

Specific Comments to Authors: This is a well written overview of current gaps in estimating CV risk in cancer survivors and appropriate management or risk reduction of future CV events. Please find attached a few minor comments to word document.

Thank you for your positive comments.

Comment 1. Please comment on role of CV imaging in assessing risk in cancer survivors- cardiac MRI, role of early detection?

An area of active research is assessing the utility of various CV imaging technique for early detection of individuals at a higher risk of future CV events following cardiotoxic therapy. Myocardial strain assessment through echocardiography and cardiac magnetic resonance (CMR) to detect myocardial fibrosis when other imaging techniques are nondiagnostic have been an important addition to the existing diagnostic tools to detect early myocardial injury and follow-up CTRCD¹.

Comment 2.) Please comment on CV risk profile of different systemic agents and challenges associated with the same. For instance, trastuzumab associated cardiomyopathy is quite different from doxorubicin or radiation associated HF.

Anthracycline and trastuzumab are one of the most commonly used chemotherapeutic agents known to cause CTRCD. Anthracyclines lead to a dose-dependent irreversible structural damage to cardiomyocytes (Type I CTRCD) resulting in heart failure, whereas trastuzumab causes inhibition of signal transduction predominantly (reversible injury, type II) and has additive effect to the cardiotoxicity from other modalities when used in combination². Radiation induced heart disease (RIHD), from radiation treatment given to prevent recurrences is another cause for major cardiovascular events among long term cancer survivors that needs to be accounted for where assessing CVD risk among patients³.

Comment 3. Please comment on role of primary prophylaxis with BB/ ACE inhibitors in risk reduction. RCT evidence exists for trastuzumab associated cardiomyopathy in breast cancer survivors.

The traditional therapy for heart failure including Beta-blockers and ACE inhibitors have both been demonstrated to be protective against CTRCD from anthracyclines and trastuzumab and prevent progression of the ventricular dysfunction when given prior to or during chemotherapy in patients with early signs of cardiac injury^{4,5}.

Comment 4. Important to address weight gain from chemotherapy or metabolic syndrome seen with certain anti-cancer treatments may impact CV risk

Up to 40% of cancer survivors become obese placing them at an increased risk of adverse cardiovascular outcomes and secondary cancers in future. Growing evidence suggests the importance of adequate weight management in improving overall health and wellbeing especially cardiovascular health among survivors. In a study of breast cancer patients treated with anthracyclines and trastuzumab, obesity was found to be an independent risk factor associated with greater cardiotoxicity when compared to non-obese patients⁶. Given the high

prevalence of obesity and associated inactivity in cancer survivors, energy balance interventions need to be incorporated in the treatment plan right from the time of first diagnosis. A motivated diet plan and exercise induced weight management led to clinically meaningful weight loss and subsequent control of risk factors related to cardiovascular health⁷.

Comment 5. Consider adding that CV events are most common cause of death in BC survivors.

Interestingly, cardiovascular disease is now one of the leading causes of death among long-term breast cancer survivors⁸.

Comment 6. please highlight importance of cardio-oncology and need for close collaboration between different specialties to improve patient outcomes.

Cardio-Oncologist care must be initiated right from the pre-treatment stage for identifying high risk patients and mitigating the factors known to contribute to cardiotoxicity to after treatment phase where future cardiovascular risk is frequently assessed and appropriate measures are undertaken to maintain long-term cardiovascular health.

Comment 7. In the absence of valid CV risk estimator in cancer survivors, readers would like to know how to best to approach this issue. Please highlight institutional practices or expert opinion (perhaps a flowchart or diagram) in addressing this unmet need

While researchers continue to develop a tool to estimate the cardiovascular risk among adult cancer survivors, the physician should focus on managing these patients by utilizing the ABCDE steps to prevent heart disease which has been largely applied to breast and prostate cancer survivors but can be adapted for all types of cancer survivors^{9,10}. A, being Awareness of risks of heart disease and symptoms associated with the cardiovascular illness, and Aspirin prophylaxis for eligible patients. B, being maintaining Blood pressure below cutoffs. C, being controlling Cholesterol levels and promoting Cigarette/tobacco smoking cessation, D being Diet and Diabetes management and E being Exercise (Figure.1).

Comment 8. What should future studies focus on to address this unmet need? how is this field evolving? Please consider adding this to your conclusion.

Recent progress in terms of utilizing advanced imaging techniques and identifying role of cardioprotective medications to prevent progression of ventricular dysfunction has been a step in the right direction, and now the urgent need is to direct future studies with the focus to develop an accurate cardiovascular risk prediction and assessment tool for adult cancer survivors to continue to provide comprehensive cancer.

Reference:

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