Chapter 9b

Heart disease and cancer –
Are the two killers colluding?

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EDITORIAL COMMENT

This chapter refers to ‘Heart Failure Stimulates Tumor Growth by Circulating Factors’, by W.C. Meijers et al., Chapter 9a of this thesis.

Noncommunicable diseases kill 40 million people each year, accounting for 70% of all deaths globally. In this context, 17.7 million people die annually as a consequence of cardiovascular diseases, whereas cancer accounts for 8.8 million deaths per year.\(^1\) Evidence linking cardiovascular diseases with a higher incidence of cancer has been suggested previously in community-based observational trials.\(^2\) In 2013, Hasin et al.\(^3\) found an interconnection between heart failure and consequent cancer diagnosis. These findings were reproduced in a prospective cohort study of patients with myocardial infarction–induced heart failure.\(^4\) Banke et al.\(^5\) observed similar results in a large Danish heart failure cohort. It is important to note, however, that these epidemiological studies do not differentiate between heart failure with preserved or reduced ejection fraction, which may be relevant because these conditions appear distinct.

Shared risk factors and biological mechanisms possibly explain this relationship. Indeed, cardiovascular risk factors such as unhealthy diet, tobacco smoking, obesity, diabetes mellitus, and hypertension have been found to be associated with an increased cancer risk.\(^6\) Moreover, it has been speculated that cardiovascular drugs (ie, angiotensin-converting enzyme inhibitors and β-blockers), radiation during diagnostic assessment, epigenetic mechanisms, and regenerative signaling are all potential links connecting both illnesses.\(^2,6\) With regard to common molecular pathways, chronic inflammation and oxidative stress are likely candidates, because they play central roles in the pathophysiology of both cardiovascular diseases and cancer.\(^6\)

Nonetheless, despite the evidence described in the aforementioned population studies and shared risk factors/biological mechanisms, the possibility that other comorbidities may explain the association between cardiovascular disease and cancer cannot be ruled out.\(^7\) Moreover, inasmuch as the clinical assessment of patients with heart failure occurs regularly, an apparent higher risk of cancer may reflect merely earlier diagnosis rather than a higher incidence.\(^7\)

The study by Meijers et al.\(^8\) in chapter 9a of this thesis presents new evidence suggesting that heart failure promotes intestinal precancerous polyp growth. The authors report compelling data using the APC\(_{\text{min}}\) mouse strain, which harbors a nonsense mutation in APC leading to persistence of β-catenin and a susceptibility to spontaneous intestinal adenoma formation.\(^9-11\) Six weeks after the induction of myocardial infarction with sub-
sequent heart failure (left ventricular ejection fraction ~32% one week after myocardial infarction), these mice developed an increased number and size of intestinal polyps in comparison with the sham-operated control. Moreover, the authors found an association between polyp growth and left ventricular ejection fraction and cardiac fibrosis, both of which correlate with the magnitude of heart failure–induced myocardial remodeling.

To exclude alterations in hemodynamics as the cause of their findings, Meijers et al. transplanted hearts from APC$^{\text{min}}$ mice subjected 1 week earlier to myocardial infarction or sham operation heterotopically into the cervical region of other APC$^{\text{min}}$ mice (HTx model). In this procedure, the external jugular vein and common carotid artery of the recipient mouse were anastomosed with the pulmonary trunk and aorta, respectively, of the transplanted heart. The performance of the recipient native heart was unaltered. It is interesting to note that 6 weeks after the procedure, APC$^{\text{min}}$ mice that were transplanted with infarcted hearts manifested elevated numbers and size of polyps in comparison with mice receiving sham-operated hearts (Figure 1).

Important questions arise from these novel findings. Can these observations be extrapolated to other precancerous or cancerous lesions? Would heart failure of non-ischemic origin elicit the same response? Does heart failure also promote metastasis?

**Figure 1. Failing heart stimulates intestinal polyp growth.**
Experimental models (Left) showed that myocardial infarction–induced heart failure (MI-HF) stimulates precancerous intestinal polyp growth in APCmin mice. Left ventricular ejection fraction was markedly decreased after myocardial infarction in MI-HF mice in comparison with sham-operated mice (Sham). MI-HF mice also developed more and larger intestinal polyps than Sham mice. Failing hearts heterotopically (HTx) transplanted to APCmin recipient mice trigger the same polyp growth. In silico studies (Middle). Exploration strategy identified SerpinA1 (alpha-1-antitrypsin), SerpinA3 (alpha-1-antichymotrypsin), FN (fibronectin), CP (ceruloplasmin), and PON1 (paraoxonase 1) as potential circulating factors responsible for promoting polyp growth. In vitro studies (Middle) showed that Serpin A1/A3 elicited proliferation of the HT-29 cancer cell line. Population studies (Right) showed that plasma levels of SerpinA1, SerpinA3, FN, CP, and PON1 were increased in patients with chronic heart failure (CHF) in comparison with healthy patients.
Pursuing mechanism, Meijers et al. reviewed the literature concerning proteins released after myocardial infarction and identified 5 proteins of potential relevance: SerpinA1 (alpha-1-antitrypsin), SerpinA3 (alpha-1-antichymotrypsin), FN (fibronectin), CP (cerculoplasmin), and PON1 (paraoxonase 1). The mRNA levels of all these proteins were elevated in the left ventricles of failing APC<sup>min</sup> mice, but this result was replicated only for SerpinA3, FN, and Pon1 in the HTx model (Figure 1). The authors went on to show that the addition of SerpinA1 and SerpinA3 to the cell culture media promoted proliferation of the colorectal cell line HT-29 (Figure 1). These findings would have been strengthened by the demonstration of increases in the protein abundance of these candidate mediators in the heart and blood. In addition, such measurements would have allowed the investigators to probe whether levels of these mediators correlate with tumor load. This limitation notwithstanding, these data are quite provocative.

Finally, this study provides evidence for the translational value of the reported results by showing increased plasma levels of their 5 candidate proteins in the plasma of 101 patients with chronic heart failure in comparison with 180 healthy patients enrolled in the PREVEND study (Prevention of Renal and Vascular End-stage Disease)<sup>12,13</sup> (Figure 1). Also, they observed that augmented heart failure biomarkers, and inflammation-related proteins, as well, were predictive of incident cancer independent of cancer risk factors.

Although the authors' findings shed light on possible molecules mediating the observed effects, a more comprehensive mechanistic assessment will be required to definitively delineate links between heart disease and cancer (Figure 2). Moreover, an unbiased proteomics approach, rather than a candidate approach, would likely be better suited to reveal the most important mediators connecting the failing heart with tumor growth. Ultimately, however, multifaceted experimental approaches to alter the abundance of these mediators will be required to prove cause and effect.

Although further research is needed to confirm and deepen these findings, these are potentially groundbreaking results that will stimulate further delineation of the connections between heart disease and cancer. This study highlights how heart disease may impact cancer just as other work has demonstrated the important effects of cancers<sup>14</sup> and cancer treatments<sup>15</sup> on cardiac structure and function. We may be at the gates of a new scientific research field.
Shared risk factors, such as unhealthy diet, tobacco smoking, obesity, diabetes mellitus, and hypertension are potential links between both diseases. Mechanistically, chronic inflammation, oxidative stress, cytokines, angiotensin II, and catecholamines are all plausible mediators contributing to this connection because they play a role in both cancer and cardiovascular diseases.

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REFERENCES


