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EDITORIAL COMMENT

Cardiac Rehabilitation During Breast Cancer Treatment*

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Cardiovascular disease is a major cause of long-term non-cancer related morbidity and mortality in patients with breast cancer due to the cardiovascular toxicity of breast cancer treatment and the higher burden of cardiac risk factors in breast cancer survivors compared with non-cancer controls.[1-3] Anthracyclines, human epidermal receptor 2 (HER2)-targeted agents, and chest radiation therapy with incidental dose to cardiac substructures can increase the risk of developing heart failure (HF) or atherosclerotic cardiovascular disease with the highest risk in patients with traditional cardiac risk factors.[4-6] Patients with breast cancer often receive combinations of these potentially cardiotoxic therapies and thus are at increased risk for cardiovascular disease. In addition to an increased risk of non-fatal cardiac events and cardiovascular mortality, peak exercise oxygen consumption (VO_2) is often reduced in early-stage breast cancer patients, which manifests as reduced exercise tolerance, physical functioning, and health related quality of life experienced by some breast cancer survivors.[7,8] In addition, weight gain and lifestyle factors are also associated with breast cancer recurrence, especially among patients with hormone receptor positive breast cancer.[9]

In observational cohort studies, higher self-reported physical activity has been associated with reduced risk of cancer and all-cause mortality[10] and reduced cardiovascular events in breast cancer survivors.[11] Given the higher prevalence of cardiac risk factors, excess risk of cardiovascular events and impaired exercise capacity demonstrated in patients with breast cancer compared with noncancer controls, interventions to treat cardiac risk factors, enhance exercise capacity, and improved adherence to healthy lifestyle habits have been encouraged.[12-14] Exercise interventions with and without multidisciplinary cardiac rehabilitation have been shown to improve functional capacity and health related quality of life in patients with established HF and coronary artery disease[15-17] and reduce morbidity and mortality in patients with coronary artery disease.[17] Based on the known benefits of cardiac rehabilitation in patients with established heart disease, cardiac rehabilitation has been recommended for patients with cancer treated with cardiotoxic chemotherapy in a recent scientific statement.[12] While there is modest quality evidence that exercise interventions can improve functional capacity and reduce fatigue in patients with cancer,[18] these recommendations for cardiac rehabilitation in cancer survivors were not based on randomized trials of multidisciplinary cardiac rehabilitation interventions.

In this issue of *JACC: Advances*, Kirkham et al[18] have addressed this gap in evidence through a well-designed and well-executed randomized trial of comprehensive cardiac rehabilitation compared with usual care in patients with breast cancer receiving potentially cardiotoxic therapy containing anthracyclines and/or trastuzumab. The study was small (n = 80); however, there was comprehensive collection of cardiac structure and function, cardiopulmonary fitness, body composition, and biomarkers. Cardiac rehabilitation consisted of: 1) cardiac risk factor assessment (blood pressure, lipids, glucose); 2) up to 2 sessions a week of moderate-intensity aerobic and resistance training in a group setting with recommendations for home-based exercise provided by an exercise physiologist; and 3) personalized

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nutrition recommendations provided by an oncology-specialized registered dietician for up to 52 weeks. Randomization to cardiac rehabilitation had no effect on the primary endpoint of cardiac magnetic resonance imaging-derived left ventricular ejection fraction (LVEF) at 52 weeks. In addition, there were no differences between the study arms in most of the secondary endpoints including cardiac biomarkers, peak VO_2, and body composition. Cardiac rehabilitation was associated with favorable changes in lipids. In addition, interesting changes in body composition were seen in both groups with an increase in total and truncal body fat percentage compared with baseline values prior to cancer therapy, but without between group differences.

There are several aspects of this study to consider when interpreting these neutral findings. First, there were no cases of cardiotoxicity, defined as LVEF decline of >10% decline in LVEF to <53% in either group, and mean declines in LVEF were modest (63% ± 6% at baseline to 61% ± 6% at 52 weeks). It is difficult to show attenuation of LVEF decline (the primary endpoint) in the absence of significant LVEF declines. The absence of significant LVEF declines seen in this study may be due to healthier patients with fewer comorbidities enrolling in a clinical trial or due to less cardiotoxic regimens used (ie, epirubicin instead of doxorubicin and few patients receiving sequential anthracyclines followed by trastuzumab). A larger study or one that enrolled an older population with more comorbidities may potentially have shown different results, especially in cardiorespiratory fitness (peak VO2). Second, while exercise interventions and multidisciplinary cardiac rehabilitation has been shown to improve symptoms and increase functional capacity in patients with established HF,[16] there is no evidence that exercise interventions improve resting LVEF in patients with HF with reduced ejection fraction and thus the cardiovascular benefits of exercise and other cardiac rehabilitation interventions may not be reflected in resting LVEF. Indeed, a recent study suggests that exercise interventions in patients treated with anthracyclines may improve measures of peak exercise cardiac function assessed by cardiac magnetic resonance imaging without significant effect on resting LVEF.[19] Third, only 70% of patients started the exercise intervention and the prescribed exercise intensity was lower than other studies of exercise interventions that have shown improvement in peak VO_2.[18,19]

The neutral findings of the TITAN (Team InterventTion in cArdio-oNcology) study should not discourage exercise interventions given several larger studies showing that exercise interventions improve cardiorespiratory fitness and reduce symptoms in patients with cancer during and after chemotherapy.[19,20] As one example, a recent study also randomized patients with breast cancer undergoing treatment with anthracyclines to an exercise intervention vs usual care; however, the exercise frequency, dose and intensity were higher in this study than in the TITAN study with improvements in peak VO_2 and peak cardiac function seen with exercise.[20] The TITAN study has advanced the field of cardio-oncology by providing the first randomized trial of cardiac rehabilitation in patients at the time of breast cancer treatment. While the conclusions are limited by sample size and specifics of the population enrolled, we have learned that the cardiac rehabilitation interventions that were designed for patients with patients with established HF or coronary artery disease may need to be modified to fit the needs of patients at risk for but who do not have established cardiovascular disease. Future randomized trials of exercise and multidisciplinary cardiac rehabilitation-type interventions can build on what we learned from this neutral study with further modifications of the exercise, dietary, and risk factor modification interventions to meet the needs of the growing population of breast cancer survivors.

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