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Full Length Article

Trends of cancer-associated venous thromboembolism (VTE) in the United States (2005–2014)

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ABSTRACT

Introduction: Cancer patients are prone to higher risk of venous thromboembolism (VTE) compared to the general population. However, the estimated incidence of cancer-associated VTE varied among the studies. The primary objective of this study was to determine the national annual incidence and examine the trend of cancer-associated VTE in the US over the years from 2005 to 2014.

Methods: A retrospective population based study was conducted using data from the Medical Expenditure Panel Survey. The study included all noninstitutionalized US adults aged ≥18 years who had a final person-weight > 0 to be representative of the national population. Simple linear regression (SLR) and Mann-Kendall (MK) tests were used to examine the trend of cancer-associated VTE over the years.

Results: On average, there were 15,570,000 adult persons living with a cancer condition every year. Female represented 53.8% of the study population, and the mean of age was 63.5 years. The overall annual incidence of cancer-associated VTE varied between 1.80 and 0.72% over the years, with an overall average of 1.18%. The study found a non-significant downward trend in the incidence of cancer-associated VTE over the years. Patients who had cancer-associated VTE were significantly older than patients without VTE (mean 68.64 vs. 62.68 years, $p < .0001$).

Conclusion: The study found cancer patients continued to have the risk of VTE over the years. The non-significant downward trend in cancer-associated VTE suggests that health care practitioners are heading in the right direction, but enhanced preventative care is needed to avoid further incidents of cancer-associated VTE.

1. Introduction

Venous thromboembolism (VTE) is a vascular disease that usually manifests as deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The Centers for Disease Control and Prevention (CDC) define DVT as a medical condition that occurs when a blood clot forms in a deep vein [1]. These clots usually develop in the lower leg, thigh, or pelvis, but they can also occur in the arm. PE occurs when a portion of the clot breaks off and travels through the bloodstream to the lungs and causes a blockage [2]. The CDC has estimated that 900,000 Americans are affected by VTE each year; even worse, 10% of these patients die because of VTE and 30% of these death events occur within one month of the VTE diagnosis [1].

Cancer patients were found to be prone to a higher risk of VTE than the general population, because cancer and cancer therapy, were among the risk factors for VTE [2]. In the United States, cancer-associated VTE events accounted for 20% of all VTE events [3,4]. Moreover, VTE and thrombotic events were the second most common causes of death in cancer patients [5–7], accounting for 9.2% of all deaths in cancer patients who were treated with chemotherapy [6]. The association between cancer and VTE had been previously established in different settings and populations [8–10].

The annual incidence of VTE in the general population was estimated to be 0.1% [11]. Cancer alone increased the risk of VTE at least fourfold, and up to 6.5-fold with chemotherapy [12,13]. The estimated incidence of cancer-associated VTE varied by type and stage of cancer, time elapsed since cancer diagnosis, type of therapy received, and co-morbidity [14,15].

Although the risk of VTE in cancer patients was well established, the estimated incidence of cancer-associated VTE varied widely among studies. As a case in point, Chew et al. estimated the incidence to be about 1 per 100 person-years [9], whereas Connolly et al. put the figure

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at 10 per 100 person-years [16]. What's more, multiple studies reported variations in the risk of cancer-associated VTE among different types of cancers based on samples of patients from participating hospitals or cancer registries. However, it was not clear whether such variation would persist at the national level. Moreover, changes to clinical practice reflecting historical findings and designed to prevent or detect these harmful events might have altered the annual incidence of cancer-associated VTE since previous estimates were established.

The primary objective of this study was to determine the national annual incidence, and examine the trends related to cancer-associated VTE in the United States over the period 2005–2014. Additionally, the study explored the incidence of cancer-associated VTE among different types of cancer with a view to assessing the risk of cancer-associated VTE for different types of cancer.

2. Methods

2.1. Data sources

A retrospective population-based cross-sectional study was conducted that used data from the Medical Expenditure Panel Survey (MEPS) to determine and examine the national annual incidence of, and trends related to cancer-associated VTE among U.S. adult cancer patients between 2005 and 2014. MEPS, a nationally representative database developed and sponsored by the Agency for Health Research and Quality (AHRQ), focuses each year on a subsample of households that participated in the previous year's National Health Interview Survey (NHIS), conducted by the National Center for Health Statistics [17].

MEPS uses a longitudinal, complex, multistage sampling methodology that features clustering and oversampling of certain groups, such as minorities. Each year a new panel is introduced to the MEPS database, subsequent to which five in-person computer-assisted personal surveys (CAPS) are conducted over 30 months to capture health and personal data for two consecutive years for each person in the panel. These collect data on health care expenditures and utilization, health status, health insurance coverage, and sociodemographic characteristics in the civilian, noninstitutionalized U.S. population. MEPS uses self-reported data collected through the in-person CAPS, with health care expenditure and utilization data verified by health care providers at doctor's offices, hospitals, and pharmacies. The AHRQ researchers assign weights to each person in each panel with a view to producing from these samples of subjects national estimates that are representative of the civilian noninstitutionalized U.S. population [17].

The MEPS-Household Component (MEPS-HC) full-year consolidated data file, medical conditions file, and prescribed medicines file were merged for each year from 2005 to 2014 to identify cancer-associated VTE cases and estimate the annual incidence in noninstitutionalized cancer patients. Then all cancer patients from 2005 to 2014 were combined by the type of cancer to estimate the average incidence of cancer-associated VTE for each type of cancer.

2.2. Subjects

The study included all noninstitutionalized U.S. adults ($\geq$18 years) having at least one type of cancer who had a final person weight > 0 as being representative of the national population at the time of the MEPS panel survey. Cancer patients were identified by the Clinical Classification Software (CCS) code, and subjects having a documented CCS code between 11 and 45 were included in this study as representing cancer patients. All health conditions reported by subjects and confirmed by health care providers were documented in MEPS by their International Statistical Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) code using a variable named ICD9CODX. The CCS codes for cancer and other health conditions were based on the ICD-9 CM code for each condition and documented in MEPS using a variable named CCCODEX in the medical condition file; this variable was used to identify cancer patients in the study.

2.3. Measures

The ICD9CODX variable from the medical condition file and variables from the prescribed medicines files (i.e., RXBEGMM, TC1S1, RXBEGYRX, RXNAME, RXQUANTY, and RXSTRENG) were used to assess the presence and validity of VTE and potential VTE cases. Cancer patients were recognized as having had a VTE event by use of the ICD-9 CM codes for VTE (415, 451, and 453). Potential VTE cases were defined as cancer patients who had used anticoagulant medication for more than one month, as recorded in the prescribed medicines file, without a specific ICD-9 CM codes for other cardiovascular conditions requiring anticoagulant therapy, such as atrial fibrillation, acute coronary syndrome, prosthetic valve replacement, and arterial thromboembolism. The VTE events documented in MEPS using ICD-9 CM codes and the potential VTE cases were combined into a single variable called VTE to represent cancer-associated VTE events in this study.

2.4. Statistical analysis

Descriptive statistics were used to describe the demographics and comorbidities of the study population. Independent *t*-testing and χ^2 testing were used to compare baseline continuous and categorical characteristics, respectively, for patients having one or multiple cancer conditions. Weighted frequencies were used to determine the prevalence of cancer and the annual incidence of cancer-associated VTE each year. The annual incidence of cancer-associated VTE was presented as the proportion of cancer patients who had VTE among all cancer patients. Moreover, annual incidence of cancer-associated VTE was further presented and analyzed based on the presence of one or multiple cancer conditions, and the relative risk was used to compare the risk of cancer-associated VTE among patients having one or multiple cancer conditions.

Trends in the annual incidence of cancer-associated VTE in cancer patients were assessed using the simple linear regression (SLR) technique. The logit-transformed of the annual proportion of VTE in cancer patients was regressed on the years from 2005 to 2014, to assess the existence and significance of a linear trend in annual incidence of cancer-associated VTE over the years. The SLR equation can be written as

$$\text{Logit}\,(p*) = \alpha + \beta\,(\text{Year})_i + \mu_i$$

where logit (p*) was the logit-transformed proportion—defined as log {p*/(1 − p*)}, where p* = 0.05 + 0.9p; p was the annual proportion of patients having VTE, with a value between 0 and 1; and log denotes the natural logarithm—and Year indicated the follow-up period for the trend, in this case 2005–2014. When no linear trend was identified from the SLR model, the non–parametric Mann–Kendall test was conducted to test for the presence of a non–linear trend.

Further analysis was conducted including patients who had only one type of cancer. Data from the ten years were combined by type of cancer, allowing examination of the average incidence of cancer-associated VTE for each type of cancer. Then the relative risk ratio was used to compare the risk of cancer-associated VTE in different types of cancer. All data extraction and statistical analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Survey weights from MEPS and survey commands in SAS were used in the analysis to account for the complex survey design thereby producing nationally representative estimates of the annual incidence of cancer-associated VTE each year and revealing the average incidence of cancer-associated VTE in each type of cancer for the duration of the study. The α level of < 0.05 was used for statistical significance.

Table 1
Descriptive characteristics of patients with one or multiple cancer conditions.

Variable	Number of cancer conditions			*p*.
	Overall	One	Multiple	
Age (*M*, [*SE*])	63.49 [0.30]	62.74 [0.30]	68.38 [0.51]	< 0.0001*
Gender (%)				0.58
Male	46.17	46.02	47.11	
Female	53.83	53.97	52.89	
Race (%)				< 0.0001*
White	90.78	90.31	93.87	
Black	5.95	6.23	4.12	
American Indian/Alaska Native	0.38	0.43	0.10	
Asian/Native Hawaiian/ Pacific Islander	1.89	2.01	1.10	
Multiple races reported	1.00	1.02	0.81	
Insurance coverage (%)				0.0005*
Private insurance	70.33	70.66	68.14	
Public insurance	26.26	25.59	30.63	
Uninsured	3.41	3.74	1.23	

* *p*-Value < .05 was statistically significant.

3. Results

3.1. Patient characteristics

On average from 2005 to 2014, 15.7 million adult persons living in the United States had at least one cancer diagnosis each year. The most common cancer diagnosis in patients having one type of cancer was that of non-epithelial skin cancer (~30% of all cancer diagnoses). The number of adults living with cancer ranged from 11.8 million in 2005 to 18.5 million in 2014. Most of these patients had a single type of cancer, which allowed determination of which types of cancer were associated with a higher risk of cancer-associated VTE in the study.

The average age of all cancer patients was 63.5 years. Patients who had multiple cancer conditions ($M = 68.38$, $SE = 0.51$) were significantly older than patients who had only one type of cancer ($M = 62.74$, $SE = 0.30$), $t(12{,}817) = 11.34$, $p < .0001$. Females represented 53.8% of the study population, and the majority of the patients were White (90.8%). The descriptive characteristics of the study population overall, as well as for patients having one or multiple cancer conditions, along with the p values for the t and χ^2 tests, were summarized in Table 1. Age was presented as mean and standard error (*M*, *SE*), and the rest of the characteristics were presented as the average frequency in each category over the period 2005–2014. Among all comorbidities, hypertension was most frequently reported, affecting as it did 50% of cancer patients in the study, followed by hyperlipidemia and osteoarthritis which affected 44% and 42% of cancer patients, respectively. The most prevalent comorbidities affecting at least 10% of the study population were reported in Table 2.

3.2. Incidence of cancer-associated VTE

Overall annual incidence of cancer-associated VTE varied between 1.80% and 0.72% in the period 2005–2014, with an overall average incidence of 1.16%. Patients who had multiple cancer conditions also had a statistically significant higher incidence of cancer-associated VTE over this period than did patients who had one cancer condition. The average annual incidence was 2.12% in patients who had multiple cancer conditions as compared to 1.02% in patients who had one cancer condition, with a relative risk (RR) of 2.08, 95% CI [2.08, 2.10]. The weighted numbers of noninstitutionalized cancer patients having one or multiple cancer conditions over the years, along with the annual and average incidence of cancer-associated VTE, were summarized in Table 3. Furthermore, patients who had cancer-associated VTE were significantly older (M = 68.64, SE = 1.41) than patients who did not have cancer-associated VTE (M = 62.68, SE = 0.31), $p < .0001$. Among patients with one cancer condition, the incidence of VTE events was higher in males, blacks, and uninsured compared to females, other races, and privately insured participants, respectively (Table S1 in the Supplementary material). The majority of the VTE events were documented in MEPS with the ICD-9 codes, and only 10% of the events were potential VTE events (Table S2 in the Supplementary material).

Table 2
Percentage of cancer patients with different comorbidities.

Comorbidity condition	% of patients with the condition
Hypertension	50%
Hyperlipidemia	44%
Osteoarthritis and other non-traumatic joint disorders	42%
COPD and asthma	30%
Mental disorders	28%
Heart conditions	27%
Disorders of the upper GIT	21%
Skin disorders	18%
Diabetes mellitus	18%
Trauma-related disorders	18%
Other CNS disorders	17%
Acute bronchitis and URI	17%
Back problems	17%
Thyroid disease	15%
Systemic lupus and connective tissues disorders	15%
Other endocrine, nutritional and immune disorder	14%
Infectious diseases	10%

Table 3
Number of cancer patients and annual incidence of VTE by year and presence of one or multiple cancer conditions.

Year	Number of patients with cancer conditions (% with VTE)		
	Overall	One	Multiple
2005	11,820,957 (1.80)	10,390,504 (1.09)	1,430,453 (6.96)
2006	11,822,758 (1.29)	10,420,154 (1.23)	1,402,604 (1.72)
2007	14,434,058 (1.29)	12,650,899 (1. 24)	1,783,159 (1. 63)
2008	16,723,627 (0.87)	14,639,150 (1.00)	2,084,477 (NA)
2009	16,467,733 (0.92)	14,543,035 (0.93)	1,924,698 (0.86)
2010	15,824,408 (1.43)	13,737,301 (1.09)	2,087,107 (3.67)
2011	17,834,285 (1.60)	15,126,245 (1.30)	2,708,040 (3.30)
2012	17,182,305 (1.17)	14,702,351 (1.06)	2,479,954 (1.84)
2013	16,824,494 (0.79)	14,666,024 (0.91)	2,158,470 (NA)
2014	18,557,435 (0.72)	15,812,301 (0.46)	2,745,134 (2.21)
Average	15,749,206 (1.16)	13,668,796 (1.02)	2,080,409 (2.12)

NA: No enough cases for cancer-associated VTE incidence estimation.

3.3. Trend in cancer-associated VTE

The data from the annual incidence of cancer-associated VTE were not steady over the period in question (Table 3), as confirmed by the lack of any significant linear trend from the SLR model. However, the fit plot output from the SLR model (Fig. 1) revealed an overall downward trend in the logit-transformed proportion over this period. Accordingly, the presence of a nonlinear monotonic trend was assessed using the Mann–Kendall test, which also revealed the presence of a downward trend in the annual incidence of cancer-associated VTE over this period, indicated by the negative sign in the Kendall Tau-b correlation coefficients (r_τ). However, this was not statistically significant: $r_\tau = -0.56$, $p = .09$.

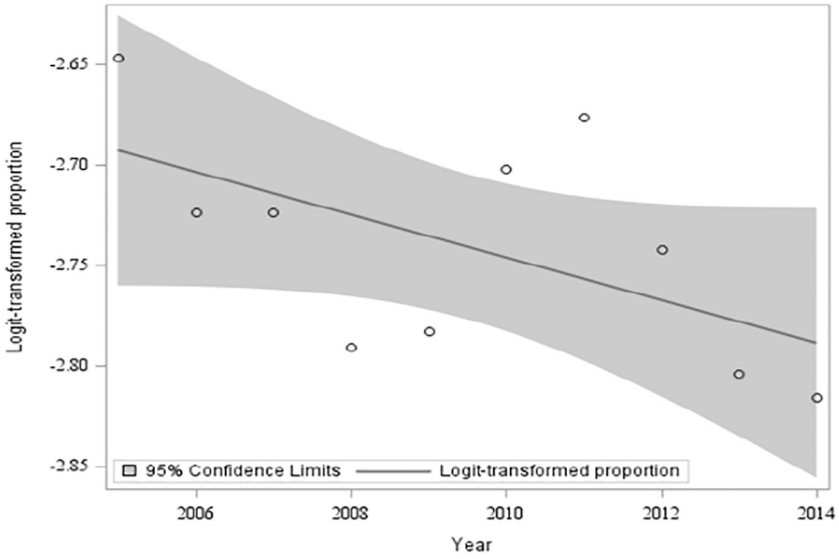

Fig. 1. Fit plot for logit-transformed proportion of cancer-associated VTE over the years of follow-up.

3.4. Incidence of VTE by type of cancer

In patients who had one type of cancer, the incidence of cancer-associated VTE was highly associated with different types of cancer. Patients who had pancreatic cancer (7.22%) followed by those who had anorectal cancer (4.81%) and kidney and renal pelvis cancer (4.19%) had the highest incidence of cancer-associated VTE (Fig. 2). Patients who had pancreatic cancer were at a significantly higher risk of developing cancer-associated VTE than were all other cancer patients combined, with an RR of 7.20, 95% CI [7.11, 7.30]. Patients who had other types of cancer, such as uterine and cervical cancers, had a much lower incidence of cancer-associated VTE (< 0.5%) than did other types of cancer, such as pancreatic and anorectal cancers—reflecting the lower risk of developing cancer-associated VTE in the former. Patients with secondary malignancies had a higher incidence and risk of having cancer associated VTE than most other types of cancer (4.45%, RR = 4.49, 95% CI [4.44, 4.53]).

4. Discussion

Cancer-associated VTE persisted as a complication that affected the life of cancer patients, influencing their survival while fighting cancer [8,18,19]. This study was conducted to address the need for updates to figures concerning the incidence of cancer-associated VTE, obtaining by taking a large weighted sample of cancer patients to represent cancer patients in the United States. It was conducted over a 10-year period with a view to identifying trends in or significant changes to the annual incidence of cancer-associated VTE during the period in question. The study also investigated differences in the incidence and risk of cancer-associated VTE among different types of cancer.

The annual incidence of cancer-associated VTE among all cancer patients in the United States varied between 1.80% in 2005 and 0.72% in 2014, with an overall average of 1.18% over this period. Chew, Wun, Harvey, Zhou and White [9] found the incidence of cancer-associated VTE among patients who had common types of cancer to be around 1.60% over two years of follow-up when relying on data for cancer patients from a cancer registry in California covering the period 1993–1995. The average annual incidence of cancer-associated VTE thus reported in patients with the same common types of cancer was 1.29%. This is similar to the findings of Chew et al. study [9], taking into consideration that they reported the cumulative incidence over two years of follow-up and identified most incidents during the first year of follow-up.

However, the overall average annual incidence in this study (1.18%) was much lower than the incidence found in the studies conducted by Khorana et al. [8] and Lyman et al. [19] (12.6% and 13.5%, respectively). Though, these two studies included only patients who used chemotherapy for the treatment of pancreatic, colorectal, lung, ovarian, bladder, or gastric cancers, and it followed these patients only during the first year after cancer diagnosis. Thus, the estimates of the annual incidence of cancer-associated VTE from these studies [8,19] were expected to be much higher than the estimates made in this study, because the population included was at much greater risk than the overall cancer population used in this study. Also, the findings from this study confirmed the higher incidence of cancer-associated VTE in patients having these types of cancer as presented in Fig. 2.

Because most weighted subjects in MEPS were followed for one year, it is perhaps reasonable to give the annual incidence in events per 1000 person-years, allowing easy comparison of the incidence rate seen in this study with those in others. Thus, the incidence rate of cancer-associated VTE in this study varied between 18 events per 1000 person-years in 2005 and 7 events per 1000 person-years in 2014, with an overall average incidence rate of 12 events per 1000 person-years. Globally, Cronin-Fenton et al. estimated the overall incidence rate of cancer-associated VTE in Denmark between 1997 and 2006, for all types of cancer, to be much lower than the average incidence rate in the United States between 2005 and 2014 (8 cases per 1000 person-years in Denmark vs. 12 cases per 1000 person-years in the United States) [15]. By contrast, Blom et al. studied the incidence rate of cancer-associated VTE in the Netherlands between 1986 and 2002 and found it to be much higher than in the United States, at 24.6 cases per 1000 person-years [20]. Likewise, in the UK, the incidence rate of cancer-associated VTE was much higher than the United States at 58 cases per 1000 person-years, as reported by Cohen et al. using cancer patients' data between 2001 and 2011 [18].

The annual incidence of cancer-associated VTE fluctuated over this period, decreasing by 60%, but overall following an insignificant non-linear downward trend, as indicated in the results produced by the SLR model and the Mann–Kendall test. Because the SLR model indicated the presence of a downward trend in the incidence of cancer-associated VTE that was not significantly linear, the Mann–Kendall test was conducted to serve as a sensitivity analysis with which to assess the presence of a nonlinear trend in the incidence of cancer-associated VTE over the period 2005–2014. The Mann–Kendall test confirmed the presence of a downward trend but, likewise, not a significant one.

Similar to other studies [15,18,19], this study identified differences

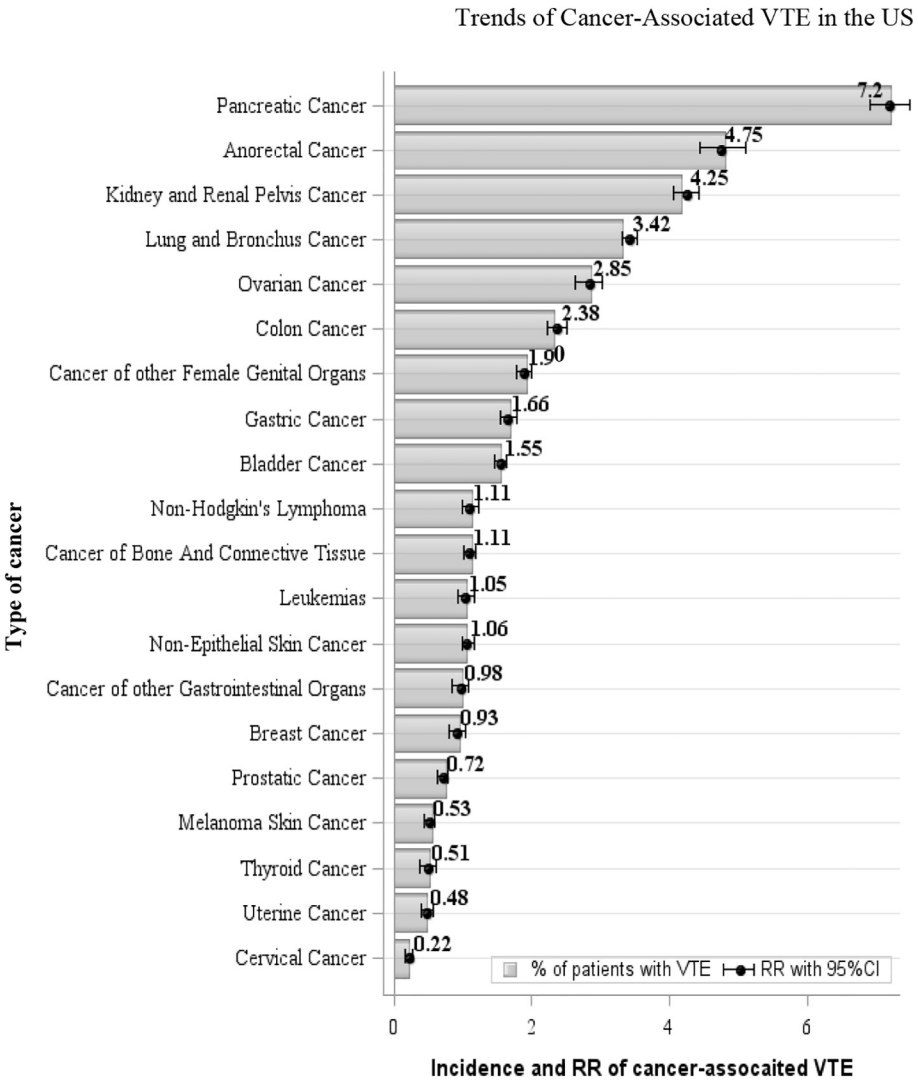

Fig. 2. The incidence (%) and relative risk (RR) of cancer-associated VTE in different types of cancer.

in the risk of cancer-associated VTE among different types of cancer. Pancreatic cancer (RR 7.20, 95%CI 6.91–7.50) and anorectal cancer (RR 4.75, 95%CI 4.65–4.86) were associated with the highest risks of cancer-associated VTE—higher than all other types of cancer combined. Other types of cancer, such as uterine cancer (RR 0.48, 95%CI 0.47–0.49) and cervical cancer (RR 0.22, 95%CI 0.21–0.23), were associated with a much lower risk of cancer-associated VTE than all other types of cancer. Even though this disparity in the risk of cancer-associated VTE among different types of cancer has been steadily documented in multiple previous studies, it is not yet reflected in the recommendations made in clinical guidelines for VTE prophylaxis in cancer patients [21–24].

Furthermore, patients who had multiple cancer conditions were at higher risk of cancer-associated VTE than were patients who had one type of cancer (RR 2.08, 95%CI 2.08–2.09). Patients who had cancer-associated VTE were significantly older than patients who did not have cancer-associated VTE (M = 68.64 vs. 62.68 years; $p < .0001$). Older age was a significant predictor for risk of VTE in the general population [11], and likewise for cancer patients in this study. Also, black persons were more likely to develop cancer-associated VTE than were other races much as reported by White et al. when evaluating the role of ethnicity as an independent risk factor for VTE in the general population [25]. Additionally, patients who were on public insurance (1.24%) or uninsured (1.30%), were more likely to have cancer-associated VTE than patients who were on private insurance (0.92%) ($p < .0001$).

This study sought to determine the annual incidence, and examine the trend, of cancer-associated VTE over a specified period, and evaluate the risk of cancer-associated VTE for different types of cancer in the United States at the national level. To do so, rather than using data from cancer registries or hospital records—which might not truly reflect national estimates or trends—this study used MEPS, which is widely accepted and commonly used to produce health care utilization and expenditure estimates at the national level. MEPS's use of complex stratified random sampling and assigned weights gives researchers the power to calculate unbiased annual estimates at the national level, and combining subjects from ten years decreases the likelihood of producing biased estimates from that seen when using data from only one year. Also, the multiple steps implemented by MEPS to verify health care utilization data collected from subjects improve the validity of the data [26]. To be inclusive, the study included all types of cancer in its general analysis and reported results for one type or a group of specific types of cancer when comparing its findings to those of other previous studies and when seeking to identify differences in the risk of cancer-associated VTE among different types of cancer.

Nonetheless, the results of this study should be interpreted in the context of the following limitations: First, to protect subjects' identity, MEPS limits the release of ICD-9 CM codes in medical condition files to the primary category code, represented by the first three digits of the

full five-digit code. The fourth and fifth digits in the ICD-9 CM code represent the subcategory and the subclassification, respectively, and both would have provided further specific information about the medical conditions in question. However, release of this data would put patients' identities at risk of being identified. Even so, this limited the researchers' ability to detect VTE events by more specific ICD-9 CM codes (i.e., 671.3, 671.4, 671.5, and 673.22); thus the detected incidence of VTE might be underestimated. Second, the use of Multum Lexicon drug classification system variables along with other variables in the prescribed medicines files as a way of detecting potential VTE cases was conservatively intended to avoid bias in overestimating the outcomes. Third, the study included all adult patients who received care for cancer conditions during the study period, regardless of whether they had active cancer or were in remission—which might produce an overestimation of the total number of cancer patients and an underestimation of the incidence of cancer-associated VTE. Fourth, MEPS surveys only the noninstitutionalized U.S. population—which, admittedly, comprises most of the U.S. population. Fifth, MEPS does not identify the primary cancer condition in patients who had multiple cancer conditions, and the random assignment of these patients to one of the multiple cancer conditions threatened to produce a biased estimate. Accordingly, only patients who had one type of cancer were included in the analysis that identified the incidence of cancer-associated VTE in different types of cancer, and data from the ten years' period were used to avoid bias that might occur if only data from one year were used. Sixth, the majority of patients with cancer in the study were from the White race (90.78%) which may limit the generalizability of the study to other races. Finally, MEPS did not include data for a sufficient number of subjects for some cancer conditions (i.e., brain cancer, esophageal cancer, multiple myeloma, and Hodgkin's disease), which limited the study's ability to generate estimates in these subgroups.

In conclusion, this study found an insignificant decrease in the incidence of cancer-associated VTE, correlated the presence of multiple cancer conditions with increased risk for cancer-associated VTE, and found that different types of cancer were at different levels of risk for cancer-associated VTE. The lack of a significant downward trend in the incidence of cancer-associated VTE indicates that cancer patients were continuously at risk for cancer-associated VTE and underscores the need for enhanced preventative techniques designed to prevent further cases of cancer-associated VTE. Accordingly, further clinical investigation is needed with which to prevent further cases of cancer-associated VTE, and additional research is recommended with a view to identifying areas for improvement in clinical care. Last, the presence of significant disparities in the risk of cancer-associated VTE between different types of cancer and in patients who had multiple cancer conditions should be reflected in future guidelines' recommendations to practitioners who provide care for cancer patients.

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Authorship

All authors had access to the data and a role in writing this manuscript.

Declaration of competing interest

All authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.08.013.

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