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EDITORIAL COMMENT

Can We Estimate Cardiorespiratory Fitness in Breast Cancer Survivors Without Exercise?*

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Advances in screening and treatment over recent decades have resulted in increasing numbers of breast cancer survivors (1). In part because of shared risk factors and potential adverse cardiac and vascular effects of cancer therapies, breast cancer survivors are at increased long-term risk for cardiovascular disease (CVD) (2,3). Despite increased attention and improved understanding of the mechanisms underlying the higher CVD risk in breast cancer survivors, risk stratification remains challenging. Impaired cardiorespiratory fitness (CRF) has recently emerged as a powerful predictor of all-cause and cardiovascular mortality in cancer survivors (4) and may identify patients most likely to benefit from interventions such as cardio-oncology rehabilitation or augmented screening approaches. Although CRF can be estimated using relatively simple tests such as exercise tolerance tests or 6-minute walk tests, these assessments do not directly account for volitional effort, can have training effects with repeated testing, and cannot delineate cardiovascular from pulmonary or musculoskeletal limitations to exercise (5). Cardiopulmonary exercise testing (CPET) provides the "gold standard" assessment of CRF (peak oxygen uptake [V_{O_2}]) through direct measurement of gas exchange and can ensure adequate volitional effort and provide complementary physiological measures of cardiovascular and pulmonary performance during exercise (5). Among breast cancer survivors, reduced peak V_{O_2} is associated with lower quality of life and increased mortality (6,7), highlighting its applicability to clinical care and the importance of defining its physiological determinants and potential modifiability.

Identifying breast cancer survivors with impaired CRF is a critical first step toward understanding its broad relevance in caring for this growing population, but pursuing CPET for peak V_{O_2} assessment is not feasible for all patients because of the requirements for specialized equipment and expertise in conducting and interpreting these tests. In this issue, Bonsignore et al (8) address this important issue by investigating whether more readily accessible clinical information—a combination of clinical, echocardiographic, and biomarker measures—can identify reduced peak V_{O_2} in women after breast cancer treatment. They enrolled 147 women with stage I to III HER2+ breast cancer treated with anthracycline chemotherapy followed by trastuzumab. Subjects were clinically assessed, had biomarkers drawn, and underwent transthoracic echocardiography and CPET between 4 and 8 weeks after completing trastuzumab. The group had a mean age of 52 years, was composed predominantly of women with stage I disease (63%), and had received a median epirubicin equivalent dose of 304 mg/m^2. The mean observed peak V_{O_2} was 19.1 mL O_2/kg/min, with 44% of the cohort demonstrating a peak V_{O_2} <18 mL O_2/kg/min (a cutoff defining functional independence). In a multivariable regression model, higher age, greater E/e′ ratio, and worse global longitudinal strain (GLS) were each associated with lower peak V_{O_2}. Notably, CVD risk factors, left ventricular ejection fraction, and clinical biomarkers (B-type natriuretic peptide and high-sensitivity troponin) were not significantly

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associated with peak Vo_2 upon multivariable adjustment. The investigators then generated a decision tree using discrete thresholds for age (≥50 years), GLS (<18%), and E/e′ ratio (≥7.8) to identify patients at highest risk for impaired CRF (defined as peak Vo_2 < 18 mL O_2/kg/min) with reasonable discrimination in their sample. Collectively, their findings show that select echocardiographic features obtained at rest are associated with CRF early after completion of breast cancer therapy.

What can the cardiovascular and oncology fields gain from this well-conducted study in a relatively uniform sample of women shortly after completing anthracycline and HER2-targeted therapy for breast cancer? Clinical measures that can be obtained at rest with relative technical ease were associated with impaired CRF in breast cancer survivors. As many patients with breast cancer may not have access to high-quality CPET, this finding may be used to identify individuals at higher risk for CVD events and mortality. By leveraging primarily cardiac features to predict peak Vo_2, the investigators have focused on the "cardiocentric" contributors to fitness, thereby providing a clear mechanistic link between subclinical cardiac dysfunction and impaired fitness in this population. In contrast, as CRF is determined by multisystem organ health (9), a focus on cardiac abnormalities may result in a large amount of unexplained variation in peak Vo_2, as observed in this study. Incorporating data from simple exercise studies that can be performed in the physician's office (eg, exercise treadmill or 6-minute walk tests) may yield models with better predictive performance in future studies.

Bonsignore et al (8) also extend our knowledge about the utility of strain imaging and GLS measurements in the breast cancer population. Already established as a reliable predictor of cancer therapeutics-related cardiac dysfunction (10), GLS may also be useful in the early prediction of CRF. The echocardiographic features of impaired CRF were apparent early—within 8 weeks—after the completion of trastuzumab, thereby providing an early opportunity to identify higher risk patients who may benefit from aggressive prevention efforts. Moreover, as resting echocardiographic measures can be obtained serially during cancer treatment when repeated exercise testing might be especially challenging because of poor patient tolerance, an echocardiography-based fitness score may have utility in guiding adjustments in treatment over time. Further work should aim to clarify if serially measured GLS and E/e′ values correlate with changes in CRF, thereby providing a convenient tool to update risk stratification assessment.

Notwithstanding these potentially important clinical implications, several additional steps are necessary before these findings can be translated to clinical care. This study was performed in a single cohort from 1 university hospital system; its findings therefore need to be validated in other cohorts with different demographic and racial/ethnic compositions. Although resting echocardiography may be more accessible than exercise testing for many patients, high-quality strain imaging data are not universally available clinically, and strain imaging measurements are known to vary among centers and across different vendors, presenting challenges for using single cutoff values (11). This study harnessed cross-sectional data, and although peak CRF is known to be strongly associated with health outcomes, the ability of a multivariable model estimate of peak Vo_2 to predict future CVD outcomes in breast cancer survivors certainly requires further study. Last, although the investigators' decision to focus on a peak Vo_2 threshold of 18 mL O_2/kg/min is understandable given lack of consensus regarding age-specific cutoff values for functional independence, the association of peak Vo_2 with CVD outcomes is linear, and a single threshold is likely insufficient to adequately describe very different clinical implications across age groups and according to pretreatment functional capacity (12).

In conclusion, the work by Bonsignore et al (8) fills an important gap in identifying early predictors of impaired CRF in breast cancer survivors. Future studies are necessary for clinical validation, including in external cohorts with broader racial and ethnic diversity, and to assess if and how impaired CRF can be modified in breast cancer survivors. By laying the groundwork for these future studies, Bonsignore et al (8) provide an important step forward in moving from passive monitoring of impaired CRF in cancer survivors to early, active, targeted intervention for this at-risk and growing population.

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