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EDITORIAL COMMENT

Physical Inactivity, Adverse Body Composition, and Cardiac Function in Breast Cancer Survivors

Triple Jeopardy?*

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Physical activity (PA) is universally recognized by the American Heart Association, the American College of Sports Medicine, and the European Society of Cardiology as an important strategy for primary prevention of cardiovascular disease (CVD).[1] Within the field of cardio-oncology, positive experimental evidence in rodent models[2] has generated enthusiasm for the role of structured exercise in the prevention of cardiotoxicity. Initial human studies have not demonstrated a significant effect of PA on cardiac function during anthracycline therapy.[3] However, PA as a CVD risk reduction therapy is a lifestyle behavior, not just a brief intervention.

In this issue of *JACC: CardioOncology*, Naaktgeboren et al[4] report their evaluation of the relationship between PA and cardiac function among breast cancer survivors. Participants were well characterized, with anthracycline dose, radiation laterality, body mass index (BMI), and cardiovascular risk factors. Echocardiographic outcomes (global longitudinal strain [GLS] and left ventricular ejection fraction [LVEF]) were prespecified as impaired vs normal and performed and analyzed at 2 core laboratories. At a median of 10 years after treatment, higher levels of self-reported PA were associated with more favorable GLS but not LVEF. No patients had heart failure with reduced ejection fraction. Treatment-related and patient-related risk factors did not influence the results.

With technical advances in echocardiography, GLS can be reliably assessed and is recognized as superior to LVEF for detecting subclinical changes.[5] GLS reflects subendocardial fiber injury and detects subtle changes in wall motion despite normal LVEF.[6] GLS and LVEF in cardio-oncology are typically evaluated in the active treatment setting.[7] However, beyond treatment completion, LVEF is rarely systematically assessed. Declines to a threshold of <50% in the 10 to 12 years postdiagnosis have been noted to be less common,[8] and Naaktgeboren et al[4] similarly note rates of 3.65% to 7.2%. The investigators' observation of impaired GLS a decade or more after definitive treatment is intriguing. To fully elucidate the contribution to physical dysfunction, GLS could be evaluated beyond the treatment phase to study the subclinical effects of risk reduction interventions.

An expected effect of physical inactivity is a corresponding low cardiorespiratory fitness, or Vo_{2peak}, an integrative measure of pulmonary, cardiovascular, and muscular systems. Physical inactivity and poor cardiopulmonary performance in breast cancer have been well documented, with survivors having Vo_{2peak} equivalent to 20 to 30 years of premature aging.[9] Bonsignore et al[10] recently reported that next to age, GLS was the strongest univariable predictor of Vo_{2peak} in 147 patients with *HER2*-positive early-stage breast cancer. Similar to the findings of Naaktgeboren

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et al, LVEF was not a predictor of Vo_{2peak}. Deeper investigation of the mechanisms of impaired Vo_{2peak} may provide insight into the reported 3-fold elevations in CVD risk in the breast cancer population.[11]

Moreover, among anthracycline-treated early-stage breast cancer survivors, we found that impaired cardiac reserve and thigh muscle fatty infiltration were associated with impaired oxygen extraction, both contributing to reduced Vo_{2peak}.[12] In a secondary analysis of the MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research) study, we observed a significant increase in fatty infiltration of skeletal muscle and increased visceral fat without concurrent change in BMI.[13] BMI categories of overweight and obese are considered CVD risk factors, but BMI cannot distinguish body fat percentage or fat location. Although all of the Naaktgeboren et al[4] models were adjusted for BMI, their least active group also had the greatest proportion of obesity. Moreover, BMI cannot distinguish body fat percentage or deposition. One in 4 obese cancer survivors are sarcopenic (low muscle mass),[14] and this accumulation of fat has major health implications. Independent of CVD risk factors, elevated visceral and intermuscular fat are prognostic factors in both breast cancer-specific and overall survival.[15,16] Accordingly, body composition represents a modifiable and therefore appealing target, particularly for PA interventions. However, promotion of PA remains a major challenge. Few breast cancer survivors achieve recommended PA levels, with participation in formal PA as low as 20%.[17] It is notable that the Naaktgeboren et al[4] study was set in the Netherlands, whose residents are known as among of the most physically active worldwide. This may account for the few inactive individuals (n = 28, or 5% of the total). These findings may not be generalizable to countries where inactivity is highly prevalent.[18]

Finally, it is worth reflecting that traditional exposures, namely anthracyclines and left-sided radiotherapy, did not influence the Naaktgeboren et al[4] results. Two hundred fifty-three patients (45.3%) received nonanthracycline regimens, possibly combination therapies including cyclophosphamide, methotrexate, and fluorouracil.[19] Radiation technologies have advanced significantly since the 2000s, now using computed tomographic planning, beam shaping, and breath-hold techniques to avoid organs at risk. It is possible that these traditional exposures have fewer long-term consequences in the modern treatment era. It is also possible that the predominance of physically active patients (95%) reduced the ability to detect these known cardiotoxic effects. Taken together, the Naaktgeboren et al[4] paper represents a significant contribution to the study of long-term effects of cancer treatments, impact of habitual PA, and utility of sensitive imaging. This work will inform future study of holistic and individualized CVD risk reduction interventions such as pharmacotherapy, nutrition, and PA at effectual time points in the disease continuum.

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