, obesity, and impaired fasting glucose, as well as in those with a 10-year risk of ASCVD of 7.5% or more, as estimated according to the American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort equation. Moreover and germane to this commentary, development of ASCVD portended a higher risk of subsequent cancer, and ASCVD increased cancer mortality.[5]

Among subjects diagnosed with cancer at follow-up, 42% had metastases at presentation. In addition to increasing the risk of nonmetastatic cancer, ASCVD was also associated with a heightened risk of metastatic cancer. This association persisted after adjusting for age, sex, and CVRF. Mortality from metastatic cancer was also enhanced when ASCVD was present.

Interestingly, the association of ASCVD with incident cancer, both metastatic and nonmetastatic, disappeared in the highest age quartile of the study population, those more than 54 years of age.

Caller et al[5] adopted a number of approaches to overcome the shortcomings intrinsic to a population-based retrospective analysis: they cross-referenced the study dataset with the nationwide Israel National Cancer Registry; they adjudicated MI and stroke cases; they accounted for the competing risk of death; they considered a 1-year blanking period at the start of follow-up to exclude possible cancers that were already present at baseline, but were clinically silent; and they performed a propensity score-based sensitivity analysis with matching by age, sex, body mass index, CVRFs, and length of follow-up.

Nonetheless, some methodological weaknesses remain. The evaluated cohort was relatively young (median age 46 years), mainly male (70%), and mostly of subjects defined as "white individuals" with high socioeconomic status. In fact, social determinants of health were not characterized and included in the

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analysis. Although MI and stroke represent the largest part of ASCVD, other manifestations of ASCVD were not evaluated. Due the predominance of males, prostate cancer was overrepresented, more than 50% of metastatic cancer cases were defined as unknown primary site (usually <10%) and about one-third were melanoma. Finally, no secondary analyses were run separating MI and stroke, or distinguishing cancer categories or specific types.

Even with these limitations acknowledged, Caller et al[5] quite convincingly conclude that ASCVD is associated with cancer incidence and mortality. They emphasize the association with metastatic cancer, as it has not previously been reported. It should also be noted that the relationship between ASCVD and cancer has been examined far less frequently than the relationship between heart failure and cancer,[6,7] and this is another aspect of originality of their work.

In a broader perspective, the article provides confirmation that impaired CV health predisposes to cancer. In Caller et al's study[5] and previous similar studies, the association of CVRF or CVD with cancer was weaker than other major drivers of tumorigenesis, such as smoking or age. In fact, predominance of age-related over CV-related cancer risk may explain why the findings of Caller et al[5] did not extend to the oldest age stratum of their cohort. On the other hand, the high prevalence of CVRF and CVD amplifies their impact on cancer outcomes, to the point that they may be viewed as actionable modifiers of cancer risk.

Largescale primary and even primordial CV prevention campaigns are globally run and could be exploited for oncological prevention. The general population is given the message that smoking predisposes to heart attacks and cancer: likewise, it should be informed that chronic kidney disease, obesity, and impaired fasting glucose—just to name the conditions highlighted by Caller et al[5]—also put individuals at risk of either condition, and that CVD connotes a status of cancer susceptibility.

Prevention of CVD and cancer also requires the identification of common causal pathways to be targeted. Inflammation promotes the development of both CVD and cancer,[8] thus anti-inflammatory therapies could halt both diseases. This has been demonstrated in principle by the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), in which interleukin-1β blockade with canakinumab reduced both CV events and lung cancer incidence in patients who had suffered from MI and had elevated concentrations of high-sensitivity C-reactive protein.[9,10] Social determinants of health are as important as biological factors in the occurrence of CVD and cancer, hence efforts to tackle them are another pillar of prevention in cardio-oncology.[11,12]

It may also be argued that the detection of CVD could be a trigger to screen for most common malignancies, particularly in younger individuals. The presence of CVD could justify changes to established screening programs for breast, cervical, prostate, colon, and lung cancer, such as lowering age thresholds. Clearly, the implications in term of resources would be significant and more data are needed, especially from populations with larger representation of women and non-White ethnicities, before making any claim.

In conclusion, the work by Caller et al[5] buttresses the consideration that CVD may anticipate cancer and that early cancer recognition should be part of CVRF and CVD management. In this regard, joint initiatives by cardiologists and onco-hematologists appear fundamental and would complete the bidirectionality of cardio-oncology, encompassing CV prevention in cancer patients and cancer prevention in CV patients.

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