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Commentary: The relationship of cancer and heart disease—it's complicated

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Both cardiovascular disease (CVD) and cancer are among the leading causes of death globally. More importantly, they share many risk factors, including genetics, sex, age, diabetes, obesity, and radiation, among others. Although often thought of as separate entities, cancer and CVD are tightly intertwined with shared causal pathways such as inflammation or oxidative stress promoting CVD and carcinogenesis.¹ Furthermore, common treatment strategies for cancer increase cardiovascular risk; plus, a significant proportion of deaths in patients with cancer are, in fact, cardiovascular deaths.² This proportion of cardiovascular death grows significantly with more indolent forms of cancer (eg, most prostate cancer). The insidious onset, chronicity, complex interaction, and shared causes between CVD and cancer pose significant challenges for observational studies on the relationship between them. Given the sheer prevalence and coexistence of the 2 disease processes, more research and a better understanding when invasive therapies such as revascularization are beneficial are desperately needed.

In this edition of the *Journal*, Mennander and colleagues³ present an analysis of more than 82,000 patients undergoing isolated, first-time coronary artery bypass grafting (CABG) in Sweden using national registry data. In their study, they compare subjects with a previous medical history of cancer (18% having a cancer diagnosis more than 10 year before CABG) to those without such a history over a median

CENTRAL MESSAGE

Significant progress in oncology has led to a growing number of cancer survivors requiring coronary revascularization with expected good outcome.

follow-up time of 5.9 years in the cancer group and 9.3 years in the comparison group.

In their paper, they share some interesting observations from these data. Arguably, the most important finding is that over time an increasing number of patients with a history of cancer were offered CABG, and those patients have similar 30-day mortality (2.4%) compared with the control group (1.7%). These are encouraging data that CABG may be safely performed in a select group of patients with a history of cancer. This trend is likely explained by significant progress made in oncology, rather than cardiac surgery, allowing a growing number of patients to survive long enough to require coronary revascularization. The authors report that cancer history was independently associated with increased all-cause mortality during follow-up; this association was also more pronounced in patients with a history of hematologic malignancies compared with solid tumors. Furthermore, this association was stronger if the cancer diagnosis was in closer temporal proximity to CABG. All this is rather expected.

Finally, the authors explore cause-specific mortality and conclude that cardiovascular prognosis after CABG is the same for patients with and without a history of cancer. We feel less certain about these conclusions. Several points about the study design and analysis are worth noting. The cancer-history-cohort enters this study after a significant survivorship bias; patients with the worst cancer and CVD burden simply did not survive or qualify for CABG. On the flip side, the control group enters this study with no similar previous selection

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process (in terms of survival probability). This notion is supported by the spline analysis associating remoteness of the cancer diagnosis with better outcomes as well as the finding that patients with a cancer history were older and had more comorbidities than their counterparts. Statistical modeling can hardly make up for that difference between the 2 groups. Further, cause-specific mortality is often difficult to study. For one, adjudication of the cause of death is often insufficient, and misclassification is common (eg, missed cancer in the control group vs biased adjudication due to previous cancer history). Notably, the authors do not account for cancer diagnosed after CABG, and therefore the comparison should not be seen as one strictly comparing subjects with and without cancer altogether. Eventually, the combined proportion of CVD- and cancer-death amount to almost the same in both groups (78% vs 72%), as a substantial proportion of patients also develop cancer during follow up (undisclosed) and die a cancer death during follow-up (18%).

A final word of caution concerns the competing risk analysis with subhazard estimation. The authors find a significantly increased subhazard for cancer death in patients with a history of cancer but also a significantly lower subhazard for cardiovascular mortality. A causal interpretation of this would be that a cancer history is protective against dying a cardiovascular

death. Substantial literature would suggest otherwise.⁴ Rather, the explanation here is given by a peculiarity of this popular methodology (Fine and Gray competing risk models), which was not actually devised for causal interpretations. To estimate the subhazards, an unnatural assumption that subjects remain part of the risk set, after a competing event has occurred, must be made. Consequently, any variable that increases the cause-specific risk of event A will appear to decrease the subdistribution hazard for event B. Because whenever a type A event occurs, it eliminates the possibility that a type B event will happen. We commend the authors for presenting this large cohort study with some important findings but also caution against a conclusion that suggests cardiovascular prognosis is the same for patient with and without a cancer.

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Commentary: Are all cancers equal?

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Cardiovascular disease and cancer are the 2 leading causes of death in the United States to date. In 2018, in the United States, the age-adjusted death rate from cardiovascular

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CENTRAL MESSAGE

Long-term cardiovascular and cancer-related mortality are important outcomes after CABG in patients with coexistent cancer but may differ with respect to cancer type.

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