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Risk of Arterial Thromboembolism in Patients With Cancer

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CME/MOC Objective for This Article: After reading this article, the reader should be able to: 1) define the short-term risk of myocardial infarction and ischemic stroke in elderly patients with newly diagnosed solid or hematological cancer; 2) identify the effects of cancer stage on the risk of arterial thromboembolic events; and 3) explain the impact of arterial thromboembolism on cancer patients' survival.

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ABSTRACT

BACKGROUND The risk of arterial thromboembolism in patients with cancer is incompletely understood.

OBJECTIVES The authors aimed to better define this epidemiological relationship, including the effects of cancer stage.

METHODS Using the Surveillance Epidemiology and End Results–Medicare linked database, the authors identified patients with a new primary diagnosis of breast, lung, prostate, colorectal, bladder, pancreatic, or gastric cancer or non-Hodgkin lymphoma from 2002 to 2011. They were individually matched by demographics and comorbidities to a Medicare enrollee without cancer, and each pair was followed through 2012. Validated diagnosis codes were used to identify arterial thromboembolism, defined as myocardial infarction or ischemic stroke. Cumulative incidence rates were calculated using competing risk survival statistics. Cox hazards analysis was used to compare rates between groups at discrete time points.

RESULTS The authors identified 279,719 pairs of patients with cancer and matched control patients. The 6-month cumulative incidence of arterial thromboembolism was 4.7% (95% confidence interval [CI]: 4.6% to 4.8%) in patients with cancer compared with 2.2% (95% CI: 2.1% to 2.2%) in control patients (hazard ratio [HR]: 2.2; 95% CI: 2.1 to 2.3). The 6-month cumulative incidence of myocardial infarction was 2.0% (95% CI: 1.9% to 2.0%) in patients with cancer compared with 0.7% (95% CI: 0.6% to 0.7%) in control patients (HR: 2.9; 95% CI: 2.8 to 3.1). The 6-month cumulative incidence of ischemic stroke was 3.0% (95% CI: 2.9% to 3.1%) in patients with cancer compared with 1.6% (95% CI: 1.6% to 1.7%) in control patients (HR: 1.9; 95% CI: 1.8 to 2.0). Excess risk varied by cancer type (greatest for lung), correlated with cancer stage, and generally had resolved by 1 year.

CONCLUSIONS Patients with incident cancer face a substantially increased short-term risk of arterial thromboembolism.
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About 40% of Americans will develop cancer in their lifetimes (1). In addition, more than 13 million Americans currently live with invasive cancer and this number will likely increase over time as continued advances in cancer treatments lead to longer survival (1). Patients with cancer face an increased risk of medical complications, especially venous thromboembolism, which is increased roughly 7-fold in patients with cancer and affects up to 20% of the cancer population (2,3). Reasons for this heightened risk include frequent immobility, invasive procedures, and alterations in coagulation, platelet, and endothelial function (3). Nevertheless, despite these well-known alterations in clotting function and the greatly heightened risk of venous thromboembolism, incident cancer is not an established independent risk factor for arterial thromboembolism, and patients with cancer do not routinely receive therapies to prevent myocardial infarction and stroke (4–6).

Ischemic heart disease and stroke are leading causes of death and disability worldwide (7). Clinical series have suggested that these arterial thromboembolic events may be common in patients with cancer (8–12). Population-based data, however, are scarce regarding the association between cancer, broadly defined, and arterial thromboembolism, with most previous investigations focused on individual cancer types or specific arterial events (13–26). In addition, the effect of cancer stage on arterial thromboembolism risk is uncertain, as is the impact of arterial thromboembolism on the survival of patients with cancer. Therefore, we aimed to define these epidemiological relationships by using population-based Medicare claims data to evaluate the risk of myocardial infarction and ischemic stroke in patients with new diagnoses of the most common solid and hematologic cancers. Our hypothesis was that a new diagnosis of cancer is associated with an

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

ICD-9-CM = International Classification of Diseases-Ninth Revision-Clinical Modification

IQR = interquartile range

SEER = Surveillance, Epidemiology, and End Results

increased short-term risk of arterial thromboembolism, and that the risk is highest in patients with advanced-stage disease.

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METHODS

DESIGN. This was a retrospective matched-cohort study using Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims from 2002 to 2012. The SEER-Medicare dataset comprises American population-based cancer registries linked to Medicare enrollment and claims files, and provides detailed clinical information about a heterogeneous population of patients with cancer (27). The SEER registries include about 28% of all patients diagnosed with cancer in the United States. The SEER program also provides data from a 5% random sample of Medicare beneficiaries without cancer residing in SEER geographic regions, which enabled us to compare the risk of arterial thromboembolism in patients with cancer versus matched patients without cancer. Medicare data used for this study included the physician and supplier file, the outpatient standard analytic file, and the Medicare provider analysis and review file. The Memorial Sloan Kettering institutional review board deemed this study exempt from review and waived the need for informed consent.

CANCER STUDY GROUP. Cancer cases consisted of all patients aged 66 years of age or older diagnosed with primary breast, lung, prostate, colorectal, bladder, pancreatic, or gastric cancer or non-Hodgkin lymphoma from January 1, 2002, to December 31, 2011. We a priori chose breast, lung, prostate, colorectal, and bladder cancers because these are the 5 most common malignant cancer types in the United States and thus are most representative of cancer in general (27).

TABLE 1 Baseline Characteristics of Pairs of Patients With Cancer and Matched Control Patients, 2002-2011, Stratified by Cancer Type

	All Cancer Cohorts (N = 279,719)	Breast Cohort (n = 62,977)	Lung Cohort (n = 56,941)	Prostate Cohort (n = 64,164)	Colorectal Cohort (n = 43,827)	Bladder Cohort (n = 17,637)	NHL Cohort (n = 15,669)	Pancreas Cohort (n = 12,279)	Gastric Cohort (n = 6,225)
Age, yrs	75 ± 7	75 ± 7	75 ± 7	74 ± 6	77 ± 7	77 ± 7	76 ± 7	77 ± 7	77 ± 7
Sex									
Women	146,729 (52)	62,608 (99)	31,226 (55)	0 (0)	26,446 (60)	6,062 (34)	9,505 (61)	7,794 (63)	3,088 (50)
Men	132,990 (48)	369 (1)	25,715 (45)	64,164 (100)	17,381 (40)	11,575 (66)	6,164 (39)	4,485 (37)	3,137 (50)
Race									
White	238,094 (85)	55,685 (88)	48,676 (85)	52,393 (82)	36,960 (84)	16,063 (91)	13,977 (89)	10,040 (82)	4,300 (69)
Other race	41,625 (15)	7,292 (12)	8,265 (15)	11,771 (18)	6,867 (16)	1,574 (9)	1,692 (11)	2,239 (18)	1,925 (31)
Geographic region									
Northeast	53,409 (19)	12,580 (20)	9,954 (17)	11,618 (18)	8,880 (20)	3,776 (21)	3,062 (20)	2,357 (19)	1,182 (19)
Midwest	47,207 (17)	10,411 (17)	9,085 (16)	11,275 (18)	7,799 (18)	2,926 (17)	2,843 (18)	1,966 (16)	902 (14)
South	72,352 (26)	15,339 (24)	17,311 (30)	15,768 (25)	11,615 (27)	4,127 (23)	3,689 (24)	3,081 (25)	1,422 (23)
West	106,751 (38)	24,647 (39)	20,591 (36)	25,503 (40)	15,533 (35)	6,808 (39)	6,075 (39)	4,875 (40)	2,719 (44)
Charlson comorbidities									
0	209,973 (75)	49,312 (78)	37,350 (66)	52,958 (83)	33,023 (75)	13,129 (74)	11,694 (75)	8,171 (67)	4,336 (70)
1 or more	69,746 (25)	13,665 (22)	19,591 (34)	11,206 (17)	10,804 (25)	4,508 (26)	3,975 (25)	4,108 (33)	1,889 (30)
HTN or AF	170,880 (61)	41,422 (66)	34,033 (60)	35,268 (55)	27,439 (63)	10,753 (61)	9,749 (62)	8,259 (67)	3,957 (64)
Census tract poverty level <10%*	151,621 (54)	36,409 (58)	28,069 (49)	35,465 (55)	23,027 (53)	10,118 (57)	8,991 (57)	6,501 (53)	3,041 (49)
Cancer stage†									
0	20,089 (7)	10,193 (16)	39 (0)	22 (0)	2,826 (6)	6,926 (39)	NA	24 (0)	59 (1)
1	85,539 (31)	25,842 (41)	8,474 (15)	31,444 (49)	8,708 (20)	5,370 (30)	3,915 (25)	651 (5)	1,135 (18)
2	60,964 (22)	15,333 (24)	2,025 (4)	26,226 (41)	10,855 (25)	1,958 (11)	2,145 (14)	1,977 (16)	445 (7)
3	33,811 (12)	4,587 (7)	13,567 (24)	1,566 (2)	9,595 (22)	876 (5)	2,414 (15)	729 (6)	477 (8)
4	51,309 (18)	3,337 (5)	24,733 (43)	2,035 (3)	8,134 (19)	1,414 (8)	5,339 (34)	4,629 (38)	1,688 (27)
Unknown	28,007 (10)	3,685 (6)	8,103 (14)	2,871 (5)	3,709 (8)	1,093 (6)	1,856 (12)	4,269 (35)	2,421 (39)

Values are mean ± SD or n (%). Total numbers represent the total number of matched pairs. Cancer patients and matched control patients without cancer had equal values for age, sex, race, geographic region, Charlson comorbidities, and hypertension or atrial fibrillation. Due to rounding, some values do not add to 100. *Number and proportion of patients who live in areas where <10% of people are below the poverty line according to the 2000 census. †Refers to the American Joint Committee on Cancer (AJCC) staging schema, except for patients with prostate cancer, who were staged according to the T (clinical) staging classification and patients with non-Hodgkin lymphoma (NHL), who were staged according to the Ann Arbor staging classification. Cancers diagnosed from 2002 to 2003 were staged according to the AJCC third edition definitions, whereas cancers diagnosed from 2004 to 2011 were staged according to the sixth edition. There is a higher proportion of patients with pancreatic and gastric cancer with an unknown stage because AJCC staging before 2004 is not available in the Surveillance, Epidemiology, and End Results data for these patients.

AF = atrial fibrillation; HTN = hypertension; NA = not applicable.

Similarly, we chose non-Hodgkin lymphoma because it is the most common hematologic cancer (27). We also included pancreatic and gastric cancers because these cancers are thought to carry the highest risk of venous thromboembolism (28). In total, these 8 cancers account for approximately 64% of all incident malignant cancer in the United States (27). Patients who were diagnosed with multiple primary cancers during the study period were assigned the cancer type diagnosed first.

We used site record definitions from the SEER Patient Entitlement and Diagnosis Summary File to define our cancer cohorts (27). The specific site definitions used to define our cancer cohorts are based on the International Classification of Diseases for Oncology, Third Edition site recode classification and are as follows: breast (site C500 to 509; recode 26000); lung (sites C300 to C301, C310 to C319, C320 to C329, C339, C340 to C349, C381 to 383, C384, C388, C390, C398, C399; recodes 22010, 22020, 22030, 22050, 22060); prostate (site C619; recode 28010); colorectal (sites C180 to C189, C199, C209, C210 to C212, C218, C260; recodes 21041 to 21049, 21051, 21052, 21060); bladder (sites C670 to 679; recode 29010); non-Hodgkin lymphoma (sites C024, C098, C099, C111, C142, C379, C422, C770 to 779; recodes 33041, 33042); pancreas (sites C250 to 259; recode 21100); and gastric (sites C160 to C169; recode 21020).

We excluded patients with cancer if they lacked Part A or B Medicare coverage or belonged to a health maintenance organization in the year before their cancer diagnosis or during follow-up, their cancer was diagnosed at autopsy, their month of cancer diagnosis was missing, their cancer diagnosis was made before 2001 or after 2011, their first cancer diagnosis during the study period was not their first-ever cancer, their age at the time of cancer diagnosis was <66 years (to provide sufficient time to evaluate comorbidities in the year before cancer diagnosis), or we could not identify a control patient without cancer matched on our predefined factors. To minimize ascertainment bias and restrict our evaluation to first-ever myocardial infarction and ischemic stroke, we also excluded patients with any inpatient or outpatient Medicare claim for coronary heart disease (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM] codes 410 to 414) or cerebrovascular disease (ICD9-CM codes 430 to 438) in any diagnosis position in the year before cancer diagnosis.

CONTROL STUDY GROUP. Each patient with cancer was individually matched to a cancer-free control patient in Medicare by year of birth, sex, race (white or other race [black, Asian, Pacific Islander, other]), SEER registry (a surrogate for geographic region categorized into Northeast, South, Midwest, and West regions), and Charlson Comorbidity Index in the year before study entry (dichotomized into 0 or ≥1) (29). As the Charlson Comorbidity Index does not include 2 important vascular risk factors, hypertension and atrial fibrillation, we also matched each patient by ICD-9-CM codes for hypertension (401 to 405, 437.2) and atrial fibrillation (427.31, 427.32) in the year before study entry. Control patients without cancer were ineligible for matching if they lacked Medicare Part A or B coverage, belonged to a health maintenance organization, or had a Medicare claim for coronary heart disease or cerebrovascular disease in the year before study entry.

MEASUREMENTS. Patients with cancer and their matched control patients entered the study at the date of the cancer patient's cancer diagnosis. The primary outcome was a composite of arterial thromboembolism, defined as any inpatient or

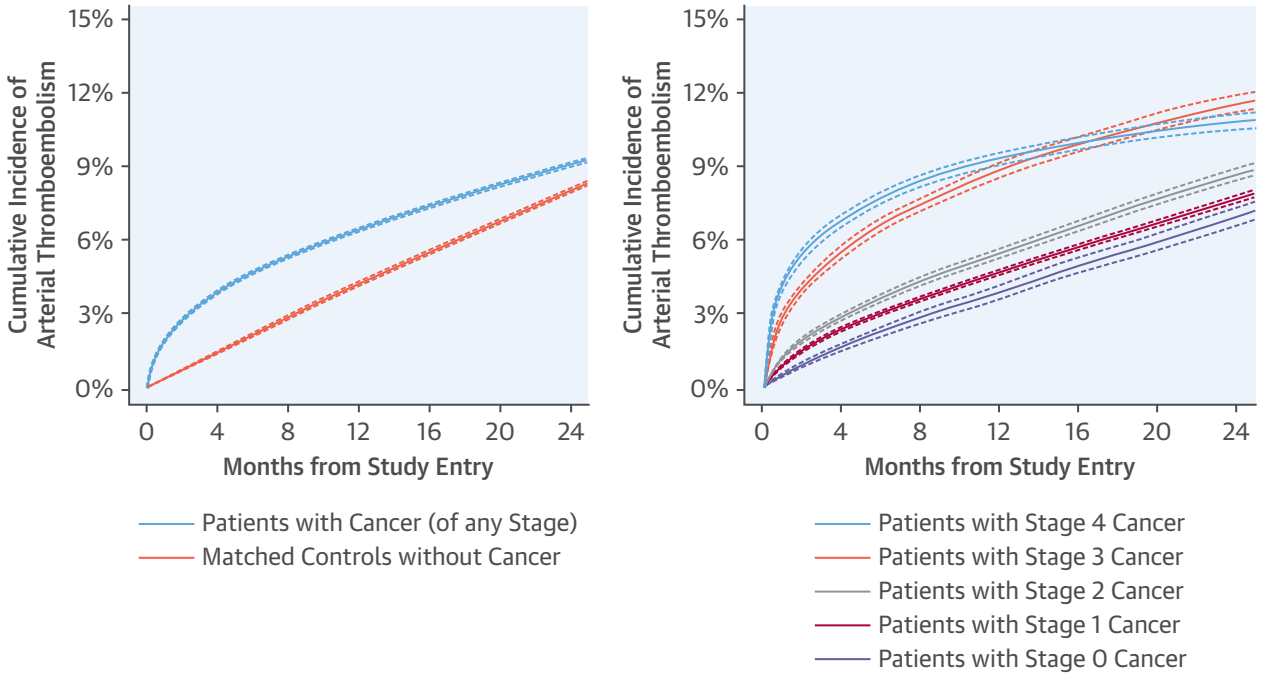
TABLE 2 Cumulative Incidence of Arterial Thromboembolism, Stratified by Cancer Type

Cancer Type	Time Since Diagnosis of Cancer*			
	3 Months	6 Months	1 Yr	2 Yrs
All cancer				
Patients	3.4 (3.4–3.5)	4.7 (4.6–4.8)	6.5 (6.4–6.6)	9.1 (9.0–9.2)
Control patients	1.1 (1.1–1.1)	2.2 (2.1–2.2)	4.2 (4.2–4.3)	8.1 (8.0–8.2)
Breast				
Patients	1.7 (1.6–1.8)	2.6 (2.5–2.7)	4.2 (4.0–4.3)	7.1 (6.9–7.3)
Control patients	1.0 (1.1–1.1)	1.9 (1.8–2.0)	3.8 (3.6–3.9)	7.3 (7.1–7.5)
Lung				
Patients	6.5 (6.3–6.7)	8.3 (8.0–8.5)	10.3 (10.1–10.6)	–
Control patients	1.2 (1.1–1.3)	2.4 (2.3–2.5)	4.5 (4.3–4.6)	–
Prostate				
Patients	1.3 (1.2–1.4)	2.3 (2.2–2.4)	3.9 (3.8–4.1)	7.0 (6.8–7.2)
Control patients	1.0 (0.9–1.1)	2.0 (1.9–2.1)	3.9 (3.7–4.0)	7.5 (7.3–7.7)
Colorectal				
Patients	4.5 (4.3–4.7)	5.9 (5.7–6.1)	7.7 (7.4–7.9)	10.4 (10.1–10.7)
Control patients	1.3 (1.2–1.4)	2.5 (2.4–2.7)	4.7 (4.5–4.9)	9.0 (8.7–9.3)
Bladder				
Patients	3.2 (2.9–3.5)	4.7 (4.4–5.0)	7.1 (6.7–7.5)	10.4 (9.9–10.9)
Control patients	1.1 (0.9–1.2)	2.3 (2.1–2.5)	4.5 (4.2–4.8)	8.5 (8.1–8.9)
NHL				
Patients	3.7 (3.4–3.9)	5.4 (5.1–5.8)	7.4 (7.0–7.8)	10.3 (9.9–10.8)
Control patients	1.0 (0.9–1.2)	2.2 (2.0–2.4)	4.2 (3.9–4.5)	8.2 (7.8–8.6)
Pancreas				
Patients	4.7 (4.4–5.1)	5.9 (5.5–6.4)	–	–
Control patients	1.2 (1.0–1.3)	2.4 (2.1–2.7)	–	–
Gastric				
Patients	4.9 (4.4–5.5)	6.5 (5.9–7.1)	7.9 (7.3–8.6)	–
Control patients	1.2 (0.9–1.5)	2.2 (1.8–2.5)	4.7 (4.2–5.2)	–

Values are % (95% confidence interval). *Data are shown through the median follow-up period for patients with cancer for each cancer type up to a maximum of 2 yrs.

NHL = non-Hodgkin lymphoma.

CENTRAL ILLUSTRATION **Cumulative Incidence of Arterial Thromboembolism in Cancer Patients**



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Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in patients with cancer compared to matched control patients **(left panel)** and when stratified by cancer stage at the time of cancer diagnosis **(right panel)**. Competing risk survival statistics were used to calculate incidence. Dashed lines are used to indicate 95% confidence intervals.

outpatient diagnosis of myocardial infarction or ischemic stroke. Previously validated diagnosis codes were used to identify these outcomes (30,31). Myocardial infarction was identified by ICD-9-CM code 410 in any diagnosis position (30). Using Medicare data, this diagnostic code algorithm has 94% positive predictive value for the World Health Organization definition of acute myocardial infarction when compared to detailed chart review, and includes all forms of cardiac infarction, including coronary artery plaque rupture, embolism, occlusion, vasospasm, and other forms of thrombosis. This outcome did not include unstable angina. Ischemic stroke was identified by ICD-9-CM codes 433.x1, 434.x1, or 436 in any diagnosis position without concurrent codes for rehabilitation (V57) in the primary diagnosis position or trauma (800 to 804, 850 to 854) or hemorrhagic stroke (430, 431) in any diagnosis position (31). Our secondary outcomes were myocardial infarction alone and ischemic stroke alone. We did not include systemic embolism or mesenteric ischemia in our composite outcome because these are uncommon events that lack validated diagnostic codes.

ANALYSIS. Descriptive statistics were used to evaluate baseline characteristics. As death is a frequent competing risk in patients with cancer and can prevent arterial thromboembolic events from being observed, competing risk survival statistics accounting for death were used to calculate the cumulative incidence of arterial thromboembolism (32). Visual inspection of the cumulative incidence curves, as well as formal statistical testing, demonstrated that the risks of arterial thromboembolism in the cancer groups varied over time, meaning that the proportional hazards assumption was violated. Therefore, hazard ratios (HRs) were not calculated for the entirety of patient follow-up, but rather during discrete time periods for which the proportional hazards assumption was generally met. The 6-month cumulative incidence of arterial thromboembolism between groups was formally assessed by performing the nonparametric Gray test (33).

TABLE 3 Relative Hazards of Arterial Thromboembolism During Discrete Time Periods, Stratified by Cancer Type and Thromboembolism Type

	Time Periods After Cancer Diagnosis*				
	0–1 Month	1–3 Months	3–6 Months	6–9 Months	9–12 Months
Arterial thromboembolism					
All cancer	5.2 (4.9–5.6)	2.1 (2.0–2.2)	1.4 (1.3–1.5)	1.1 (1.1–1.2)	1.1 (1.0–1.1)
Breast	2.3 (2.0–2.7)	1.3 (1.1–1.4)	1.1 (1.0–1.2)	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Lung	9.6 (8.4–10.9)	3.6 (3.2–4.0)	2.3 (2.1–2.6)	1.9 (1.7–2.1)	2.2 (1.9–2.5)
Prostate	1.7 (1.5–2.0)	1.1 (1.0–1.3)	1.0 (0.9–1.1)	0.9 (0.8–1.0)	0.8 (0.7–0.9)
Colorectal	6.7 (5.7–7.8)	2.1 (1.9–2.4)	1.3 (1.2–1.5)	1.0 (0.9–1.2)	1.0 (0.9–1.1)
Bladder	4.6 (3.5–6.0)	2.2 (1.8–2.7)	1.4 (1.1–1.6)	1.4 (1.1–1.7)	1.1 (0.9–1.3)
NHL	6.1 (4.6–8.1)	2.3 (1.8–2.9)	1.8 (1.5–2.1)	1.3 (1.0–1.6)	1.2 (1.0–1.6)
Pancreas	6.8 (5.1–9.2)	3.0 (2.3–3.7)	1.7 (1.4–2.2)	–	–
Gastric	6.0 (4.1–8.9)	3.0 (2.2–4.3)	2.4 (1.7–3.2)	1.1 (0.7–1.5)	1.1 (0.8–1.6)
Myocardial infarction					
All cancer	7.3 (6.5–8.2)	3.0 (2.7–3.3)	1.8 (1.6–1.9)	1.3 (1.2–1.4)	1.0 (1.0–1.1)
Breast	3.8 (2.8–5.0)	1.8 (1.4–2.2)	1.6 (1.3–1.9)	1.0 (0.8–1.2)	0.7 (0.5–0.8)
Lung	10.1 (8.0–12.8)	4.8 (4.0–5.8)	2.8 (2.4–3.3)	2.4 (2.0–2.8)	2.5 (2.1–3.0)
Prostate	1.9 (1.5–2.6)	1.7 (1.4–2.1)	1.2 (1.0–1.4)	0.9 (0.8–1.1)	0.7 (0.6–0.9)
Colorectal	12.6 (9.5–16.7)	3.3 (2.7–4.1)	1.8 (1.4–2.2)	1.2 (0.9–1.5)	1.0 (0.8–1.3)
Bladder	5.6 (3.6–8.6)	2.6 (1.9–3.6)	1.5 (1.1–1.9)	1.8 (1.3–2.4)	1.2 (0.9–1.7)
NHL	9.1 (5.4–15.6)	3.3 (2.2–4.9)	2.1 (1.5–2.8)	1.4 (1.0–2.0)	1.0 (0.7–1.5)
Pancreas	13.9 (7.7–25.0)	4.0 (2.6–6.1)	2.1 (1.4–3.0)	–	–
Gastric	11.0 (5.3–22.6)	8.0 (4.0–16.0)	3.3 (1.9–5.5)	1.0 (0.5–1.8)	1.0 (0.5–2.0)
Ischemic stroke					
All cancer	4.5 (4.1–4.8)	1.7 (1.6–1.8)	1.3 (1.2–1.3)	1.0 (1.0–1.1)	1.1 (1.0–1.2)
Breast	1.8 (1.5–2.2)	1.1 (1.0–1.3)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	1.0 (0.9–1.1)
Lung	9.3 (8.0–10.9)	3.1 (2.7–3.5)	2.1 (1.9–2.4)	1.7 (1.5–2.0)	2.0 (1.8–2.4)
Prostate	1.6 (1.3–2.0)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Colorectal	4.6 (3.9–5.6)	1.7 (1.5–2.0)	1.2 (1.1–1.4)	1.0 (0.8–1.1)	1.0 (0.8–1.1)
Bladder	4.1 (2.9–5.8)	2.0 (1.5–2.5)	1.3 (1.1–1.7)	1.2 (0.9–1.5)	1.1 (0.8–1.4)
NHL	4.7 (3.4–6.6)	1.9 (1.5–2.5)	1.5 (1.2–1.9)	1.2 (0.9–1.5)	1.3 (1.0–1.7)
Pancreas	5.0 (3.6–6.9)	2.6 (2.0–3.4)	1.6 (1.2–2.1)	–	–
Gastric	4.5 (2.9–7.1)	1.9 (1.3–2.9)	1.9 (1.3–2.8)	1.2 (0.8–1.7)	1.1 (0.7–1.8)

Values are hazard ratio (95% confidence interval). *Data are shown through the median period of follow-up for each cancer type up to a maximum of 1 yr.
NHL = non-Hodgkin lymphoma.

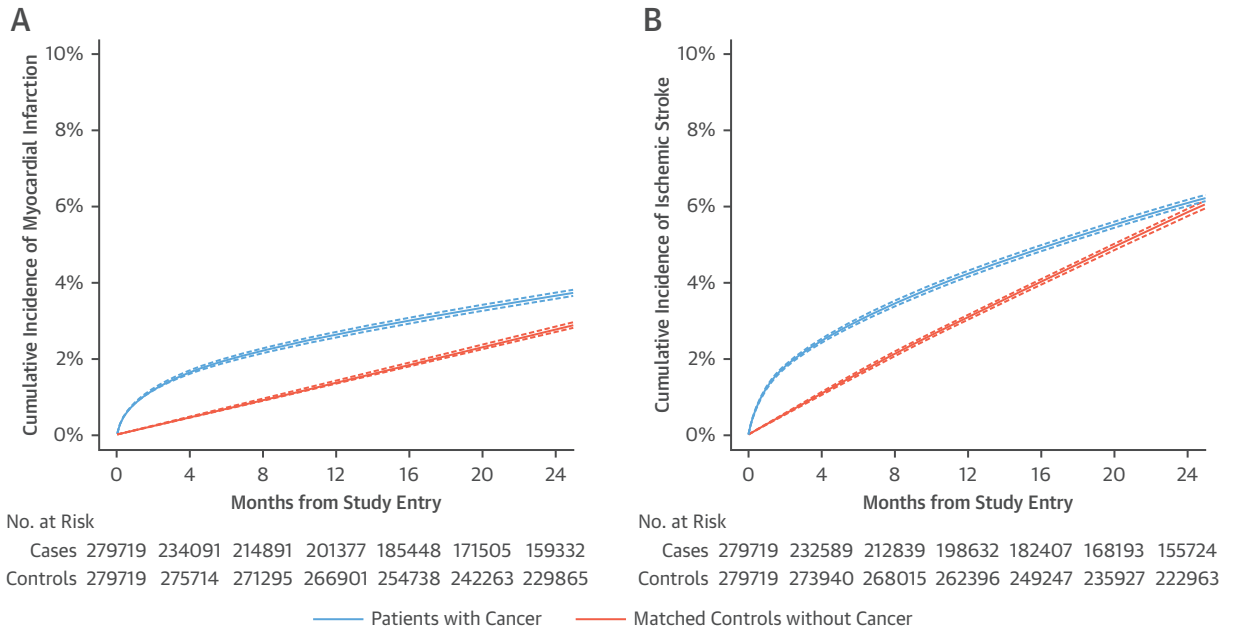
To estimate a global summary statistic for cancer in general, while also accounting for variable risks across individual cancer types, we analyzed data for each of the 8 cancer types separately and in combination. Follow-up was calculated from the case patient's date of cancer diagnosis until myocardial infarction, ischemic stroke, death, or end of study on December 31, 2012 (whichever occurred first). Myocardial infarction, ischemic stroke, and deaths were considered events, and patients without these events were censored.

In subgroup analyses aiming to evaluate the effects of cancer stage on arterial thromboembolism risk, the cumulative incidence function was stratified by the cancer patients' stage at the time of cancer diagnosis. We used the American Joint Committee on Cancer classification, except for prostate cancer, which was staged according to the T (clinical) classification, similar to other SEER-Medicare studies, and non-Hodgkin lymphoma, which was staged according to the Ann Arbor staging classification (34–36). Patients with unknown cancer stage (and their matched control patients) were excluded from this analysis.

To evaluate the association between arterial thromboembolism and survival in patients with cancer, we performed several Cox proportional hazards regression analyses with arterial thromboembolism inserted as a time-varying covariate. This included models that adjusted for the clinical factors used to match patients and cancer stage.

In a post hoc sensitivity analysis, we used inpatient and outpatient Medicare claims data in the year before study entry to evaluate differences in the frequency of cardiovascular risk factors between groups. We determined that peripheral vascular

FIGURE 1 Cumulative Incidence of Myocardial Infarction and Ischemic Stroke in Cancer Patients and Matched Control Patients



(A) Cumulative incidence of myocardial infarction in patients with cancer (all types combined) compared to matched control patients. **(B)** Cumulative incidence of ischemic stroke in patients with cancer (all types combined) compared to matched control patients.

disease, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, and liver disease were more common among patients with cancer, whereas diabetes mellitus and congestive heart failure were more common among control patients. To account for these differences, we performed an additional analysis whereby cancer cases and cancer-free control patients were matched by these 7 cardiovascular risk factors, in addition to the variables previously matched by in our primary analysis. Statistical analyses were performed by B.B.N., A.S.R., and K.S.P. and using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) or R version 3.2.4 (R Project for Statistical Computing, Vienna, Austria) software.

RESULTS

CHARACTERISTICS. Among 279,719 pairs of patients with cancer and matched control patients, the median age was 74 years (interquartile range [IQR]: 70 to 80 years) and 48% were men (**Table 1**). Stage of cancer varied greatly by malignancy type, although among the entire cohort, 18% had stage 4 disease at cancer diagnosis. Because of reduced survival, median follow-up time was 2.8 years (IQR: 0.9 to 5.8 years) in patients with cancer versus 5.0 years (IQR: 2.7 to 7.6 years) in control patients.

PRIMARY OUTCOME. At 6 months, the cumulative incidence of the composite outcome of arterial thromboembolism was 4.7% (95% confidence interval [CI]: 4.6% to 4.8%) in patients with cancer (all types combined) compared with 2.2% (95% CI: 2.1% to 2.2%) in control patients (HR: 2.2; 95% CI: 2.1 to 2.3; $p < 0.001$) (**Table 2, Central Illustration**). Risks varied by cancer type and were generally higher in patients with typically more advanced cancers at diagnosis (Online Figure 1). The greatest excess risk was seen in lung cancer, with a 6-month cumulative incidence of 8.3% (95% CI: 8.0% to 8.5%) compared with 2.4% (95% CI: 2.3% to 2.5%) in control patients ($p < 0.001$). Among patients with non-Hodgkin lymphoma, the only hematologic cancer studied, the 6-month cumulative incidence of arterial thromboembolism was 5.4% (95% CI: 5.1% to 5.8%) compared with 2.2% (95% CI: 2.0% to 2.4%) in control patients ($p < 0.001$). Excess risks attenuated in patients with cancer over time and generally had resolved by 1 year (**Table 3**).

SECONDARY OUTCOMES. Among this relatively older population, ischemic stroke was slightly more

TABLE 4 Cumulative Incidence of Secondary Outcomes, Stratified by Cancer Type

	Time Since Diagnosis of Cancer*							
	Myocardial Infarction				Ischemic Stroke			
	3 Months	6 Months	1 Yr	2 Yrs	3 Months	6 Months	1 Yr	2 Yrs
All cancer								
Patients	1.4 (1.4–1.5)	2.0 (1.9–2.0)	2.6 (2.6–2.7)	3.7 (3.6–3.7)	2.1 (2.1–2.2)	3.0 (2.9–3.1)	4.3 (4.2–4.3)	6.1 (6.0–6.2)
Control patients	0.3 (0.3–0.3)	0.7 (0.6–0.7)	1.4 (1.3–1.4)	2.8 (2.7–2.8)	0.8 (0.8–0.8)	1.6 (1.6–1.7)	3.1 (3.0–3.1)	5.8 (5.7–5.9)
Breast								
Patients	0.7 (0.6–0.7)	1.0 (1.0–1.1)	1.5 (1.4–1.6)	2.5 (2.4–2.6)	1.1 (1.0–1.1)	1.7 (1.6–1.8)	2.9 (2.8–3.0)	5.1 (4.9–5.2)
Control patients	0.3 (0.2–0.3)	0.5 (0.5–0.6)	1.1 (1.0–1.2)	2.3 (2.2–2.4)	0.8 (0.7–0.9)	1.5 (1.4–1.6)	2.8 (2.7–3.0)	5.4 (5.3–5.6)
Lung								
Patients	2.4 (2.3–2.5)	3.2 (3.0–3.3)	4.0 (3.9–4.2)	–	4.4 (4.2–4.5)	5.6 (5.4–5.7)	6.9 (6.7–7.1)	–
Control patients	0.4 (0.3–0.4)	0.8 (0.7–0.8)	1.5 (1.4–1.6)	–	0.9 (0.8–1.0)	1.7 (1.6–1.8)	3.2 (3.1–3.4)	–
Prostate								
Patients	0.6 (0.5–0.6)	1.0 (0.9–1.0)	1.5 (1.4–1.6)	2.8 (2.7–2.9)	0.8 (0.7–0.8)	1.4 (1.3–1.5)	2.5 (2.4–2.6)	4.6 (4.5–4.8)
Control patients	0.3 (0.3–0.4)	0.7 (0.6–0.7)	1.4 (1.3–1.5)	2.8 (2.7–2.9)	0.7 (0.6–0.8)	1.4 (1.3–1.5)	2.7 (2.6–2.8)	5.1 (4.9–5.3)
Colorectal								
Patients	2.3 (2.1–2.4)	2.8 (2.6–2.9)	3.4 (3.3–3.6)	4.4 (4.3–4.6)	2.5 (2.3–2.6)	3.5 (3.3–3.7)	4.8 (4.6–5.0)	6.7 (6.5–7.0)
Control patients	0.4 (0.3–0.4)	0.7 (0.6–0.8)	1.4 (1.3–1.5)	2.9 (2.7–3.1)	0.9 (0.8–1.0)	1.9 (1.8–2.0)	3.6 (3.4–3.7)	6.7 (6.5–6.9)
Bladder								
Patients	1.4 (1.3–1.6)	2.0 (1.8–2.2)	3.1 (2.8–3.3)	4.5 (4.2–4.9)	1.9 (1.7–2.1)	2.9 (2.6–3.1)	4.4 (4.1–4.7)	6.6 (6.2–6.9)
Control patients	0.4 (0.3–0.5)	0.9 (0.7–1.0)	1.6 (1.5–1.8)	3.1 (2.9–3.4)	0.7 (0.6–0.9)	1.5 (1.3–1.7)	3.1 (2.8–3.3)	6.0 (5.6–6.3)
NHL								
Patients	1.5 (1.3–1.7)	2.2 (1.9–2.4)	2.8 (2.6–3.1)	4.0 (3.7–4.3)	2.3 (2.0–2.5)	3.4 (3.2–3.7)	4.9 (4.6–5.3)	6.9 (6.5–7.3)
Control patients	0.3 (0.2–0.4)	0.7 (0.5–0.8)	1.4 (1.2–1.6)	2.9 (2.6–3.1)	0.8 (0.6–0.9)	1.7 (1.5–1.9)	3.2 (2.9–3.4)	6.0 (5.6–6.4)
Pancreas								
Patients	2.1 (1.8–2.4)	2.6 (2.3–2.8)	–	–	3.0 (2.7–3.3)	3.8 (3.5–4.2)	–	–
Control patients	0.3 (0.2–0.4)	0.7 (0.6–0.9)	–	–	1.0 (0.8–1.1)	1.8 (1.6–2.1)	–	–
Gastric								
Patients	2.4 (2.0–2.8)	3.1 (2.7–3.6)	3.6 (3.1–4.1)	–	2.8 (2.4–3.2)	3.7 (3.3–4.2)	4.8 (4.3–5.3)	–
Control patients	0.3 (0.1–0.4)	0.6 (0.4–0.8)	1.4 (1.1–1.7)	–	0.9 (0.7–1.2)	1.7 (1.4–2.0)	3.4 (3.0–3.9)	–

Values are % (95% confidence interval). *Data are shown through the median follow-up period for patients with cancer for each cancer type up to a maximum of 2 yrs.
NHL = non-Hodgkin lymphoma.

common than myocardial infarction, but the HR for myocardial infarction was consistently higher than for ischemic stroke (Figure 1, Table 4). The 6-month cumulative incidence of myocardial infarction was 2.0% (95% CI: 1.9% to 2.0%) in all patients with cancer compared with 0.7% (95% CI: 0.6% to 0.7%) in control patients (HR: 2.9; 95% CI: 2.8 to 3.1; $p < 0.001$). The 6-month cumulative incidence of ischemic stroke was 3.0% (95% CI: 2.9% to 3.1%) in all patients with cancer compared with 1.6% (95% CI: 1.6% to 1.7%) in control patients (HR: 1.9; 95% CI: 1.8 to 2.0; $p < 0.001$). Among the different cancer types, patients with lung cancer had the highest 6-month cumulative incidence of myocardial infarction (3.2%; 95% CI: 3.0% to 3.3%) and ischemic stroke (5.6%; 95% CI: 5.4% to 5.7%). Excess risks of both myocardial infarction and ischemic stroke attenuated over time, but the heightened risk of myocardial infarction persisted for longer and several cancer types were associated with an increased risk of myocardial infarction beyond 1 year.

STAGE ANALYSES. The cumulative incidence and relative hazards of arterial thromboembolism steadily increased with increasing cancer stage at diagnosis and were especially high in cancer patients with stages 3 and 4 disease; however, even patients with stage 0 or 1 disease demonstrated excess risk (Central Illustration, Tables 5 and 6). At 6 months, the relative hazard of arterial thromboembolism in patients with cancer was 1.6 (95% CI: 1.5 to 1.7) for patients with stage 1 disease and 3.6 (95% CI: 3.3 to 3.8) for patients with stage 4 disease. The cumulative incidence and relative hazards of myocardial infarction alone and ischemic stroke alone also correlated with cancer stage, with results mirroring that of all arterial thromboembolism.

MORTALITY ANALYSIS. Median survival was 5.2 years (IQR: 0.9 years to not reached) for the entire cancer cohort and was not reached for matched control patients. Among patients with cancer, the

TABLE 5 Relative Hazards of Arterial Thromboembolism During Discrete Time Periods, Stratified by Cancer Stage and Thromboembolism Type

	Time Periods After Cancer Diagnosis*				
	0-1 Month	1-3 Months	3-6 Months	6-9 Months	9-12 Months
Arterial thromboembolism					
Stage 0	2.1 (1.6-2.8)	1.2 (0.9-1.5)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.8 (0.6-0.9)
Stage 1	2.9 (2.5-3.3)	1.6 (1.5-1.8)	1.1 (1.0-1.2)	1.0 (0.9-1.1)	0.9 (0.9-1.0)
Stage 2	3.6 (3.1-4.1)	1.5 (1.4-1.7)	1.3 (1.1-1.4)	1.0 (0.9-1.1)	0.9 (0.8-1.0)
Stage 3	6.5 (5.4-7.7)	2.7 (2.4-3.2)	1.9 (1.6-2.1)	1.5 (1.3-1.7)	1.6 (1.4-1.9)
Stage 4	11.2 (9.6-13.0)	3.4 (3.0-3.8)	2.3 (2.1-2.6)	1.8 (1.6-2.0)	–
Myocardial infarction					
Stage 0	3.0 (1.8-5.0)	1.6 (1.0-2.5)	0.9 (0.7-1.3)	1.3 (0.9-1.9)	0.7 (0.5-0.9)
Stage 1	4.7 (3.7-6.0)	2.6 (2.2-3.2)	1.4 (1.2-1.6)	1.2 (1.0-1.4)	0.9 (0.8-1.1)
Stage 2	5.2 (4.0-6.7)	2.3 (1.9-2.8)	1.6 (1.3-1.9)	0.9 (0.7-1.1)	0.7 (0.6-0.9)
Stage 3	9.7 (7.1-13.2)	3.5 (2.7-4.4)	2.6 (2.1-3.2)	1.6 (1.3-2.1)	1.7 (1.3-2.2)
Stage 4	13.1 (10.0-17.1)	4.3 (3.5-5.2)	3.1 (2.6-3.7)	2.1 (1.7-2.6)	–
Ischemic stroke					
Stage 0	1.8 (1.3-2.6)	0.8 (0.6-1.1)	0.9 (0.7-1.1)	0.7 (0.6-0.9)	0.8 (0.7-1.1)
Stage 1	2.2 (1.9-2.6)	1.3 (1.1-1.5)	1.0 (0.9-1.1)	0.9 (0.8-1.0)	1.0 (0.9-1.1)
Stage 2	2.9 (2.4-3.4)	1.3 (1.1-1.4)	1.1 (1.0-1.3)	1.0 (0.8-1.1)	0.9 (0.8-1.1)
Stage 3	5.3 (4.3-6.5)	2.4 (2.0-2.9)	1.6 (1.4-1.9)	1.4 (1.2-1.7)	1.6 (1.4-2.0)
Stage 4	10.4 (8.7-12.3)	3.1 (2.7-3.5)	2.0 (1.8-2.3)	1.7 (1.4-1.9)	–

Values are hazard ratio (95% confidence interval). Staging is defined according to the American Joint Committee on Cancer staging schema, except for patients with prostate cancer, who were staged according to the T (clinical) staging classification and patients with non-Hodgkin lymphoma, who were staged according to the Ann Arbor staging classification. Cancers diagnosed from 2002 to 2003 were staged according to the American Joint Committee on Cancer third edition definitions, whereas cancers diagnosed from 2004 to 2011 were staged according to the sixth edition. This analysis includes combined data from all evaluated cancer sites. Patients with unknown cancer stage (and their matched control patients) were excluded from this analysis. *Data are shown through the median period of follow-up for each cancer stage up to a maximum of 1 yr.

development of arterial thromboembolism was associated with an increased hazard for mortality (HR: 4.0; 95% CI: 4.0 to 4.1). This association remained significant after adjusting for all matching factors (HR: 3.5; 95% CI: 3.4 to 3.5) and all matching factors and cancer stage (HR: 3.1; 95% CI: 3.0 to 3.1). The 30-day cumulative incidence of death after arterial thromboembolism was 17.6% (95% CI: 17.3% to 18.0%) among patients with cancer versus 11.6% (95% CI: 11.3% to 11.9%) among matched control patients ($p < 0.001$).

SENSITIVITY ANALYSIS. When cancer cases and cancer-free control patients were matched by a broader set of cardiovascular risk factors, 117,574 pairs of patients were identified (42% of the original cohort). The association between incident cancer and arterial thromboembolism was materially unchanged with this additional matching schema (Online Table 1). Among these patients, the 6-month cumulative incidence of arterial thromboembolism was 3.9% (95% CI: 3.7% to 4.0%) in patients with cancer compared with 1.6% (95% CI: 1.5% to 1.7%) in control patients (HR: 2.5; 95% CI: 2.3 to 2.6; $p < 0.001$).

DISCUSSION

SUMMARY OF FINDINGS. In a large, heterogeneous, population-based sample, we found that patients newly diagnosed with common solid or hematologic cancers faced a considerably increased short-term risk of arterial thromboembolism. Within 6 months of diagnosis, more than twice as many patients with cancer had experienced arterial thromboembolism as compared with matched control patients without cancer. The risks of both myocardial infarction and ischemic stroke were increased in patients with cancer, although the excess risk of myocardial infarction was higher and persisted for longer. In addition, the risk of arterial thromboembolism varied by cancer type, with lung, gastric, and pancreatic cancers conferring the highest risk. Furthermore, advanced cancer stage was associated with increased risk, directly relating arterial thromboembolism to overall tumor burden and extent of disease. Finally, arterial thromboembolism among patients with cancer carried a poor prognosis, with a 3-fold increased hazard for death.

COMPARISON WITH PRIOR KNOWLEDGE. An increased risk of cardiovascular events has been previously reported in patients with lymphoma and breast, lung, cervical, prostate, gastric, ovarian, and head and neck cancers (13-20). Among Swedish patients diagnosed with any cancer type between 1987 and 2009, the 6-month relative risk of an inpatient diagnosis of coronary heart disease was 1.7 (21), and the 6-month relative risk of an inpatient diagnosis of ischemic stroke was 1.6 (26). In these Swedish studies, most individual cancer types were associated with an increased risk of arterial thromboembolism, including hematologic cancers and non-smoking-related solid cancers, although, similar to our study, the risks were highest with generally more advanced cancer types. Our study builds on these prior reports by including data on outpatients, cancer stage, and mortality after arterial thromboembolism, and by performing detailed individual matching to minimize the risk of confounding bias in a large, demographically heterogeneous population.

CLINICAL IMPLICATIONS. Our findings raise the question of whether patients with newly diagnosed malignant cancer, particularly those with advanced disease, should be considered for antithrombotic and statin medicines for primary prevention of cardiovascular disease. Given that patients with cancer are also prone to bleeding due to frequent coagulopathy and invasive procedures, carefully designed clinical trials are needed to answer these

questions. Several primary prevention trials in high-risk patients with cancer are currently underway. This includes a phase 2, randomized, placebo-controlled trial evaluating 6 months of anticoagulation with low-dose apixaban (NCT02048865) and a phase 1, randomized, parallel-assignment trial evaluating short-term antiplatelet and statin therapy with aspirin and simvastatin (NCT02285738). In the meantime, physicians treating patients with cancer should manage general cardiovascular risk factors such as hypertension, and they should be vigilant for symptoms or signs of heart disease or stroke.

The optimal antithrombotic strategy to treat acute arterial thromboembolism in patients with cancer is also uncertain. Besides standard acute recanalization therapies when indicated, these patients sometimes receive empiric long-term anticoagulation because of concerns for cancer-mediated hypercoagulability, and low-molecular-weight heparins are generally preferred over vitamin K antagonists because of extrapolation from randomized trials of venous thromboembolism treatment in patients with cancer (37). However, low-molecular-weight heparins are daily injections, which can be onerous, and are associated with increased bleeding risk, including intracranial hemorrhage (38), which is a major concern for patients with ischemic stroke. Direct oral anticoagulants are another option for cancer-associated thrombosis, although oncological guidelines recommend against their routine use outside of clinical trials (39). A pilot randomized trial of anticoagulation with enoxaparin versus antiplatelet therapy with aspirin for the treatment of acute ischemic stroke in patients with active cancer is nearing completion (NCT01763606). Such trials will be instrumental in determining the optimal antithrombotic treatment strategy for patients with cancer with arterial thromboembolism.

POTENTIAL MECHANISMS FOR FINDINGS. Several reasons may account for the increased short-term risk of arterial thromboembolism in patients with cancer. First, cancer and cardiovascular disease share several risk factors, including age, smoking, and obesity. Although we matched on age and several comorbidities, it is possible that differences in smoking or other factors contributed to the differences in outcomes between groups. However, this is unlikely to fully explain our findings because several cancer types not associated with smoking, such as breast cancer and non-Hodgkin lymphoma, also demonstrated heightened risks of arterial

TABLE 6 Cumulative Incidence of Arterial Thromboembolism, Stratified by Cancer Stage

	Time Since Diagnosis of Cancer*			
	3 Months	6 Months	1 Yr	2 Yrs
Arterial thromboembolism				
Stage 0				
Patients	1.4 (1.3–1.6)	2.3 (2.1–2.6)	4.0 (3.7–4.2)	7.0 (6.7–7.4)
Control patients	0.9 (0.8–1.1)	2.0 (1.8–2.2)	4.0 (3.7–4.2)	7.5 (7.1–7.8)
Stage 1				
Patients	2.0 (1.9–2.1)	3.0 (2.9–3.1)	4.7 (4.6–4.9)	7.7 (7.5–7.8)
Control patients	1.0 (0.9–1.0)	2.0 (1.9–2.0)	3.8 (3.7–3.9)	7.4 (7.2–7.6)
Stage 2				
Patients	2.5 (2.3–2.6)	3.7 (3.5–3.8)	5.5 (5.3–5.6)	8.7 (8.5–8.9)
Control patients	1.1 (1.0–1.2)	2.1 (2.0–2.2)	4.2 (4.1–4.4)	8.0 (7.7–8.2)
Stage 3				
Patients	4.8 (4.6–5.1)	6.6 (6.4–6.9)	8.9 (8.6–9.2)	11.6 (11.2–11.9)
Control patients	1.2 (1.1–1.3)	2.4 (2.2–2.5)	4.4 (4.2–4.6)	8.3 (8.0–8.6)
Stage 4				
Patients	6.2 (6.0–6.4)	7.7 (7.5–8.0)	9.4 (9.1–9.6)	–
Control patients	1.1 (1.0–1.2)	2.2 (2.1–2.4)	4.4 (4.2–4.5)	–
Myocardial infarction				
Stage 0				
Patients	0.6 (0.5–0.7)	0.9 (0.8–1.0)	1.5 (1.3–1.7)	2.6 (2.4–2.9)
Control patients	0.3 (0.2–0.3)	0.6 (0.5–0.7)	1.3 (1.1–1.5)	2.5 (2.3–2.7)
Stage 1				
Patients	0.9 (0.8–1.0)	1.3 (1.2–1.4)	1.9 (1.8–2.0)	3.0 (2.9–3.1)
Control patients	0.3 (0.2–0.3)	0.6 (0.5–0.6)	1.2 (1.1–1.2)	2.5 (2.4–2.6)
Stage 2				
Patients	1.1 (1.1–1.2)	1.6 (1.5–1.7)	2.2 (2.1–2.4)	3.5 (3.4–3.6)
Control patients	0.4 (0.3–0.4)	0.7 (0.6–0.7)	1.4 (1.4–1.5)	2.8 (2.7–3.0)
Stage 3				
Patients	2.1 (1.9–2.2)	2.8 (2.7–3.0)	3.7 (3.5–3.9)	4.8 (4.6–5.0)
Control patients	0.4 (0.3–0.4)	0.7 (0.6–0.8)	1.4 (1.3–1.6)	2.9 (2.7–3.0)
Stage 4				
Patients	2.4 (2.3–2.5)	3.0 (2.9–3.2)	3.7 (3.5–3.8)	–
Control patients	0.4 (0.3–0.4)	0.7 (0.6–0.8)	1.4 (1.3–1.5)	–
Ischemic stroke				
Stage 0				
Patients	0.9 (0.8–1.0)	1.5 (1.4–1.7)	2.6 (2.4–2.8)	4.8 (4.5–5.1)
Control patients	0.7 (0.6–0.8)	1.4 (1.3–1.6)	2.8 (2.6–3.1)	5.5 (5.1–5.8)
Stage 1				
Patients	1.2 (1.1–1.2)	1.9 (1.8–1.9)	3.1 (3.0–3.2)	5.1 (5.0–5.3)
Control patients	0.7 (0.7–0.8)	1.4 (1.4–1.5)	2.8 (2.7–2.9)	5.3 (5.2–5.5)
Stage 2				
Patients	1.4 (1.3–1.5)	2.2 (2.1–2.3)	3.5 (3.4–3.7)	5.8 (5.6–6.0)
Control patients	0.8 (0.7–0.9)	1.6 (1.5–1.6)	3.0 (2.9–3.1)	5.7 (5.5–5.9)
Stage 3				
Patients	3.0 (2.8–3.2)	4.2 (4.0–4.4)	5.8 (5.5–6.0)	7.6 (7.3–7.9)
Control patients	0.9 (0.8–1.0)	1.8 (1.6–1.9)	3.2 (3.0–3.3)	5.9 (5.7–6.2)
Stage 4				
Patients	4.2 (4.0–4.3)	5.2 (5.0–5.4)	6.3 (6.1–6.5)	–
Control patients	0.8 (0.7–0.9)	1.6 (1.5–1.8)	3.2 (3.0–3.3)	–

Value are % (95% confidence interval). Staging is defined according to the American Joint Committee on Cancer staging schema, except for patients with prostate cancer, who were staged according to the T (clinical) staging classification and patients with non-Hodgkin lymphoma, who were staged according to the Ann Arbor staging classification. Cancers diagnosed from 2002 to 2003 were staged according to the American Joint Committee on Cancer third edition definitions, whereas cancers diagnosed from 2004 to 2011 were staged according to the sixth edition. This analysis includes combined data from all evaluated cancer sites. Patients with unknown cancer stage (and their matched control patients) were excluded from this analysis. *Data are shown through the median follow-up period for patients with cancer for each cancer stage up to a maximum of 2 yrs.

thromboembolism. In addition, the clear correlation between cancer stage and arterial thromboembolism risk suggests a biological gradient between cancer activity and arterial thromboembolism risk. Furthermore, the temporal pattern of arterial thromboembolism risk among patients with cancer, whereby risk was highest soon after cancer diagnosis, when cancer activity and treatments are most intense, and then attenuated over time, supports the biological plausibility of our hypothesis because confounding factors would not be expected to attenuate in this fashion. Second, cancer can induce a hypercoagulable state through circulating microparticles, secretion of procoagulant factors, and alterations in platelet activity and endothelial function (3,40). In fact, there are numerous reports of stroke or myocardial infarction serving as the initial manifestation of cancer (41,42). In addition, several cancer treatments, particularly platinum-based compounds, may increase thrombotic risk (3,43,44). Third, invasive procedures and thrombocytopenia are common in patients with cancer, and sometimes necessitate interruption of preventative antithrombotic medicines, which could precipitate thromboembolism. Fourth, it is possible that patients with cancer were monitored more closely, resulting in more detected events. However, this seems unlikely given the pattern of associations we found. For example, pancreatic cancer was more strongly associated with stroke than was breast cancer, even though the care of pancreatic cancer rarely involves brain imaging, whereas patients with breast cancer often undergo brain imaging to rule out metastases.

STUDY LIMITATIONS. First, it was retrospective and relied on administrative diagnosis codes for outcome assessments, and although the codes we used were previously validated, some arterial thromboembolism diagnoses might have been misclassified, particularly among patients with advanced-stage disease, whereby metastases could have mimicked symptoms or signs of stroke or myocardial infarction. Additionally, we lacked granular data on clinical characteristics such as electrocardiogram and imaging findings, laboratory data, severity of events, and administered medications. This lack of detailed clinical information prevented us from determining the specific pathophysiology of arterial thromboembolic events, including the proportion of myocardial infarction events caused by acute plaque rupture versus other mechanisms. Second, our use of SEER-Medicare data required us to exclude patients younger than 66 years of age and patients enrolled in primary insurance plans other than traditional Medicare. In addition, SEER program-based research has several known limitations, including incomplete data regarding adjuvant therapies, lack of reliable data on functional status and quality of life measures, migration from SEER catchment areas, and selection bias towards better outcomes (45). The SEER program also lacks central histology review; therefore, coding reliability can vary for distinct cancer types. Furthermore, claims-based data, including Medicare, can be affected by changes in coding patterns and diagnostic reclassifications over time (46). These factors could have led to overcoding of outcomes, which could have hampered the precision of our absolute risk estimates. Third, although we matched on demographics, several comorbidities, and, in a sensitivity analysis, most cardiovascular risk factors, it is possible that unmeasured confounders were responsible for the heightened arterial thromboembolism risk seen in patients with cancer. However, the fact that arterial thromboembolism risk increased considerably after cancer diagnosis and then decreased with time argues against this, as residual confounding would be expected to produce uniform risk differences between groups over time. Fourth, patients with cancer likely received more medical attention than cancer-free control patients, which could have led to increased endpoint detection among the cancer group.

CONCLUSIONS

We found that patients with a new diagnosis of cancer faced an increased risk of arterial thromboembolism, especially during the first 6 months after diagnosis. Our results suggest that malignant cancer may be an underappreciated, yet common risk factor for arterial thromboembolism. Future research should aim to investigate the mechanistic basis for these findings, the utility of including cancer in cardiovascular risk prediction instruments, and optimal strategies to prevent arterial thromboembolism in patients with cancer.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with cancer face a high short-term risk of arterial thromboembolism, particularly those with advanced disease or historically aggressive cancer types, although even early stage disease or indolent cancer types heighten risk. Arterial thromboembolism in cancer patients carries a 3-fold increased risk of death.

TRANSLATIONAL OUTLOOK: Future research should investigate the mechanisms responsible for the association between cancer and arterial thromboembolism, the predictive value of including cancer in risk prediction models, and strategies to prevent arterial thromboembolism in patients with cancer.

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KEY WORDS ischemic stroke, myocardial infarction, thrombosis

APPENDIX For a supplemental figure and table, please see the online version of this article.

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