JACC: CARDIOONCOLOGY VOL. 6, NO. 6, 2024

EDITORIAL COMMENT

Cardiovascular Disease and Breast Cancer

Exploring 2 Interconnected Landscapes

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As early detection and treatments improve, there is a growing number of breast cancer survivors, constituting nearly one-third of all female cancer survivors worldwide.[1] These women face an increased risk for long-term cardiovascular disease (CVD) attributable to shared cancer and CVD risk factors (eg, late menopause, obesity, smoking) and treatment-related side effects such as cardiotoxicity from anthracyclines, trastuzumab, and chest radiotherapy.[2-4] Intriguingly, a bidirectional relationship between cancer and CVD has been suggested, with some studies reporting increased cancer risks among patients with CVD.[5] However, little is known about this phenomenon in cancer survivors, specifically, how new-onset CVD after a cancer diagnosis might influence patient outcomes. Given the overlapping risk factors between cancer and CVD, understanding the bidirectional relationship between cancer and CVD is a critical research area to inform the complexities of cardio-oncology care and to optimize outcomes for breast cancer survivors.

In a study reported in this issue of *JACC: CardioOncology*, Calvillo-Argüelles et al[6] expand upon the overlap between cancer and CVD among an insured population of 30,694 breast cancer survivors in Ontario, Canada. The investigators revealed that patients who developed new-onset CVD after breast cancer diagnosis had a higher risk for adverse cancer outcomes, including non-breast cancer second malignancies (39% higher risk), subsequent chemotherapy initiation as a proxy for breast cancer recurrence (25% higher risk), and cancer-related deaths (nearly 4 times higher risk), compared with women without CVD.

The investigators should be commended for their thoughtful methodology and consideration of competing events (eg, non-cancer deaths) when estimating the cumulative incidence of cancer outcomes and their important use of time-varying exposure for new-onset cardiomyopathy and heart failure. Internal validity was carefully considered when the study was designed to reduce surveillance bias, determine potential confounders, identify possible reverse causation, and assess falsification endpoints to confirm residual confounding.

To improve our understanding of bidirectional cardio-oncology, there are a few additional considerations. It would be interesting to understand whether the relationship between CVD and second cancers also applies to risk for contralateral breast cancer, as this is the most common type of second cancer among breast cancer survivors.[7] The study did not apply validated algorithms that account for inpatient vs outpatient CVD admissions to optimize sensitivity and specificity, potentially contributing to an imprecise exposure definition.[8-10] In this case of nondifferential misclassification, estimates would be biased toward the null. The investigators relied on landmark analysis, and the analytical population was restricted to women who survived and were cancer free for at least 2 years after their initial breast cancer diagnosis to allow the completion of cancer treatment. Landmark analysis is commonly used in cancer survivorship research to reduce immortal-time bias,[11] which results from applying conventional survival

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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.2024.10.008

analysis to compare survival between responders and nonresponders. Doing so is biased in favor of responders because responders must live long enough to eventually be evaluated as responders, whereas no such requirement is present for nonresponders. Landmark analysis, although a sound approach in this setting, impedes our knowledge of a selected population, potentially the acutely ill, as patients can develop cardiotoxicity during cancer treatment. These data are largely lacking but clinically necessary.

An important research opportunity is to assess these associations by cardiotoxic cancer treatments (anthracyclines, trastuzumab),[8] as effect modification is possible. Patients who develop worsened cancer outcomes because of treatment-related cardiotoxicity likely require different clinical considerations compared with patients who developed CVD because of multiple comorbidities and risk factors and did not receive cardiotoxic treatment. Disentangling this would be important for medical care implications and risk stratification. For example, systematic evaluation of individual CVD risk among breast cancer survivors could optimize breast cancer outcomes. Currently available risk prediction tools include the pooled cohort equations and the PREVENT (Predicting Risk of Cardiovascular Disease Events) tool, both endorsed by the American Heart Association and the American College of Cardiology. These tools integrate data on established CVD risk factors to estimate the risk for CVD, but not breast cancer treatment, despite clinical guidelines labeling cardiotoxic treatments as "risk enhancing." The performance of these models for CVD risk prediction among breast cancer survivors is not known, and examining the additional predictive value of breast cancer-related biomarkers for CVD risk is therefore warranted to fully integrate into care processes.[12,13]

This study reports important hypothesis-generating observations. Given the inherently multidisciplinary nature of cardio-oncology, future studies should strive to comprehensively capture the medical presentation and outcomes of these patients. Studies that leverage electronic medical record linkage can provide the comprehensive appraisal needed in cardio-oncology[14] and allow more holistic insights to health and disease. However, it is important to underscore that electronic medical record data are not "fit for purpose" in clinical research because of their primary design for billing and documentation rather than structured data collection. Inconsistent data entry, variability in coding practices, and the lack of standardized formats across institutions can introduce significant biases and errors. Additionally, crucial research variables such as lifestyle factors, social determinants of health, and granular clinical phenotypes may be incompletely or not captured. Analytically, researchers must be mindful of the unique methodological challenges of electronic medical record-based research (eg, missingness, biases related to care-seeking behaviors, care delivery approaches, and inequities in care delivery, including race/ethnicity, rural vs urban residence, and income).[15]

The external validity of the present study conducted in an insured population must be considered before generalizing research findings. Several studies have reported cardio-oncology disparities by race and ethnicity and socioeconomic status,[16-19] likely perpetuated by barriers in accessing health care or specialized cardio-oncology clinics, which are generally concentrated at urban, academic centers. Equitable cardio-oncology care requires successful multidisciplinary partnerships across both health care and research, understanding how and when new research is incorporated into contemporary clinical practices, and scaling the high-quality CVD practices to underserved populations.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors are supported by the Intramural Research Program of the National Institutes of Health. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS breast cancer, cardio-oncology, heart disease