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ORIGINAL ARTICLE

Cancer-associated venous thromboembolism: Incidence and features in a racially diverse population

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Abstract

Background: Data on the population-based incidence of cancer-associated venous thromboembolism (VTE) from racially diverse populations are limited.

Objective: To evaluate the incidence and burden of cancer-associated VTE, including demographic and racial subgroups in the general population of Oklahoma County—which closely mirrors the United States.

Design: A population-based prospective study.

Setting: We conducted surveillance of VTE at tertiary care facilities and outpatient clinics in Oklahoma County, Oklahoma, from 2012–2014. Surveillance included reviewing all imaging reports used to diagnose VTE and identifying VTE events from hospital discharge data and death certificates. Cancer status was determined by linkage to the Oklahoma Central Cancer Registry.

Measurements: We used Poisson regression to calculate crude and age-adjusted incidence rates of cancer-associated VTE per 100 000 general population per year, with 95% confidence intervals (95% CI).

Results: The age-adjusted incidence (95% CI) of cancer-associated VTE among adults age ≥ 18 was 70.0 (65.1–75.3). The age-adjusted incidence rates (95% CI) were 85.9 (72.7–101.6) for non-Hispanic Blacks, 79.5 (13.2–86.5) for non-Hispanic Whites, 18.8 (8.9–39.4) for Native Americans, 15.6 (7.0–34.8) for Asian/Pacific Islanders, and 15.2 (9.2–25.1) for Hispanics. Recurrent VTE up to 2 years after the initial diagnosis occurred in 38 of 304 patients (12.5%) with active cancer and in 34 of 424 patients (8.0%) with a history of cancer > 6 months previously.

Conclusion: Age-adjusted incidence rates of cancer-associated VTE vary substantially by race and ethnicity. The relatively high incidence rates of first VTE and of recurrence warrant further assessment of strategies to prevent VTE among cancer patients.

KEYWORDS
cancer, deep vein thrombosis, incidence rate, pulmonary embolism, venous thromboembolism

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1 | INTRODUCTION

As the treatment of cancer continues to improve, efforts to prevent complications among cancer survivors are increasingly important. Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a complication that is associated with increased mortality and morbidity in cancer patients, including ambulatory patients receiving chemotherapy.[1-10] The risk of VTE is highest for patients with pancreatic, brain, lung, or ovarian cancer[2,4,5,6,7,8,9,11,12] and is greatest for patients with metastatic disease and those receiving chemotherapy.[1,2,3,4,5,6,7,8,9,11,12]

Current population-based incidence data on cancer-associated VTE from racially diverse populations in the United States are limited.[1,13] Such data are important to inform prevention strategies because the nature and burden of VTE in cancer patients may change over time,[4,15,16,17,18] and some cancer treatments (such as some immunotherapy agents) may predispose the patient to the development of thrombosis.[2,5,12,14] Data on the association of race and ethnicity with the incidence of VTE in cancer patients are also limited.[2,4,13] The available data suggest that non-Hispanic Blacks have higher rates of cancer-associated VTE, and people of Hispanic or Asian/Pacific Islander origin have lower rates of cancer-associated VTE, compared to other races and ethnicities.[2,4,13]

We have recently reported that, among a prospective population-based study in the racially and ethnically diverse population of Oklahoma County, Oklahoma, the age-adjusted VTE incidence and mortality rates vary substantially by race.[19,20] We used the data from this population-based study to assess the incidence and burden of cancer-associated VTE among adults (age ≥ 18 years), including the outcomes of recurrent VTE and case fatality. We also assessed the demographic and risk factor profile of the patients with cancer-associated VTE. Because the distributions of age, sex, race/ethnicity, and cancer types[21] in Oklahoma County are very similar to the overall US population, our results are likely to be informative of the burden and features of cancer-associated VTE in the US population.

Essentials

- Venous thromboembolism (VTE) contributes to mortality and morbidity in cancer patients.
- There are limited data on cancer-associated VTE among racially diverse populations in the United States.
- This prospective population-based study in a racially diverse population closely mirrors the United States.
- Age-adjusted cancer-associated VTE incidence rates varied substantially by race/ethnicity.

2 | METHODS

2.1 | Venous thromboembolism data

A detailed description of the methods and overall results of our VTE surveillance system have been published.[19,20] In collaboration with the Centers for Disease Control and Prevention (CDC) and the Oklahoma State Department of Health, we conducted VTE surveillance in accordance with federal statutes[22] and Title 310, Oklahoma State Department of Health, Chapter 515-1-6 for public health disease surveillance. The Oklahoma Commissioner of Health authorized VTE as a reportable condition during the surveillance period and delegated disease surveillance responsibilities to the authors at the University of Oklahoma Health Sciences Center. The present study was approved by the institutional review boards at the University of Oklahoma Health Sciences Center and the Oklahoma State Department of Health. Surveillance was conducted from April 1, 2012 through March 31, 2014 using both active and passive methods. Active surveillance consisted of regularly visiting all tertiary care facilities and outpatient clinics in Oklahoma County to review the text from all imaging studies from chest computed tomography (CT) or magnetic resonance imaging (MRI), lung perfusion scans, and compression ultrasonography (CUS) of the extremities to identify patients with VTE. We identified the relevant imaging studies at each facility using International Classification of Diseases Ninth Revision Clinical Modification procedure codes, current procedural terminology (CPT) codes, and free text, depending on the facilities' medical record system.[19,20] Passive surveillance comprised accessing health records from the hospital discharge dataset and death certificate records from the Oklahoma State Department of Health for 2010 through 2015.

VTE reports from each data source were linked by name, birthdate, social security number, and ZIP code, which enabled the identification of unique patients meeting the case definition (published previously).[19] Population denominator data for 2013 (surveillance midpoint) were obtained from the US Census Bureau.[23]

2.2 | Cancer data

Cancer data were obtained from the Oklahoma Central Cancer Registry, part of the National Program of Cancer Registries, CDC cancer programs.[24] The Oklahoma Central Cancer Registry maintains a population-based cancer database of all cancer diagnosed or treated in Oklahoma since January 1, 1997. This statewide population-based registry enables both private and public health agencies to study cancer trends and to develop and assess cancer prevention and control programs with data. The Oklahoma Central Cancer Registry follows standards developed by the North American Association of Central Cancer Registries. All cancer (excluding cervix in situ and basal cell or squamous cell skin cancer) was used. The cancer data were linked to VTE data using Registry Plus™ Link Plus software version 2.0 (CDC), through a probabilistic linkage method. Double visual review and reconciliation was completed.

2.3 | Case definition

We categorized a VTE event as cancer-associated if the patient had any history of cancer prior to the date of VTE diagnosis, other than basal cell or squamous cell skin cancer. Active cancer was defined as documented cancer that was either metastatic or diagnosed within 6 months prior to VTE diagnosis.

Incident VTE events were defined as the first VTE event detected during the 2-year surveillance period. A recurrent event was defined as a new VTE occurring ≥ 72 h after the incident VTE but detected within the surveillance period. All-cause case fatality rates were calculated at 30, 90, and 180 days after the diagnosis date of the incident VTE event.

We also categorized VTE events as persistent provoked, transient provoked, or unprovoked according to the recommendations of the International Society on Thrombosis and Haemostasis.[25] Persistent provoking factors were further subclassified as either associated with cancer (active or any history of cancer, as defined above) or with other persistent factors, which included inflammatory bowel disease, anti-phospholipid syndrome, and systemic lupus erythematosus. Transient provoking factors included a history of hospitalization (past 2 months); immobilization, surgery, trauma, central venous catheterization, congestive heart failure, myocardial infarction, or stroke (past 3 months); pregnancy (past 2 months, or past 3 months if cesarean delivery); and select medications (past 2 months). The medications included estrogen- and progesterone-containing drugs, raloxifene, tamoxifen, erythropoietin, romiplostim, oprelvekin, eltrombopag thalidomide, and lenalidomide. We also documented whether the patient was receiving anticoagulant therapy at the time of their VTE event.

2.4 | Statistical analysis

SAS 9.4 was used for all analyses. Crude and stratified incidence rates and all-cause case fatality rates and the corresponding 95% confidence intervals (CI) were calculated using Poisson regression.

Age was divided into the following strata: 18–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years. Age-adjusted incidence rates were calculated overall and stratified by sex and race/ethnicity by using PROC STDRATE, using the direct standardization method with the 2013 US population as the reference. All incidence rates were given per 100 000 population per year.

Race/ethnicity was categorized as non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic Native American, and non-Hispanic White. Persons of multiple and unknown race were excluded from the race/ethnicity-stratified analyses.

The distribution of age group, race/ethnicity, presenting symptoms, and provoking risk factors are reported among all VTE patients identified through this surveillance system in Oklahoma County and stratified by those without a history of cancer, metastatic/active cancer, and a history of cancer > 6 months previous. Cumulative incidence of the first recurrent VTE event during the surveillance period was calculated for VTE patients without a history of cancer, with metastatic/active cancer, and with a > 6-month history of cancer. In addition, the cumulative incidence was further stratified among those without a history of cancer by persistent provoked, transient provoked, and unprovoked.

3 | RESULTS

The age and race/ethnicity distribution of Oklahoma County and the United States for the year 2013, the midpoint year of our surveillance period, are similar (Table 1). We screened 56 967 imaging reports from 14 inpatient facilities and seven outpatient facilities. This surveillance identified a total of 3815 VTE events among 3422 unique patients with and without cancer. Among these, 167 patients had incomplete data on cancer history and/or VTE risk factors, and 20 patients were less than 18 years of age. Of the remaining 3235 patients, a total of 730 patients (22.6%) were linked to the cancer registry as having a history of cancer, of which 306 patients (9.5%) had active cancer, and 424 (13.1%) had a history of cancer more than 6 months previously. Among these 424 patients, the precise date of cancer diagnosis was known in 181 patients, and in 243 patients the precise date of cancer diagnosis was unknown. Cancer was diagnosed > 6 and < 12 months previously to the VTE diagnosis in 20 patients, between 12 and < 24 months in 33 patients, between 24 and < 36 months in 27 patients, between 36 and < 48 months in 12 patients, between 48 and < 60 months in 12 patients, and ≥ 60 months previously in 77 patients.

Of the 306 patients classified as having active cancer, VTE was the presenting complaint which led to the diagnosis of cancer in 23 patients (7.5%). Cancer was diagnosed on the same day as VTE in 13 of these 23 patients and between 1 and 105 days after the diagnosis of VTE in 10 patients. Of the total 730 patients with a history of cancer, 10 were missing information on race/ethnicity and were excluded from the race/ethnicity-stratified analyses.

3.1 | Incidence of cancer-associated VTE

The annual crude incidence per 100 000 population of all cancer-associated VTE among adults age 18 years or more was 64.8 (95% CI: 60.3–69.7). The age-adjusted incidence rate was 70.0 (95% CI: 65.1–75.3).

The annual crude; age-adjusted; and the age-, sex-, and race/ethnicity-stratified incidence rates for all cancer-associated VTE, and for clinical presentation as either DVT or PE, are listed in Table 2. Among the 454 patients with cancer-associated VTE who presented with DVT, 234 (51.5%) had proximal DVT of the leg, 43 (9.5%) had isolated calf DVT, 169 (37.2%) had upper extremity DVT, and 8 (1.8%) had an unknown location. Of the patients with upper extremity thrombosis, 87 (51.5%) had a central venous catheter within the past 6 months. There was an increasing incidence as age

TABLE 1 Distribution of age and race/ethnicity in the United States and Oklahoma County from the 2013 American Community Survey

	United States		Oklahoma County	
Demographic characteristic	***N***	**%**	***N***	**%**
Total	316 128 839	100.0	755 639	100.0
Age (years)				
<18	73 585 872	23.3	192 960	25.5
18–39	93 906 010	29.7	241 263	31.9
40–49	42 057 226	13.3	90 239	11.9
50–59	43 753 656	13.8	97 987	13.0
60–69	32 730 718	10.4	70 674	9.4
70–79	18 285 930	5.8	37 633	5.0
≥80	11 809 427	3.7	24 883	3.3
Race/ethnicity				
Non-Hispanic White	230 592 579	72.9	501 213	66.3
Non-Hispanic Black	39 167 010	12.4	109 245	14.5
Native American	2 540 309	0.8	22 738	3.0
Asian	15 231 962	4.8	22 536	3.0
Pacific Islander	526 347	0.2	500	0.1
Other race	14 746 054	4.7	27 886	3.7
Two or more races	8 732 333	2.8	48 000	6.4
Missing	4 592 545	1.5	23 521	3.1
Hispanic[a]	54 203 686	17.1	121 309	16.0

[a]Not a mutually exclusive category with the race categories.

increased, with high incidences of 138, 235, and 313 per 100 000 population among those aged 60 to 69, 70 to 79, and 80 years or more, respectively.

The annual crude; age-adjusted; and the age-, sex-, and race/ethnicity-stratified VTE incidence rates for patients with active cancer, and for those with a history of cancer more than 6 months previously, are given in Table 3.

The incidence rates of VTE for both all cancer-associated and among patients only with active cancer were highest among non-Hispanic Blacks and non-Hispanic Whites, and lower among people of non-Hispanic Asian/Pacific Islander, Hispanic, and non-Hispanic Native American descent (Tables 2 and 3).

Among the 730 patients with cancer-associated VTE, documentation regarding VTE prophylaxis prior to their event was present in 574 patients (78.6%) and absent in 156 patients (21.4%). Of the 574 patients, 391 patients received anticoagulant prophylaxis only, 114 patients were using mechanical prophylaxis only, and 69 patients were receiving both.

3.2 | Patient features, symptoms at presentation, and risk factors for venous thromboembolism

The distribution of age, race/ethnicity, symptoms at presentation, and risk factors for the incident VTE diagnosis are summarized in Table 4. Those with metastatic/active cancer and a > 6-month history of cancer tended to be older (age 60–79 years) than those without cancer. Patients with metastatic/active cancer also tended to have a higher proportion of symptoms in the arms, whereas patients without a history of cancer tended to have a higher proportion of symptoms in the legs. Among patients with cancer-associated VTE, 60% and 51% of patients with metastatic/active cancer and a > 6-month history of cancer, respectively, had at least one other provoking risk factor. Similarly, among those without any history of cancer, 49% had at least one provoking risk factor. Hospitalization was the most common provoking risk factor among all three patient populations. Central venous catheterization was more common among patients with metastatic/active cancer (23%) than those with a > 6-month history of cancer (13%) or no history of cancer (9.2%). The distribution of tumor types among the patients with VTE is shown in Table 5. Cancers of the breast, lung, colorectal, and prostate were most common among patients with cancer-associated VTE. When stratified by timing of cancer, there was a higher proportion of lung cancer tumors among patients with metastatic/active cancer, whereas there was a higher proportion of breast cancer among those with a > 6-month history of cancer.

3.3 | Recurrent VTE

A total of 319 (9.9%) of the total population of 3235 patients with VTE had ≥ 2 unique VTE events during our 2-year surveillance period of which 267 patients had two events, 36 patients had three

TABLE 2 Annual incidence rate per 100000 population of cancer-associated VTE, DVT and PE, among adults age ≥ 18 years in Oklahoma County, Oklahoma

	VTE				DVT				PE ± DVT			
Measure	***n***	**IR**	**95% CI**		***n***	**IR**	**95% CI**		***n***	**IR**	**95% CI**	
Crude overall	730	64.8	60.3	69.7	454	40.3	36.8	44.2	276	24.5	21.8	27.6
Age-adjusted overall[a]		70	65.1	75.3		43.5	39.7	47.7		26.5	23.6	29.9
Sex[a]												
Male	334	67.4	60.5	75	205	41.3	36	47.4	129	26.1	21.9	31
Female	396	72.8	66	80.3	249	45.7	40.3	51.7	147	27.1	23.1	31.9
Age												
18–39	26	5.4	3.7	7.9	19	3.9	2.5	6.2	7	1.5	0.7	3
40–49	50	27.7	21	36.6	30	16.6	11.6	23.8	20	11.1	7.2	17.2
50–59	126	64.2	53.9	76.5	79	40.3	32.3	50.2	47	24	18	31.9
60–69	195	137.8	119.8	158.6	125	88.4	74.1	105.3	70	49.5	39.1	62.5
70–79	177	235.1	202.9	272.5	102	135.5	111.6	164.5	75	99.6	79.5	124.9
≥ 80	156	313.4	267.9	366.6	99	198.9	163.3	242.2	57	114.5	88.3	148.4
Race/ethnicity[a]												
Asian/Pacific Islander	6	15.6	7	34.8	5	13	5.4	31.2	1	2.7	0.4	18.9
Non-Hispanic Black	138	85.9	72.7	101.6	90	55.5	45.1	68.3	48	30.4	22.9	40.4
Hispanic	17	15.2	9.2	25.1	6	6.1	2.6	14	11	9.1	4.9	17
Native American	7	18.8	8.9	39.4	3	8.3	2.7	25.8	4	10.5	3.9	27.9
Non-Hispanic White	552	79.5	73.2	86.5	343	49.3	44.4	54.8	209	30.2	26.4	34.6

[a]Age-adjusted to the US 2013 population.

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; PE, pulmonary embolism; VTE, venous thromboembolism.

TABLE 3 Annual incidence rate per 100000 population of cancer-associated VTE, stratified by cancer history, among adults age ≥ 18 years in Oklahoma County, Oklahoma

	VTE: Any Hx of cancer				VTE: Active cancer only				VTE: > 6 month Hx cancer			
Measure	*n*	IR	95% CI		*n*	IR	95% CI		*n*	IR	95% CI	
Crude overall	730	64.8	60.3	69.7	306	27.2	24.3	30.4	424	37.7	34.2	41.4
Age-adjusted overall[a]		70	65.1	75.3		29.2	26.1	32.7		40.8	37.1	44.9
Sex[a]												
Male	334	67.4	60.5	75	135	26.9	22.7	31.9	199	40.5	35.2	46.5
Female	396	72.8	66	80.3	171	31.4	27.1	36.5	225	41.4	36.3	47.1
Age												
18–39	26	5.4	3.7	7.9	10	2.1	1.1	3.9	16	3.3	2	5.4
40–49	50	27.7	21	36.6	33	18.3	13	25.7	17	9.4	5.9	15.2
50–59	126	64.2	53.9	76.5	67	34.1	26.9	43.4	59	30.1	23.3	38.8
60–69	195	137.8	119.8	158.6	89	62.9	51.1	77.4	106	74.9	61.9	90.6
70–79	177	235.1	202.9	272.5	73	97	77.1	122	104	138.2	114	167.4
≥ 80	156	313.4	267.9	366.6	34	68.3	48.8	95.6	122	245.1	205.2	292.6
Race/ethnicity[a]												
Asian/Pacific Islander	6	15.6	7	34.8	3	7.7	2.5	24	3	7.9	2.5	24.5
Non-Hispanic Black	138	85.9	72.7	101.6	66	40.9	32.1	52	72	45.1	35.8	56.9
Hispanic	17	15.2	9.2	25.1	8	5.6	2.7	11.3	9	9.6	4.9	19
Native American	7	18.8	8.9	39.4	3	8	2.6	24.9	4	10.7	4	28.7
Non-Hispanic White	552	79.5	73.2	86.5	225	32.5	28.5	37	327	47	42.2	52.4

[a]Age-adjusted to the US 2013 population.

Abbreviations: CI, confidence interval; Hx, history; IR, incidence rate; VTE, venous thromboembolism.

events, and 16 patients had four or more events. The median time between the first and second episodes was 61 days (range 4–427 days) in patients with active cancer and 72.5 days (range 7–673 days) in patients with a history of cancer more than 6 months previously. The cumulative incidence of the first recurrent VTE event according to cancer status is highest among patients with metastatic/active cancer, and most instances of recurrences occurred in the first 6 months (Figure 1). At the time of the first recurrent VTE event, the number of patients receiving anticoagulant medication were 14 (36.8%), 13 (38.2%), and 104 (42.1%) for those with active cancer, those with cancer more than 6 months previously, and those without cancer, respectively. The cumulative incidence of the first recurrent VTE is highest among patients with a persistent provoking risk factor[25] excluding cancer, and patients with metastatic/active cancer have the next highest cumulative incidence of recurrent VTE (Figure 2).

As a sensitivity analysis, we calculated the cumulative incidence of recurrence while treating death as a competing risk factor, shown in Figures S1 and S2 in supporting information. The overall trends were similar to the primary results. The notable difference between the two approaches is that when death is treated as a competing risk factor, the cumulative incidence for each group of patients is slightly higher, with the most pronounced increase being among patients with a > 6-month history of cancer at ≥ 600 days follow-up.

3.4 | Case-fatality

The all-cause case fatality rates stratified by age, sex, and race/ethnicity are provided in Table 6. The case fatality rate among those with active cancer was higher at each time point (i.e., 0–30, 31–90, 91–180, and > 180 days) than for those with a history of cancer > 6 months previously, and the case fatality rate among those with > 6-month history of cancer was higher than for those without any history of cancer at each time point (data not shown). While case fatality rates varied by race/ethnicity, data were limited for several groups (i.e., Non-Hispanic Asian/Pacific Islander, Hispanic, and Non-Hispanic Native American), and there was substantial overlap in all confidence intervals.

TABLE 4 Distribution of demographic characteristics, symptoms, and risk factors among cases of VTE age ≥ 18 in Oklahoma County, Oklahoma

	All VTE patients		VTE no cancer		VTE active cancer		VTE history of cancer > 6 months previous	
Demographic factors	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Total	3235	100	2505	77.4	306	9.5	424	13.1
Age (years)								
18–39	384	12	358	14	10	3.3	16	3.8
40–49	383	12	333	13	33	11	17	4
50–59	636	20	510	20	67	22	59	14
60–69	684	21	489	20	89	29	106	25
70–79	556	17	379	15	73	24	104	25
≥ 80	592	18	436	17	34	11	122	29
Race/ethnicity								
Non-Hispanic White	2244	69	1692	68	225	74	327	77
Non-Hispanic Black	704	22	566	23	66	22	72	17
Hispanic	100	3.1	83	3.3	8	2.6	9	2.1
Native American	59	1.8	52	2.1	3	1	4	0.9
Asian/Pacific Islander	29	0.9	23	0.9	3	1	3	0.7
Missing/unknown	97	3	87	3.5	1	0.3	9	2.1
Multiple	2	0.1	2	0.1				
Symptoms								
Any symptoms	2754	85	2134	85	251	82	369	87
Arm symptoms	389	12	260	10	60	20	69	16
Leg symptoms	1522	47	1252	50	97	32	173	41
Cardio-respiratory symptoms	1317	41	998	40	132	43	187	44
No symptoms (i.e., incidental)	481	15	371	15	55	18	55	13
Provoking risk factors								
Any risk factor	1619	50	1218	49	184	60	217	51
Hospitalization	1165	36	871	35	140	46	154	36
Immobilization	324	10	267	11	15	4.9	42	9.9
Surgery	105	3.3	79	3.2	18	5.9	8	1.9
Trauma	245	7.6	209	8.3	12	3.9	24	5.7
Central venous catheterization	354	11	230	9.2	69	23	55	13
Congestive heart failure	58	1.8	45	1.8	4	1.3	9	2.1
Myocardial infarction	25	0.8	20	0.8	1	0.3	4	0.9
Stroke	55	1.7	50	2	2	0.7	3	0.7
Pregnancy	17	0.5	17	0.7	0	0	0	0
Medications	118	3.7	101	4	8	2.6	9	2.1
No other risk factors	1616	50	1287	51	122	40	207	49

Abbreviation: VTE, venous thromboembolism.

4 | DISCUSSION

The results of this population-based study document the disease burden of cancer-associated VTE and describe the demographic and risk factor profile of these patients, which can help inform strategies to reduce this disease burden. Cancer-associated VTE comprised 21% of all cases of VTE detected during the surveillance period, underscoring its major contribution to the total burden of venous thromboembolic disease. The age-adjusted incidence of 70 per 100 000 adult population (Table 2) indicates cancer-associated

TABLE 5 Distribution of cancer type among adults age ≥ 18 years with cancer-associated VTE

	All history of cancer		Active cancer		History of cancer > 6 months previous	
	N = 730	%	*n* = 306	%	*n* = 424	%
Cancer type						
Anal	2	0.3	1	0.3	1	0.2
Bladder	13	1.8	5	1.6	8	1.9
Brain	11	1.5	4	1.3	7	1.7
Breast	138	18.9	46	15.1	92	22.0
Cervical/uterus	34	4.7	15	4.9	19	4.5
Colorectal	73	10.0	32	10.5	41	9.8
Esophageal/gastric	31	4.2	19	6.3	12	2.9
Head/neck	18	2.5	6	2.0	12	2.9
Kidney/renal cell	31	4.2	19	6.3	12	2.9
Leukemia	21	2.9	3	1.0	18	4.3
Liver	10	1.4	4	1.3	6	1.4
Lung	91	12.5	55	18.1	36	8.6
Lymphoma	25	3.4	10	3.3	15	3.5
Melanoma	7	1.0	3	1.0	4	1.0
Myeloma	14	1.9	8	2.6	6	1.4
Other digestive	6	0.8	3	1.0	3	0.7
Ovarian	23	3.2	13	4.3	10	2.4
Pancreatic	19	2.6	13	4.3	6	1.4
Prostate	69	9.5	12	3.9	57	13.6
Sarcoma	10	1.4	7	2.3	3	0.7
Testicular	7	1.0	4	1.3	3	0.7
Other	18	2.5	4	1.3	14	3.3
Multiple	40	5.5	14	4.6	26	6.2
Unknown	19	2.6	6	2.0	13	3.1

Abbreviation: VTE, venous thromboembolism.

VTE is an important public health burden. Applying this incidence rate to the most current US population estimates (2020) suggests an estimated annual number of new cases of cancer-associated VTE among adults nationally of 179 777. This estimate indicates cancer-associated VTE is more common than all new cases of colorectal cancer (147 950 cases) in the United States in 2020, as estimated by the National Cancer Institute.[26] For additional perspective, the estimated numbers of new cases of breast, lung, and prostate cancer in the United States in 2020 were 276 000, 229 000, and 192 000, respectively.[26] Cancer-associated VTE is 1.7 to 3 times more common than each of the remaining cancers in the list of the 13 most common cancers. Similar to VTE incidence among patients without cancer,[19] there was a clear gradient of increasing incidence as age increased. Among those age 65 years or older, the incidence was 239 per 100 000—making cancer-associated VTE an important public health burden in the US Medicare population, with an estimated 130 692 new cases in 2020.

The observed differences in incidences by race/ethnicity are substantial, with the highest incidence among non-Hispanic Blacks and non-Hispanic Whites, and similar incidences among people from other races/ethnicities (Table 2). To our knowledge, this is the first study to estimate the population incidence of cancer-associated VTE among American Indian/Alaskan Native people in the general population. Our results documenting the highest incidence among non-Hispanic Blacks, and lower incidences among Hispanics and non-Hispanic Asian/Pacific Islanders, are consistent with previous studies.[2,4,13] The reasons for the substantial variance in incidence by race/ethnicity are not completely understood. Likely contributing factors are genomic differences, socioeconomic factors, and differences in access to health care and the quality of care received—particularly related to cancer screening and prevention and to thrombosis prevention. Misclassification of race/ethnicity is an inherent source of error in data from medical records, and stratum-specific results could be affected, particularly those with the smallest cell sizes. However, the differences in some of the race/ethnicity rates are sufficiently large that the results are fairly robust. For example, there were seven cancer-associated VTE events among Native American people. There would have needed to be an additional 10 events among Native Americans (e.g., if some persons who were Native American and had a VTE were mistakenly classified as

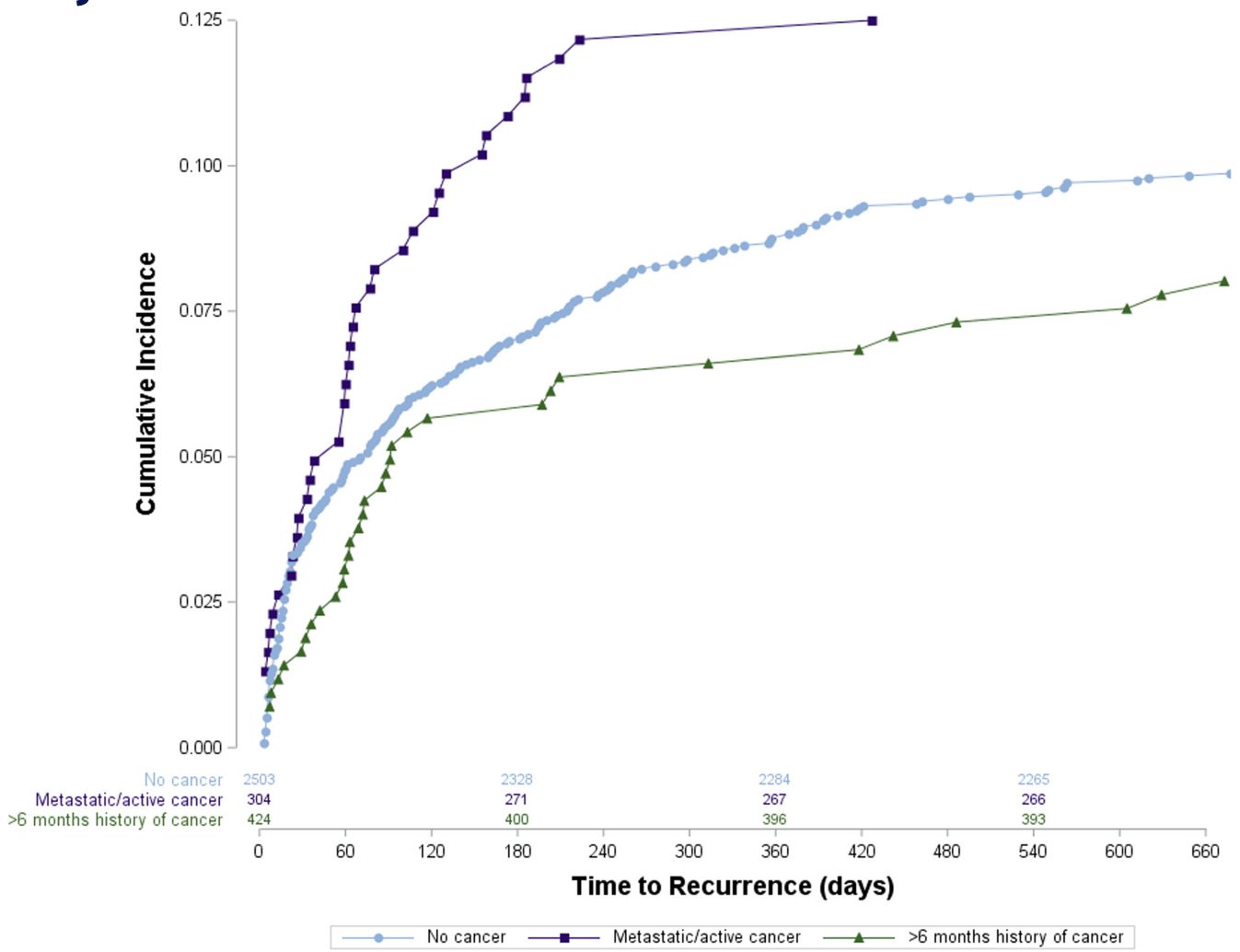

FIGURE 1 Cumulative incidence of the first recurrent venous thromboembolic event among adults age ≥ 18 years detected during the surveillance period (April 1, 2012 through March 31, 2014) among all incident events (n = 3231), stratified by cancer history.

non-Hispanic White) to sufficiently impact the findings such that the confidence intervals for age-adjusted incidence would overlap for non-Hispanic Whites and Native Americans. Further research is needed to understand and reduce the racial/ethnic disparities in cancer-associated VTE.

The incidence of recurrent VTE was high (12.5%) among patients with active cancer, with most recurrences occurring within 6 months (180 days) of diagnosis (Figure 1). This observation is consistent with previous studies.[2,3,6] Of interest is the appreciable cumulative rate of recurrent VTE of 8% among patients with a history of cancer more than 6 months previously (Figure 1). The majority of these recurrences occur within the first 6 months, but approximately one third of recurrences accumulate later throughout the 2-year observation period (Figure 1). While patients with cancer may be followed more closely than other patients, this trend is similar in all subgroups. About two thirds of these patients with recurrent VTE were not receiving anticoagulant therapy at the time of recurrence. Further analysis of recurrent VTE according to the patient's provoking status shows that the time course of recurrent VTE for patients with a history of cancer more than 6 months previously was similar to that of patients with unprovoked VTE (Figure 2). Of note, 49% of the patients with a history of cancer more than 6 months previously had no identifiable provoking factors for VTE at the time of diagnosis (Table 4).

Taken together, the above findings support the inference that a clinically important incidence of recurrence among patients with cancer-associated VTE persists beyond the period of active cancer and cancer treatment. Practice guidelines generally recommend that anticoagulant treatment be continued in patients with metastatic or unresolved cancer, and in patients continuing cancer treatment. It is common practice to discontinue anticoagulant treatment in patients with cancer-associated VTE after 6 months if the cancer is resolved (e.g., resected colon or breast cancer) and the patient has completed active cancer therapy. Extended anticoagulant therapy has become safer in recent years, with an annual incidence of major bleeding for the direct oral anticoagulants of approximately 0.2% to 0.5% and a low risk of fatal bleeding.[27,28] Further clinical trials evaluating the benefit and risk of extended anticoagulant therapy among patients

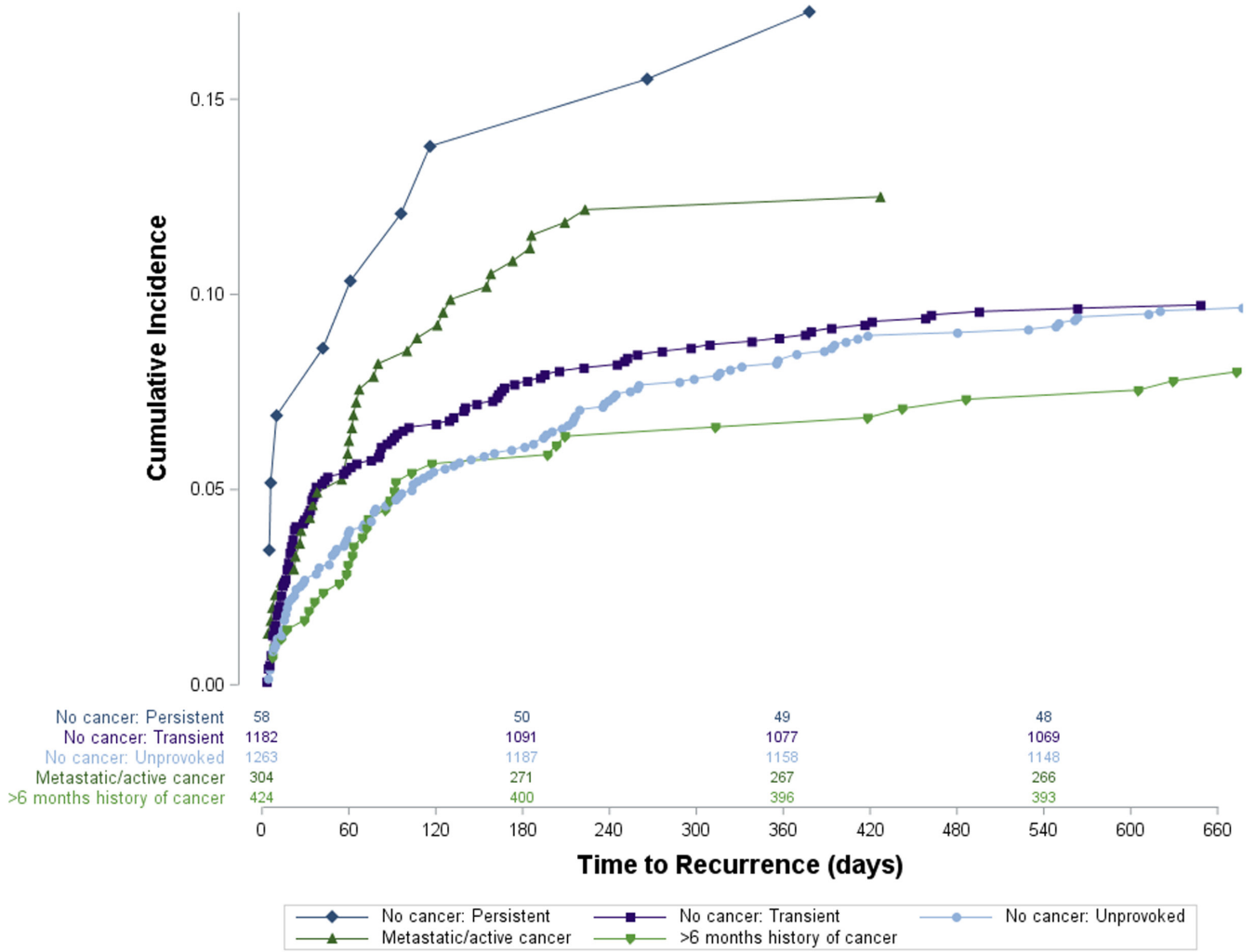

FIGURE 2 Cumulative incidence of the first recurrent venous thromboembolic event among adults age ≥ 18 years detected during the surveillance period (April 1, 2012 through March 31, 2014), stratified by status of cancer and provoking risk factor status.

with cancer-associated VTE in whom cancer is no longer active could have a potentially important impact for reducing the burden from recurrent VTE.

The VTE cases in this study were associated with a broad range of tumor types (Table 5). The rank order of cancer type in this study is similar to the rank order of the estimates of the most common cancers in 2020 of breast, lung, prostate, and colorectal, respectively.[21,26] Breast cancer, although the most common cancer, has historically been considered to be associated with much lower risk of VTE than, for example, lung cancer. Yet, breast cancer was the associated cancer for about one in five of the cases of VTE in our study (Table 5). Improved survival of breast cancer patients through early detection and improved treatment is likely a contributing reason these patients are at risk for VTE. This also underscores the importance of preventing complications such as VTE.[29] The data in Table 5 suggest that further research targeting the four most common solid tumors, as well as hematologic cancer, could inform new prevention strategies for 59% of the burden of cancer-associated VTE. Continued understanding of increased risk of rare tumor types associated with VTE is also warranted.

Our study has several strengths as well as some limitations. Strengths include the prospective population-based design, performance of the study under federal and state public health disease surveillance statutes, surveillance in both hospitals and outpatient clinics, and the use of active surveillance to supplement case-finding through hospital discharge and death records data. These design features enabled us to document unique patient events and minimized the possibility of unidentified events, as hospital refusal to participate did not occur. The racially and ethnically diverse population of Oklahoma County and its close similarity to the US population indicate the results might be generalizable to the US population. Oklahoma City was ranked as the seventh most representative city in the United States, according to a poll used to determine ideal markets for companies to test their products.[30] However, the generalizability of our results to other countries is uncertain and could be influenced by differences between the United States and other countries (e.g., lack of universal health insurance; access to health care; and documented health disparities according to race/ethnicity, socioeconomic status, and quality of care received). Additional limitations include the quality of the race/ethnicity data in the medical

TABLE 6 Number of deaths (*n*) and all-cause case fatality (%) among patients with cancer-associated VTE during intervals of 30, 90, and 180 days after incident VTE diagnosis, and cumulatively during the surveillance period April 1, 2012 through March 31, 2014

	0–30 days			31–90 days			91–180 days			>180 days			Cumulative		
Demographic	***n***	**rate**	**95% CI**	***n***	**rate**	**95% CI**	***n***	**rate**	**95% CI**	***n***	**rate**	**95% CI**	***n***	**rate**	**95% CI**
Overall	127	17.4	14.6–20.7	88	14.6	11.8–18	62	12.0	9.4–15.4	95	21.0	17.2–25.6	372	51.0	46.0–56.4
Age															
18–39	1	3.8	0.5–27.3	1	4.0	0.6–28.4	2	8.3	2.1–33.3	4	18.2	6.8–48.4	8	30.8	15.4–61.5
40–49	7	14.0	6.7–29.4	8	18.6	9.3–37.2	1	2.9	0.4–20.3	5	14.7	6.1–35.3	21	42.0	27.4–64.4
50–59	22	17.5	1.5–26.5	14	13.5	8–22.7	17	18.9	11.7–30.4	10	13.7	7.4–25.5	63	50.0	39.1–64
60–69	35	17.9	12.9–25	28	17.5	12.1–25.3	15	11.4	6.9–18.8	20	17.1	11–26.5	98	50.3	41.2–61.3
70–79	33	18.6	13.3–26.2	23	16.0	10.6–24	13	10.7	6.2–18.5	27	25.0	17.1–36.5	96	54.2	44.4–66.2
≥80	29	18.6	12.9–26.8	14	11.0	6.5–18.6	14	12.4	7.3–20.9	29	29.3	20.4–42.2	86	55.1	44.6–68.1
Sex															
Male	65	19.5	15.3–24.8	41	15.2	11.2–20.7	36	15.8	11.4–21.9	48	25.0	18.8–33.2	190	56.9	49.3–65.6
Female	62	15.7	12.2–20.1	47	14.1	10.6–18.7	26	9.1	6.2–13.3	47	18.0	13.5–24	182	46.0	39.7–53.1
Race/ethnicity															
Asian/Pacific Islander	2	33.3	8.3–133.3	3	75.0	24.2–232.5	0	0.0	0–0	0	0.0	0–0	5	83.3	34.7–200
Non-Hispanic Black	26	18.8	12.8–27.7	20	17.9	11.5–27.7	14	15.2	9–25.7	18	23.1	14.5–36.6	78	56.5	45.3–70.6
Hispanic	2	11.8	2.9–47	1	6.7	0.9–47.3	2	14.3	3.6–57.1	2	16.7	4.2–66.6	7	41.2	19.6–86.4
Native American	1	14.3	2.0–101.4	1	16.7	2.3–118.3	0	0.0	0–0	1	20.0	2.8–142	3	42.9	13.8–133
Non-Hispanic White	96	17.4	14.2–21.2	61	13.4	10.4–17.2	45	11.4	8.5–15.3	73	20.9	16.6–26.2	275	49.8	44.3–56.1
Cancer history															
Active cancer	69	22.5	17.8–28.5	53	22.4	17.1–29.3	32	17.4	12.3–24.6	44	28.9	21.5–38.9	198	64.7	56.3–74.4
>6-month history of cancer	58	13.7	10.6–17.7	35	9.6	6.9–13.3	30	9.1	6.3–13	51	16.9	12.9–22.3	174	41.0	35.4–47.6

Abbreviations: CI, confidence interval; VTE, venous thromboembolism.

record and some incompleteness of the data on risk factors, prophylaxis use, and the exact date of cancer diagnosis in those with a history of cancer more than 6 months previously. In recognition that some people travel out of state for cancer care, it is possible that we missed some cases of cancer-associated VTE if the thrombotic event occurred and was diagnosed at that out-of-state facility, in which case our results would underestimate the true burden of cancer-associated VTE. Another limitation is that we did not collect information on therapy for patients' cancer treatment and therefore cannot comment on their impact on the thrombotic process. Underreporting of American Indian or Alaskan Native race,[31] particularly in the East and Southern Plains,[32] and Hispanic ethnicity in medical records has been documented;[33] the true incidence of VTE may be higher in these populations. Finally, our study evaluated an urban population and therefore differences with rural populations were not measured.

In conclusion, our results suggest an annual incidence of cancer-associated VTE of 70 per 100 000 of the general adult population, resulting in more than 175 000 cases each year in the United States. The incidence increased with each decade of age. The four most common solid tumors (breast, lung, colorectal, and prostate), together with hematologic malignancy, accounted for approximately 60% of the cancer-associated VTE disease burden. The incidence, together with the appreciable rate of recurrent VTE, contribute to an important disease burden. Further studies toward implementing effective prevention (e.g., in those undergoing ambulatory chemotherapy) are warranted. Additionally, clinical trials are warranted to evaluate (1) the benefits and risks of extended anticoagulant treatment for a greater proportion of patients and (2) whether this is a strategy that could have a potentially important impact on reducing the burden of cancer-associated VTE disease.

AUTHOR CONTRIBUTIONS

G. Raskob, A. Wendelboe, and J. Campbell were responsible for the study conception and design. G. Raskob and A. Wendelboe wrote the manuscript. K. Ding, L. Ford, A. Wendelboe, J. Campbell, M. McCumber, A. Adamski, M. Beckman, and N. Reyes collected and analyzed the data. All authors edited and reviewed the final manuscript.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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