

## EDITORIAL COMMENT

# What Cardio-Oncology Lessons Can We Learn From Population-Based Data?\*



Harry Klimis, MBBS, PhD,<sup>a</sup> Som D. Mukherjee, MD,<sup>b</sup> Darryl P. Leong, MBBS, MPH, M.Biostat, PhD<sup>a</sup>

The maturation of administrative data—collected over the past few decades thanks to major advances in data collection processes and storage—has led to a rapid growth of analyses in which “big,” “real-world” data are mined for epidemiologic associations. In this issue of *JACC: CardioOncology*, Bertero et al<sup>1</sup> present their findings from an analysis of administrative data from Puglia, Italy, in which adults at least 50 years of age with heart failure were matched to control subjects without heart failure to investigate the link between heart failure and the risk of developing cancer.<sup>1</sup> The study authors concluded that heart failure patients are at increased risk of incident cancer (including both solid organ and hematologic malignancies) and cancer mortality. To determine what can be robustly inferred from this finding and from analyses of big real-world data more broadly, one must carefully consider the limitations of administrative data.<sup>2</sup>

The first limitation is unmeasured confounding. Key known cancer-causing exposures, such as obesity, heavy alcohol consumption, smoking, poor diet quality, physical inactivity, and occupational risk factors,<sup>3</sup> are not captured in administrative data. These exposures are also important risk factors for heart failure, or coronary artery disease that could lead to heart failure. Therefore, the extent to which

these risk factors could be confounding the association between heart failure and cancer risk cannot be accurately determined given the lack of information on several key cancer risk factors.

The second limitation is selection of control subjects. Any association identified in an observational matched study can be driven by the control subjects equally as by the cases. The authors should be commended for matching on the data available to them as best as possible. However, patients in the health care system (for reasons other than heart failure) will include individuals who highly value their health, whereby their health care system encounter is part of general health maintenance, rather than because of severe illness, in the same way that some bring their cars to a mechanic to ensure that it runs well while others bring their cars to a mechanic when it is failing. This bias would increase any effects observed.

The third limitation is missing or unavailable data. The authors acknowledge that they did not have access to data on cancer therapies and thus could not exclude the possibility that heart failure patients had higher cancer mortality caused by less intensive cancer therapy or different treatment goals (ie, palliative vs curative intent) than patients without heart failure.

Acknowledging these limitations, what conclusions can we confidently draw from the analysis of Bertero et al? The clearest is that, whatever the reason, patients with heart failure are at increased risk of developing cancer and have a poorer prognosis. The clinical implication of this finding is that physicians treating patients with heart failure should maintain a high index of suspicion that a previously undiagnosed cancer may be responsible for unexplained symptoms and signs. Indeed, some clinical features of heart failure, such as fatigue, dyspnea, pleural effusions, and cachexia, can also be caused by various malignancies, which could lead to undesirable delays in cancer diagnosis if not suspected.

\*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 <sup>a</sup>Population Health Research Institute and the Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; and the <sup>b</sup>Department of Oncology, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada.

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](#).

A natural hypothesis that arises from the present analysis—one that the authors speculate on and cite evidence to support—is that heart failure in and of itself predisposes to cancer. When evaluating the possibility of causal association in observational data, the key principles described by Hill<sup>4</sup> are useful to methodically evaluate these inferences.

The first is strength of association. For cancer incidence, the authors report an HR of 1.76. To put this HR into context, the adjusted HR for current smoking and lung cancer incidence has been reported to be 19.12 (95% CI: 15.78-23.18) in men and 13.63 (95% CI: 11.83-15.70) in women.<sup>5</sup> Therefore, the HR of 1.76, which notably is not adjusted for important cancer determinants, is not strong enough to be confident of a causal association.

The second is consistency of association. Epidemiological and case-control studies evaluating the association between heart failure and cancer incidence have been inconsistent. Earlier reports found an independent relationship with adjusted risk estimates ranging from 1.24 to 2.16,<sup>6-8</sup> while more recent reports have found no association after multivariable adjustment.<sup>9,10</sup> Therefore, there is insufficient consistency of association to be confident of a causal role of heart failure in cancer development.

The third is biological gradient (ie, a “dose-response” relationship). The authors were not able to assess heart failure severity directly; however, they used the dose of loop diuretic agents as a surrogate for heart failure severity. Cancer incidence and mortality were higher in patients taking a high-dose loop diuretic, although this finding was not consistent across different cancer subtypes.

The fourth is biological plausibility. There is interesting evidence demonstrating that myocardial infarction leads to increased intestinal tumor burden in genetically predisposed mice and that *SERPINA3*, whose levels are higher in patients with heart failure, can stimulate in vitro colon cancer cell proliferation.<sup>11</sup> The present research is consistent epidemiologically with these data. However, the authors found fairly early divergence of cancer cumulative incidence curves (which start to separate from around 1.5 to 2 years after a first heart failure presentation and are statistically significantly divergent by 6 years). Given that most causes of cancer in humans require many years of exposure, it seems unlikely that heart failure

could be the major cause of cancer within a short time frame. Rather, it would be more plausible that long-standing exposures that are known causes of both heart failure and cancer, such as obesity, confound their association.

The fifth is experimental evidence. The gold standard for establishing or refuting a causal relationship is the randomized clinical trial. While it is not feasible to randomize individuals to heart failure or not, some useful insights could come from positive heart failure therapy trials. In a recent systematic review of phase 3 trials involving participants with heart failure with reduced left ventricular ejection fraction, cancer mortality was reported in 15 (25%) of 61 trials (N = 33,709) and accounted for 6% to 14% of all deaths and 17% to 67% of non-cardiovascular deaths.<sup>12</sup> The pooled cancer mortality rate was 0.58 (95% CI: 0.46-0.71) per 100-patient years, and heart failure therapies did not reduce cancer mortality, with a pooled odds ratio of 1.08 (95% CI: 0.92-1.28). Cancer incidence, however, was not reported in these trials.

Taken altogether, we feel there is little evidence that heart failure in and of itself causes cancer. More generally, administrative data have important strengths and limitations for cardio-oncology research. Their strength lies in the large sample sizes available and the large number of outcome events. These are important in any new field of clinical research, especially when absolute numbers of patients with individual cancers or with cancer therapy-related cardiotoxicity are modest. This strength is particularly useful when evaluating the rates of select outcomes that are well documented in administrative datasets, such as deaths or hospitalizations. Their limitations have been described in part in this editorial. It is important that researchers and clinicians avoid overstating the effect sizes observed in such data or drawing causal inferences from them. It must be recognized that large sample sizes with many outcome events do not address unmeasured confounding, but as in all retrospective analyses, they carry a risk of bias. Therefore, large sample sizes, which decrease CIs surrounding estimates, have the potential to lead to estimates that are very precisely biased. Thus, while further research into the factors underlying the association between heart failure and cancer incidence reported may be interesting, based on the present data, we cannot yet

conclude that heart failure in and of itself causes cancer.

### FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Darryl Leong, Hamilton General Hospital, C2-237 David Braley Building, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: [darryl.leong@phri.ca](mailto:darryl.leong@phri.ca). Twitter: [@DarrylLeong](https://twitter.com/DarrylLeong), [@PHRIResearch](https://twitter.com/PHRIResearch).

### REFERENCES

- Bertero E, Robusto F, Rulli E, et al. Cancer incidence and mortality according to pre-existing heart failure in a community-based cohort. *J Am Coll Cardiol CardioOnc*. 2022;4:98-109.
- Jairam V, Park HS. Strengths and limitations of large databases in lung cancer radiation oncology research. *Transl Lung Cancer Res*. 2019;8:S172-S183.
- Koene RJ, Prizment AE, Blaes A. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133:1104-1114.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.
- Hansen MS, Licaj I, Braaten T, et al. Sex differences in risk of smoking-associated lung cancer: results from a cohort of 600,000 Norwegians. *Am J Epidemiol*. 2018;187:971-981.
- 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;18:260-266.
- Hasin T, Gerber Y, McNallan SM, et al. Patients with heart failure have an increased risk of incident cancer. *J Am Coll Cardiol*. 2013;62:881-886.
- 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;68:265-271.
- Selvaraj S, Bhatt DL, Claggett B, et al. Lack of association between heart failure and incident cancer. *J Am Coll Cardiol*. 2018;71:1501-1510.
- Schwartz B, Schou M, Gislason GH, et al. Prevalence and incidence of various Cancer subtypes in patients with heart failure vs matched controls. *Int J Cardiol*. 2020;316:209-213.
- Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. *Circulation*. 2018;138:678-691.
- Tini G, Bertero E, Signori A, et al. Cancer mortality in trials of heart failure with reduced ejection fraction: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e016309.

**KEY WORDS** administrative, cardio-oncology, heart failure, real-world