

EDITORIAL

Revealing the Complex Interplay Between Cancer and Cardiovascular Disease: Can Cardiac Magnetic Resonance Lead the Way?

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Cardiovascular disease (CVD) and cancer are associated with the highest burdens of disease and mortality globally as well as in both the United States and the United Kingdom.^{1–3} Although they are 2 separate disease entities, the association between CVD and cancer is a complex one.

See Article by Labib et al.

First, a number of studies have now established that patients with heart failure are at an increased risk of incident cancer. Hasin et al⁴ first demonstrated this in 2013 in their study of 961 patients with heart failure without a prior diagnosis of cancer, who had a 60% increased risk of developing cancer (hazard ratio, 1.60; 95% CI, 1.14–2.26) when compared against 961 matched controls. This has been further corroborated by a number of subsequent studies, including the big data analysis from Banke et al⁵ of 9307 patients with heart failure without a prior diagnosis of cancer from the Danish National Registries; risk of any type of cancer was increased compared with the background population incidence, with an incidence rate ratio of 1.24 (95% CI, 1.15–1.33; $P < 0.0001$).

Second, the converse is also true that cardiovascular risk and mortality are elevated in survivors of

cancer. Indeed, from the inquiry by Sturgeon et al² of the Surveillance, Epidemiology and End Results database of more than 3.2 million patients with cancer, 11% died of CVD, representing an average 2 to 6 times higher CVD mortality risk than the general population. However, while much of the focus thus far has been in defining the diagnosis, treatment, and surveillance of cancer treatment related CVD, there is an increasing appreciation that this does not account for the full picture. The question is no longer limited to how and why cancer treatments affect CVD but how active malignancy itself influences CVD. In other words, do cancer and CVD represent final pathways of a common pathophysiology, or perhaps is cancer itself cardiotoxic?

The complex interaction between cancer and CVD is at least in part due to both the shared risk factors and our increasing understanding of common pathophysiological pathways. The incidence of CVD and cancer are both associated with hypertension, obesity, smoking, diabetes mellitus, and poor lifestyle choices.⁶ Additionally, both disease processes are driven by inflammation and dysregulation of the immune system resulting in dysregulated T cells, changes in the macrophage population, and influx of other inflammatory cells such as neutrophils, monocytes, and mast cells, along increased oxidative stress and activation of neurohormonal systems.⁷ Furthermore, prospective data

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from a small Italian cohort (Danese et al⁸) of 75 patients with either one of untreated ovarian cancer, endometriosis, or a benign mass showed that women with untreated cancer had significantly higher troponins compared with the latter 2 groups and therefore raises the question of whether myocardial injury is implicated in oncogenesis.

In this issue of the *Journal of the American Heart Association (JAHA)*, new work by Labib et al⁹ describes the cardiac phenotype of patients with treatment-naïve breast and lymphoma cancer who prospectively underwent assessment with cardiac magnetic resonance (CMR) imaging before the initiation of any cancer treatment. This cohort of 381 patients was compared against 102 healthy volunteers. Patients with an underlying cardiovascular diagnosis were excluded from the study.

The investigators should be congratulated for their success in recruiting the largest cohort of this type to date in order to obtain a broad and comprehensive range of CMR data that have made this both a novel and important study. The key findings of their analysis found that patients with treatment-naïve, active cancer had smaller cardiac chamber volumes, higher myocardial strain values, and elevated native myocardial T1, compared with the healthy volunteer cohort.

The differences in cardiac chamber volumes and myocardial strain values observed by Labib et al are an intriguing, and perhaps surprising, observation. If subclinical, early phenotypes of CVD were to accompany cancer either because of the purported shared risk factors, pathophysiology, or cardiotoxicity, then the prediction might have been for an *increase* in cardiac chamber sizes and *decrease* in myocardial strain measurements.

The small cardiac chamber sizes noted in cancer by Labib et al point to cardiac remodeling, although the mechanism for this and its implications are unclear. In a cohort of 137 patients with preserved ejection fraction undergoing exercise stress echocardiography presented by Meyer et al,¹⁰ poor exercise capacity (as measured by their metabolic equivalent of tasks and New York Heart Association functional class) was similarly associated with small left ventricular cavity sizes as compared with those with good exercise capacity. Could poorer performance status and exercise capacity in the context of cancer be one of the drivers of cardiac remodeling and small cardiac chamber sizes? Additionally, concentric cardiac remodeling resulting in a small left ventricular cavity size can be seen in diastolic dysfunction and restrictive cardiomyopathies. Pilot data by Cochet et al¹¹ have suggested that baseline diastolic dysfunction could be predictive of trastuzumab-mediated cardiotoxicity, and the question will be whether baseline CMR measurements such as cardiac chamber sizes can similarly predict at-risk cohorts.

One of the most interesting findings of this study was the higher native T1 values (imaged with a 3.0-T scanner) demonstrated in patients with cancer when compared with the healthy volunteers; women had a median elevation of 23 ms ($P<0.001$) in the septum and 19 ms ($P=0.02$) in the lateral wall, whereas men had a median elevation of 69 ms ($P=0.001$) in the septum and 59 ms ($P<0.001$) in the lateral wall.⁹

Diao et al¹² have previously demonstrated in a systematic analysis of 308 patients pooled from 15 studies that elevated myocardial T1 measurements have a significant correlation with histological confirmation of myocardial fibrosis. Interestingly, Labib et al⁹ in the discussion of their findings thought that myocardial fibrosis was unlikely in their cohort because of the short time frame of the recently diagnosed cancer and the lack of associated adverse chamber remodeling and reductions in contractile performance. However, interstitial fibrosis that is associated with native T1 elevation (as differentiated from replacement fibrosis), occurs earlier in the course, can be reversible, and has been shown to possibly precede the development of heart failure.^{13,14} Furthermore, although the median time from diagnosis to undertaking CMR in the Labib et al⁹ cohort was only 1.2 months, cancer perhaps represents only the final pathway and snapshot in time of a longer pathophysiological process of inflammation and immune dysregulation as discussed earlier in this editorial.

Of course, it is important to note that prolongation of native T1 is also associated with anemia^{15,16} and that cancer is one of the most common causes of anemia with a prevalence of 30% to 90%, dependent on cancer type and disease stage.¹⁷ Subsequently, the differences between the cohort with cancer and healthy volunteers may simply reflect this rather than myocardial fibrosis.

The caution with which we must approach the significant native T1 findings highlights the missed opportunity of this study—omitting the use of gadolinium contrast. This would have allowed for acquisition of late gadolinium sequences and contrast-enhanced T1 mapping to provide an estimation of extracellular volume fraction, the additive data lending themselves to better detection of myocardial fibrosis.¹³ Indeed, in comparing the correlation between different analyses of myocardial T1 (native, contrast enhanced, and extracellular volume), Diao et al¹² found native T1 to have the lowest correlation value with myocardial fibrosis and extracellular volume the highest.

The important data from this study by Labib et al are a good start to describing the cardiac phenotype associated with cancer and better definition of the complex relationship between cancer and CVD. However, it perhaps leaves the reader with more questions than answers at this stage.

The mechanism of change and injury that produces the cardiac phenotype in patients who are treatment naïve is important to define. This should better allow cardio-oncologists to predict the patient cohort more susceptible to cancer treatment related CVD based on CMR findings. Ultimately this will help determine whether earlier institution of cardioprotective therapies or increased cardiac surveillance in this cohort will improve cardiac outcomes. Additionally, it also begs the question of whether worse baseline CMR findings in patients with cancer may predict worse cancer outcomes and whether CMR may have a role in deciding cancer treatment regimens. Going forward, answering these gaps in our current understanding of the relationship and interplay between cancer and CVD will empower cardio-oncologists and oncologists alike in delivering personalized cancer and cardiac treatments to ensure the best outcomes for patients.

ARTICLE INFORMATION

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Disclosures

None.

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