Research Article

Cancer Epidemiology, Biomarkers & Prevention

Venous Thromboembolism and Cancer Risk among Elderly Adults in the United States

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Abstract

Background: Few studies have evaluated cancer risk following venous thromboembolism (VTE). Both VTE and cancer disproportionately affect older adults.

Methods: Using linked Surveillance, Epidemiology, and End Results (SEER)–Medicare data, we evaluated 1.2 million cancer cases and 200,000 controls (66–99 years old, 1992–2005). VTEs occurring before selection were identified using Medicare claims. Logistic regression was used to estimate ORs.

Results: VTE was present in 2.5% of cases and 2.2% of controls. VTE was associated with risk of cancers of the lung [OR = 1.18; 95% confidence interval (CI), 1.12–1.23], stomach (OR = 1.19; 95% CI, 1.09–1.30), small intestine (OR = 1.42; 95% CI, 1.17–1.71), colon (OR = 1.25; 95% CI, 1.18–1.31), gallbladder (OR = 1.39; 95% CI, 1.16–1.67), pancreas (OR = 1.53; 95% CI, 1.43–1.64), soft tissue (OR = 1.43; 95% CI, 1.21–1.68), ovary (OR = 1.35; 95% CI, 1.22–1.50), and kidney/renal pelvis (OR = 1.34; 95% CI, 1.23–1.46), and melanoma (OR = 1.17; 95% CI, 1.08–1.27), non-Hodgkin lymphoma (OR = 1.27; 95% CI, 1.20- 1.35), myeloma (OR = 1.48; 95% CI, 1.35–1.63), and acute myeloid leukemia (OR = 1.35; 95% CI, 1.19–1.54). Strongest risks were observed within 1 year of VTE diagnosis, but risks were elevated more than 6 years after VTE for colon cancer (OR = 1.24; 95% CI, 1.12–1.37), pancreatic cancer (OR = 1.33; 95% CI, 1.15–1.54), and myeloma (OR = 1.35; 95% CI, 1.10–1.66). Few differences in risk were observed by VTE subtype. Cancers of the lung, stomach, and pancreas were more likely to have distant metastases within one year after VTE.

Conclusion: Among elderly adults, cancer risk is elevated following VTE diagnosis.

Impact: Short-term associations with cancer are likely driven by enhanced screening following VTE and reverse causation. While obesity, other comorbidities, and smoking cannot be excluded as explanations, longer-term elevations for select cancers suggest that some VTEs may be caused by cancer precursors. *Cancer Epidemiol Biomarkers Prev; 23(5); 774–83. ©2014 AACR.*

Introduction

Venous thromboembolism (VTE) involves obstruction of blood flow caused by the presence of clots and includes pulmonary emboli and both deep venous thromboses (DVT) and superficial venous thromboses (SVT). VTE affects nearly 500,000 individuals each year (1, 2). The incidence of VTE increases steeply with age, with rates of 450 to 600 cases per 100,000 person-years among individuals >65 years of age (3, 4). Furthermore, VTE risk is 4- to 6-fold higher in individuals diagnosed and treated for cancer (5, 6). VTE also contributes significant morbidity and mortality among patients with cancer, with VTE detected within 1 year before cancer diagnosis being associated with advanced stage and poorer posttreatment survival (7).

Although much work has focused on understanding the sources of VTE and its management (1, 5, 7–10), only a handful of studies have assessed the association of VTE with the subsequent development of malignancies. Population and hospital-based studies have demonstrated a strong risk of cancer within a very short follow-up time interval after VTE (typically less than 1 year; refs. 11–15). Interestingly, prior studies show that those individuals with a longer follow-up time of 2 or more years after VTE also have elevated risk for certain malignancies such as cancers of the digestive tract, ovarian cancer, and lymphomas (11, 14, 16, 17). These associations seem to be similar across VTE subtypes of pulmonary embolism, DVT, and SVT (18).

Individuals older than 65 years have a disproportionately high burden of both cancer and VTE. We therefore, investigated the relationship of VTE with subsequent development of cancer in a large case–control study of elderly adults in the United States using data from cancer registries and Medicare claims files. The large number of cancer cases and controls in this study afforded us the

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opportunity to assess the relationship of VTE overall and subtypes of VTE with a wide range of solid-organ and hematologic malignancies.

Materials and Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program comprises population-based state and metropolitan cancer registries that ascertain cancers occurring in approximately 26% of the U.S. population (19). Medicare is a federally funded program that provides health insurance for 97% of the U.S. population ages older than 65 years. All Medicare beneficiaries are entitled to coverage for inpatient care (Part A), and most purchase additional coverage for physician and outpatient services (Part B). The SEER–Medicare data set was created by electronically linking SEER and Medicare data (19). The resulting match links 94% of SEER cancer cases ages 65 years and older to Medicare data. In addition, data are available for a 5% random sample of Medicare beneficiaries living in SEER regions. The SEER–Medicare dataset contains demographic and clinical information, and Medicare claims data (Part A beginning in 1986, Part B beginning in 1991) on these individuals.

The current study is a population-based case–control study derived from the SEER–Medicare data, as previously described (20). Cases were defined as individuals with first cancers identified in SEER, ages 66 to 99 years between the years 1992 to 2005. Cases identified solely at autopsy or by death certificates were excluded. Cases also were required to have at least 13 months of Part A and Part B Medicare coverage, during which they were not enrolled in a health maintenance organization (HMO), before diagnosis. Cancers were categorized based on the SEER program "site recode with Kaposi sarcoma and mesothelioma," which we modified to collapse some rare categories. Non-Hodgkin lymphoma (NHL) was classified based on the World Health Organization scheme and included chronic lymphocytic leukemia (21).

Controls ($N = 200{,}000$) were selected from the 5% random sample of Medicare beneficiaries living in SEER areas and were frequency-matched to cases by sex, age (66–69, 70–74, 75–79, 80–84, and 85–99 years), and calendar year of selection. As of July 1 of the calendar year of selection, controls were alive, cancer-free, and had at least 13 months of Part A, Part B, and non-HMO Medicare coverage. Controls could have been selected multiple times in different calendar years or could later have become a case.

The first recorded VTE was assessed using Medicare claims in hospital, outpatient, and provider files. We defined VTE based on International Classification of Diseases, 9th revision (ICD-9) codes for pulmonary embolism (415.1), DVT (451.1, 451.2, 451.81, 451.83, 453.2, 453.3, and 453.4), SVT (451.0, and 451.82), and venous thrombosis not otherwise specified (VTE NOS; 451.84, 451.89, 453.1, 453.8, and 453.9).

Table 1. Subject characteristics

Characteristic	Case ($N = 1{,}138{,}390$) *N* (%)	Control ($N = 200{,}000$) *N* (%)
Age, y		
65–69	192,272 (16.9)	33,780 (16.9)
70–74	296,027 (26.0)	52,008 (26.0)
75–79	287,109 (25.2)	50,440 (25.2)
80–84	205,451 (18.1)	36,097 (18.1)
85+	157,531 (13.8)	27,675 (13.8)
Sex		
Male	604,333 (53.1)	106,172 (53.1)
Female	534,057 (46.9)	93,828 (46.9)
Year of diagnosis or selection		
1992–1994	178,515 (15.7)	31,364 (15.7)
1995–1998	226,785 (19.9)	39,843 (19.9)
1999–2002	414,976 (36.5)	72,903 (36.5)
2003–2005	318,114 (27.9)	55,890 (27.9)
Race/ethnicity		
White	973,236 (85.5)	166,827 (83.4)
Black	89,893 (7.9)	13,949 (6.9)
Asian	29,038 (2.6)	8,097 (4.1)
Hispanic	18,286 (1.6)	5,199 (2.6)
Native American	2,580 (0.2)	656 (0.3)
Other	21,965 (1.9)	4,713 (2.4)
Unknown	3,389 (0.3)	558 (0.3)
Duration of medicare coverage, mo		
13–60	319,446 (28.1)	57,440 (28.7)
61–120	556,095 (48.9)	97,485 (48.7)
121–180	210,858 (18.5)	35,805 (17.9)
181–240	51,991 (4.6)	9,270 (4.6)

Unconditional logistic regression models were used to estimate ORs and 95% confidence intervals (CI), comparing the prevalence of VTE in cases and controls. Given the incidence density sampling of cases and controls from the Medicare cohort, the odds ratios calculated in this study can be interpreted as estimates of relative risk. We accounted for the repeated sampling of controls and the fact that some controls later became cases in the variance calculation (20). All analyses were adjusted for sex, age, and calendar year of diagnosis/selection. Given the large number of cancer types assessed in this study, a conservative Bonferroni P value of <0.001 was used as the cut-off for statistical significance.

For cancers that were associated with VTE, we created additional models to evaluate the strength of the association with cancer in different latency intervals after VTE (<1, 1–2.5, 2.6–4.0, 4.1–6, and >6 years). The interaction of VTE and cancer risk across latency intervals was assessed by including a product term in the logistic regression model. We also fit logistic regression models to evaluate associations for each VTE subtype and used likelihood ratio tests to assess the differential effect of VTE subtypes on cancer risk (i.e., to compare the effects of pulmonary embolism or DVT vs. SVT, or of pulmonary embolism vs.

Table 2. Associations of venous thromboembolism and cancer

	Total	Percentage of subjects with VTE	OR (95% CI)	*P* value
Controls	200,000	2.2	1.0	
All cancers	**1,138,390**	**2.5**	**1.15 (1.11–1.20)**	**<0.001**
Head and neck				
Lip	2,340	2.1	0.98 (0.74–1.30)	0.874
Tongue	4,486	2.0	0.96 (0.78–1.19)	0.706
Salivary gland	2,482	2.5	1.07 (0.83–1.39)	0.600
Floor of mouth	1,412	2.2	1.12 (0.78–1.60)	0.546
Gum and other mouth	3,796	2.5	1.12 (0.91–1.37)	0.287
Nasopharynx	779	—	0.68 (0.36–1.26)	0.219
Tonsil	1,583	2.0	1.13 (0.79–1.61)	0.494
Oropharynx	543	—	0.86 (0.44–1.66)	0.654
Hypopharynx	1,660	1.7	0.92 (0.63–1.34)	0.664
Larynx	8,234	1.9	1.00 (0.85–1.18)	0.995
Nasal cavity	1,451	2.2	0.98 (0.69–1.40)	0.924
Respiratory tract				
Lung	**179,880**	**2.5**	**1.18 (1.12–1.23)**	**<0.001**
Pleura	78	–	0.53 (0.08–3.79)	0.530
Mesothelioma	3,333	2.4	1.08 (0.86–1.35)	0.520
Gastrointestinal tract				
Esophagus	11,442	2.4	1.15 (1.01–1.30)	0.033
Stomach	**22,860**	**2.8**	**1.19 (1.09–1.30)**	**<0.001**
Small intestine	**3,694**	**3.2**	**1.42 (1.17–1.71)**	**<0.001**
Appendix	687	2.9	1.35 (0.86–2.12)	0.187
Colon	**107,265**	**2.9**	**1.25 (1.18–1.31)**	**<0.001**
Rectosigmoid junction	11,800	2.1	0.98 (0.86–1.11)	0.735
Rectum	24,762	2.1	0.93 (0.85–1.03)	0.151
Anus	2,633	3.0	1.35 (1.08–1.70)	0.010
Hepatobiliary sites				
Liver	10,219	2.5	1.19 (1.04–1.35)	0.010
Intrahepatic bile duct	1,988	2.7	1.14 (0.87–1.50)	0.338
Gallbladder	**3,777**	**3.4**	**1.39 (1.16–1.67)**	**<0.001**
Pancreas	**33,135**	**3.5**	**1.53 (1.43–1.64)**	**<0.001**
Bone and soft tissue				
Bones and joints	760	—	0.64 (0.35–1.16)	0.139
Soft tissue including heart	**4,728**	**3.3**	**1.43 (1.21–1.68)**	**<0.001**
Melanoma	**27,059**	**2.6**	**1.17 (1.08–1.27)**	**<0.001**
Retroperitoneum	772	3.1	1.46 (0.97–2.20)	0.072
Kaposi sarcoma	652	3.7	1.54 (1.02–2.33)	0.039
Reproductive organs				
Breast	134,274	2.3	1.01 (0.95–1.07)	0.683
Cervix	4,033	2.3	1.05 (0.85–1.29)	0.674
Uterus	26,889	2.4	1.11 (1.02–1.22)	0.022
Ovary	**16,112**	**3.1**	**1.35 (1.22–1.50)**	**<0.001**
Vagina	927	3.3	1.36 (0.95–1.96)	0.096
Vulva	3,288	2.4	0.90 (0.72–1.14)	0.391
Prostate	215,219	1.7	0.92 (0.87–0.98)	0.009
Penis	836	2.4	1.11 (0.71–1.74)	0.638

(Continued on the following page)

Table 2. Associations of venous thromboembolism and cancer (Cont'd)

	Total	Percentage of subjects with VTE	OR (95% CI)	*P* value
Urinary tract				
Urinary bladder	61,751	2.5	1.11 (1.04–1.18)	0.001
Kidney/renal pelvis	**24,611**	**2.8**	**1.34 (1.23–1.46)**	**<0.001**
Ureter	1,476	3	1.29 (0.95–1.75)	0.099
Neurologic/endocrine sites				
Eye and orbit	1,461	2.7	1.27 (0.92–1.74)	0.140
Brain	9,552	2.2	1.06 (0.92–1.22)	0.440
Thyroid	5,923	2.3	1.15 (0.97–1.37)	0.115
Hematologic malignancies				
Hodgkin lymphoma	1,915	2.8	1.31 (0.99–1.72)	0.057
NHL	**55,195**	**2.9**	**1.27 (1.20–1.35)**	**<0.001**
Myeloma	**15,318**	**3.3**	**1.48 (1.35–1.63)**	**<0.001**
Acute lymphocytic leukemia	736	3.5	1.61 (1.08–2.38)	0.018
AML	**8,489**	**3.1**	**1.35 (1.19–1.54)**	**<0.001**
Chronic myeloid leukemia	3,626	2.9	1.23 (1.01–1.50)	0.041
Acute monocytic leukemia	508	—	0.74 (0.38–1.44)	0.382
NHL subtypes				
Diffuse large B-cell lymphoma	**15,883**	**3.3**	**1.41 (1.28–1.55)**	**<0.001**
CLL/SLL/PLL	14,571	2.7	1.19 (1.07–1.33)	0.001
Follicular lymphoma	7,264	2.3	1.06 (0.90–1.24)	0.468
Marginal zone lymphoma	3,223	2.7	1.14 (0.92–1.42)	0.226
T-cell NHL	2,813	3.0	1.37 (1.10–1.71)	0.005
Mantel cell lymphoma	1,553	2.4	1.13 (0.82–1.56)	0.467
LPL/Waldenstrom	693	2.6	1.13 (0.71–1.82)	0.607
Burkitt lymphoma	260	—	1.31 (0.65–2.67)	0.454

NOTE: Bolded entries indicate a significant association of VTE with cancer at a *P* value of <0.001. In accordance with the SEER–Medicare data use agreement, the percentage of cases with VTE is not shown for cancers when the number of cases with VTE is fewer than 11.

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; PLL, T-cell prolymphocytic leukemia; LPL, lymphoplasmacytic lymphoma.

DVT). A *P* value of <0.05 was used as the cut-off to determine whether the effect on cancer risk varied by latency or VTE subtype. Finally, among cases with solid-organ cancers, we compared the distribution of SEER cancer stage (local vs. regional vs. distant) among those with a VTE detected <1 year before cancer diagnosis, ≥1 year before cancer diagnosis, and those without a VTE.

Results

The characteristics of cases and controls are presented in Table 1. The majority of subjects were male, white, and selected between 1999 and 2002. Cases and controls were matched with respect to age, sex, and year of diagnosis/selection; they differed slightly by race/ethnicity and duration of Medicare coverage.

VTE was observed among 2.5% of cases and 2.2% controls. Overall, VTE was associated with a 15% increased risk of any cancer (OR = 1.15; 95% CI, 1.11–1.20; Table 2). Among the 45 solid-organ cancers assessed, 10 were associated with VTE ($P < 0.001$), including cancers of the lung (OR = 1.18; 95% CI, 1.12–1.23), stomach (OR = 1.19; 95% CI, 1.09–1.30), small intestine (OR = 1.42; 95% CI, 1.17–1.71), colon (1.25; 95% CI, 1.18–1.31), gallbladder (OR = 1.39; 95% CI, 1.16–1.67), pancreas (OR = 1.53; 95% CI, 1.43–1.64), soft tissue including the heart (OR = 1.43; 95% CI, 1.21–1.68), ovary (OR = 1.35; 95% CI, 1.22–1.50), and kidney/renal pelvis (OR = 1.34; 95% CI, 1.23–1.46), and melanoma (OR = 1.17; 95% CI, 1.08–1.27). Among 7 evaluated hematologic malignancies, VTE was associated with an increased risk of NHL (OR = 1.27; 95% CI, 1.20–1.35), myeloma (OR = 1.48; 95% CI, 1.35–1.63), and acute myeloid leukemia (AML; OR = 1.35; 95% CI, 1.19–1.54). Among NHL subtypes, there was a significant association with diffuse large B-cell lymphoma (OR = 1.41; 95% CI, 1.28–1.55).

We also investigated the association of VTE and cancer risk across different follow-up times (i.e., latency intervals) after VTE (Table 3). For most cancers, risk was strongest <1 year following VTE and significantly attenuated with longer time intervals ($P < 0.001$); an exception was melanoma, for which risk did not vary by time

Table 3. Associations of VTE with cancer in different latency intervals following VTE

		Period within 1 year before cancer diagnosis or selection		Period from 1 to 2.5 years before cancer diagnosis or selection		Period from 2.6 to 4 years before cancer diagnosis or selection		Period from 4.1 to 6 years before cancer diagnosis or selection		Period more than 6 years before cancer diagnosis or selection		
	Total	% with VTE	OR (95% CI)	% with VTE	OR (95% CI)	% with VTE	OR (95% CI)	% with VTE	OR (95% CI)	% with VTE	OR (95% CI)	P^a
Controls	200,000	0.4	1.0	0.5	1.0	0.4	1.0	0.4	1.0	0.5	1.0	—
All cancers	1,138,390	0.6	**1.51 (1.41–1.63)**	0.5	1.04 (0.97–1.11)	0.4	1.06 (0.98–1.15)	0.4	1.09 (1.01–1.18)	0.5	1.10 (1.02–1.19)	<0.001
Lung	179,880	0.7	**1.75 (1.60–1.92)**	0.5	1.06 (0.97–1.16)	0.4	1.04 (0.94–1.15)	0.4	1.07 (0.96–1.18)	0.5	1.01 (0.92–1.12)	<0.001
Stomach	22,860	0.8	**1.75 (1.47–2.07)**	0.5	1.09 (0.91–1.31)	0.4	0.99 (0.80–1.23)	0.4	1.02 (0.83–1.26)	0.6	1.15 (0.96–1.38)	0.003
Small intestine	3,694	1.1	**2.42 (1.74–3.38)**	0.7	1.49 (1.02–2.17)	0.3	0.76 (0.42–1.39)	0.7	**1.72 (1.16–2.54)**	0.4	0.79 (0.48–1.33)	0.002
Colon	107,265	0.7	**1.64 (1.48–1.82)**	0.6	1.15 (1.04–1.27)	0.4	1.06 (0.94–1.19)	0.5	1.17 (1.04–1.31)	**0.7**	**1.24 (1.12–1.37)**	0.002
Gallbladder	3,777	1.5	**3.28 (2.47–4.35)**	0.4	0.78 (0.48–1.28)	0.4	1.02 (0.62–1.67)	0.6	1.29 (0.84–1.97)	0.5	0.89 (0.56–1.41)	<0.001
Pancreas	33,135	1.2	**2.75 (2.43–3.12)**	0.6	1.19 (1.02–1.38)	0.5	1.26 (1.06–1.49)	0.5	1.27 (1.08–1.50)	0.7	**1.33 (1.15–1.54)**	<0.001
Soft tissue	4,728	1.0	**2.27 (1.67–3.07)**	0.7	1.39 (0.99–1.96)	0.6	**1.59 (1.10–2.30)**	0.6	1.44 (1.00–2.10)	0.4	0.67 (0.41–1.08)	<0.001
Melanoma	27,059	0.5	1.10 (0.91–1.34)	0.6	1.21 (1.02–1.42)	0.4	1.02 (0.83–1.26)	0.6	1.38 (1.16–1.65)	0.6	1.14 (0.96–1.35)	0.570
Ovary	16,112	1.2	**2.79 (2.35–3.32)**	0.5	0.95 (0.75–1.21)	0.5	1.17 (0.91–1.50)	0.4	0.84 (0.64–1.11)	0.6	1.13 (0.90–1.42)	<0.001
Kidney/renal pelvis	24,611	0.9	**2.18 (1.87–2.54)**	0.5	1.16 (0.97–1.39)	0.4	1.15 (0.94–1.41)	0.4	1.07 (0.87–1.32)	0.6	1.20 (1.00–1.44)	<0.001
NHL	55,195	0.9	**2.06 (1.83–2.31)**	0.5	1.01 (0.88–1.15)	0.5	1.19 (1.03–1.37)	0.4	1.05 (0.91–1.21)	0.6	1.16 (1.02–1.32)	<0.001
Myeloma	15,318	0.9	**2.14 (1.78–2.58)**	0.6	1.34 (1.09–1.64)	0.5	1.29 (1.02–1.63)	0.6	1.35 (1.08–1.69)	0.7	**1.35 (1.10–1.66)**	0.006
AML	8,489	0.9	**2.00 (1.57–2.56)**	0.5	1.11 (0.83–1.48)	0.5	1.17 (0.85–1.62)	0.8	**1.80 (1.40–2.33)**	0.5	0.86 (0.63–1.18)	0.009

NOTE: Bolded entries indicate a significant association of VTE with cancer at a P value of <0.001.

[a]P value for the test of whether OR differs according to time since VTE.

Table 4. Associations of pulmonary embolism, DVT, and SVT with cancer

		Pulmonary embolism		DVT		SVT			
	Total	% Pulmonary embolism	OR (95% CI)	% DVT	OR (95% CI)	% SVT	OR (95% CI)	P1[a]	P2[b]
Controls	200,000	0.6	1.0	0.3	1.0	0.1	1.0	—	—
All cancers	1,138,390	0.7	1.14 (1.06–1.22)	0.4	**1.22 (1.11–1.34)**	0.1	1.24 (1.05–1.46)	0.199	0.412
Lung	179,880	0.7	**1.21 (1.11–1.32)**	0.3	1.08 (0.96–1.22)	0.1	1.27 (1.04–1.55)	0.119	0.385
Stomach	22,860	0.7	1.19 (1.01–1.41)	0.5	1.31 (1.06–1.63)	0.1	1.20 (0.82–1.76)	0.462	0.883
Small intestine	3,694	0.9	1.42 (0.99–2.02)	0.4	1.32 (0.80–2.18)	—	**2.16 (1.10–4.23)**	0.824	0.250
Colon	107,265	0.8	**1.27 (1.15–1.39)**	0.5	**1.27 (1.12–1.45)**	0.2	1.35 (1.08–1.67)	0.926	0.581
Gallbladder	3,777	0.8	1.24 (0.86–1.79)	0.6	1.59 (1.04–2.45)	0.2	1.68 (0.82–3.44)	0.391	0.602
Pancreas	33,135	0.9	**1.47 (1.29–1.68)**	0.6	**1.66 (1.41–1.97)**	0.2	1.33 (0.98–1.82)	0.245	0.374
Soft tissue	4,728	0.5	0.84 (0.56–1.25)	0.5	1.36 (0.89–2.08)	0.2	1.65 (0.84–3.23)	0.112	0.224
Melanoma	27,059	0.7	1.24 (1.07–1.45)	0.4	1.27 (1.03–1.57)	0.1	1.03 (0.70–1.52)	0.869	0.323
Ovary	16,112	0.9	**1.44 (1.19–1.73)**	0.5	**1.49 (1.16–1.91)**	0.1	1.13 (0.71–1.79)	0.825	0.281
Kidney/renal pelvis	24,611	0.8	**1.36 (1.16–1.59)**	0.5	**1.53 (1.25–1.88)**	0.2	**1.73 (1.24–2.41)**	0.361	0.264
NHL	55,195	0.7	1.11 (0.98–1.25)	0.6	**1.65 (1.43–1.91)**	0.2	**1.50 (1.17–1.93)**	<0.001	0.273
Myeloma	15,318	1.0	**1.65 (1.39–1.96)**	0.5	1.37 (1.07–1.77)	0.1	1.26 (0.81–1.97)	0.230	0.371
AML	8,489	0.6	0.96 (0.73–1.28)	0.7	**1.92 (1.46–2.54)**	—	1.51 (0.89–2.58)	0.001	0.597

NOTE: Bolded entries indicate a significant association of VTE with cancer at a P value of <0.001. In accordance with the SEER–Medicare data use agreement, percentages are not shown for groups with fewer than 11 subjects.

[a]P1 = P value for test of difference in OR between pulmonary embolism and DVT.

[b]P2 = P value for test of difference in OR between the combination of pulmonary embolism/DVT and SVT.

interval. Most associations were not significant >6 years after VTE. However, cancers for which risk was elevated >6 years after VTE included colon cancer (OR = 1.24; 95% CI, 1.12–1.37), pancreatic cancer (OR = 1.33; 95% CI, 1.15–1.54), and myeloma (OR = 1.35; 95% CI, 1.10–1.66).

In total, 0.7%, 0.4%, 0.1%, and 1.3% of cases and 0.6%, 0.3%, 0.1%, and 1.2% of controls were diagnosed with pulmonary embolism, DVT, SVT, or VTE NOS, respectively. Overall, for most cancers, risk seemed similar following pulmonary embolism and DVT, or for the combination of pulmonary embolism or DVT compared with SVT (Table 4). NHL and AML were exceptions in that risk was significantly higher following DVT as compared with pulmonary embolism.

The stage distribution of solid-organ cancers in relation to VTE diagnosis is shown in Table 5. A significantly higher proportion of distant stage diagnoses were observed among individuals with VTE diagnosed <1 year before cancer diagnosis, compared with cases without VTE for cancers of the lung (60.5% vs. 52.9%, $P < 0.001$), stomach (44.7% vs. 35.5%, $P = 0.024$), and pancreatic cancer (74.4% vs. 59.7%, $P < 0.001$).

Discussion

In our case–control study of over 1 million cancer cases of elderly individuals in the United States, we demonstrate a 15% increased risk of any cancer diagnosis associated with a prior diagnosis of VTE. This increased risk was not present for all cancers but instead was restricted to a large and somewhat heterogeneous subgroup of malignancies: cancers of the lung, stomach, small intestine, colon, gallbladder, pancreas, soft tissue, ovary, and kidney/renal pelvis, as well as for melanoma, NHL, myeloma, and AML. The elevated risks were generally stronger in the 1-year period following VTE diagnosis. Nonetheless, the risk of colon cancer, pancreatic cancer, and myeloma remained significantly elevated after more than 6 years of follow-up time.

The strongly elevated risk of cancer less than 1 year after VTE diagnosis observed in this study is consistent with results from prior population- and hospital-based studies (11–15). These previous studies have also shown distinct associations with cancers of digestive tract, pancreas, and NHL, as observed in our study. The short-term associations may be because of medical practice patterns in which clinicians search for cancer in people presenting with VTE. Prompted by VTE, screening tests such as colonoscopy or chest and abdominal/pelvic computed tomography scans could lead to diagnosis of previously unsuspected and asymptomatic malignancies.

Because cancer can itself cause VTE, an additional explanation is that VTE is a presenting manifestation of cancer and is diagnosed simultaneously with or slightly before the cancer. Many of the cancers diagnosed concurrently with VTE present at an advanced stage (7, 14). Indeed, we demonstrated that a larger proportion of lung, stomach, and pancreatic cancers diagnosed within 1 year of VTE presented with distant metastases, compared with when there was no history of VTE. Conversely, several

Table 5. Frequency and distribution of cancers by stage among those with and without VTE

Cancer type	Local	Regional	Distant	*P* value
Lung				
No VTE	31,317 (19.7)	43,671 (27.4)	84,299 (52.9)	
VTE detected <1 year before cancer	205 (18.4)	236 (21.1)	676 (60.5)	
VTE detected ≥1 year before cancer	571 (20.2)	736 (25.9)	1,527 (53.9)	<0.001
Stomach				
No VTE	5,876 (31.4)	6,187 (33.1)	6,646 (35.5)	
VTE detected <1 year before cancer	36 (27.3)	37 (28.0)	59 (44.7)	
VTE detected ≥1 year before cancer	135 (37.6)	106 (29.5)	118 (32.9)	0.024
Small intestine				
No VTE	1,091 (33.9)	1,165 (36.2)	962 (29.9)	
VTE detected <1 year before cancer	14 (43.8)	10 (31.3)	8 (25.0)	
VTE detected ≥1 year before cancer	28 (39.4)	25 (35.2)	18 (25.4)	0.652
Colon				
No VTE	41,919 (41.9)	39,974 (40.0)	18,040 (18.1)	
VTE detected <1 year before cancer	288 (42.2)	259 (37.9)	135 (19.8)	
VTE detected ≥1 year before cancer	979 (43.6)	909 (40.4)	360 (16.0)	0.077
Gallbladder				
No VTE	1,194 (34.6)	1,097 (31.7)	1,165 (33.7)	
VTE detected <1 year before cancer	12 (24.5)	12 (24.5)	25 (51.0)	
VTE detected ≥1 year before cancer	26 (38.2)	20 (29.4)	22 (32.4)	0.140
Pancreatic				
No VTE	2,745 (10.6)	7,716 (29.7)	15,524 (59.7)	
VTE detected <1 year before cancer	27 (8.7)	53 (16.9)	232 (74.4)	
VTE detected ≥1 year before cancer	72 (11.3)	172 (27.1)	391 (61.6)	<0.001
Soft tissue				
No VTE	2,368 (57.1)	1,134 (27.4)	643 (15.5)	
VTE detected <1 year before cancer	19 (47.5)	11 (27.5)	10 (25.0)	
VTE detected ≥1 year before cancer	59 (60.8)	26 (26.8)	12 (12.4)	0.430
Melanoma				
No VTE	20,073 (79.9)	3,781 (15.0)	1,281 (5.1)	
VTE detected <1 year before cancer	88 (77.2)	20 (17.5)	6 (5.3)	
VTE detected ≥1 year before cancer	423 (78.5)	91 (16.9)	25 (4.6)	0.719
Ovary				
No VTE	1,485 (10.5)	940 (6.7)	11,706 (82.8)	
VTE detected <1 year before cancer	16 (9.4)	13 (7.7)	141 (82.9)	
VTE detected ≥1 year before cancer	23 (8.6)	14 (5.2)	231 (86.2)	0.637
Kidney/renal pelvis				
No VTE	11,920 (53.7)	5,224 (23.6)	5,040 (22.7)	
VTE detected <1 year before cancer	97 (51.6)	45 (23.9)	46 (24.5)	
VTE detected ≥1 year before cancer	234 (53.7)	93 (21.3)	109 (25.0)	0.684

NOTE: Cases with missing stage information are excluded from the table.

large registry-based studies documented a significantly higher risk of VTE following diagnosis and treatment of these cancer types as well as kidney cancer, ovarian cancer, NHL, and myeloma (5, 6, 22). Furthermore, a separate study of over 66,000 cancer cases identified a near 2-fold increased risk of VTE associated with distant metastases as compared with a localized malignancy (23). Mechanistic studies have shown higher concentrations of pro-coagulant factors among individuals diagnosed with cancer (24, 25). Therefore, the short-term associations of VTE with cancer risk are most likely driven by a combination of enhanced screening for cancer among individuals with VTE (which would lead to detection of early stage cancers) and reverse causation (i.e., cancer causing VTE, with some cases manifesting aggressive biology and advanced stage).

In contrast, the long-term association of VTE with risk of cancer of the digestive tract and hematologic malignancies, for a period of greater than 6 years following VTE, cannot be readily explained by screening or reverse

causation. Unlike the short-term associations with cancer risk, these longer-term associations have not been observed consistently in prior studies (11, 14, 16–18). Nonetheless, one plausible explanation is that the VTE may be caused by small, slow-growing tumor precursors that exist for extended periods of time. Such precursor tumors may induce procoagulant activity, possibly through production of cytokines and other molecular factors (26). Of interest, the 3 cancers in our study that were associated with VTE over a long latency period have a prolonged precancerous phase. Specifically, colon cancer is preceded by preneoplastic polyps, pancreatic cancer develops over more than a decade, and myeloma is preceded by monoclonal gammopathy of underdetermined significance (MGUS; refs. 27–29). Indeed, an elevated rate of VTE and arterial thrombosis has been reported among those diagnosed with MGUS, which persists for up to 10 years after MGUS diagnosis (30–32). Furthermore, elevated serum concentrations of prothrombin fragments 1 and 2 are associated with increased risk of digestive tract cancers (33).

We found very little difference in cancer risk by VTE subtype. This observation is mostly in agreement with a previous study that also assessed VTE subtype-specific associations (18). However, we observed a higher risk of NHL and AML associated with DVT than pulmonary embolism. While pulmonary embolism is a more severe VTE event that results in higher mortality than DVT, a biologic basis for these differences in cancer risk is unclear. Notably, the otherwise general lack of difference in cancer risk by VTE subtype reinforces the need to consider all VTEs, including SVT, with equal importance as they relate to cancer risk.

This study also has several limitations. First, we lacked information on some risk factors that could confound the observed associations. Smoking and obesity both increase the risk of VTE in general and are identified risk factors for the development of cancers of the lung, stomach, pancreas, colon, and ovary (2, 34–43). In addition to smoking and obesity, other comorbid conditions that occur at an elevated rate in this elderly population may also play a role as potential confounders. Second, our study was limited to people ages 66 years and older, and we could not ascertain the occurrence of VTE before the age of 65 years. The high prevalence of other cancer risk factors in this elderly Medicare population may explain why the associations observed in our study are weaker than relative risks estimated in other, mostly younger, populations (11, 17). Third, because information on VTE subtype was based on billing claims submitted by health care providers, rather than a detailed medical record abstraction, there may be some misclassification of VTE subtypes.

This study has several strengths, including the large sample size and population-based selection of cases and controls. Furthermore, because we included a large representative sample of elderly adults, our results are directly relevant to this population, among whom both VTE and cancer are disproportionately common. In addition, the large sample of this study allowed for systematic evaluation across a range of multiple cancer types. However, given the rarity of VTE, some true associations may have failed to reach statistical significance.

The association of VTE with subsequent diagnosis of cancer, as well as the increased mortality of individuals with cancer who were previously diagnosed with VTE, has led to the suggested use of enhanced cancer screening strategies among individuals diagnosed with VTE. This approach may be most relevant for those cancers with an asymptomatic precursor condition and for which we observed associations with VTE over a latency period of several years (i.e., colon and pancreatic cancers, myeloma). A number of prospective and retrospective studies have indeed demonstrated that the use of basic screening strategies such as physical examination, computed tomography scans, or targeted laboratory testing among individuals diagnosed with unprovoked or idiopathic VTE results in early detection of malignancies, particularly those of the pelvis and abdomen (44–46). However, a small randomized trial assessing the effect of targeted screening among individuals with VTE showed no increased benefit of early detection on survival (47). Therefore, cancer screening among individuals with VTE may only increase the lead-time in detecting cancer and may not improve survival among individuals diagnosed early with cancer.

In conclusion, we observed an elevated risk of specific solid-organ and hematologic cancers. The associations were most notable within 1 year following VTE diagnosis, and several cancers were more likely to present with distant metastases when they manifested in this short interval. The elevated risk of 3 cancers (colon and pancreatic cancers, myeloma) was significant at a period of more than 6 years following VTE diagnosis. Our study lends epidemiologic support to the view that cancer is related to the development of VTE. Additional studies are needed to better understand the underlying biologic mechanisms and evaluate the potential clinical role of VTE as an early predictor for the development of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.A. Engels
Development of methodology: E.A. Engels
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.A. Marks, E.A. Engels
Writing, review, and/or revision of the manuscript: M.A. Marks, E.A. Engels
Study supervision: E.A. Engels

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