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

EDITORIAL COMMENT

Exercise as Medicine

Can We Preserve Cardiac Health Through Physical Activity?*

Melinda R. Stolley, PhD, David Lewandowski, MD

Breast cancer (BC) is the most frequently diagnosed cancer among women in the United States, with 279,790 new cases estimated in 2023.[1] With advances in prevention, early detection, and treatment, BC mortality has decreased by nearly 40% during the last 4 decades. Although most women with nonmetastatic disease survive their BC, a subset faces adverse treatment effects that can diminish length and quality of life. Among these, cardiotoxicity is a significant challenge and is associated with common therapies including anthracyclines, human epidermal growth factor receptor 2 (HER2)-targeted therapies, and chest radiation. Although the cardiac effects of HER2-targeted therapies often resolve with therapy discontinuation, the damage associated with anthracyclines can result in a progressive decline in left ventricular function, potentially leading to overt heart failure.[2] In a study of cancer patients receiving anthracyclines (51% BC), the median cardiotoxicity onset was at 3.5 months; 98% of all cases occurred within 1 year.[3] The estimated incidence of clinical cardiotoxicity for anthracyclines is 10% to 15%.[4] These adverse effects are more pronounced in Black/African-American women, with a 3-fold increase in risk for cardiotoxicity after anthracyclines.[5] Importantly, cardiotoxicity can limit BC treatment options and contributes significantly to cardiovascular (CV) morbidity and mortality in BC survivors. Cardiovascular disease (CVD) is now the leading cause of noncancer death among women treated for BC.[6]

Adherence to national exercise guidelines is associated with a reduced risk of CV complications among women exposed to BC treatments.[7] However, physical activity (PA) can be negatively impacted by BC and its treatments, often never returning to pretreatment levels.[8] Relatedly, post-treatment weight gain is common, with increases in fat mass accompanied by losses of lean mass.[9] These conditions further reduce PA and increase the risk for adverse CV outcomes.[8] Notable scientific gaps remain because most studies to date focus on PA in women after treatment; have study samples lacking diversity; do not always specify PA intensity; and do not examine relationships between PA, exercise capacity, and cardiac function.

In this issue of *JACC: CardioOncology*, Bellisimo et al[10] address several gaps with results from their prospective study examining the trajectory of self-report leisure time physical activity (LTPA, Godin Leisure Time Activity Questionnaire), submaximal exercise capacity (6-minute walk), and cardiac function (cardiac magnetic resonance) among 223 (77% White and 17% Black) women undergoing treatment for nonmetastatic BC from pretreatment to 3 months after treatment initiation. These data are compared to those of 126 noncancer controls (80% White and 14% Black). At baseline, BC patients were similar to controls in LTPA, exercise capacity, and cardiac function. After 3 months of treatment, BC patients reported a significant decline in LTPA across activity levels (sufficiently active, moderately active, or insufficiently active) compared to controls. Exercise capacity and cardiac function also reduced over time but not significantly. Notably, a dose-response relationship was observed between LTPA, activity category, and exercise capacity. Higher LTPA was associated

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

From the Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

Jennifer A. Ligibel, MD, served as the Guest Associate Editor for this paper. Kathryn J. Ruddy, MD, MPH, served as the Guest Editor-in-Chief for this paper.

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.2023.08.006

JACC: CARDIOONCOLOGY, VOL. 5, NO. 5, 2023
OCTOBER 2023:653–655

with greater exercise capacity and a lower risk of cardiac dysfunction. Additionally, women in the "active" category at baseline had higher exercise capacity and preserved cardiac function at 3 months compared to the insufficiently active group who exhibited statistically significant decreases in exercise capacity and cardiac function.

The study by Bellisimo et al[10] confirms previous work supporting decreased LTPA among women treated for BC and the benefits of LTPA. Sabiston and colleagues[8] examined moderate and vigorous PA using actigraphy in 199 nonmetastatic BC survivors over 12 months following treatment completion. Women demonstrated consistently high rates of sedentary activity, along with significant reductions in moderate and vigorous PA over time.[8] In a prospective post-treatment study, Jones et al[7] reported a 23% reduction in new CVD events (new diagnosis of coronary heart disease, heart failure, valve abnormality, arrhythmia, stroke, or CVD death) among women (N = 2,973) with BC who adhered to national exercise guidelines compared to those who did not. The results were consistent across age, CVD risk factors, menopausal status, and treatment type.[7] Bellisimo et al[10] extend the existing evidence base by targeting women on treatment, providing data on the impact of treatment on PA and CV function, and documenting the protective effects of exercise during treatment. The study is limited by self-report LTPA and a brief follow-up period. Given that the study duration was shorter than the mean onset of anthracycline cardiotoxicity, longer follow-up periods could demonstrate larger differences in the incidence of cardiomyopathy across activity groups. Additionally, it is not clear if women exposed to multiple cardiotoxic treatments (ie, anthracyclines ± HER2+-targeted therapies ± chest radiotherapy ± aromatase inhibitors) appreciate similar protections. Furthermore, although the prevalence (14%-17%) of Black participants is greater compared to other studies in cardio-oncology, the study lacks sufficient representation of racially diverse women, particularly given the higher risk Black women face. However, the prospective design, the inclusion of a noncancer control group, and the measurement of cardiac function with cardiac magnetic resonance reflect methodological strengths. Notably, the study results have important clinical implications, allowing clinicians to talk with patients about the potential value of increasing LTPA to guideline-concordant levels to reduce cardiotoxicity risk.

The next steps are critical to leverage the strengths of work to date and address ongoing gaps. Given the high rates of inactivity and resulting cardiac damage as well as the documented benefits of exercise on cardiorespiratory fitness,[7,8,11] efforts are needed to better understand mechanistic pathways linking exercise to reduced risk, to describe longer-term benefits of exercise for CV outcomes, and to integrate exercise interventions into oncologic care.

Longer duration studies may help solidify exercise as a preventative strategy for the development of cardiotoxicity and the resulting impact on cardiac function. These studies would also further elucidate the mechanisms by which exercise mitigates the toxic effects of BC treatments. Multiple pathways are being examined; yet, evidence from clinical studies remains insufficient to reach any conclusions. Using a preventative rather than reactive approach could minimize interruptions in cancer therapy, which result in a higher risk of disease recurrence[12] and the need for often poorly tolerated cardioprotective medications. In 2018, the American Society of Clinical Oncology published guidelines recommending oncology providers to advise patients on active treatment with curative intent to engage in aerobic and resistance training.[13] However, with the psychological and physical challenges of maintaining PA during cancer therapy, patients need support. This need could be addressed by the 2019 American Heart Association recommendation to implement cardio-oncology rehabilitation for cancer patients across the care continuum, a model based on multidisciplinary cardiac rehabilitation programs for non-cancer cardiology patients.[14] Providing individualized exercise programs would help identify the optimal level of exercise for each patient based on their course of therapy[11] and might also enhance patient motivation.

Future work must be more intentional about including diverse samples of patients. Racial disparities are prevalent in cardiology and oncology. Black/African American adults have the greatest mortality rates attributable to CVD and stroke and, for women, BC compared to non-Hispanic Whites. Furthermore, Black/African American women are at higher risk for anthracycline-based cardiotoxicity, contributing to worse outcomes compared to non-Hispanic White women. Given the challenges of multiple social determinants of health driven by structural racism, Black/African American women often enter their cancer experience at increased risk for CVD with higher psychosocial stress, multiple comorbidities, and lower PA levels. Pursuing adequate representation in exercise trials requires a diverse workforce, patient engagement in trial development, careful consideration of eligibility criteria to increase

inclusivity, and considerate intervention development to facilitate access and efficacy.

In closing, transdisciplinary teams that include behavioral scientists, cardiologists, oncologists, exercise physiologists, and BC patients are needed to establish the robust research infrastructure: 1) to understand best practices to promote exercise in women facing what could be the most challenging period of their lives; 2) to gain a comprehensive understanding of the effects of exercise on cardiotoxicity and mechanisms therein; and 3) to successfully engage and address the needs and interests of the many communities of women facing BC.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Supported by American Heart Association Scientific Focused Research Network Cardio-Oncology and Disparities: Understanding and Addressing Disparities in Cancer Therapy Induced Inflammation and Associated Endothelial Dysfunction. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Melinda R. Stolley, Medical College of Wisconsin Cancer Center, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226-3548, USA. E-mail: mstolley@mcw.edu.

REFERENCES

1. Cancer Facts & Figures 2023. Atlanta: American Cancer Society, Inc. 2022.

2. Khouri MG, Douglas PS, Mackey JR, et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. *Circulation*. 2012;126(23):2749–2763.

3. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131(22):1981–1988.

4. Narayan HK, Finkelman B, French B, et al. Detailed Echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. *Circulation*. 2017;135(15):1397–1412.

5. Addison D, Branch M, Baik AH, et al. Equity in cardio-oncology care and research: a scientific statement from the American Heart Association. *Circulation*. 2023;148(3):297–308.

6. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016;27(1):6–13.

7. Jones LW, Habel LA, Weltzien E, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. *J Clin Oncol*. 2016;34(23):2743–2749.

8. Sabiston CM, Brunet J, Vallance JK, Meterissian S. Prospective examination of objectively assessed physical activity and sedentary time after breast cancer treatment: sitting on the crest of the teachable moment. *Cancer Epidemiol Biomarkers Prev*. 2014;23(7):1324–1330.

9. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. *J Clin Oncol*. 2005;23(4):774–782.

10. Bellisimo MP, Canada JM, Jordan JH, et al. Physical activity during breast cancer therapy associates with preserved exercise capacity and cardiac function (WF97415). *J Am Coll Cardiol CardioOnc*. 2023;5:641–652.

11. Scott JM, Zabor EC, Schwitzer E, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2018;36(22):2297–2305.

12. Copeland-Halperin RS, Al-Sadawi M, Patil S, et al. Early trastuzumab interruption and recurrence-free survival in ERBB2-positive breast cancer. *JAMA Oncol*. 2020;6(12):1971–1972.

13. Ligibel JA, Bohlke K, May AM, et al. Exercise, diet, and weight management during cancer treatment: ASCO guideline. *J Clin Oncol*. 2022;40(22):2491–2507.

14. Gilchrist SC, Barac A, Ades PA, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation*. 2019;139(21):e997–e1012.

KEY WORDS breast cancer, cardiac magnetic resonance, heart failure, lifestyle risk factors, treatment