JACC: CARDIOONCOLOGY VOL. 2, NO. 4, 2020

EDITORIAL COMMENT

Cancer and Cardiovascular Disease

Finding the Signal Through the Noise*

Wendy Bottinor, MD, MSCI, W. Gregory Hundley, MD

The complexity of the relationship between cancer and cardiovascular disease is increasingly evident. The ability of traditional cancer therapeutics including anthracyclines and radiation treatment to potentiate cardiovascular disease has been well established (1,2). Novel agents, including immune checkpoint inhibitors, angiogenic inhibitors, and chimeric antigen receptor T cell therapy have also been associated with cardiovascular toxicities (3–5). The increased risk for cardiovascular disease among individuals with cancer extends beyond the acute treatment period. Cardiovascular disease is the most common noncancer cause of death among breast cancer survivors more than 10 years from diagnosis (6). In addition, clonal hematopoiesis of indeterminate potential, an acquired genetic mutation that portends an increased risk for hematologic malignancy, has been associated with an approximately 2-fold increased risk for coronary heart disease (7). This suggests the link between cancer and cardiovascular disease is not mediated through treatment toxicities alone.

Evidence suggesting a bi-directional relationship between cancer and cardiovascular disease has also emerged. A large population study by Banke et al. (8) demonstrated an increased incidence of cancer in individuals diagnosed with heart failure. In women with heart failure, the risk for breast cancer is elevated with a hazard ratio of 1.36 (8). Several other groups (**Table 1**) have also demonstrated an association between heart failure and subsequent cancer, and it is postulated that this relationship may be due to systemic inflammation, oxidative stress, or neurohormonal dysregulation (9–13). However, work from the Physicians' Health Studies, the largest study to date, did not find an association between heart failure and cancer (14).

The study by Lam et al. (15), presented in this issue of *JACC: CardioOncology*, further investigates the relationship between cancer and heart failure among postmenopausal women within the Women's Health Initiative. Among a cohort of >44,000 women, with approximately 15 years of follow-up, Lam et al. (15) examined associations between prevalent heart failure and an incident invasive breast cancer diagnosis as well as prevalent invasive breast cancer and an incident heart failure hospitalization. Interestingly, the authors found no association between prevalent heart failure and a subsequent invasive breast cancer diagnosis and vice versa. However, the authors did find higher mortality rates among women with prevalent or interim breast cancer who were hospitalized for heart failure. Similarly, among women with prevalent and interim heart failure, survival was worse after an incident breast cancer diagnosis. Although the lack of an association between prevalent cancer and incident heart failure is divergent from previous studies, the higher mortality rate among individuals with both cancer and heart failure is consistent with previous work (8).

Several methodological limitations are important to consider when interpreting the results of this study. First, the baseline prevalence of breast cancer and heart failure relied on self-reported data, which may impact the true incidence of disease, particularly Stages I to IV breast cancer. Many women may consider a diagnosis of ductal carcinoma in situ

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

From the Department of Internal Medicine, Division of Cardiovascular Medicine, Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA.

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 *JACC: CardioOncology* author instructions page.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2020.09.003

TABLE 1 Publications Investigating the Relationship Between Heart Failure and Cancer

First Author, Year (Ref. #)	Study Design	Study Population	N	Study Objectives	Study Findings
Positive association between prevalent heart failure and incident cancer					
Banke et al., 2016 (8)	Prospective cohort study	Adults with newly diagnosed HFrEF referred to Danish heart failure clinics	9,307	Assess the incidence and risk of cancer and all-cause mortality in a large cohort with HFrEF	Risk of any type of cancer was increased among individuals with HFrEF (IRR: 1.24) Increased risk for breast cancer among women with HFrEF (HR: 1.36; 95% CI: 1.02 to 1.81)
Hasin et al., 2013 (9)	Case-control study	Adults diagnosed with HF between 1979 and 2002	596 pairs	Evaluate the risk of cancer in patients with HF	Individuals with HF had a higher risk of developing cancer (HR:1.68; 95% CI: 1.13 to 2.50)
Sakamoto et al., 2017 (10)	Retrospective cohort study	Individuals with HF hospitalized between 2001 and 2013	5,238	Investigate whether HF induces or reduces the incidence of cancer	HF increased the incidence of cancer >3.85 times
Hasin et al., 2016 (12)	Prospective cohort study	Individuals with incident myocardial infarction between 2002 and 2010	1,081	Examine whether HF was associated with an increased risk of subsequent cancer among survivors of a first myocardial infarction	Individuals with HF had an increased risk of cancer (HR: 1.71; 95% CI: 1.07 to 2.73)
Meijers et al., 2018 (13)	Prospective cohort study	28- to 75-year-old inhabitants of the city of Groningen, the Netherlands	8,319	Investigate whether a causal relationship exists between HF and the development of cancer	Cardiac and inflammatory markers are associated with predication of new-onset cancer N-terminal pro-B-type natriuretic peptide (HR 1.06; 95% CI: 1.00 to 1.12) High-sensitivity troponin T (HR: 1.10; 95% CI: 1.02 to 1.19) High-sensitivity C-reactive protein (HR: 1.08; 95% CI: 1.04 to 1.13)
No association between prevalent heart failure and incident cancer					
Selvaraj et al., 2018 (14)	Retrospective cohort study	Men enrolled in Physicians' Health Study I and II	28,341	Determine whether HF is associated with cancer incidence and cancer-specific mortality	HF was not associated with cancer incidence (HR: 1.05; 95% CI: 0.86 to 1.29)

CI = confidence interval; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR= hazard ratio; IRR= incidence rate ratio.

(DCIS) as breast cancer. DCIS is treated surgically and women in general do not receive many of the cardiotoxic therapies associated with the development of heart failure. Given the lower association of heart failure with DCIS, if women with DCIS were included in this analysis, this could lead to a lower percentage of heart failure diagnoses among the women enrolled in the study relative to a study population comprised of women with Stage I to IV breast cancer.

Second, incident heart failure was defined as definite or possible hospitalization for heart failure. Among the 5.8 million people in the United States diagnosed with heart failure, only approximately 1 million are hospitalized each year, therefore the authors likely underestimated the incidence of symptomatic heart failure within this population (16). Individuals with Stage B heart failure as defined by American College of Cardiology/American Heart Association guidelines, a population 4 times larger than those with symptomatic heart failure, were certainly not identified (17). This limitation is particularly noteworthy, as evidence suggests one-third of women treated with anthracyclines and trastuzumab develop Stage B heart failure within 3 months of treatment (18).

Third, anthracyclines, radiation, and trastuzumab are often used in the treatment of breast cancer. Given the well-established risk for adverse cardiovascular events associated with exposure to these agents, as well as the increased likelihood of developing cardiovascular risk factors in postmenopausal women treated for breast cancer, the authors' finding of no association between prevalent breast cancer and incident heart failure is surprising (19). Unfortunately, the significance of this result is unclear, as the authors did not account for cancer therapy in their analysis. Therefore, it is unknown what cancer therapeutics were used in this cohort and it is possible that a disproportionate number of women did not receive cardiotoxic therapy.

Finally, the study design does not account for the implementation of strategies in high-risk women to avoid the development of heart failure. For example, in women receiving trastuzumab for HER2+ breast cancer, serial transthoracic echocardiograms are performed to identify those with subclinical deteriorations in left ventricular ejection fraction or longitudinal strain for the purpose of implementing angiotensin-converting enzyme inhibitors or other combinations of medications to prevent heart failure. In the current study, we are uncertain of the utilization of strategies or therapies designed to reduce heart failure admissions among the study participants. Simply stated, are the authors testing the efficacy of therapies administered to women with breast cancer that would prevent the development of heart failure?

In summary, we commend the authors for recognizing the importance of further investigation into the link between cancer and cardiovascular disease. Importantly, however, significant limitations exist pertaining to the study design that may underestimate: 1) the diagnosis of breast cancer; 2) the true incidence of heart failure; and 3) the use of therapies to avoid hospitalization for heart failure within the study population. As such, caution is advised when reviewing the conclusions set forth by the authors, mainly the absence of an association between breast cancer and the development of heart failure. Moreover, these study results highlight the importance of performing additional investigations to determine the relationship between breast cancer, heart failure, and other forms of cardiovascular disease in postmenopausal women.

AUTHOR DISCLOSURES

This publication is supported in part by the To-morrow's Research Fund St. Baldrick's Scholar Award (Award Number 636214); the American Heart Association (Award Number (19CDA34760181); and the National Institutes of Health (Award Numbers 1R01HL118740, 1R01CA199167, R21CA226960-01A1). The content is solely the responsibility of the authors and does not necessarily represent the official views of St. Baldrick's Foundation, the American Heart Association, or the National Institutes of Health, respectively. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. W. Gregory Hundley, Virginia Commonwealth University, Gateway Building, 1200 E. Marshall Street, Richmond, Virginia 23298. E-mail: greg.hundley@vcuhealth.org.

REFERENCES

1. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302–14.

2. Brosius FC 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med 1981;70:519–30.

3. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749–55.

4. Li W, Croce K, Steensma DP, et al. Vascular and metabolic implications of novel targeted cancer therapies: focus on kinase inhibitors. J Am Coll Cardiol 2015;66:1160–78.

5. Aldoss I, Khaled SK, Budde E, Stein AS. Cytokine release syndrome with the novel treatments of acute lymphoblastic leukemia: pathophysiology, prevention, and treatment. Curr Oncol Rep 2019;21:4.

6. Afifi AM, Saad AM, Al-Husseini MJ, Elmehrath AO, Northfelt DW, Sonbol MB. Causes of death after breast cancer diagnosis: a US population-based analysis. Cancer 2020;126:1559–67.

7. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med 2017;377:111–21.

8. Banke A, Schou M, Videbaek L, et al. Incidence of cancer in patients with chronic heart failure: a long-term follow-up study. Eur J Heart Fail 2016;18:260–6.

9. Hasin T, Gerber Y, McNallan SM, et al. Patients with heart failure have an increased risk of incident cancer. J Am Coll Cardiol 2013;62:881–6.

10. Sakamoto M, Hasegawa T, Asakura M, et al. Does the pathophysiology of heart failure prime the incidence of cancer? Hypertens Res 2017;40:831–6.

11. Bertero E, Canepa M, Maack C, Ameri P. Linking heart failure to cancer: background evidence and research perspectives. Circulation 2018;138:735–42.

12. Hasin T, Gerber Y, Weston SA, et al. Heart failure after myocardial infarction is associated with increased risk of cancer. J Am Coll Cardiol 2016;68:265–71.

13. Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. Circulation 2018;138:678–91.

14. Selvaraj S, Bhatt DL, Claggett B, et al. Lack of association between heart failure and incident cancer. J Am Coll Cardiol 2018;71:1501–10.

15. Lam PH, Barac A, Nohria A, et al. Temporal associations and outcomes of breast cancer diagnosis and heart failure hospitalization in postmenopausal women. J Am Coll Cardiol CardioOnc 2020;2:567–77.

16. Hall M, Levant S, DeFrances CJ. 2012. Available at: https://www.cdc.gov/nchs/products/databriefs/db108.htm. Accessed September 15, 2020.

17. Frigerio M, Oliva F, Turazza FM, Bonow RO. Prevention and management of chronic heart failure in management of asymptomatic patients. Am J Cardiol 2003;91:4f–9f.

18. Jones DN, Jordan JH, Meléndez GC, et al. Frequency of transition from stage A to stage B heart failure after initiating potentially cardiotoxic chemotherapy. J Am Coll Cardiol HF 2018;6:1023–32.

19. Buttros DAB, Branco MT, Orsatti CL, Almeida-Filho BS, Nahas-Neto J, Nahas EAP. High risk for cardiovascular disease in postmenopausal breast cancer survivors. Menopause 2019;26:1024–30.

KEY WORDS breast cancer, cardio-oncology, cardiovascular disease, heart failure