12-1-2023

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ORIGINAL RESEARCH

Risk profiles and incidence of cardiovascular events across different cancer types

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Available online 17 November 2023

Background: Cancer survivors are at increased risk for cardiovascular (CV) disease, although additional data are needed to better understand the incidence of CV events across different malignancies. This study sought to characterize the incidence of major adverse CV events [myocardial infarction, stroke, unstable angina (MACE), or heart failure (HF)] across multiple cancer types after cancer diagnosis.

Patients and methods: Patients were identified from a USA-based administrative claims database who had index cancer diagnoses of breast, lung, prostate, melanoma, myeloma, kidney, colorectal, leukemia, or lymphoma between 2011 and 2019, with continuous enrollment for ≥12 months before diagnosis. Baseline CV risk factors and incidence rates of CV events post-index were identified for each cancer. Multivariable Cox hazards models assessed the cumulative incidence of MACE, accounting for baseline risk factors.

Results: Among 839 934 patients across nine cancer types, CV risk factors were prevalent. The cumulative incidence of MACE was highest in lung cancer and myeloma, and lowest in breast cancer, prostate cancer, and melanoma. MACE cumulative incidence for lung cancer was 26% by 4 years (2.7-fold higher relative to breast cancer). The incidence of stroke was especially pronounced in lung cancer, while HF was highest in myeloma and lung cancer.

Conclusions: CV events were especially increased following certain cancer diagnoses, even after accounting for baseline risk factors. Understanding the variable patient characteristics and associated CV events across different cancers can help target appropriate CV risk factor modification and develop strategies to minimize adverse CV events and improve patient outcomes.

Key words: cancer, cardio-oncology, cardiovascular disease, major adverse cardiovascular event, real-world data, risk assessment

INTRODUCTION

Cancer and cardiovascular (CV) disease (CVD) account for >40% of disease-related deaths globally.[1] These diseases are often encountered in the same patients because of shared risk factors such as tobacco use,[2,3] a bidirectional mechanistic relationship between cancer and CVD,[4,5] and CV side-effects of cancer treatments.[6-10] Cancer therapies, including radiation therapy, are associated with a myriad of CV toxicities,[11] including cardiomyopathy, development and progression of coronary artery disease (CAD),[10,12] direct CV injury,[13,14] myocarditis,[15] and arrhythmia.[16,17] Cancer is known to induce increased platelet activation and aggregability, which can increase the incidence of CVD.[18,19] Cachexia, chronic inflammation, and cardiotoxic oncometabolites have also been shown to increase the risk of CVD in patients with cancer.[5]

In recent decades, cancer survival after diagnosis has improved significantly, with half of people diagnosed with cancer in high-income settings surviving >10 years.[20] Given the improved prognoses now possible following a cancer diagnosis, it is imperative to understand the risk and impact of CVD in people with cancer.[21,22] On average, these patients have a two- to sixfold higher CVD mortality rate than the general population, with the highest risk in the first year after cancer diagnosis.[23,24] The CV risk factors or CVD that are often present in patients with cancer tend to persist or worsen during cancer therapy.[21] Conversely, a patient's CV health can also impact cancer treatment. CV risk factors and

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CVD increase the risk of cardiac events during and after cancer therapy, and therefore can compromise the use of cancer regimens and clinical outcomes.[21,25]

While our previous understanding of CVD in cancer is largely based on studies in breast cancer and survivors of childhood cancers, more recent studies have begun to explore the seemingly marked difference in CV risk among different cancer types.[23,26-29] These studies have leveraged large electronic health record (EHR), administrative, or tumor registry databases to explore the differences in CV risk among specific cancer demographics. However, important gaps in our understanding remain.

An analysis using the USA-based Kaiser Permanente Surveillance, Epidemiology, and End Results (SEER)-affiliated cancer registry found that the risk of CVD [ischemic heart disease, stroke, or cardiomyopathy/heart failure (HF)] in 2-year cancer survivors compared with age- and sex-matched controls varied by cancer subtype and by the presence of CV risk factors (i.e. hypertension, diabetes, or dyslipidemia).[27] After accounting for CV risk factors, survivors of multiple myeloma (MM), lung/bronchus carcinoma, non-Hodgkin's lymphoma, and breast cancer had a significantly higher CVD risk compared with matched non-cancer controls; other evaluated cancer types did not have an increased CV risk. Notably, this study did not evaluate CV events in the first 2 years after cancer diagnosis but focused on cancer survivors.[27]

Another recent study used EHR databases from the UK Clinical Research Practice Datalink to compute incidence rates and adjusted hazard ratios (aHRs) for CV events in patients with different cancer types starting 1 year after cancer diagnosis and compare outcomes with the general population.[26] This analysis similarly demonstrated that aHRs for CV events varied across survivors of different cancer types compared with the control population, including increased risks for HF and cardiomyopathy in patients with lung cancer, lymphoma, and MM.[26]

While these prior studies helped shape our understanding of CV events in cancer survivors at least 1 year after cancer diagnosis, neither was designed to account for CV events during the first year post-cancer diagnosis—a period when the increased risk of CV mortality is highest.[23] More recently, an analysis of a Canadian administrative database helped define the relative risk of CV events and mortality for different cancer types at the time of diagnosis.[28]

Yet, to date, no study has reported on the cumulative incidence of CV events over time across different initial cancer diagnoses while accounting for baseline CV risk factors. Such information is valuable to help guide CV screening and prevention strategies at the time of cancer diagnosis, with the aim of reducing the risk of adverse cardiac events and minimizing interruptions to cancer treatment. Thus, we sought to use a large administrative claims database to characterize the background prevalence and variability of CV risk factors and CVD in patients across cancer types and estimate the relative incidence of CV events while accounting for baseline CV risk factors and CVD.

PATIENTS AND METHODS

Data source

Data for this study were derived from IQVIA PharMetrics® Plus, a de-identified, integrated administrative claims database of paid medical and pharmacy claims for >210 million members since 2006 from health insurance plans across the United States. The database, which is representative of the commercially insured USA population aged <65 years, includes both inpatient and outpatient claims, diagnoses, and procedures based on the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) and Current Procedural Terminology codes, as well as retail and mail order pharmacy claims.

Study design

This non-interventional, longitudinal, retrospective, observational study was conducted using cohorts of patients diagnosed with one of nine cancers—breast, lung, prostate, melanoma, myeloma, kidney, colorectal, leukemia, or lymphoma—in the PharMetrics® Plus database from 1 June 2011 until 31 December 2019.

Study population

Patients (aged ≥18 years) included in the study were required to have at least two diagnosis claims for the same cancer within a 60-day period, to have baseline data available for 12 months before their initial cancer diagnosis (index date) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101830), and could not have more than one type of cancer on the index date. Follow-up occurred until the end of the study period (31 December 2019) or health plan disenrollment.

Study variables and outcomes

Patient demographics, comorbidities, and baseline use of statins were extracted. The baseline prevalence of CV risk factors and CVD was assessed within the 12-month pre-index (baseline) period before cancer diagnosis using ICD-9/10-CM codes (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101830). Where appropriate, Elixhauser diagnoses codes were used to define each comorbidity.[30] Evaluated outcomes included the incidence of major adverse CV events (MACE), defined as myocardial infarction (MI), stroke, unstable angina, or HF by ICD-9/10-CM codes (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101830), as well as the individual CV events of the MACE outcome along with deep vein thrombosis (DVT) and pulmonary embolism (PE).

For each analysis, patients were excluded if the event of interest was recorded in the 12-month baseline period in order to prevent recounting of previous events during follow-up visits. For example, patients with MI before index were not included in the incident MI analysis, and patients with MACE before index were not included in the incident MACE analysis. Both inpatient and outpatient diagnoses were included to document all events, while a sensitivity analysis explored the

impact of limiting events to primary inpatient diagnoses only. MI was specified as acute MI (initial episode of care), while stroke was evaluated as the combination of ischemic, hemorrhagic, and non-specified stroke. In prior analyses of administrative claims databases, the ICD-9/10-CM codes for inpatient MI and stroke were found to have a ≥90% positive predictive value (PPV) for adjudicated events,[31-34] and the codes for HF were found to have a specificity of 83%-99% and a PPV of 84%-96%.[35]

Statistical considerations

Patient demographics, baseline prevalence rates of CV risk factors and CVD within 12 months before index, and baseline statin use were analyzed descriptively. Incidence rates of each CV event after index per 1000 person years were identified for each cancer type. Multivariable Cox hazards models across cancer types assessed the adjusted hazard for MACE over the follow-up period that was attributable to baseline CV risk factors and CVD. Covariates included in the multivariable models were selected a priori from accepted CV risk factors and established CVD, and consisted of age (continuous), sex, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco use (current or former), peripheral vascular disease, CAD, cerebrovascular disease, and renal failure. Year of diagnosis was also included in the multivariable model to account for changing treatment patterns over time. Additional multivariable Cox hazards models assessed the cumulative incidence of MACE, MI, stroke, and HF comparatively across cancer types while accounting for the same covariates. Cumulative incidence curves were obtained from the models by applying overall marginal frequencies and mean values for covariates. As prior research on cancer-associated CV risk primarily focused on breast cancer, this cancer type was used as the reference for comparative purposes. A power analysis confirmed the data had sufficient power to detect associations between CV events and covariates of interest (Supplementary Figures S2 and S3, available at https://doi.org/10.1016/j.esmoop.2023.101830).

Statistics were carried out using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Study cohort

A total of 839 934 patients across nine cancer types met inclusion criteria (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101830).

Baseline characteristics

Baseline demographics and characteristics of the study population across cancer types are shown in Table 1. Mean age ranged from 55 years in patients with lymphoma and melanoma to 64 years in patients with prostate cancer. Other than the sex-specific cancers (breast cancer: 99% female; prostate cancer: 100% male), there was a relatively even split between sexes across cancer types, with a small male preponderance in kidney cancer (64% male) and leukemia (58% male). Patients with melanoma had the lowest Charlson Comorbidity Index score [median 0, interquartile range (IQR) 0-1], and patients with lung cancer had the highest score (median 2, IQR 1-5).

Follow-up duration

Patients with lung cancer had the shortest follow-up duration (median 282 days, IQR 118-617 days), while patients with breast cancer had the longest follow-up (median 668 days, IQR 293-1315 days) (Table 1).

Baseline CV risk factors and CVD

During the baseline period, the most prevalent CV risk factors were hypertension (36%-62%) and hyperlipidemia (35%-56%) across all cancer types (Figure 1 and Table 1). The baseline prevalence of almost all CV risk factors was lowest in patients with breast cancer and melanoma, and was highest in kidney, prostate, and lung cancers, as well as myeloma. Baseline CAD was most prevalent in patients with lung cancer (21%) and prostate cancer (15%), and was least prevalent in breast cancer (4%).

CV events

The incidence of CV events post-index varied by cancer diagnosis, and was especially increased in lung cancer, myeloma, and leukemia (Figure 2 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101830). Relative to breast cancer, the incidence rate of HF in lung cancer was 4.5-fold higher, the incidence rates of MI and stroke were both over 7-fold higher, and the incidence rate of PE was almost 10-fold higher. HF and DVT were the most common CV complications across all cancer types over the study period; HF was especially common in lung cancer and myeloma.

For each cancer type, multivariable Cox proportional hazard models were used to determine the independent association between baseline risk factors and incidence of MACE. Across all cancer types, baseline CAD (aHR 1.36-2.25) followed by renal failure (aHR 1.37-1.71) were the greatest risk factors for MACE post-index (Supplementary Table S4 and Figure S4, available at https://doi.org/10.1016/j.esmoop.2023.101830).

Cancer diagnoses with the greatest risk for incident MACE relative to breast cancer after adjusting for baseline CV risk factors and CVD were lung cancer [aHR 2.67, 95% confidence interval (CI) 2.60-2.74, $P < 0.001$], myeloma (aHR 2.21, 95% CI 2.12-2.31, $P < 0.001$), and leukemia (aHR 2.08, 95% CI 2.01-2.14, $P < 0.001$) (Figure 3, Table 2 and Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101830). The cumulative incidence of MACE post-index was lowest for patients with breast cancer, prostate cancer, and melanoma. By 4 years, the cumulative incidence of MACE reached 26%, 22%, and 21% for lung cancer, myeloma, and leukemia, respectively, while the incidence for breast cancer, prostate cancer, and melanoma reached 11%, 9%, and 8%, respectively.

Regarding individual CV events, stroke was especially pronounced in lung cancer relative to breast cancer

Table 1. Baseline demographics and comorbidities

	Breast	Lung	Prostate	Melanoma	Myeloma	Kidney	Colorectal	Leukemia	Lymphoma
Patients, *n*	262 654	74 067	178 742	82 652	16 095	39 624	81 073	37 480	67 547
Total cohort, %	31.3	8.8	21.3	9.8	1.9	4.7	9.7	4.5	8.0
Mean age, years (SD)	56.8 (10.0)	62.2 (9.5)	63.7 (7.9)	54.8 (12.2)	60.7 (10.0)	57.7 (10.5)	58.4 (10.7)	57.1 (14.0)	54.7 (14.0)
Age group, %									
18-40	5.3	1.8	0.3	13.2	2.9	6.0	5.1	12.4	16.2
41-64	76.4	62.3	60.2	69.0	65.8	72.1	70.7	60.4	62.2
65+	18.3	35.8	39.5	17.9	31.3	21.9	24.2	27.2	21.6
Female, %	99.1	48.9	0.3	48.8	44.6	36.0	46.6	41.7	46.1
Median CCI score (IQR)	1 (0-2)	2 (1-5)	1 (0-2)	0 (0-1)	2 (0-3)	2 (0-3)	1 (0-2)	2 (0-2)	2 (0-2)
Median follow-up, days (IQR)	668 (293-1315)	282 (118-617)	604 (271-1206)	672 (282-1326)	517 (222-1044)	542 (231-1115)	523 (223-1073)	526 (214-1127)	595 (253-1218)
CV risk factor									
Hypertension	36.5	**61.9**	**56.7**	**56.1**	55.5	46.6	44.1	39.5	35.5
Hyperlipidemia	35.4	**50.1**	**55.5**	**47.4**	44.3	39.4	39.6	37.2	36.5
Statin use	22.3	**35.2**	**41.2**	**35.6**	29.2	26.2	27.2	25.0	24.6
Diabetes mellitus	12.5	**24.8**	19.3	**20.0**	**21.6**	19.3	18.9	15.8	10.6
Tobacco use	7.2	**17.6**	9.0	**40.8**	12.8	**12.9**	10.4	11.3	6.6
Obesity	9.8	**18.1**	8.8	9.5	**12.4**	**12.0**	10.4	10.4	8.7
Renal failure	1.6	**10.3**	4.0	**4.6**	**13.2**	3.7	4.5	3.9	1.8
CVD									
CAD	4.4	**14.4**	**15.1**	**20.6**	14.0	10.5	11.9	10.6	7.2
PVD	2.5	**8.1**	6.0	**13.5**	**7.5**	5.8	5.8	5.2	2.9
HF	2.1	5.5	3.9	**8.3**	**8.9**	4.5	**5.5**	5.0	2.0
Cerebrovascular disease	2.4	4.4	4.5	**9.0**	**5.8**	3.8	**4.4**	4.1	2.6
Prior stroke	0.9	1.9	1.6	**3.6**	**2.5**	1.8	**2.0**	1.8	1.1
Acute MI	0.2	**1.1**	0.7	**1.6**	**1.4**	0.9	1.0	0.8	0.4
Prior PCI	0.2	**0.9**	0.6	**1.0**	**0.6**	0.6	**0.6**	0.6	0.3
Prior CABG	0.0	0.2	**0.2**	**0.3**	**0.2**	0.2	0.2	0.2	0.1

Baseline prevalence (%) of CV risk factors and CVD within 12 months before cancer diagnosis. Bold indicates the three highest prevalence rates of each CV risk factor among nine cancer types.
CABG, coronary artery bypass graft; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation.

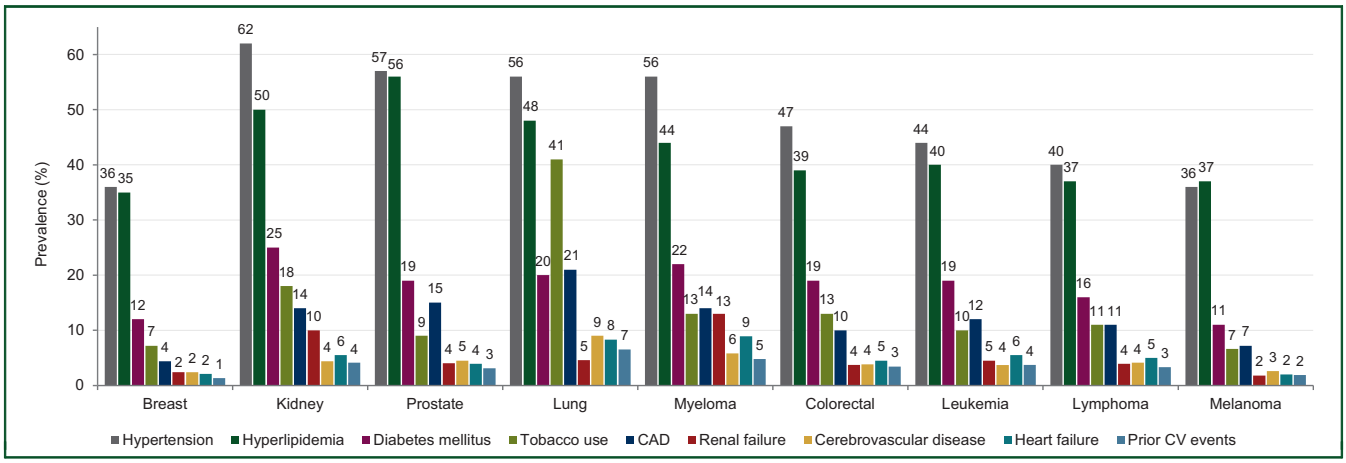

Figure 1. Baseline prevalence of CV risk factors and CVD by cancer type. Baseline prevalence of CV risk factors and CVD within 12 months before cancer diagnosis. Prior CV events include prior coronary revascularization, myocardial infarction, and/or stroke.
CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease.

(Figure 3 and Table 2). The cumulative incidence of HF was highest in myeloma, followed closely by lung cancer and leukemia. Malignancies with the highest risk for MI were lung cancer, myeloma, and leukemia. Prostate cancer, breast cancer, and melanoma were consistently the cancers with the lowest risk for each individual CV event.

Unlike other traditional CV risk factors, hyperlipidemia was associated with a lower hazard for MACE (aHR 0.88, 95% CI 0.87-0.90, $P < 0.001$) (Table 2). However, hyperlipidemia was highly correlated with baseline statin use (correlation coefficient 0.76, $P < 0.0001$). A subsequent *post hoc* analysis adjusted the model by replacing hyperlipidemia with baseline statin use (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2023.101830). This model did not substantially affect other HRs but showed a mild protective benefit for baseline statin use (aHR 0.97, 95% CI 0.96-0.99, $P = 0.001$).

An a priori sensitivity analysis assessed the impact of limiting the diagnosis of MACE to only primary inpatient diagnoses, versus the use of all diagnostic positions in both inpatient and outpatient care settings in the main analysis. This limitation would be expected to improve PPV but reduce sensitivity. In this sensitivity analysis, the overall trend and relationship between cancer types was generally maintained, despite the lower number of incident MACE. When limited to primary inpatient diagnoses, the cumulative incidence of MACE at 4 years after diagnosis of lung cancer was 13%, compared with 26% in the main analysis. For breast cancer, the cumulative incidence of MACE at 4 years was 4% when limited to primary inpatient diagnoses, compared with 11% in the main analysis (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.101830).

DISCUSSION

It is increasingly recognized that CVD in patients with cancer, including cancer survivors, has a tremendous impact on overall patient outcomes.[36] In our study of >800 000 patients across nine cancer types (breast, lung, prostate,

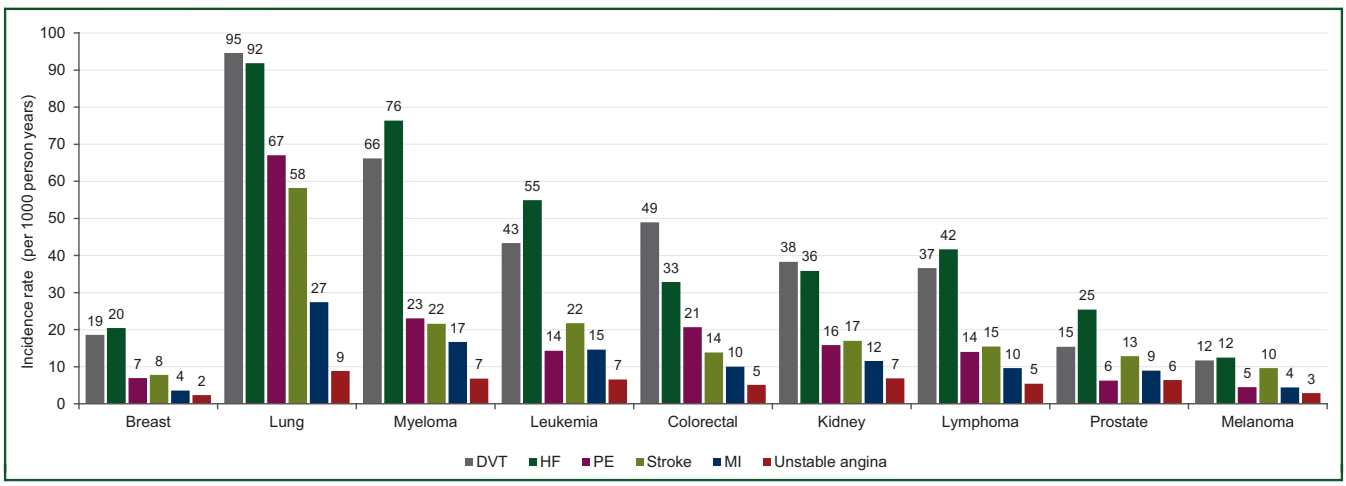

Figure 2. Incidence rate (per 1000 person years) of CV events after cancer diagnosis by cancer type. Incidence rate (%) of CV events per 1000 person years following cancer diagnosis until the end of study period or disenrollment from health plan.
CV, cardiovascular; DVT, deep vein thrombosis; HF, heart failure; MI, myocardial infarction; PE, pulmonary embolism.

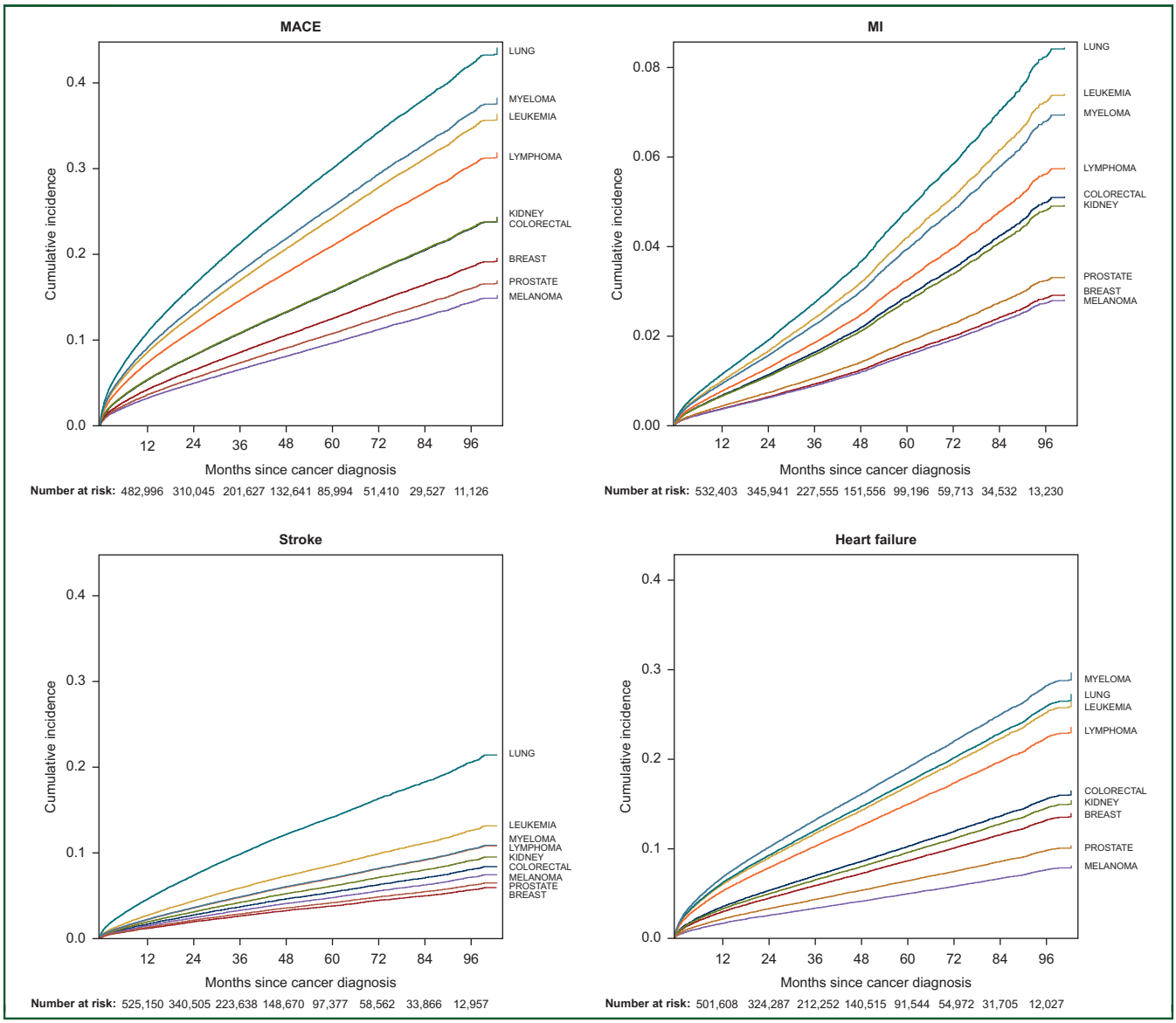

Figure 3. Cumulative incidence of MACE, MI, stroke, and heart failure by cancer type, adjusted for baseline CV risk factors and CVD. Cumulative incidence of MACE (MI, stroke, unstable angina, or heart failure) and individual CV events following cancer diagnosis, adjusted for baseline CV risk factors and CVD. (Reference = breast cancer.) Note *y*-axis for MI has been adjusted relative to other cumulative incidence plots for ease of interpretation.
CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular event; MI, myocardial infarction.

melanoma, myeloma, kidney, colorectal, leukemia, and lymphoma), modifiable CV risk factors were prevalent across all cancer types and were especially common in patients with kidney, prostate, and lung cancers, and in those with myeloma. Following cancer diagnosis, the incidence of CV events was markedly increased in patients with certain malignancies, especially lung cancer, myeloma, and leukemia, even after accounting for baseline CV risk factors. To our knowledge, this is the first study to analyze the comparative cumulative incidence of CV events across cancer types, thereby illustrating the marked variation in CV risk across cancer types.

Overall, the results of our study are in alignment with data reported in prior studies. In another study of cancer survivors starting at 1 year after diagnosis, the risk of CV events was substantially increased in patients with lung cancer and MM compared with matched general population controls, including a >65% increased risk of HF in patients with leukemia, compared with a 14% increased risk in patients with breast cancer.[26] Additionally, in cancer survivors at 2 years after diagnosis, the highest cumulative incidence of MACE occurred in patients with MM, bladder cancer, lung, and leukemia.[27] However, the reported number of CV events in our study was substantially higher than in several prior studies, predominantly because we included events in the first year after cancer diagnosis, when the risk of increased CV mortality is highest.[23] Our study adds to previous work by analyzing the comparative cumulative

Table 2. Adjusted hazard of CV events independently associated with baseline CV risk factors, CVD, age, and sex in multivariable analyses across cancer types

Parameter	MACE	MI	Stroke	HF
Cancer type				
Lung	2.7 (2.6-2.7)	3.0 (2.8-3.2)	3.9 (3.7-4.1)	2.1 (2.0-2.2)
Myeloma	2.2 (2.1-2.3)	2.4 (2.2-2.7)	1.9 (1.7-2.0)	2.3 (2.2-2.4)
Leukemia	2.1 (2.0-2.1)	2.6 (2.4-2.8)	2.3 (1.2-2.4)	2.0 (2.0-2.1)
Lymphoma	1.8 (1.7-1.8)	2.0 (1.9-2.2)	1.9 (1.8-2.0)	1.8 (1.7-1.8)
Kidney	1.3 (1.2-1.3)	1.7 (1.6-1.9)	1.6 (1.5-1.7)	1.1 (1.1-1.2)
Colorectal	1.3 (1.2-1.3)	1.8 (1.7-1.9)	1.4 (1.4-1.5)	1.2 (1.2-1.2)
Prostate	0.9 (0.8-0.9)	1.1 (1.1-1.2)	1.1 (1.0-1.2)	0.7 (0.7-0.8)
Melanoma	0.8 (0.7-0.8)	1.0 (0.9-1.0)	1.3 (1.2-1.3)	0.6 (0.5-0.6)
CV risk factor and CVD				
CAD	1.9 (1.8-1.9)	2.4 (2.3-2.4)	1.3 (1.2-1.3)	2.0 (2.0-2.1)
Renal failure	1.5 (1.5-1.6)	1.5 (1.4-1.6)	1.4 (1.3-1.5)	1.7 (1.7-1.8)
Cerebrovascular disease	1.4 (1.3-1.4)	1.2 (1.1-1.3)	1.9 (1.8-2.0)	1.2 (1.1-1.2)
Diabetes mellitus	1.4 (1.3-1.4)	1.4 (1.3-1.4)	1.3 (1.3-1.4)	1.4 (1.4-1.5)
Hypertension	1.4 (1.3-1.4)	1.3 (1.3-1.4)	1.3 (1.3-1.4)	1.4 (1.4-1.4)
PVD	1.3 (1.2-1.3)	1.2 (1.2-1.3)	1.2 (1.1-1.2)	1.3 (1.3-1.4)
Tobacco use	1.2 (1.2-1.2)	1.4 (1.3-1.4)	1.2 (1.2-1.3)	1.2 (1.1-1.2)
Hyperlipidemia	0.9 (0.9-0.9)	0.9 (0.9-0.9)	0.9 (0.9-0.9)	0.8 (0.8-0.9)
Age (per 10-year increase)	1.4 (1.4-1.4)	1.5 (1.5-1.5)	1.5 (1.5-1.5)	1.5 (1.4-1.5)
Sex (female)	0.9 (0.9-0.9)	0.7 (0.7-0.8)	1.0 (1.0-1.0)	0.9 (0.9-0.9)

Data listed are aHR (95% CI). Multivariable Cox proportional hazards models were analyzed for the entire cohort for each CV event and adjusted for baseline CV risk factors and CVD as listed, as well as age, sex, and year of cancer diagnosis. Breast cancer was used as the reference cancer. Male sex was used as the reference sex. $P < 0.001$ for all comparisons except for risk factor of melanoma for MI ($P = 0.329$) and risk factor of female sex for stroke ($P = 0.228$). MACE comprised the first event of MI, stroke, unstable angina, or HF. Patients with the CV event of interest in the 12-month baseline period were excluded from that event analysis.
aHR, hazard ratio; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; PVD, peripheral vascular disease.

incidence of CV events over time while accounting for baseline CV risk factors.

In line with previous research,[27] the differences in CV risk across cancer types remained after adjusting for CV risk factors. This remaining increased CV risk can be attributed to cancer treatment effects and the impact of cancer pathophysiology and inflammation, as well as residual confounding. The cancer-specific incidence and prevalence reported in our study ultimately reflects the average risk a patient for each specified cancer faces at the time of diagnosis. Within each cancer population, any given cancer treatment can further impact that risk. Radiation, for instance, is known to increase the risk of vascular damage, cardiomyopathy, pericardial disease, and valvular disease.[37] Anthracyclines and anti-human epidermal growth factor receptor 2 (HER2) therapy will increase the risk of cardiomyopathy and HF.[37] Many cancer treatment agents can be associated with venous and/or arterial thromboembolism.[18]

Interestingly, the variation in CV events observed across cancer types was substantially greater than any predicted differences that would arise from specific treatments alone. For example, the risk of HF was highest in myeloma, which is not typically treated with anthracyclines, radiation, or HER2 antagonists—the cancer therapies known to have a large attributable HF risk.[37] There is increasing interest in the multiple interplays between cancer and CVD, and the potential impact of cancer biology on CV risk. Preclinical and clinical studies continue to explore the potential pathways linking cancers associated with cachexia, sarcopenia, inflammatory cytokines, and oncometabolites to CVD development or progression.[5]

While multiple pathways may be involved, CV risk factor optimization remains a tangible strategy to mitigate CV events. Furthermore, strategies for primary prevention or early detection of CV risk factors would likely have an important impact on patients who are at highest risk for CV events, such as those with lung cancer, myeloma, or leukemia. Although CAD and renal failure were associated with the highest hazard for MACE after any cancer diagnosis, more modifiable risk factors such as hypertension and diabetes mellitus were also independently associated with a significantly increased hazard for MACE. Consistent with some previous findings, hypertension, hyperlipidemia, and diabetes mellitus were generally the most common risk factors in patients before cancer diagnosis across all cancer types.[19] While hyperlipidemia was consistently protective for MACE in our study, it was highly correlated with baseline statin use, which provides support for the expected positive impact of risk factor modification and the value of statin use, specifically.[38]

Of interest, the incidence of CV events following a diagnosis of prostate cancer was relatively lower than for other cancer types during 4 years of follow-up, both before and after adjusting for baseline CV risk factors. These results are in line with previous findings from the SEER registry showing that the overall CV risk for patients with prostate cancer was lower than for non-cancer controls.[27] There has been growing interest in the occurrence of CV events in patients with prostate cancer who are on anti-androgen therapy, especially whether gonadotropin-releasing hormone (GnRH) agonists confer greater CV risk relative to GnRH antagonists. The PRONOUNCE trial, designed to compare CV events between degarelix (GnRH antagonist) and leuprolide (GnRH agonist), was notably stopped early—in part due to a lower than expected number of CV events.[39] However, patients with prostate cancer have been

shown to remain at higher risk for CV mortality over long-term follow-up, and some newer agents have been associated with an increased risk for hypertension and CV events.[23,40]

Improved understanding of the overall risk of CV events in patients with certain cancers can help treating practitioners inform prevention and monitoring strategies. While current guidance on baseline CV risk assessment is largely derived from the cancer therapy planned for a patient,[36,41] our study data suggest that cancer type may also be a critical consideration in the risk assessment process. In patients with cancers associated with a high CV risk, such as lung cancer (26% cumulative incidence of MACE at 4 years after diagnosis), CV risk factor optimization should be integral to the overall treatment plan. Adverse CV events in patients with cancer have also been connected to interruptions and discontinuation of cancer therapy, as well as reductions in disease-free survival and overall survival.[42] Optimal CV risk mitigation strategies would thus be expected to improve both cancer and CV outcomes.

The 2022 European Society of Cardiology guidelines on cardio-oncology, as well as the International Cardio-Oncology Society expert consensus statement for cancer survivors after radiation therapy, recommend yearly assessment and optimization of CV risk factors.[14,43] Additional screening can often take the form of imaging modalities (e.g. echocardiogram, cardiac magnetic resonance imaging), biomarkers, and/or ischemic testing.[14,43,44] Screening recommendations and intervals are generally based on the patient's risk of future cardiomyopathy or CVD, with the goal of early detection and mitigation. Further study is needed to delineate the optimal screening strategy and management plan for each cancer type and treatment, but the results of our study suggest that cancer type may play a more important role than previously thought.

Our results should not be misinterpreted to direct decisions on cancer therapy. The risk of cancer-specific mortality remains high in patients with lung cancer, MM, and leukemia,[45] and therapeutic regimens should continue to prioritize maximal treatment response in line with patient goals. However, appropriate CV preventive therapy should also be integral to care. Patients with cancers associated with high CV risk may benefit from referral to cardio-oncology specialists and closer monitoring with imaging and/or biomarkers.[36,41,46,47] Additionally, despite the lower risk of CV events for breast cancer, CV risk assessment and optimization remains important given the generally favorable cancer prognosis and increased risk of future CV mortality in breast cancer survivors.[23,45]

Study limitations

Inherent limitations in any administrative data analysis include the potential for inaccurate covariate or outcome assessment. ICD-9/10-CM codes have been extensively studied for CV outcomes, and the diagnostic codes for MI, stroke, and HF have been shown to have high predictive value for adjudicated events in prior claims analyses. There is an inherent tradeoff in restricting outcomes to inpatient-only codes (higher specificity, especially if limited to the primary diagnosis) as opposed to using both inpatient and outpatient codes (higher sensitivity). The higher sensitivity approach of using both inpatient and outpatient codes was chosen for the primary analysis to better understand the breadth of CV risks. A sensitivity analysis restricted to primary inpatient diagnosis codes helped confirm the results of the primary analysis. Coding algorithms for covariates are generally less sensitive. While we used the most validated approaches, including Elixhauser where applicable and a 12-month baseline period, there remains a risk for underestimating baseline CV risk prevalence.

The large administrative claims database utilized in this study is representative of the United States commercially insured population aged $<$65 years. Given that data available for patients aged $\geq$65 years were limited, older patients included in the study may not be representative of other older patient populations. Information on individual patient race was also not available and no assessment of racial differences could be ascertained. Similarly, cancer stage could not be assessed, and further study will be needed to determine whether the higher CV rate seen in some cancers, such as lung cancer, varies significantly across cancer stage at presentation. We could not account for the relative severity of comorbid disorders or calculate atherosclerotic CVD risk scores. Mortality is also not recorded in the claims database, and a competing risk analysis for noncardiac (i.e. cancer) death could not be conducted.

This study did not account for the cancer therapies patients received and is not intended to influence cancer treatment. The residual CV risk for each cancer type after adjusting for baseline CV comorbidities reflects the inherent CV risk of the cancer, the toxicity of any treatments received, and residual confounding. Further study will be required to understand the impact of each factor. The contribution of the current study lies in the demonstration of high CV risk in certain cancers, highlighting the need for CV risk optimization during cancer treatment.

Conclusions

The incidence of MACE and other CV events in this study varied significantly across cancer types, with an especially high rate of MACE in patients with lung cancer, myeloma, and leukemia. Stroke was substantially more common in lung cancer, while the risk of HF was highest in lung cancer, myeloma, and leukemia.

Baseline CV risk factors, particularly hypertension, hyperlipidemia, and diabetes, were prevalent across multiple cancer types, suggesting a readily available opportunity for targeted preventive therapy to reduce the risk of short-term CV events and long-term CV morbidity and mortality. The stark difference in CV events between cancer types persisted even after adjustment for CV risk factors. Further research should continue to investigate the potential contribution of other etiologies for increased CVD in certain

cancers. A better understanding of the wide variation of CV events across different cancer types, in addition to cancer treatments, can help inform CV screening, risk factor modification strategies, and cardioprotective measures to minimize cardiac events while maximizing cancer therapy outcomes.

ACKNOWLEDGEMENTS

Medical writing and editorial support was provided by LATITUDE (Powered by AXON) and was funded by Bristol Myers Squibb.

FUNDING

This work was supported by Bristol Myers Squibb (no grant number). Research reported in this publication was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health [grant number UL1TR002345]. All financial support was unrestricted—the authors had full control of the study design, execution, analysis, and interpretation of the data.

DISCLOSURES

JDM: research funding: Pfizer, Longer Life Foundation, Children's Discovery Institute, Myocardial Solutions, Abbott Laboratories. Consultant: Pfizer (modest), BridgeBio (modest). **ML**: stock owner: Bristol Myers Squibb. Current affiliation: Mirati Therapeutics. **QX**: stock owner: Bristol Myers Squibb. Current affiliation: Regeneron. **BD**: stock owner: Bristol Myers Squibb. **DL**: stock owner: Bristol Myers Squibb, Humana. **DJL**: research funding: Myocardial Solutions. Consultant: Clementia, Eidos, Prothena, Astra-Zeneca, OncXerna, SecuraBio, Bristol Myers Squibb (all consultancy remuneration modest). All other authors have declared no conflicts of interest.

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