Incidence rates of cardiovascular outcomes in a community-based population of cancer patients

Rajeev Masson | Lina Titievsky | Douglas A. Corley | Wei Zhao | Alfredo R. Lopez | Jennifer Schneider | Jonathan G. Zaroff

1Kaiser Permanente San Francisco Medical Center, San Francisco, CA, USA
2Department of Epidemiology, Pfizer Inc., New York, NY, USA
3Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

Correspondence
Jonathan G. Zaroff, 2425 Geary Boulevard, 8th Floor Cardiology Department, San Francisco, CA 94115, USA.
Email: Jonathan.G.Zaroff@kp.org

Funding information
The study was funded by Pfizer Inc., New York, NY.

Abstract
Background: There are limited data on the incidence of cardiovascular disease among cancer patients in the pre-tyrosine kinase inhibitor (TKI) era. Such data are important in order to contextualize the incidence of various cardiovascular outcomes among cancer patients enrolled in clinical trials of new agents and for postmarketing surveillance.

Methods: A retrospective cohort study was conducted using data from the Kaiser Permanente Northern California (KPNC) population of cancer patients. The inclusion criterion was a KPNC Cancer Registry diagnosis of any of several selected solid and hematologic tumors between 1997 and 2009 not treated with a TKI. Endpoints were identified using ICD-9 codes and included acute coronary syndrome, heart failure, stroke, cardiac arrest, hypertension, venous thromboembolism, all-cause mortality, and cardiovascular mortality. Event rates were calculated according to type of cancer and number of cardiovascular risk factors.

Results: The study included almost 165,000 individuals with a broad variety of tumor types. The parent cohort was 54% female and 35% were ≥70 years old. Cardiovascular risk factors such as diabetes mellitus (14% of patients with solid tumors, 15% of patients with liquid tumors), dyslipidemia (33%, 31%), hypertension (50%, 49%), and smoking (35%, 32%) were common. The most frequent adverse outcomes were incident hypertension (26.8–61.0 cases per 1000 person-years, depending on the type of cancer), heart failure (9.4–78.7), and acute coronary syndrome (2.6–48.1). These event rates are high compared to what has been reported in prior KPNC cohort studies of patients without cancer. The rates of acute coronary syndrome, heart failure, and ischemic stroke increased with increasing numbers of cardiovascular risk factors.

Conclusions: In a population of patients with cancer not exposed to TKIs, cardiovascular risk factors and outcomes are very common, regardless of cancer type. These data can inform the evaluation of potential excess cardiovascular risks from new interventions.

KEYWORDS
cancer, heart failure, hypertension, myocardial infarction, venous thromboembolism
1 | INTRODUCTION

With the advent of new chemotherapy agents, cancer patients are surviving longer but experiencing increased morbidity and mortality from cardiovascular disease. The number of cancer survivors in the United States has grown to over 10 million and there are limited data on the prevalence and incidence of cardiovascular disease in this population. Chemotherapy agents, including increasingly popularized tyrosine kinase inhibitors (TKIs), may have cardiotoxic effects but limitations of clinical trials (sample size, follow-up time) and post-marketing surveillance studies have made it difficult to determine to what extent the newer agents increase cardiovascular risk above the background level. The objective of this study was to quantify the incidence rates of cardiovascular outcomes among patients diagnosed with different types of cancer in the pre-TKI and bevacizumab treatment era.

2 | METHODS

2.1 | Data sources

Kaiser Permanente Northern California (KPNC) is an integrated health program that included 3.2 million members at the time of this analysis. KPNC provides comprehensive care to its members, has high member retention rates (more than 80% at 10 years postcancer diagnosis), and is thus uniquely positioned to study cancer treatment, outcomes, and survivorship. The membership’s demographics closely resemble the underlying census population of Northern California. Data were combined from a variety of KPNC research databases, including a cancer registry which includes specific cancer diagnoses, stages, and treatments.

2.2 | Study population

For this study, patients were identified with selected solid tumor (excluding non-melanoma skin cancer) and liquid tumor cancer diagnoses between 1997 and 2009 from the cancer registry. Patients with gaps in membership greater than 12 months, unknown cancer stage, or treatment with either a TKI or bevacizumab were excluded from the analysis. The timeline used for cohort inclusion, covariates, and outcomes is shown in Figure 1.

2.3 | Risk factors for cardiovascular disease

Cardiovascular risk factors of interest included: hypertension (ICD-9 codes 401.0, 401.1, 401.9), hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.4), diabetes mellitus (ICD-9 codes 250.0-250.9, 250.0-250.3), and a history of coronary artery disease (ICD-9 code 414). The code of interest was required to be present between 1/1/1996 and the day before the cancer diagnosis (see Appendix Table S1 for coding details).

2.4 | Demographic and clinical characteristics

Demographic factors and clinical characteristics such as smoking status, history of heart failure, and types of cancer treatment received were obtained from KPNC research databases (see Appendix Table S1 for coding details).

Primary endpoints were required to occur after the cancer diagnosis and included the following: Acute coronary syndrome (ACS, ICD9 codes 411.1 or 410), heart failure (428, 402.01, 402.11, 402.91), stroke (ischemic, 433.1, 434.1, 436 and hemorrhagic, 430-432), cardiac arrest or sustained ventricular arrhythmia (427.1, 427.4-5), hypertension (401.0-1, 401.9), venous thromboembolism (deep venous thrombosis, 451.11, 451.19, 451.2, 451.40-42, 451.81, 451.83, 451.89, 453.4 and pulmonary embolism, 415.1), all-cause mortality, and CV-specific mortality (ie death with one of the CV endpoints listed above as the primary cause or ICD10 death codes I00-I99). Please see Appendix Table S1 for the detailed endpoint coding methodology.

Incidence rates of cardiovascular outcomes were also stratified by the type and number of risk factors (ie no risk factors, hypertension, hyperlipidemia, diabetes mellitus, two risk factors, three risk factors, and prior coronary artery disease).

2.5 | Outcome adjudication

At least 100 cases with each of the cardiovascular outcomes were assessed by chart review to evaluate the accuracy of ICD-9 coding. The chart review process included charts from throughout the study’s 13-year follow-up period. An initial pilot phase was completed and the medical abstractors received feedback from the investigators, resulting in optimization of the coding algorithm. In addition, the sensitivity of the
2.6 | Statistical analysis

The incidence of each cardiovascular endpoint was measured as the rate per 1000 person-years occurring at any time after the cancer diagnosis. Using the score interval technique, 95% confidence limits were calculated for each rate. The rates of all-cause and cancer-related mortality were also calculated for the larger solid tumor cohort. Next, incidence rates were calculated for each specific solid and liquid tumor of interest. Patients experiencing one endpoint were not excluded from the analysis of the other endpoints such that any individual could be counted as having more than one endpoint.

3 | RESULTS

3.1 | Overview of cohort

The study population included 156,610 with solid tumors and 8036 with liquid tumors. Figure 2 illustrates the impact of the inclusion and exclusion criteria. The distribution of specific cancer types is shown in Table 1.

3.2 | Cardiovascular endpoints stratified by cancer type

The incidence rates of cardiovascular endpoints according to individual cancer types of interest are shown in Table 4. ACS was most common in patients with small cell or non-small cell lung cancer. Heart failure and hypertension occurred at a high rate across the spectrum of cancer types. Deep venous thrombosis and pulmonary embolism endpoints were particularly common in patients with lung cancer.

3.3 | Cause of death

The all-cause mortality rate among the patients with solid tumors was 74.7 deaths per 1000 person-years (Table 5). The majority of these deaths were attributed to cancer (54.2 deaths per 1000 person-years) and a minority were coded as CV deaths (7.6 per 1000 person-years).
TABLE 2  Demographic and clinical characteristics for patients with solid tumors

| Variable                      | Total 156,610 |          | Men 71,648 |          | Women 84,962 |          |
|-------------------------------|---------------|----------|------------|----------|--------------|----------|
|                               | N  | %   | N  | %   | N  | %   |
| **Age distribution**          |    |      |    |      |    |      |
| <18 y                         | 725 | 0.5 | 299 | 0.4 | 426 | 0.5 |
| 18-39                         | 13,029 | 8.3 | 1852 | 2.6 | 11,177 | 13.2 |
| 40-49                         | 15,644 | 10.0 | 4174 | 5.8 | 11,470 | 13.5 |
| 50-59                         | 31,072 | 19.8 | 13,740 | 19.2 | 17,332 | 20.4 |
| 60-69                         | 41,224 | 26.3 | 22,804 | 31.8 | 18,420 | 21.7 |
| 70+                           | 54,915 | 35.1 | 28,779 | 40.2 | 26,136 | 30.8 |
| Age, mean (SD)                | 62.2 (15.4) | — | 65.7 (12.5) | — | 59.3 (16.9) | — |
| **Follow-up time (y), mean (SD)** | 4.3 (3.7) | — | 4.1 (3.6) | — | 4.5 (3.8) | — |
| **Race/ethnicity**            |    |      |    |      |    |      |
| African American              | 11,992 | 7.7 | 5723 | 8.0 | 6269 | 7.4 |
| Asian                         | 14,957 | 9.6 | 5907 | 8.2 | 9050 | 10.7 |
| Latino                        | 12,253 | 7.8 | 5517 | 7.7 | 6736 | 7.9 |
| Non-latio-no white            | 116,391 | 74.3 | 54,119 | 75.5 | 62,272 | 73.3 |
| Other or unknown              | 1017 | 0.7 | 382 | 0.5 | 635 | 0.8 |
| **Body mass index >25**       | 67,136 | 42.9 | 31,423 | 43.9 | 35,713 | 42.0 |
| Diabetes mellitus             | 22,201 | 14.2 | 12,322 | 17.2 | 9879 | 11.6 |
| Dyslipidemia                  | 52,086 | 33.3 | 28,540 | 39.8 | 23,546 | 27.7 |
| Hypertension                  | 77,730 | 49.6 | 39,660 | 55.4 | 38,070 | 44.8 |
| Smoking                       | 54,575 | 34.9 | 29,880 | 41.7 | 24,695 | 29.1 |
| Coronary artery disease       | 19,003 | 12.1 | 12,702 | 17.7 | 6301 | 7.4 |
| Acute coronary syndrome       | 8689 | 5.6 | 5690 | 7.9 | 2999 | 3.5 |
| Heart failure                 | 11,062 | 7.1 | 6161 | 8.6 | 4901 | 5.8 |
| Atrial fibrillation/flutter   | 10,937 | 7.0 | 6526 | 9.1 | 4411 | 5.2 |
| Ischemic stroke               | 5833 | 3.7 | 3159 | 4.4 | 2674 | 3.2 |
| Hemorrhagic stroke            | 813 | 0.5 | 470 | 0.7 | 343 | 0.4 |
| Cardiac arrest                | 1928 | 1.2 | 1288 | 1.8 | 640 | 0.8 |
| Deep venous thrombosis        | 839 | 0.5 | 410 | 0.6 | 429 | 0.5 |
| Pulmonary embolism            | 1140 | 0.7 | 534 | 0.8 | 606 | 0.7 |
| **SEER Stage**                |    |      |    |      |    |      |
| 0: In situ                    | 25,824 | 16.5 | 5717 | 8.0 | 20,107 | 23.7 |
| 1: Localized                  | 69,626 | 44.5 | 37,073 | 51.7 | 32,553 | 38.3 |
| 2: Regional by direct extension | 10,061 | 6.4 | 5796 | 8.1 | 4265 | 5.0 |
| 3: Regional lymph nodes involved | 11,546 | 7.4 | 2797 | 3.9 | 8749 | 10.3 |
| 4: Regional by direct extension & lymph nodes | 5884 | 3.8 | 2861 | 4.0 | 3023 | 3.6 |
| 5: Regional, not specified    | 435 | 0.3 | 231 | 0.3 | 204 | 0.2 |
| 7: Distant site(s)/node(s)    | 25,427 | 16.2 | 12,915 | 18.0 | 12,512 | 14.7 |
| 9: Unknown                    | 7807 | 5.0 | 4258 | 5.9 | 3549 | 4.2 |
| **Cancer treatments**         |    |      |    |      |    |      |
| Chemotherapy                  | 37,778 | 24.1 | 13,376 | 18.7 | 24,402 | 28.7 |
| Immunotherapy                 | 1890 | 1.2 | 1291 | 1.8 | 599 | 0.7 |
| Radiation therapy             | 40,666 | 26.0 | 19,775 | 27.6 | 20,891 | 24.6 |
| Surgical resection            | 106,538 | 68.0 | 36,930 | 51.5 | 69,608 | 81.9 |
3.4 | Cardiovascular endpoints according to risk factor profile

The effects of different cardiovascular risk factors on the incidence rates of the various study outcomes are shown in Table 6. Hypertension, hyperlipidemia, diabetes mellitus, and a history of established coronary artery disease (CAD) were associated with endpoints related to atherosclerosis: ACS, heart failure, ischemic stroke, and cardiovascular death. The effects of these risk factors on the rates of DVT, pulmonary embolism, and hemorrhagic stroke were less marked. Table 6 also demonstrates increasing incidence rates for some outcomes as the number of cardiovascular risk factors increases. For example, the rate of ACS was 12.4 cases per 1000 person-years in the absence of any risk factors, 22.3 with two risk factors, 34.1 with three risk factors, and 50.4 with a prior history of CAD. There were much smaller differences observed for the venous thromboembolic outcomes, for which atherosclerosis is not a causative mechanism. The incidence of new-onset hypertension did not increase with the number of cardiovascular risk factors as previous hypertension was an exclusion criterion for this endpoint.

3.5 | Endpoint adjudication results

A total of 1052 charts were reviewed, including at least 100 cases for each cardiovascular endpoint. The confirmed endpoint diagnosis rates (true positive rates) ranged from 76% to 91%. The true positive rates for the coding algorithm were stable over time. For the 250-patient sample without coded outcomes, chart review confirmed the absence of an outcome in 98% of cases.

4 | DISCUSSION

This analysis offers a comprehensive description of the incidence of cardiovascular outcomes among patients with multiple cancer types. Hypertension and heart failure occurred in high rates among patients with all the cancer types whereas ACS and thromboembolic events occurred most frequently in lung cancer patients. The risk of hemorrhagic stroke was especially high in patients with liquid tumors such as acute and chronic myeloid leukemia. Mortality was common, but a minority of deaths occurred due to cardiovascular causes. Finally, the incidence rates of cardiovascular outcomes were higher among patients with increasing numbers of cardiovascular risk factors.

4.1 | Comparison with current knowledge

This study showed that new-onset hypertension was common among patients with cancer; this is not surprising since hypertension has been reported to occur at rates of 10%-40% among cancer patients, depending on the type and dose of treatment. Variations in reported hypertension rates may be related to the pathophysiology of different cancer types, variable detection and documentation of previously undiagnosed disease during periods of intensive medical observation, specific treatments used for each cancer, differing rates of comorbidities, and varying study follow-up times.

Prior studies suggest that there is an increased risk of vascular disease such as stroke and ACS among cancer patients. In this study, this was particularly evident in lung cancer patients, who had a particularly high incidence of stroke, consistent with prior studies. In comparison, an older (1996-1999) KPNC cohort study of patients with COPD reported an incident stroke rate of approximately 8 per 1000 person-years versus 17 (non-small cell) to 23 (small cell) per 1000 person-years among patients with lung cancer in this study. A prior KPNC study of population trends in myocardial infarction rates reported an incidence of 2.9 per 1000 person-years in 1999 which decreased to 2.1 by 2008. Those rates are low compared to what was observed in the lung cancer population in this study: 34.5 ACS (unstable angina plus MI) cases per 1000 person-years among patients with non-small cell cancer and 48.1 among those with small-cell cancer. Tumor embolism, cerebral metastases, cerebral infections, coagulation disorders, and therapeutic-side effects all may contribute to cerebrovascular events and ACS in cancer patients.

In this study, heart failure endpoints were common, regardless of cancer type, ranging from 9.4 to 78.7 cases per 1000 person-years. In comparison, a prior KPNC cohort study of patients with diabetes mellitus reported a HF incidence of 4.5 to 9.2 per 1000 person-years. In some of the cancers included in this analysis, such as breast cancer and non-Hodgkin’s lymphoma, cardiotoxic medications such as anthracyclines, daunorubicin and doxorubicin, are first line treatments. In a prior study of 700 breast cancer patients taking anthracyclines, 52 cases of treatment-induced cardiomyopathy occurred. Other studies reported a 5-year cumulative risk of cardiac events including systolic dysfunction and clinical heart failure of 19%-20% in non-Hodgkin’s lymphoma patients. The cardiotoxicity of anthracyclines partly occurs due to the production of free radicals and reactive oxygen species (ROS) in response to tumor injury resulting in mitochondrial DNA and myocyte damage.

4.2 | Causes of mortality in the study cohort with solid tumors

The incidence rate of cardiovascular mortality was 7.60 per 1000 PY vs. 54.15 per 1000 PY for cancer-related mortality. Notably, the mean number of days from cancer diagnosis to death was higher in those experiencing cardiovascular mortality compared to cancer-related mortality (1398 vs...
## Table 3  Demographic and clinical characteristics for patients with liquid tumors

| Variable                        | Total  |       | Men  |       | Women |       |
|---------------------------------|--------|-------|------|-------|-------|-------|
|                                 | N      | %     | N    | %     | N     | %     |
| **Age distribution**            |        |       |      |       |       |       |
| <18                             | 401    | 5.0   | 246  | 5.7   | 155   | 4.2   |
| 18-39                           | 528    | 6.6   | 299  | 6.9   | 229   | 6.2   |
| 40-49                           | 794    | 9.9   | 462  | 10.6  | 332   | 9.0   |
| 50-59                           | 1433   | 17.8  | 785  | 18.0  | 648   | 17.6  |
| 60-69                           | 1754   | 21.8  | 979  | 22.5  | 775   | 21.0  |
| 70+                             | 3126   | 38.9  | 1581 | 36.3  | 1545  | 41.9  |
| **Age, mean (SD)**              |        |       |      |       |       |       |
|                                 | 61.2 (19.3) | — | 60.1 (19.6) | — | 62.5 (18.9) | — |
| **Follow-up time (y), mean (SD)** | 3.8 (3.6) | — | 3.7 (3.5) | — | 4.0 (3.6) | — |
| **Race/ethnicity**              |        |       |      |       |       |       |
| African American                | 474    | 5.9   | 242  | 5.6   | 232   | 6.3   |
| Asian                           | 851    | 10.6  | 464  | 10.7  | 387   | 10.5  |
| Latino                          | 751    | 9.4   | 419  | 9.6   | 332   | 9.0   |
| Non-latino White                | 5923   | 73.7  | 3208 | 73.7  | 2715  | 73.7  |
| Other or unknown                | 37     | 0.5   | 19   | 0.4   | 18    | 0.5   |
| **Body mass index >25**         | 3170   | 39.5  | 1632 | 37.5  | 1538  | 41.8  |
| **Diabetes Mellitus**           | 1182   | 14.7  | 679  | 15.6  | 503   | 13.7  |
| **Dyslipidemia**                | 2487   | 31.0  | 1397 | 32.1  | 1090  | 29.6  |
| **Hypertension**                | 3932   | 48.9  | 2055 | 47.2  | 1877  | 51.0  |
| **Smoking**                     | 2604   | 32.4  | 1617 | 37.2  | 987   | 26.8  |
| **Coronary artery disease**     | 1128   | 14.0  | 775  | 17.8  | 353   | 9.6   |
| **Acute coronary syndrome**     | 535    | 6.7   | 341  | 7.8   | 194   | 5.3   |
| **Heart failure**               | 726    | 9.0   | 421  | 9.7   | 305   | 8.3   |
| **Atrial fibrillation/flutter** | 702    | 8.7   | 446  | 10.3  | 256   | 7.0   |
| **Ischemic stroke**             | 309    | 3.9   | 166  | 3.8   | 143   | 3.9   |
| **Hemorrhagic stroke**          | 59     | 0.7   | 39   | 0.9   | 20    | 0.5   |
| **Cardiac arrest**              | 153    | 1.9   | 99   | 2.3   | 54    | 1.5   |
| **Deep venous thrombosis**      | 53     | 0.7   | 24   | 0.6   | 29    | 0.8   |
| **Pulmonary embolism**          | 61     | 0.8   | 21   | 0.5   | 40    | 1.1   |
| **SEER Stage**                  |        |       |      |       |       |       |
| 1: Localized                    | 1901   | 23.7  | 1009 | 23.2  | 892   | 24.2  |
| 2: Regional by direct extension | 80     | 1.0   | 38   | 0.9   | 42    | 1.1   |
| 3: Regional lymph nodes involved| 12     | 0.2   | 6    | 0.1   | 6     | 0.2   |
| 4: Regional by direct extension & lymph nodes | 8 | 0.1 | 5 | 0.1 | 3 | 0.1 |
| 5: Regional, not specified      | 988    | 12.3  | 507  | 11.7  | 481   | 13.1  |
| 7: Distant site(s)/node(s)      | 4767   | 59.3  | 2635 | 60.6  | 2132  | 57.9  |
| 9: Unknown                      | 280    | 3.5   | 152  | 3.5   | 128   | 3.5   |
| **Cancer treatments**           |        |       |      |       |       |       |
| Chemotherapy                    | 5281   | 65.7  | 2944 | 67.7  | 2337  | 63.4  |
| Immunotherapy                   | 652    | 8.1   | 350  | 8.0   | 302   | 8.2   |
| Radiation therapy               | 1397   | 17.4  | 704  | 16.2  | 693   | 18.8  |
| Surgical resection              | 3667   | 45.6  | 1975 | 45.4  | 1692  | 45.9  |
| Outcome                                | N    | Person-time (y) | Incidence rate (95% CI)a | N    | Person-time (y) | Incidence Rate (95% CI)a |
|----------------------------------------|------|-----------------|--------------------------|------|-----------------|--------------------------|
| Acute coronary syndrome                | 256  | 12 383.4        | 20.7 (18.3-23.3)         | 201  | 10 098.9        | 19.9 (17.4-22.8)         |
| Heart failure                          | 354  | 12 177.6        | 29.1 (26.2-32.2)         | 280  | 9921.6          | 28.2 (25.1-31.7)         |
| Ischemic stroke                        | 122  | 12 746.0        | 9.6 (8.0-11.4)           | 95   | 10 390.2        | 9.14 (7.5-11.2)          |
| Hemorrhagic stroke                     | 52   | 12 986.9        | 4.0 (3.1-5.3)            | 46   | 10 580.4        | 4.35 (3.3-5.8)           |
| Cardiac arrest                         | 132  | 12 910.1        | 10.2 (8.6-12.1)          | 103  | 10 524.8        | 9.79 (8.1-11.9)          |
| Hypertension                           | 347  | 11 586.3        | 30.0 (27.0-33.2)         | 270  | 9451.1          | 28.6 (25.4-32.1)         |
| Deep venous thrombosis                 | 59   | 12 968.5        | 4.55 (3.5-5.9)           | 42   | 10 579.7        | 3.97 (2.9-5.4)           |
| Pulmonary embolism                     | 92   | 12 865.3        | 7.15 (5.8-8.8)           | 77   | 10 490.0        | 7.34 (5.9-9.2)           |
| Cardiovascular death                   | 172  | 14 460.1        | 11.9 (10.3-13.8)         | 135  | 11 817.0        | 11.42 (9.7-13.5)         |
| **Colorectal cancer**                  |      |                 |                          |      |                 |                          |
| Acute coronary syndrome                | 914  | 55 258.6        | 16.5 (15.5-17.6)         | 82   | 1705.8          | 48.1 (38.9-59.3)         |
| Heart failure                          | 1372 | 54 256.4        | 25.3 (24.0-26.6)         | 122  | 1643.1          | 74.3 (62.5-87.9)         |
| Ischemic stroke                        | 543  | 56 486.7        | 9.6 (8.8-10.5)           | 40   | 1720.7          | 23.3 (17.1-31.5)         |
| Hemorrhagic stroke                     | 150  | 57 550.9        | 2.6 (2.2-3.1)            | 22   | 1743.0          | 12.6 (8.4-19.0)          |
| Cardiac arrest                         | 561  | 57 081.0        | 9.8 (9.1-10.7)           | 86   | 1729.3          | 49.7 (40.5-61.0)         |
| Hypertension                           | 1901 | 49 098.6        | 38.7 (37.1-40.5)         | 80   | 1645.2          | 48.6 (39.2-60.1)         |
| Deep venous thrombosis                 | 348  | 57 081.3        | 6.1 (5.5-6.8)            | 22   | 1734.7          | 12.7 (8.4-19.1)          |
| Pulmonary embolism                     | 369  | 57 074.2        | 6.5 (5.8-7.2)            | 46   | 1712.1          | 26.9 (20.2-35.7)         |
| Cardiovascular death                   | 810  | 63 546.3        | 12.8 (11.9-13.7)         | 38   | 1888.6          | 20.1 (14.7-27.5)         |
| **Non-small cell lung cancer**         |      |                 |                          |      |                 |                          |
| Acute coronary syndrome                | 501  | 14 525.4        | 34.5 (31.6-37.6)         | 1089 | 166 799.3      | 6.5 (6.2-6.9)            |
| Heart failure                          | 738  | 14 151.6        | 52.2 (48.6-55.9)         | 2239 | 163 420.7      | 13.7 (13.2-14.3)         |
| Ischemic stroke                        | 263  | 14 890.4        | 17.7 (15.7-19.9)         | 877  | 167 609.2      | 5.2 (4.9-5.6)            |
| Hemorrhagic stroke                     | 93   | 15 085.3        | 6.2 (5.0-7.6)            | 262  | 169 485.9      | 1.6 (1.4-1.8)            |
| Cardiac arrest                         | 357  | 15 003.9        | 23.8 (21.5-26.4)         | 540  | 169 137.8      | 3.2 (2.9-3.5)            |
| Hypertension                           | 589  | 13 590.7        | 43.3 (40.0-46.9)         | 5187 | 144 629.4      | 35.9 (34.9-36.8)         |
| Deep venous thrombosis                 | 197  | 14 991.8        | 13.1 (11.4-15.1)         | 485  | 168 915.3      | 2.9 (2.6-3.1)            |
| Pulmonary embolism                     | 401  | 14 862.3        | 27.0 (24.5-29.7)         | 467  | 168 774.5      | 2.8 (2.5-3.0)            |
| Cardiovascular death                   | 248  | 16 286.6        | 15.2 (13.5-17.2)         | 926  | 187 480.1      | 4.9 (4.6-5.3)            |
| **Prostate cancer**                    |      |                 |                          |      |                 |                          |
| Acute coronary syndrome                | 2165 | 137 258.2       | 15.8 (15.1-16.5)         | 1    | 194.7          | 5.1 (0.9-28.5)           |
| Heart failure                          | 2536 | 137 066.0       | 18.5 (17.8-19.2)         | 4    | 194.8          | 20.5 (8.0-51.6)          |
| Ischemic stroke                        | 1002 | 141 479.3       | 7.1 (6.7-7.5)            | 0    | 196.1          | 0 (0-19.2)               |
| Hemorrhagic stroke                     | 350  | 143 740.3       | 2.4 (2.2-2.7)            | 0    | 196.1          | 0 (0-19.2)               |
| Cardiac arrest                         | 921  | 142 934.4       | 6.4 (6.0-6.9)            | 3    | 195.9          | 15.3 (5.2-44.1)          |
| Hypertension                           | 3621 | 127 510.9       | 28.4 (27.5-29.3)         | 9    | 147.5          | 61.0 (32.4-111.9)        |
| Deep venous thrombosis                 | 464  | 143 382.7       | 3.2 (3.0-3.5)            | 0    | 196.1          | 0 (0-19.2)               |
| Pulmonary embolism                     | 439  | 143 304.5       | 3.1 (2.8-3.4)            | 2    | 195.9          | 10.2 (2.8-36.5)          |
| Cardiovascular death                   | 1286 | 160 053.1       | 8.0 (7.6-8.5)            | 0    | 218.9          | 0 (0-17.3)               |

(Continues)
| Outcome                  | N   | Person-time (y) | Incidence rate (95% CI)a | N   | Person-time (y) | Incidence Rate (95% CI)a |
|--------------------------|-----|----------------|--------------------------|-----|----------------|--------------------------|
| Renal cancer (all types) |     |                |                          |     |                |                          |
| Hepatocellular carcinoma | 32  | 1650.4         | 19.4 (13.8-27.2)         |     |                |                          |
| Renal cell carcinoma     | 4   | 255.6          | 15.7 (6.1-39.6)          |
| Pancreatic neuroendocrine tumor |     |                |                          | 9   | 260.1          | 34.6 (18.3-64.4)         |
| acute coronary syndrome  | 78  | 1603.5         | 48.7 (39.2-60.3)         | 1   | 275.6          | 3.6 (0.6-20.3)           |
| Heart failure            | 11  | 1666.2         | 6.6 (3.7-11.8)           | 1   | 275.6          | 3.6 (0.6-20.3)           |
| Ischemic stroke          | 19  | 1656.9         | 11.5 (7.4-17.8)          | 1   | 275.6          | 3.6 (0.6-20.3)           |
| Hemorrhagic stroke       | 60  | 1555.0         | 38.6 (30.1-49.4)         | 7   | 260.8          | 26.8 (13.1-54.4)         |
| Cardiac arrest           | 42  | 1655.7         | 25.4 (18.8-34.1)         | 6   | 261.0          | 23.0 (10.6-49.2)         |
| Hypertension             | 14  | 1664.0         | 8.4 (5.0-14.1)           | 1   | 273.7          | 3.7 (0.7-20.4)           |
| Deep venous thrombosis   | 22  | 1843.5         | 11.9 (7.9-18.0)          | 2   | 294.4          | 6.8 (1.9-24.4)           |
| Pulmonary embolism       |     |                |                          | 9   | 1659.1         | 5.4 (2.9-10.3)           |
| Cardiovascular death     |     |                |                          | 1   | 1555.0         | 3.6 (0.6-20.3)           |
| Non-Hodgkin's lymphoma   |     |                |                          | 11  | 1702.4         | 10.0 (6.2-15.9)          |
| - nodal                  |     |                |                          | 124 | 1704.2         | 78.7 (66.4-93.1)         |
| - extranodal             |     |                |                          | 17  | 1702.4         | 78.7 (66.4-93.1)         |
| Acute myeloid leukemia   |     |                |                          | 11  | 1702.4         | 78.7 (66.4-93.1)         |
| Chronic myeloid leukemia |     |                |                          | 18  | 1702.4         | 78.7 (66.4-93.1)         |
| Acute lymphoblastic leukemia |   |                |                          | 18  | 1702.4         | 78.7 (66.4-93.1)         |

Note: An individual patient may experience multiple outcomes. The occurrence of a specific type of outcome censors that patient from experiencing the same outcome again but not other types of outcomes.

a Per 1000 person-years.
614 respectively. Due to competing risks, it is reasonable to presume that patients with very aggressive cancers experience cancer-related mortality sooner than cardiovascular-related mortality and thus a substantial number of patients with the potential to develop cardiovascular disease were censored from the analysis. However, the number of cancer survivors is expected to increase by approximately 70% until the year 2040 and as survival time increases, the number of patients succumbing to cardiovascular disease is also likely to increase. One prior study reported late cardiac toxicity in 30% of patients 13 years after initiation of cancer treatment.

### 4.3 Risk factors for cardiovascular outcomes

This study shows a trend towards an increased incidence of cardiovascular outcomes among cancer patients with

| TABLE 5 | All-cause, cancer-related, and cardiovascular death among patients with solid tumors |
|------------------|---------------------------------|---------------------------------|
|                   | N  | Person-time (years) | Incidence Rate (95% CI) | Days from Cancer Diagnosis to Death<sup>b</sup> |
| All-cause mortality | 57,846 | 774,671.0 | 74.7 (74.1-75.3) | 832 ± 1008, 401 |
| Cardiovascular death | 5888 | 774,671.4 | 7.6 (7.4-7.8) | 1398 ± 1187, 112 |
| Cancer-related death | 41,949 | 774,671.4 | 54.2 (53.7-54.7) | 614 ± 813, 285 |

<sup>a</sup>Per 1000 person-years.  
<sup>b</sup>Or censoring.

| TABLE 6 | Cardiovascular outcome rates according to the type and number of risk factors and a history of coronary artery disease |
|------------------|---------------------------------|---------------------------------|---------------------------------|
|               | Incidence rates (95% CI)<sup>a</sup> |               |               |               |               |
|                 | No risk factors | Hypertension | Hyperlipidemia | Diabetes mellitus |
| Acute coronary syndrome | 12.4 (12.1-12.7) | 20.2 (19.7-20.7) | 21.7 (21.0-22.4) | 29.5 (28.3-30.7) |
| Heart failure | 18.9 (18.5-19.2) | 32.0 (31.4-32.7) | 29.0 (28.3-29.8) | 43.7 (42.2-45.3) |
| Ischemic stroke | 7.0 (6.8-7.2) | 10.9 (10.5-11.3) | 9.0 (8.5-9.4) | 13.8 (13.0-14.6) |
| Hemorrhagic stroke | 2.6 (2.4-2.7) | 3.7 (3.5-4.0) | 3.6 (3.4-3.9) | 4.3 (3.8-4.8) |
| Cardiac arrest | 6.8 (6.7-7.0) | 10.6 (10.2-11.0) | 10.2 (9.8-10.7) | 14.4 (13.5-15.2) |
| Hypertension | 32.7 (32.3-33.2) | 12.6 (12.2-13.0) | 22.1 (21.4-22.8) | 20.5 (19.5-21.6) |
| Deep venous thrombosis | 4.6 (4.5-4.8) | 6.3 (6.0-6.6) | 6.8 (6.4-7.2) | 6.8 (6.2-7.4) |
| Pulmonary embolism | 5.2 (5.0-5.4) | 7.1 (6.8-7.5) | 7.4 (7.0-7.8) | 6.9 (6.3-7.5) |
| All-cause mortality | 74.7 (74.1-75.3) | 109.8 (108.7-110.9) | 100.3 (99.0-101.6) | 133.5 (131.2-135.8) |
| Cardiovascular death | 7.6 (7.4-7.8) | 13.6 (13.2-14.0) | 11.6 (11.2-12.1) | 17.1 (16.2-18.0) |

<sup>a</sup>Per 1000 person-years.  
<sup>b</sup>2/3 of hypertension, hyperlipidemia, and diabetes mellitus.  
<sup>c</sup>Hypertension, hyperlipidemia, and diabetes mellitus.
one or more cardiovascular risk factors, a novel finding compared with prior studies which focused on individual risk factors.\textsuperscript{22,26} A history of CAD was associated with the highest incidence rates of the cardiovascular outcomes of interest.

4.4 | Strengths

The strengths of this study include a large sample size, a long follow-up period, a robust endpoint adjudication process, and generalizability to the local population. Another strength is the use of data from a cancer registry which provides unbiased population data regarding cancer treatments and survival.

4.5 | Limitations

This was a retrospective cohort study with intrinsic limitations including missing data, censorship of patients who are lost to follow-up, and difficulties in comparing outcome timing and variables such as cancer treatment timing. The study was conducted using a cohort of patients selected from 1997 to 2009. However, this cohort was intentionally chosen to quantify the rates of cardiovascular outcomes among cancer patients before the use of newer therapeutic agents. Additionally, it is unclear to what extent KPNC cancer and cardiovascular treatments are generalizable to other health care systems though generalizability may be superior in comparison with studies from academic and/or tertiary care centers.

5 | CONCLUSIONS

The rates of cardiovascular outcomes among cancer patients included in this analysis were high, regardless of cancer type. Although a majority of deaths during the study period were due to cancer-related causes, it is important to note that death from cardiovascular causes occurred later after cancer diagnosis, which may be explained by the late effects of therapy-related cardiotoxicity on cancer survivors. Furthermore, cardiovascular events appeared to occur more commonly in cancer patients with increasing numbers of cardiovascular risk factors and, in particular, a prior history of CAD. Future research is warranted to investigate the role of early cardiovascular screening and the use of cardio-protective agents in reducing cardiovascular-related complications in cancer patients.

ACKNOWLEDGMENTS

L Titievsky was an employee of Pfizer at the time this work was conducted and holds Pfizer stocks.

CONFLICT OF INTEREST

None of the study authors have conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Jonathan G. Zaroff [D] https://orcid.org/0000-0002-2513-0464

REFERENCES

1. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. \textit{N Engl J Med}. 2000;342:1077-1084.
2. Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. \textit{J Clin Oncol}. 2010;28:2280-2285.
3. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. \textit{Arch Intern Med}. 2006;166:458-464.
4. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio- oncological prevention. \textit{J Natl Cancer Inst}. 2010;102:14-25.
5. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. \textit{J Am Coll Cardiol}. 2009;53:2231-2247.
6. Zoller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. \textit{Eur J Cancer}. 2012;48:1875-1883.
7. Zoller B, Ji J, Sundquist J, Sundquist K. Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden. \textit{Eur J Cancer}. 2012;48:121-128.
8. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. \textit{J Clin Oncol}. 2007;25:3991-4008.
9. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. \textit{Lancet}. 2007;370:2011-2019.
10. Iribarren C, Tolstykh I, Somkin CP, et al. Sex and racial/ethnic disparities in outcomes after acute myocardial infarction: a cohort study among members of a large integrated health care delivery system in northern California. \textit{Arch Intern Med}. 2005;165:2105-2113.
11. Agresti A, Coull BA. Approximate is better than “exact” for interval estimation of binomial proportions. \textit{Am Stat}. 1998;52:119-126.
12. Moughayar E, Salahudeen A. Hypertension in cancer patients. \textit{Tex Heart Inst J}. 2011;38:263-265.
13. Fraeman KH, Nordstrom BL, Luo W, Landis SH, Shantakumar S. Incidence of new-onset hypertension in cancer patients: a retrospective cohort study. \textit{Int J Hypertens}. 2013;2013:379252.
14. Stefan O, Vera N, Otto B, Heinz L, Wolfgang G. Stroke in cancer patients: a risk factor analysis. \textit{J Neurooncol}. 2009;94:221-226.
15. Chen PC, Miao CH, Lee YT, Yu YH, Sung FC. Lung cancer and incidence of stroke: a population-based cohort study. *Stroke*. 2011;42:3034-3039.
16. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. *Acta Neurol Scand*. 2009;119:1-16.
17. Navi BB, Reichman JS, Berlin D, et al. Intracerebral and subarachnoid hemorrhage in patients with cancer. *Neurology*. 2010;74:494-501.
18. Park JY, Guo W, Al-Hijji M, et al. Acute coronary syndromes in patients with active hematologic malignancies – incidence, management, and outcomes. *Int J Cardiol*. 2019;275:6-12.
19. Sidney S, Sorel M, Quesenberry CP, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest*. 2005;128:2068-2075.
20. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165.
21. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation*. 2001;103:2668-2673.
22. Reinbolt RE, Patel R, Pan X, et al. Risk factors for anthracycline-associated cardiotoxicity. *Support Care Cancer*. 2016;24:2173-2180.
23. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol*. 2013;112:1980-1984.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.