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EDITORIAL COMMENT

Redefining Heart Failure in Breast Cancer*

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The Women's Health Initiative study began in 1992, investigating various health aspects among women. In 2002, the landmark study revealed that estrogen plus progestin given to postmenopausal women resulted in an increase in cardiovascular events and invasive breast cancers (BCs).[1] In this issue of *JACC: CardioOncology*, Reding et al[2] report on their evaluation of lifestyle and cardiovascular risk factors associated with the 2 heart failure (HF) subtypes in the subgroup of patients who developed invasive BC after study initiation. They found that among the 2,272 racially diverse BC survivors, the incidence of hospitalizations for HF with preserved ejection fraction (HFpEF) was higher than that for HF with reduced ejection fraction (HFrEF), and both were associated with increased mortality risk.

Some BC therapies increase the risk for HFrEF, but this study showed that among BC survivors, more patients were hospitalized for HFpEF than for HFrEF.[2] Unfortunately, HFpEF represents one of the greatest unmet needs in medicine, given the paucity of treatment strategies.[3] Recently, some drugs have shown promise in HFpEF. Sodium-glucose cotransporter 2 inhibitors, renin-angiotensin-aldosterone blockers, and angiotensin-neprilysin inhibitors reduce HF hospitalizations.[4] However, there were no significant HFpEF-associated mortality benefits with all drug classes. The present study by Reding et al[2] is pivotal because many of the HF studies in BC and other cancers have focused on HFrEF.[5]

Anthracycline use in adjuvant BC therapy is known to cause decreases in left ventricular ejection fraction (LVEF).[6] This is exacerbated by the addition of trastuzumab in 15% to 20% of early-stage BCs with human epidermal growth factor receptor 2 (HER2) overexpression.[7,8] Age, hypertension (HTN), and previous coronary artery disease are established risk factors for LVEF decrease.[9] The present study confirms age as a significant risk factor, as the cohort had a median age of >70 years, with more than 80% of women diagnosed with BC after the 65 years of age.[2]

Moreover, in this study, approximately 12% of participants were HER2 positive. Adjuvant trastuzumab was approved in 2006, and therefore some patients in this study were eligible to receive this drug. It would be interesting to know what role trastuzumab played in the development of hospitalizations for HFpEF or HFrEF. Specifically, it would be interesting to further explore whether HFpEF or HFrEF was higher in the anthracycline-trastuzumab arm.[2] In considering these data in the context of the modern treatment era, the impact of newer anti-HER2 therapies (eg, trastuzumab and pertuzumab, trastuzumab emtansine, and trastuzumab deruxtecan) on HFpEF risk would also be of interest.

A key result in this study is that HF symptoms still occurred in the setting of preserved LVEF following BC treatment. This finding suggests that when discussing risk for HF with BC treatment, especially in elderly patients, additional diagnostic variables should be considered, including biomarkers (eg, natriuretic peptides), diastolic function, global longitudinal strain, and management of modifiable cardiovascular risk factors.

Approximately 78% of participants were estrogen receptor positive or progesterone receptor positive,

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many of whom would have been receiving antiestrogen therapy. Consequently, a limitation was not identifying the impact of antiestrogen therapy, specifically the role of aromatase inhibitors (AIs) on HF admissions, especially HFpEF. Through meta-analyses, it is recognized that HTN can arise from prolonged AI use, and there is evidence to support extended AI use (>5 years) in BC survivors at higher risk for recurrence.[10] In the study by Reding et al,[2] obesity, elevated waist circumference, and waist/hip ratio were associated with an almost 2-fold increased risk for HF hospitalization; waist circumference, in particular, was associated with HFpEF in the population studied. In general, AIs increase the risk for HTN and obesity, so specific associations between endocrine therapy (AIs vs tamoxifen) and HFpEF would be of interest in future studies.

Last, with the current use of extended endocrine therapies and the recent addition of cyclin-dependent kinases inhibitors (eg, abemaciclib) for high-risk BC, there may be an increased risk for coronary artery disease with HF in the long term. Moreover, with advances in cancer treatment, specific immune checkpoint inhibitors have also been approved to treat certain BCs. The future of these agents, which could cause immune-related myocarditis or pericarditis in HFpEF (and HFrEF) among patients with BC, is important to understand.

Although the median age of this study was >70 years for both populations of patients hospitalized with HFpEF and HFrEF, the findings demonstrate that HF decreased after 2010 compared with 1994 to 2004. This decline may have been due to less anthracycline use or lower cumulative dosages. It would have been interesting to know how many women received additional systemic therapies, specifically as treatment and management have evolved (serial cardiac imaging with trastuzumab, less radiation, more AI use, less anthracycline use). Finally, this cohort had a higher risk for cardiovascular complications because of baseline older age: 65% had family histories of myocardial infarction, 76% had histories of HTN, 49% had smoking histories, 50% had body mass index ≥30 kg/m^2, and 59% had large waist circumference. Consequently, the study revealed a concerning 12- and 10-fold higher risk for cardiovascular disease-specific mortality in those patients with BC who developed HFpEF and HFrEF, respectively, with wide confidence intervals. Both HF subtypes were associated with a nonsignificant 2-fold higher risk for BC-specific mortality. Although the wide confidence intervals call for a larger study population, the comparable mortality data associated with both HF subtypes mirror the general population and highlight the importance of studying and generating more data for HFpEF. Until now, the focus has been on HFrEF in this population.

Although this was a population free of HF at baseline, it would be intriguing to know the proportion of the population with stage B (subclinical) HF prior to BC treatment, which could have influenced this study's eventual outcomes. Interestingly, in an exploratory analysis, the present study did not reveal significant associations between radiation therapy and HF, unlike other studies.[11] The fact that anthracycline use was only marginally associated with hospitalized HFrEF in this same population suggests that more robust data in a larger population would provide further insight.

In this small population, this study demonstrated no significant associations between race/ethnicity and socioeconomic status and HF risk. This finding adds data to the currently limited body of research on disparities in cardiovascular disease among patients with cancer.

The investigators are to be congratulated on this study demonstrating important findings about hospitalizations for understudied HFpEF compared with well-studied HFrEF in a BC population. With the shift away from LVEF as the main definition of HF in patients with cancer, additional and larger studies of HFpEF in BC and other cancers are paramount. In the emerging world of multimodality imaging, a redefinition of HF among patients with cancer is likely imminent. A multidisciplinary approach among cardiology, oncology, primary care, additional specialties, and the patient is necessary to improve modifiable risk factors, determine better risk stratification and imaging modalities that can predict HF, and improve overall mortality in cancer survivors.

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MARCH 2022:66–68

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