JACC: CARDIOONCOLOGY VOL. 4, NO. 2, 2022

EDITORIAL COMMENT

Hearts on the Minds of Oncologists

Building Evidence to Ensure Implementation*

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Cancer mortality rates have declined over the past 30 years.[1] As a result, the number of cancer survivors has swelled, with expectations that this number will grow to 20 million by 2026.[2] Although this is excellent news, there are competing sources of morbidity and mortality for cancer survivors, many of which arise as long-term adverse effects of cancer treatment. One key example is cardiotoxicity after exposure to chemotherapy (eg, anthracyclines), radiation, or targeted therapies.[3,4] The risks from these exposures are exacerbated by pre-existing cardiovascular risk factors, including age, hypertension, and diabetes. The American Heart Association (AHA) recently issued a statement endorsed by the American Cancer Society, proposing the development of a cardio-oncology rehabilitation (CORE) comprehensive model for cancer survivors to address such adverse treatment effects.[5] The AHA statement presents a targeted approach to identify patients at high risk for cardiovascular disease (CVD) and the use of a multimodal approach of cardiac rehabilitation to prevent or mitigate cardiovascular events. The statement highlights knowledge gaps in the field of cardio-oncology, including the need for further development of the evidence base and to discern best practices for implementation of CORE. In addition, the National Comprehensive Cancer Network released guidelines in 2020 with the intention to integrate cardiovascular risk assessment into cancer care, toward the goal of promoting cardiovascular wellness of cancer survivors.[6] The release of 2 recent statements from major organizations about cardiovascular risk assessment and interventions to address cardiotoxic effects of cancer therapies signals strong interest of the fields of oncology and cardiology to prevent and treat adverse cardiovascular outcomes among people living with and beyond cancer. In this issue of *JACC: CardioOncology*, Fakhraei et al[7] present evidence that more robust randomized controlled trial data are needed to support the stated goals of the recent AHA and National Comprehensive Cancer Network statements.

Fakhraei et al[7] conducted a rigorous systematic review and meta-analysis on the topic of research quality and the impact of cardiac rehabilitation among cancer survivors. Their process started with adherence to published guidelines for such research from Preferred Reporting Items for Systematic Reviews and Meta-Analyses and A Measurement Tool to Assess Systematic Reviews.[2] The review methods were published prior to full-text extraction. The work was conducted with the highest rigor and transparency, from design to searches, from evaluations to data synthesis, analysis, and conclusions.

The investigators included randomized and nonrandomized trials, single-arm trials, and prospective and retrospective studies, in acknowledgment of the limitations of the available evidence. Although more than 23,000 records were identified, only 10 studies were deemed eligible for full review. Designs of the included studies included 3 retrospective and 6 prospective single-arm cohorts and 1 randomized controlled trial. There was a total of 741 participants, 685 of whom had had cancer diagnoses. The majority received interventions ranging from 6 to 26 weeks, but the frequency, intensity, time, and type of exercise interventions varied across studies. The majority of the participants (61%) were breast cancer survivors.

*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 author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution 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.2022.05.006

JACC: CARDIOONCOLOGY, VOL. 4, NO. 2, 2022
JUNE 2022:207–209

The quality of the studies was relatively low, as noted by multiple metrics calculated by Fakhraei et al.[7] For example, more than half of the studies were rated as having moderate to critical values of risk for bias using well-established methods of assessment. The only randomized controlled trial had a high risk for bias arising from adherence and missingness of data. Overall, identified studies were found lacking in reporting of key details regarding intervention and harm, as well as having a high risk for bias.

Benefit was documented, particularly for cardiorespiratory fitness (CRF), a finding that is in agreement with prior reviews. A recent meta-analysis by Scott et al[8] of 46 trials evaluating the impact of exercise on CRF in individuals with cancer showed that exercise increased CRF relative to control both during ($+1.37$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 0.58-2.16 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) and after ($+2.45$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 1.71-3.19 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) cancer treatment. Combined with the present study, existing evidence supports the conclusion that exercise improves CRF in patients with cancer. However, most trials to date have been small, enrolling fewer than 100 participants. Additionally, most exercise interventional trials in patients with cancer and survivors have precluded enrollment of individuals with preexisting CVD, depressed ejection fraction, and diabetes, because of concerns over the risk for major adverse cardiovascular events during exercise training.

The effectiveness of cardiac rehabilitation for patients who have had myocardial infarction or heart failure is well established, and appropriate third-party payer coverage is available for these services. Unfortunately, as shown by Fakhraei et al,[7] the available evidence is insufficient to expand third-party payer coverage to patients with cancer at risk for cardiovascular events. However, there is consensus that the development of CORE interventions tailored to the needs of patients with cancer with pre-existing CVD and/or CVD risk factors is important in reducing CVD risk and mortality in this population.

Given the well-established benefits of exercise on CRF, patient-reported outcomes, and other endpoints among cancer survivors, guidelines increasingly call for the incorporation of exercise into oncology care.[9-11] However, third-party payers do not support exercise consultation or training for patients with cancer, and there is no established infrastructure to support the delivery of exercise training as a part of cancer care. Some oncology facilities have developed oncology rehabilitation programs, but these programs largely focus on functional limitations or adverse effects of cancer treatment, such as neuropathy or lymphedema, rather than improvements in CRF and reduction of CVD risk factors. Consideration of using the well-developed, pre-existing infrastructure for cardiac rehabilitation, currently used for patients who have had myocardial infarction or heart failure, in the setting of cancer is appealing because cardiac rehabilitation delivers exercise as its core program with the long-term goal of improving CVD outcomes. It allows the systematic application of exercise and risk factor reduction under close supervision and guidance from a well-organized, multidisciplinary team of health care professionals.[12,13] Cardiac rehabilitation also has the advantage of being standardized, available across thousands of community and academic sites, and could be immediately scalable to cancer patients across the United States. Although the available evidence broadly suggests feasibility and potential benefits of cardiac rehabilitation in patients with cancer, more work is needed to determine whether cardiac rehabilitation could be a model to effectively and consistently improve CVD risk factors and reduce the risk for major adverse cardiovascular events in cancer survivors.

There is a clear and pressing need to assess the efficacy of cardiac rehabilitation to reduce CVD in cancer survivors at elevated risk because of treatment-related exposures. Efficient and broad dissemination of positive trials requires that such trials include implementation science elements to ensure that we understand both the barriers and facilitators at the levels of the patient, oncology care team, and health care system. Widespread, systematic adoption will require buy-in from both multidisciplinary care teams and patients. Evidence-based discussions between care teams and patients regarding the benefits of exercise will be an important aspect of widespread adoption, and education of providers will help catalyze meaningful discussions with patients.

There is clearly strong interest in the development of exercise interventions to address cardiotoxicity after cancer treatment. The way forward will need to include well-designed and rigorous efficacy assessment with appropriate infusion of implementation science elements to speed the translation of results to

practice, to address CVD risk and outcomes in cancer survivors.

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 bias, biomedical research standards, cardiology, data reporting, exercise therapy, oncology