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Incident Cancer in Heart Failure Patients and the Need for Additional Investigations

We read with interest the paper by Bertero et al,[1] which evaluated the risk of cancer in heart failure (HF) patients. This study examined 104,020 patients aged >50 years in Italy over a 16-year time frame. The results indicated an increased incidence rate of cancer in HF patients compared with control subjects (hazard ratio [HR]: 1.76, 95% CI: 1.71-1.81). However, an important variable not considered in this study was ethnicity because the population was limited to 1 area of Italy.[1]

The conclusion of this study is corroborated by Roderburg et al,[2] in 2021, who found a similar association between HF and cancer (HR: 1.76 [95% CI: 1.71-1.81]; $P < 0.001$). However, the study by Roderburg et al evaluated additional cancer types and additional confounders, and found the strongest associations between HF and cancers of the pharynx, lip, and oral cavity (HR: 2.1 [95% CI: 1.66-2.17]; $P < 0.001$). HF was also associated with lung cancer and female gynecologic cancers (HR:1.91 [95% CI: 1.74-2.10] and 1.86 [95% CI: 1.56-2.17], respectively; $P < 0.001$).[2] These cancer types warrant further investigation.

Leedy et al,[3] in 2021, found a significant association between incident cancer in post-menopausal women aged 50 to 79 years with HF (HR: 1.28, 95% CI: 1.02-1.51) in lung, colorectal, and obesity-related cancers. Furthermore, there was an overall increased risk of incident cancer in patients with HF with preserved ejection fraction (HR: 1.34, 95% CI: 1.06-1.67).[3] In future investigations, it will be important to incorporate various HF subtypes, and include men as well as younger patients.

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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.

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REPLY: Perspectives and Limitations of the Studies of the Association Between Heart Failure and Cancer

We thank Drs Brahmbhatt and colleagues and Dr Menon and Mr Ahmad for their constructive comments on our paper.[1]

We agree with Dr Brahmbhatt and colleagues that clonal hematopoiesis of indeterminate potential (CHIP) may be a possible mechanism linking cancer and cardiovascular disease. Indeed, CHIP-related variants both confer a proliferative advantage to hematopoietic progenitors and amplify the inflammatory response of the innate immune system. The proinflammatory phenotype of mature myeloid cells carrying CHIP-related variants might contribute to the enhanced atherosclerotic burden and increased risk for cardiovascular events observed in animal models and patients with CHIP.[2] Accordingly, one recent exploratory analysis suggested that in the CANTOS (Cardiovascular Risk Reduction Study [Reduction in Recurrent Major CV Disease Events]) trial, the effect of interleukin-1-beta inhibition with canakinumab on major adverse cardiovascular events was greater in patients with CHIP due to *TET2* variants.[3] In addition, in rodent models of pressure overload-induced heart failure (HF), CHIP-related activation of the Nod-like receptor protein 3 inflammasome worsened maladaptive left ventricular remodeling, indicating that the inflammatory state associated with CHIP has detrimental effects on cardiac function even in the absence of atherosclerosis.[4] Overall, experimental and clinical evidence implicates CHIP in the pathogenesis of both cardiovascular disease and hematologic malignancies.

As pointed out by Dr Menon and Mr Ahmad, one limitation of our analysis is that our study population is rather homogeneous with respect to ethnicity and