EDITORIAL COMMENT

Incident Cancer in Patients With Heart Failure

Causation or Mere Association?*

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Heart failure (HF) and cancer are becoming increasingly prevalent as our population ages. Both conditions are associated with significant mortality and morbidity. Although the increased risk of incident HF in patients with cancer receiving chemotherapy has been well documented (1), little is currently known about the risk of incident cancer in patients with HF. In this issue of the Journal, Hasin et al. (2) explore this association, with interesting results. The investigators compared patients with incident HF to age-, sex-, and date-matched community controls without HF (961 pairs, 1979 to 2002) in Olmsted County, Minnesota. They found that the prevalence of prior cancer was similar in newly diagnosed HF patients compared with controls. They further evaluated the cohort without any history of cancer at index (596 pairs) for the development of incident cancer.

Over 9,203 person-years of follow-up and a mean follow-up of 7.7 years, patients with HF were found to have a 68% higher risk of being diagnosed with cancer compared with controls, after adjusting for body mass index, smoking, and comorbidities (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.13 to 2.5). Patients with HF that were diagnosed with cancer also had a 56% higher risk of death compared with HF patients without cancer (HR: 1.56; 95% CI: 1.22 to 1.99) compared with a 93% increased mortality risk in non–HF controls diagnosed with cancer compared with controls without cancer (HR: 1.93; 95% CI: 1.51 to 2.46, p = 0.18 for interaction between HF patients and controls). On the basis of these findings, the authors emphasized the importance of cancer surveillance in patients with HF.

The study addresses a novel question that may have public health implications. Noncardiac comorbidities in patients with HF are being increasingly recognized as having a significant impact on mortality and hospitalizations in HF patients, with the effect being even more pronounced in patients with HF and preserved ejection fraction (3). The study by Hasin et al. (2) addresses the comorbidity of cancer in patients with HF. A significant strength of the investigation is the comprehensive database utilized. Olmstead County, Minnesota, is isolated from other urban centers, and medical records from all providers are indexed and accessible through the Rochester Epidemiology Project, thus providing an ideal setting for epidemiological research.

The first finding for discussion is that the risk of cancer may be increased in individuals with HF compared with non–HF controls. Before we conclude that HF itself causes an increased risk for cancer, several alternative explanations need to be considered. Studies on cancer epidemiology are especially prone to lead-time bias, which is the amount of time by which the diagnosis of an asymptomatic or less advanced cancer has been advanced by screening (4). In the current study, no data are available to compare healthcare utilization by HF cases and controls. However, on the basis of the fact that HF patients have more comorbidities and are almost certainly sicker than non–HF controls, it is reasonable to assume that they had more frequent encounters with their primary care physicians, as well as with specialists in both the inpatient and outpatient settings. This may have contributed to more frequent screening tests for cancer, as well for other medical testing, compared with non–HF controls, which may have led to earlier diagnoses of cancer. This effect of lead-time bias is substantiated by the Kaplan-Meier curves for the cumulative incidence of cancer in HF patients versus controls over the entire study period (Fig. 1 in Hasin et al. [2]). The increased hazard of diagnosis of cancer in HF patients compared with controls did not appear to be constant over time. The curve for the HF patients diverges from that of controls (with a higher risk of cancer in HF patients), beginning at approximately 2 years after the diagnosis of HF, with the greatest divergence at ~4 years, followed by the curves coming together at ~7 years, and later crossing over such that the cumulative incidence of cancer in patients with HF appears to fall below that of controls. This suggests that an earlier diagnosis of cancer may have occurred in HF patients. In addition, because the development of cancer is usually a slow process, it would be unlikely that HF itself would be the causal factor for the relatively early increase of cancer.

Furthermore, some of the risk factors for developing cancer and cardiovascular disorders, including HF, are similar, such as cigarette smoking. Although the analyses show that the risk of cancer is independent of a history of smoking, a dose-response effect of the duration and amount of smoking (5) would not be accounted for in this analysis, as would not other unmeasured factors. For example, patients with HF also have more cardiac and noncardiac
comorbidities that could have led to greater radiation exposure from medical imaging, even before the development of HF, possibly contributing to an increased risk of cancer (6). Interestingly, a study utilizing the ARIC (Atherosclerosis Risk in Communities) cohort had suggested that adherence to heart-healthy behaviors at baseline is associated with a lower incidence of cancer long term (7), again supporting a lower incidence of cancer in patients with a lesser risk of cardiovascular disease. The study by Hasin et al. (2) also lacked data on medications. Although medications that are used in HF, as well as in pre-existing cardiovascular comorbidities, namely, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, have been implicated for potentially carcinogenic effects in some experimental and observational studies, there is a lack of convincing evidence that any of these medications, in the current doses and durations tested, lead to an increased risk of cancer (8). Hasin et al. (2) also observed a trend toward a higher risk of cancer in patients with incident HF in the second half of the study period (1991 to 2002) compared with the earlier half (1979 to 1990). Although the authors suggest that this may parallel the increased use over time of HF medications such as angiotensin–converting enzyme inhibitors and angiotensin receptor blockers, it is also possible that these observations are related to increased diagnoses of cancer due to more aggressive screening or medical testing, as well as a possible increase in cancer over time due to exposure to radiation from increased medical imaging in patients with pre-existing cardiac and noncardiac comorbidities (6).

The second important finding of the study by Hasin et al. (2) is that the diagnosis of cancer in HF patients was associated with increased mortality compared with HF patients without cancer. This suggests that the comorbidity of cancer itself may independently contribute to increased mortality in HF patients, and it is possible that adequate surveillance and treatment of cancers in this population of patients may have a beneficial effect on outcomes. However, because data regarding the treatment of the cancers once they are diagnosed, or the cause of the increased mortality, that is, whether it is cancer related, are not available in the current study, future studies are needed to examine these issues. Concordant with findings of a prior study (3), the prognostic impact of cancer on mortality appeared similar in HF patients with preserved versus reduced ejection fraction in the subgroup of patients for whom ejection fraction data were available.

In summary, these findings of an association of incident cancer in patients with HF, although novel, should be interpreted with caution. Further studies are needed to corroborate these findings and to answer several important questions raised by this study. Temporal trends in the incidence of cancer in patients with HF should be investigated, as should the effect of cancer surveillance on the diagnosis of cancer, as well as the impact of cancer treatment on mortality in patients with HF. Lastly, if it is confirmed that HF is indeed associated with an increased risk of cancer, the role of various factors, including medications, dietary habits, radiation exposure, telomere shortening (9,10), and inflammation, will need to be investigated.

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