MINI-FOCUS ISSUE: EPIDEMIOLOGIC AND BIOLOGIC LINKS BETWEEN CANCER AND CV DISEASE

ORIGINAL RESEARCH

Incident Cardiovascular Disease Among Adults With Cancer

A Population-Based Cohort Study

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ABSTRACT

BACKGROUND Patients with cancer and cancer survivors are at increased risk for incident heart failure, but there are conflicting data on the long-term risk for other cardiovascular events and how such risk may vary by cancer site.

OBJECTIVES The aim of this study was to determine the impact of a new cancer diagnosis on the risk for fatal and nonfatal cardiovascular events.

METHODS Using administrative health care databases, a population-based retrospective cohort study was conducted among 4,519,243 adults residing in Alberta, Canada, from April 2007 to December 2018. Participants with new cancer diagnoses during the study period were compared with those without cancer with respect to risk for subsequent cardiovascular events (cardiovascular mortality, myocardial infarction, stroke, heart failure, and pulmonary embolism) using time-to-event survival models after adjusting for sociodemographic data and comorbidities.

RESULTS A total of 224,016 participants with new cancer diagnoses were identified, as well as 73,360 cardiovascular deaths and 470,481 nonfatal cardiovascular events during a median follow-up period of 11.8 years. After adjustment, participants with cancer had HRs of 1.33 (95% CI: 1.29-1.37) for cardiovascular mortality, 1.01 (95% CI: 0.97-1.05) for myocardial infarction, 1.44 (95% CI: 1.41-1.47) for stroke, 1.62 (95% CI: 1.59-1.65) for heart failure, and 3.43 (95% CI: 3.37-3.50) for pulmonary embolism, compared with participants without cancer. Cardiovascular risk was highest for patients with genitourinary, gastrointestinal, thoracic, nervous system and hematologic malignancies.

CONCLUSIONS A new cancer diagnosis is independently associated with a significantly increased risk for cardiovascular death and nonfatal morbidity regardless of cancer site. These findings highlight the need for a collaborative approach to health care for patients with cancer and cancer survivors. (J Am Coll Cardiol CardioOnc 2022;4:85–94) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Advances in early diagnosis and treatment have substantially improved clinical outcomes for most patients with cancer in the past 2 decades. As the life expectancy of cancer survivors has increased, so has the likelihood of developing other illnesses after cancer diagnosis. Cancer and cardiovascular (CV) disease share many risk factors, including smoking, lower socioeconomic status, and obesity. This suggests that patients with cancer constitute a high-risk population for CV disease. Furthermore, many cancer therapies, including chest irradiation as well as systemic therapies such as chemotherapy, are associated with incident CV disease during treatment and in survivorship. It has been hypothesized that the excess CV morbidity of cancer treatments is mediated by direct myocardial and/or vascular injury as well as indirectly through adverse effects on lifestyle behaviors.

However, recent population studies have yielded conflicting results on the long-term CV risk of cancer survivors. One study using data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated a higher risk for CV death among 234,256 cancer survivors compared with the U.S. general population, particularly in the first year after cancer diagnosis. However, another SEER-based study showed that cardiac mortality in a cohort of 347,476 patients with breast cancer was not increased compared with age-matched control subjects during long-term follow-up. Although these studies considered the effects of age, ethnicity, and cancer-related variables, they did not adjust for other risk modifiers, including prior CV disease, hypertension, diabetes mellitus, and dyslipidemia. Indeed, administrative databases confirm a high prevalence of CV disease in patients with cancer relative to cancer-free control subjects. Prior work on CV risk in cancer survivors has also been limited in scope and has typically included study of only 1 cancer type and 1 CV outcome.

Access to multiple health data repositories in Alberta, Canada, permits the construction of well-characterized, population-based cohorts with extensive profiling of cancer and CV disease. Therefore, we designed this study to investigate the risk for incident CV events among people with histories of cancer compared with those without cancer after adjustment for baseline CV risk and other potential confounders. We hypothesized that CV risk is increased in all cancer types and is not limited to incident heart failure.

**METHODS**

We reported this retrospective population-based cohort study according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The Health Research Ethics Board of Alberta (HREBA.CC-16-0164) provided institutional approval and waived the requirement for participants to provide consent.
DATA SOURCES AND COHORT. We used an existing database, which incorporates patient registry, physician claims, hospitalizations, and ambulatory care utilization data from all adults registered with Alberta Health (the provincial health ministry) and links it with data from provincial clinical laboratories and vital statistics. This database has been widely used because of its population-based coverage of a geographically defined area, including demographic characteristics, health services utilization, and clinical outcomes. Additional information on the database is available elsewhere, including the validation of selected data elements. All Alberta residents are eligible for insurance coverage by Alberta Health, with >99% participation. The database was used to assemble cohorts of adults who resided in Alberta between April 1, 2004, and March 31, 2007 (ie, prior to the study period).

We defined other comorbidities using a previously published framework of validated algorithms as applied to Canadian physician claims, hospitalizations, and ambulatory care data, each of which had positive predictive value ≥70% compared with a gold-standard measure such as chart review. Comorbidities included CV conditions such as atrial fibrillation, heart failure, diabetes, dyslipidemia, hypertension, myocardial infarction (MI), peripheral artery disease, severe obesity, and stroke or transient ischemic attack as well as non-CV conditions such as alcohol misuse, asthma, chronic pain, chronic obstructive pulmonary disease, chronic hepatitis B, cirrhosis, severe constipation, dementia, depression, epilepsy, gout, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, Parkinson’s disease, peptic ulcer disease, psoriasis, osteoporosis, rheumatoid arthritis, and schizophrenia. Detailed methods for classifying comorbidity status and the specific algorithms used have been previously detailed. We defined dyslipidemia as an outpatient low-density lipoprotein cholesterol level ≥3.5 mmol/L (135 mg/dL). Severe obesity was defined using a fee modifier, as in our previous work. Severe chronic kidney disease was defined by sustained estimated glomerular filtration rate <30 mL/min/1.73 m² and/or registration with a renal replacement program. Participants without data on low-density lipoprotein cholesterol and estimated glomerular filtration rate were considered not to have dyslipidemia and chronic kidney disease.

CANCER, COMORBIDITIES, AND OTHER CHARACTERISTICS. We linked the primary database with data from the Alberta Cancer Registry to identify participants with cancer as well as cancer stage (0, I, II, III, IV, or not determined), site (breast, melanoma, genitourinary, gynecological, head and neck, hematologic, gastrointestinal, nervous system, thoracic [primarily lung], and other sites), and date of diagnosis. If multiple stages and/or sites were identified within the same participant and incident cancer date, then the highest stage and the most frequent site were recorded. We excluded participants from the cohort if they were diagnosed with cancer between April 1, 2004, and March 31, 2007 (ie, prior to the study period).

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| Table 2 Site and Stage of Cancers |
|-----------------------------------|
|                                | Stage |
|                                 | O   | I   | II  | III | IV  | ND  |
| All                             | 224,016 | 45,230 (20.2) | 37,303 (16.7) | 37,128 (16.6) | 22,795 (10.2) | 31,494 (14.1) | 50,066 (22.4) |
| Gynecological                   | 45,534 (20.3) | 32,832 (71.1) | 4,839 (10.6) | 851 (1.9) | 1,716 (3.8) | 890 (2.0) | 4,406 (9.7) |
| Genitourinary                   | 43,296 (19.3) | 3,560 (8.2) | 5,997 (13.9) | 17,483 (40.4) | 3,841 (8.9) | 4,237 (9.8) | 8,178 (18.9) |
| Gastrointestinal               | 36,897 (16.5) | 2,314 (6.3) | 5,281 (14.3) | 6,258 (17.0) | 6,715 (18.2) | 9,222 (25.0) | 7,107 (19.3) |
| Breast                          | 29,407 (13.1) | 3,130 (10.6) | 10,163 (34.6) | 8,602 (29.3) | 2,776 (9.4) | 1,268 (4.3) | 3,468 (11.8) |
| Thoracic                        | 21,534 (9.6) | 15 (0.1) | 3,629 (16.9) | 772 (3.6) | 4,510 (20.9) | 9,555 (44.4) | 1,053 (4.2) |
| Hematological                  | 19,558 (8.7) | 0 (0.0) | 1,617 (8.3) | 1,447 (7.4) | 1,312 (6.7) | 3,094 (15.8) | 12,088 (61.8) |
| Leukemia                       | 5,632 (2.5) | 0 (0.0) | 28 (0.5) | 39 (0.7) | 62 (1.1) | 37 (0.7) | 5,466 (97.1) |
| Lymphoma                       | 8,113 (3.6) | 0 (0.0) | 1,580 (19.5) | 1,406 (17.3) | 1,248 (15.4) | 3,051 (37.6) | 828 (10.2) |
| Other                          | 5,813 (2.6) | 0 (0.0) | 9 (0.2) | 2 (0.0) | 2 (0.0) | 6 (0.1) | 5,794 (99.7) |
| Melanoma                       | 10,140 (4.5) | 3,203 (31.6) | 1,907 (18.8) | 721 (7.1) | 590 (5.8) | 234 (2.3) | 3,485 (34.4) |
| Head and neck                  | 4,589 (2.1) | 175 (3.8) | 691 (15.1) | 387 (8.4) | 488 (10.6) | 2,133 (46.5) | 715 (15.6) |
| Nervous system                 | 2,553 (1.1) | 0 (0.0) | 6 (0.2) | 9 (0.4) | 6 (0.2) | 6 (0.2) | 2,526 (98.9) |
| Other                          | 10,508 (4.7) | 1 (0.0) | 3,173 (30.2) | 598 (5.7) | 841 (8.0) | 855 (8.1) | 5,040 (48.0) |

Values are n (%). The all-stages column shows the percentage of each cancer site. The stage-specific columns show the percentage of each stage within each cancer site. ND = not determined.
TABLE 3 Adjusted HRs for Cardiovascular Outcomes by Cancer Status: Primary and Sensitivity Analyses

| Cancer Status                  | All-Cause Mortality | CV Mortality | Acute MI | Stroke | Heart Failure | Pulmonary Embolism |
|-------------------------------|---------------------|--------------|----------|--------|---------------|-------------------|
| Cancer (reference no cancer)  | 8.34 (8.26-8.42)    | 1.33 (1.29-1.37) | 1.01 (0.97-1.05) | 1.44 (1.41-1.47) | 1.62 (1.59-1.65) | 3.43 (3.37-3.50) |
| Competing risks (sensitivity) |                     |              |          |        |               |                   |
| Cancer (reference no cancer)  | 1.05 (1.01-1.09)    | 1.40 (1.38-1.43) | 1.79 (1.75-1.82) |        |               | 2.77 (2.72-2.82) |
| Cox (sensitivity)             |                     |              |          |        |               |                   |
| Cancer (reference no cancer)  | 8.34 (8.26-8.42)    | 1.33 (1.29-1.37) | 1.01 (0.97-1.04) | 1.44 (1.41-1.47) | 1.62 (1.59-1.65) | 3.43 (3.37-3.50) |
| Age and sex 1:1 matched (sensitivity) |             |              |          |        |               |                   |
| Cancer (reference no cancer)  | 12.92 (12.72-13.13) | 1.73 (1.67-1.80) | 1.03 (0.99-1.08) | 1.38 (1.35-1.41) | 1.59 (1.55-1.62) | 3.13 (3.05-3.20) |
| Exclude participants diagnosed with stage O cancer (sensitivity) | | | | | | |
| Cancer (reference no cancer)  | 9.22 (9.13-9.31)    | 1.36 (1.32-1.40) | 1.03 (0.99-1.07) | 1.49 (1.46-1.52) | 1.69 (1.66-1.73) | 3.97 (3.89-4.04) |

Values are HR (95% CI). Reference group is the no-cancer group in all rows (HR: 1.00). Fully adjusted for baseline age, biological sex, neighborhood material deprivation quintile, rural or urban, distance to cancer center, and distance to family doctor, plus 31 comorbidities: alcohol misuse, asthma, atrial fibrillation, heart failure, severe chronic kidney disease, chronic pain, chronic pulmonary disease, dyslipidemia, viral hepatitis B, cirrhosis, severe constipation, dementia, depression, diabetes mellitus, epilepsy, gout, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, myocardial infarction, multiple sclerosis, severe obesity, osteoporosis, Parkinson’s disease, peptic ulcer disease, peripheral artery disease, psoriasis, rheumatoid arthritis, schizophrenia, and stroke or transient ischemic attack.

CV = cardiovascular; MI = myocardial infarction; RCS = restricted cubic splines.
considered as a competing risk (subdistribution hazards) to determine if the relationship found by censoring at death in our primary analyses provided different results. Third, we used a subcohort of 1:1 age-sex matched and stratified age analyses to address the imbalance in age between those with cancer and those without cancer (median 56 vs 34 years). A participant who developed cancer was matched within 1 year (of age) to a participant who did not develop cancer. Fourth, we excluded participants diagnosed with cancer at stage 0 (in situ) given that 73% of cases were gynecological and it does not apply to hematologic malignancies. Fifth, we reported associations between cancer site and CV events by biological sex. Sixth, we examined the material deprivation quintile as a possible modifier of the association between cancer and CV outcomes using an interaction term.

### RESULTS

#### CHARACTERISTICS OF PARTICIPANTS.

We identified 4,519,243 participants during the study period (after excluding 34,954 participants because of a
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Median follow-up duration was 11.8 years. Of these, 224,016 received new cancer diagnoses during follow-up. Table 1 shows the characteristics of the study populations at first contact. For participants diagnosed with cancer, the median age was 56 years (IQR: 43-67 range) and 57% were women, compared with a median age of 34 years (IQR: 23-49 years) and 49% women among those without cancer. CV disease was prevalent in the cancer group, including 32% with hypertension, 10% with diabetes, 2% with prior MI, and 3% with heart failure. Non-CV disease was also prevalent in the cancer group, including 10% with chronic obstructive pulmonary disease and 8% with depression. Participants without cancer were more than 20 years younger on average, were more likely to be male, and more commonly lived in an urban residence than those without; they also had a lower prevalence of every chronic condition.

The most frequent cancer sites were gynecological (20%), genitourinary (19%), gastrointestinal (17%), breast (13%), thoracic (10%) and hematologic (9%) (Table 2).

OUTCOMES. Median follow-up duration was 11.8 years (IQR: 6.4-11.8 years). During follow-up, there were 248,541 deaths, including 73,360 from CV causes. Nonfatal CV outcomes included 123,342 with incident heart failure, 53,496 with acute MI, 178,433 with stroke, and 115,210 with pulmonary embolism. In the cancer groups, the highest rates of CV events were as follows: hematologic cancers for CV deaths (3.7 per 1,000 participant-years), genitourinary cancers for acute MIs (2.4 per 1,000 participant-years), nervous system cancers in stroke (16.4 per 1,000 participant-years), hematologic cancers in heart failure (12.0 per 1,000 participant-years), and nervous system cancers in pulmonary embolism (16.5 per 1,000 participant-years). High rates of CV events were also noted for thoracic cancers (Supplemental Table 1).

After adjustment for age and sex, the rate of CV death in the cancer group was 3.0 per 1,000 patient-years compared with 2.9, 3.8, and 6.8 per 1,000 patient-years for participants with hypertension, diabetes, or prior MI, respectively (Supplemental Table 2).

After adjustment for baseline covariates, participants with cancer had HRs of 1.33 (95% CI: 1.29-1.37) for CV mortality, 1.01 (95% CI: 0.97-1.05) for acute MI, 1.44 (95% CI: 1.41-1.47) for stroke, 1.62 (95% CI: 1.59-1.65) for heart failure, and 3.43 (95% CI: 3.37-3.50) for pulmonary embolism, all compared with participants without cancer (Table 3). When we subcategorized stroke as hemorrhagic stroke and ischemic stroke, the HRs among participants with cancer (vs those without) were 1.41 (95% CI: 1.38-1.44) for hemorrhagic stroke and 1.51 (95% CI: 1.48-1.54) for ischemic stroke.

SENSITIVITY ANALYSES. Results from the Cox model and the Weibull model were very similar to the primary results (Table 3). The results were also similar when we excluded participants <50 years of age and when we excluded those diagnosed with stage 0 cancers. Analyses that treated mortality as a competing risk found that the risks for acute MI, stroke, and heart failure associated with cancer were similar to those from the primary analysis, although the risk for pulmonary embolism was slightly attenuated (from HR: 3.43 [95% CI: 3.37-3.50] to HR: 2.77 [95% CI: 2.72-2.82]).

Supplemental Table 3 shows that the risk for CV outcomes associated with cancer varied significantly by socioeconomic status. The excess risk for all-cause mortality (P < 0.001) and pulmonary embolism (P = 0.013) associated with cancer was smaller for participants in the least deprived neighborhoods, although their risk for heart failure was greater (P = 0.011).

Risks for CV mortality (HR: 1.02-3.24), pulmonary embolism (HR: 1.64-18.75), heart failure (HR: 1.00-3.11), and stroke (HR: 1.16-11.20) among participants with cancer were greater than among control subjects without cancer for all cancer sites except melanoma (Table 4). Two cancer sites, thoracic and hematologic, were also at greater risk for acute MI (HR: 1.60 [95% CI: 1.41-1.82] and HR: 1.23 [95% CI: 1.11-1.37], respectively). CV risks by cancer sites were qualitatively similar between the sexes.

The excess CV risk associated with cancer was greatest during the first year following the cancer diagnosis for all outcomes (HR: 1.24-8.36) and declined over time, although it remained significantly elevated for CV mortality, heart failure, and pulmonary embolism even after 10 years of follow-up (Central Illustration, Supplemental Table 4). Similarly, participants with more advanced cancer were at higher risk for CV outcomes (Supplemental Table 5). However, even patients with very early stage disease (stages 0 and I) had higher risk for CV events relative to control subjects without cancer.

Supplemental Table 6 shows the baseline characteristics of participants with and without cancer after matching for age and sex. After matching, the excess risks for nonfatal CV events associated with cancer were similar to those in the primary analysis (Table 3), and the excess risks for all-cause and CV mortality associated with cancer were accentuated (from HR: 8.34 [95% CI: 8.26-8.42] to HR: 12.92 [95% CI: 12.72-13.13]; and from HR: 1.33 [95% CI: 1.29-1.37] to HR: 1.73.
Supplemental Table 7 demonstrates that the risk for CV events in patients with cancer varies by age at cancer diagnosis. For all outcomes except MI, the excess risk was higher among younger participants.

**DISCUSSION**

In this large population-based study, we found that a new diagnosis of cancer was associated with an increased risk for fatal and nonfatal CV events, even after adjustment for baseline risk. Regardless of cancer site, patients were at increased risk for CV mortality, heart failure, stroke, or pulmonary embolism, and this risk persisted to 10 years for heart failure and pulmonary embolism (Central Illustration). Genitourinary, thoracic, hematologic, gastrointestinal, and nervous system cancers were identified as higher risk groups warranting further study.

**PREVIOUS POPULATION-BASED STUDIES OF CV OUTCOMES IN PATIENTS WITH CANCER.** Our study has several novel aspects compared with prior work. First, ours is a uniquely comprehensive study of CV risk in cancer. We have included data on cancer site, stage, and time from diagnosis in addition to evaluating several CV outcomes of interest. Prior studies of incident CV disease in cancer have often included only 1 cancer site, usually breast cancer, and have studied only CV mortality and/or incident heart failure. Second, population-based studies have shown that cancer is associated with higher risk for venous and arterial thromboembolism during the first year from cancer diagnosis, whereas our findings demonstrate that the excess risk extends to year 7 for stroke and past year 10 for heart failure and pulmonary embolism. Furthermore, prior survival analyses have adjusted only for age and sex but not other risk factors for incident CV disease. Our study demonstrates that patients with cancer were at higher risk for 5 distinct CV events, while controlling for sociodemographic data and 31 clinical covariates. Similar to Sturgeon et al, we found that the first year from cancer diagnosis was associated with the greatest excess risk for CV mortality. However, we also found an excess of nonfatal CV events during this period, which suggests that patients with cancer may benefit...
from comanagement that includes cardiologists as well as stroke and thrombosis specialists.26

**IS CANCER A RISK FACTOR FOR CV DISEASE?** Despite adjustment for covariates including age, sex, hypertension, diabetes, dyslipidemia, and prior CV disease, a new cancer diagnosis was associated with a higher risk for CV mortality, acute MI, stroke, heart failure, and pulmonary embolism. Although data were not available on smoking status, this characteristic is unlikely to account for the observed HR of 1.22 for CV mortality and 1.55 for stroke, given that the median prevalence of smoking in Canada was 20% among patients with cancer versus 19% among those without cancer during the study period.27 Another notable finding was that the HR for incident heart failure was 1.62, after adjustment for all major risk factors of heart failure (age, hypertension, diabetes, and prior MI).

We recently reported that patients with cancer have relative cardiac hypertrophy prior to receiving cancer treatment,28 and others have reported abnormal cardiac function at baseline.29 Thus, patients with cancer may be predisposed to developing CV disease independent of treatment. Indeed, a recent study using data from the SEER database found that patients with breast cancer not exposed to chemotherapy or radiotherapy were at higher risk for incident CV disease compared with the general population, especially without tumor resection.30

**HIGH-RISK CANCER SITES.** Most studies of adverse CV outcomes in cancer have reported on participants with breast cancer. Our findings suggest that the risk for incident CV disease is higher for other cancer sites, notably genitourinary, thoracic, hematologic, gastrointestinal, and nervous system. Participants with these cancers constituted 55% of the cancer cohort and accounted for more than 71% of the incident CV burden. Furthermore, the majority of these people with cancer will experience extended survival, with 5-year survival rates of 93% for prostate cancer and 44% to 86% for hematologic malignancies.31 Although median survival for lung cancer remains significantly lower than for these other forms of cancer, immune-modifying therapies now provide long-term survival in a substantial subset of patients. Thus, future work should further elucidate the CV risk in patients with these understudied cancer types.

**STUDY LIMITATIONS.** Although the cohort that we used included detailed information on sociodemographic factors and a detailed assessment of comorbidity, data on cancer therapies, patient ethnicity and some risk factors for atherosclerosis such as smoking and physical activity were not available. However, we found that the adjusted CV risk was elevated for all cancer stages, including patients with very early stage disease who were less likely to receive radiation and/or systemic treatment. Regardless, our study shows that patients with prior cancer are susceptible to a variety of CV events over a long time frame. Unfortunately, this risk is unlikely to diminish in the short term given that many newer cancer therapies are also associated with increased risk for myocardial injury and heart failure. Future work should evaluate CV events in large prospective cancer registries with enhanced phenotyping and risk modeling. Such work would potentially lead to better prediction of CV risk for patients with cancer and survivors and improved prevention and treatment strategies.

**CONCLUSIONS**

In this population-based study of 4,519,243 participants with median follow-up of nearly 12 years, we found that a new cancer diagnosis was independently associated with a significantly higher risk for CV death, stroke, heart failure, and pulmonary embolism, especially in the first year. This risk was relatively more pronounced in participants with genitourinary, thoracic, hematologic, and nervous system cancers. Future studies should evaluate other potential contributors to CV risk, including cancer therapies and emerging risk factors of cardiotoxicity.

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patients with cancer are at high risk for fatal and nonfatal CV events, including heart failure, stroke, and pulmonary embolism. Patients with genitourinary gastrointestinal, hematologic, nervous system, or thoracic malignancies accounted for the majority of CV events and were higher risk cancer subtypes.

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KEY WORDS cancer survivorship, coronary artery disease, epidemiology, heart failure

APPENDIX For supplemental tables, please see the online version of this paper.