The Association of Active Cancer With Venous Thromboembolism Location: A Population-Based Study

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OBJECTIVE: **To test active cancer for an association with venous thromboembolism (VTE) location.**

PATIENTS AND METHODS: **Using the resources of the Rochester Epidemiology Project, we identified all Olmsted County, MN, residents with incident VTE during the 35-year period 1966-2000 (N=3385). We restricted analyses to residents with objectively diagnosed VTE during the 17-year period from January 1, 1984, to December 31, 2000 (N=1599). For each patient, we reviewed the complete medical records in the community for patient age, gender, and most recent body mass index at VTE onset; VTE event type and location; and previously identified independent VTE risk factors (ie, surgery, hospitalization for acute medical illness, active cancer, leg paresis, superficial venous thrombosis, and varicose veins). Using logistic regression we tested active cancer for an association with each of 4 symptomatic VTE locations (arm or intra-abdominal deep venous thrombosis [DVT], intra-abdominal DVT, pulmonary embolism, and bilateral leg DVT), adjusted for age, gender, body mass index, and other VTE risk factors.**

RESULTS: **In multivariate analyses, active cancer was independently associated with arm or intra-abdominal DVT (odds ratio [OR], 1.76; *P*=.01), intra-abdominal DVT (OR, 2.22; *P*=.004), and bilateral leg DVT (OR, 2.09; *P*=.02), but not pulmonary embolism (OR, 0.93).**

CONCLUSION: **Active cancer is associated with VTE location. Location of VTE may be useful in decision making regarding cancer screening.**

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BMI = body mass index; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep venous thrombosis; OR = odds ratio; PE = pulmonary embolism; VTE = venous thromboembolism

The association between cancer and venous thromboembolism (VTE) is well-established and strong.[1-4] Active cancer with and without chemotherapy increases VTE risk by 5- to 6-fold.[5] Furthermore, active cancer accounts for about 20% of the entire VTE burden occurring in a community.[6] Indeed, VTE is the second most common cause of death among patients with cancer.[7] Cancer patients with VTE have a 2-fold or greater increase in mortality compared with cancer patients without VTE, even after adjusting for stage.[8,9] Nearly half of the patients with cancer-associated VTE have distant metastases at the time of VTE diagnosis.[8] The incidence of cancer in patients with recurrent idiopathic VTE is higher than that in patients with secondary VTE.[3]

Opinions differ regarding screening for an underlying occult cancer after an idiopathic VTE event.[10,11] Although a small randomized clinical trial found that more occult cancers were detected at an early stage with extensive screening, which theoretically could improve cancer treatment potential, no difference in survival was noted between this strategy and usual care.[10] Because anticoagulant therapy improves the outcomes of patients with VTE and cancer, it is still important to recognize which patients with VTE have an underlying active cancer.[12] The diagnosis of VTE may help to uncover previously occult cancer by prompting a complete physical examination and testing consistent with standard health care maintenance. However, indiscriminate cancer screening is not cost-effective.[13,14] To provide a more organized and cost-effective approach to cancer detection among patients with VTE, the VTE characteristics associated with cancer must be recognized. Although evidence shows that idiopathic VTE and bilateral deep venous thrombosis (DVT) correlate with subsequent cancer diagnosis,[3,15] there is a paucity of data regarding the association between active cancer and VTE location. The current study aims to determine whether underlying cancer is associated with particular VTE locations.

PATIENTS AND METHODS

Using the resources of the Rochester Epidemiology Project,[16] we identified the inception cohort of Olmsted County, MN, residents with a first lifetime acute DVT or pulmonary embolism (PE), or first lifetime diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), during the 35-year period 1966-2000, as previously described.[17,18] For this study, we restricted analyses to residents with an incident objectively diagnosed acute DVT and/or PE dur-

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ing the 17-year period from January 1, 1984, to December 31, 2000. The study time frame was selected to minimize variation in cancer prevalence due to change in diagnostic testing over time while maximizing sample size and associated study power. Residents with arm DVT related to a central venous catheter or transvenous pacemaker in the preceding 3 months, those with newly diagnosed CTEPH, and those in whom the VTE location was not recorded in the medical record were excluded.

Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records (inpatient and outpatient) in the community for cases and controls who provided consent to review of their medical records for research purposes. All records were reviewed from date first seen by a Rochester Epidemiology Project healthcare provider until death, date of last medical record follow-up, or 2000,[19] whichever was earliest, as previously performed.[5,20] Data were recorded on the method of diagnosis and type of incident VTE event (DVT, PE, or both; CTEPH). A DVT was categorized as objectively diagnosed when symptoms and/or signs of acute DVT were present and the diagnosis was confirmed by venography, compression venous duplex ultrasonography, impedance plethysmography, computed tomographic venography, magnetic resonance imaging, or pathology examination of a thrombus removed at surgery or autopsy. A PE was categorized as objectively diagnosed when symptoms and/or signs of acute PE were present and the diagnosis was confirmed by pulmonary angiography, a ventilation-perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, magnetic resonance imaging, or pathology examination of a thrombus removed at surgery or autopsy. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons dying within Olmsted County during the study period.

For Olmsted County residents meeting our criteria for objectively diagnosed DVT or PE, the nurse abstractors also collected data from the medical record on date of incident event; patient age at incident event; patient gender; patient location at incident event onset (3 categories: community-dwelling; confined to a hospital or community-dwelling but hospitalized in the previous 90 days; or confined to a nursing home [including long-term rehabilitation facility]); body mass index (BMI) (calculated as the weight in kilograms divided by height in meters squared); active cancer (excluding nonmelanoma skin cancer); serious neurologic disease (stroke or other disease affecting the nervous system with associated leg paresis or acute stroke with leg paresis requiring hospitalization within the previous 3 months); surgery requiring anesthesia; prior superficial venous thrombosis; and varicose veins (varicose veins or treated varicose veins [injection sclerotherapy or stripping]). Serious neurologic disease with leg paresis, all surgery variables, and anesthesia had to have been documented in the 3 months before the incident VTE event for cases or before the index episode of medical care for controls. Active cancer had to have been documented in the 3 months before or after the incident VTE event. Cancer was considered as inactive when the patient had undergone curative surgery (defined as no residual tumor and clear margins) or chemotherapy and/or radiotherapy with no evidence of residual disease. Myeloproliferative or myelodysplastic disorders, chronic myelocytic leukemia or chronic lymphocytic leukemia, and hematopoietic growth factor therapy for these disorders were considered as active cancer. A few patients had multiple primary cancers in the 3-month period on either side of the date of the incident VTE. We used the cancer in the 3 months after the incident VTE if one was before the incident VTE and one was after it. We used the more recent cancer if both were before the VTE. If both primary cancers were diagnosed on the same day, we used the one with the worse stage. One of 2 Mayo Clinic oncologists (R.S.M., A.A.A.) verified the classification for all VTE incident cases with malignancy during the time frame examined. Body mass index was based on the most recent height and weight measurements before the incident VTE event.

Statistical Analyses

Using logistic regression, we tested active cancer for an association with 4 VTE locations (4 analyses; Figure), including: (1) arm (internal jugular, axillary, subclavian, innominate, and/or superior vena cava) or intra-abdominal (hepatic, portal, splenic, superior or inferior mesenteric, renal, ovarian, and/or inferior vena cava) DVT compared with all other incident VTE (leg DVT or PE); (2) intra-abdominal DVT compared with all other incident VTE (leg DVT or PE); (3) PE (with or without leg DVT) compared with leg DVT alone with no symptomatic PE; and (4) bilateral leg DVT compared with unilateral leg DVT. All patients with leg DVT (including those with PE) were used in the fourth analysis (Figure), whereas the comparison group for the first and second analyses was the same. We tested active cancer for an association with the log odds of each VTE location univariately, adjusted for age at incident VTE, gender, as well as BMI and other known VTE risk factors (ie, hospitalization with or without major surgery, nursing home confinement, trauma or fracture, neurologic disease with leg paresis, prior superficial venous thrombosis, and varicose veins[5,20]). We investigated interactions between active cancer and age, male gender, and event year for all 4 VTE locations, and we examined residuals to check for influential points and lack of fit.

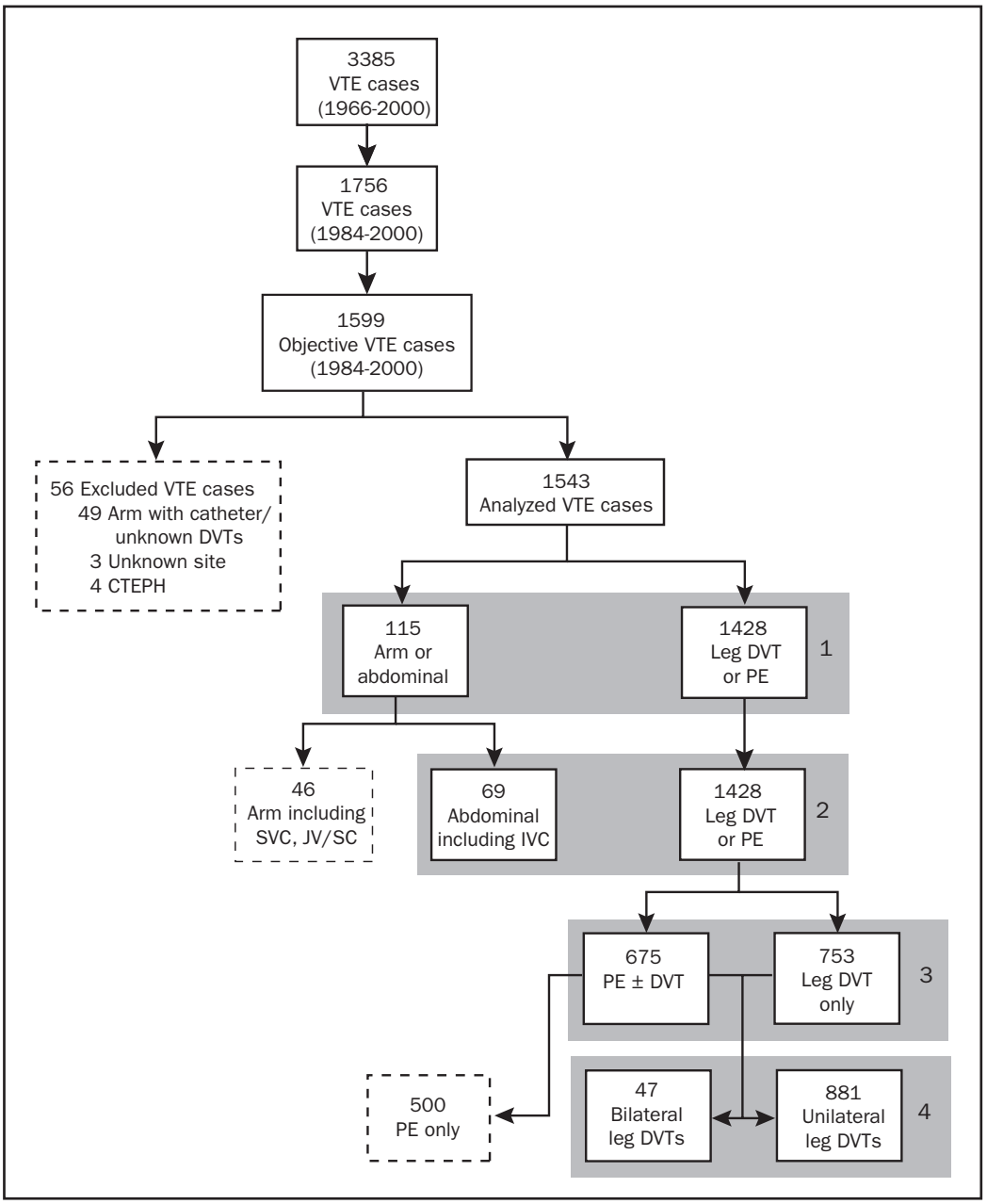

FIGURE. Study flow diagram by inclusion criteria and venous thromboembolism (VTE) location analyses. Broken line represents excluded patients. Shadowed rectangles indicate the 4 analyzed groups. CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep venous thrombosis; IVC = inferior vena cava; JV/SC = jugular vein/subclavian vein; PE = pulmonary embolism; SVC = superior vena cava.

Models were tested without potentially influential points to ensure that our conclusions were correct. Categorical data were expressed as percentages and continuous data as means ± SD. All *P* values presented are based on the analysis as completed. However, adjusting for the number of related end points (n=4), as one would do with the Bonferroni correction, suggests that a *P* value of less than .0125 (0.05 ÷ 4) should be considered significant when evaluating the results presented.

RESULTS

During the 35-year period 1966-2000, 3385 residents of Olmsted County developed a first lifetime acute DVT or

TABLE 1. **Demographic Characteristics and Active Cancer Prevalence by VTE Location Analysis**

Characteristic	Analysis 1 (N=1543)		Analysis 2 (N=1497)		Analysis 3 (N=1428)		Analysis 4 (N=928)	
	Arm or intra-abdominal DVT (n=115)	Nonarm or intra-abdominal DVT, or PE (n=1428)	Intra-abdominal DVT (n=69)	Nonarm or intra-abdominal DVT, or PE (n=1428)	PE ± DVT (n=675)	Leg DVT only (n=753)	Bilateral leg DVT (n=47)	Unilateral leg DVT (n=881)
Age (y), mean ± SD	52.0±22.8	66.0±18.3	55.4±22.7	66.0±18.3	68.8±17.4	63.5±18.8	72.3±16.4	64.2±18.6
Age (y), median	52.1	69.7	57.5	69.7	72.4	66.3	75.8	66.9
Male	49 (43)	641 (45)	31 (45)	641 (45)	303 (45)	338 (45)	21 (45)	395 (45)
Active cancer	36 (31)	335 (23)	26 (38)	335 (23)	154 (23)	181 (24)	20 (43)	206 (23)
Active cancer found after VTE	4 (11)	56 (17)	4 (15)	56 (17)	30 (19)	26 (14)	3 (15)	33 (16)

Categorical data are provided as number (percentage). DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

PE or received a diagnosis of CTEPH (Figure). Of these VTE events, 1756 occurred during the 17-year period 1984-2000, and 1599 of these 1756 (91%) were objectively diagnosed. Fifty-six VTE events were excluded (arm DVT related to a central venous catheter or transvenous pacemaker, CTEPH, or unknown site; Figure), leaving 1543 incident VTE events for analysis. There were 21 patients with an arm or intra-abdominal DVT who also had PE. The demographic characteristics and active cancer prevalence in the 4 analysis groups are shown in Table 1, and the distribution of active cancer types for each of the 4 VTE event locations tested is shown in Table 2. Gastrointestinal cancers were the most common cancers found in patients with arm or intra-abdominal DVT, intra-abdominal DVT, and bilateral leg DVT.

The results of tests for an association between each of the 4 VTE locations (4 analyses) and active cancer are presented in Table 3. After adjustment for age and gender, active cancer was associated with arm or intra-abdominal DVT (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.32-3.15; *P*=.001; Table 3) compared with the remaining VTE (leg DVT or PE; analysis 1), and after adjustment for BMI and other VTE risk factors, the association remained statistically significant (OR, 1.76; 95% CI, 1.12-2.77; *P*=.01). Younger age, lower BMI, and hospitalization for acute medical illness (no surgery) in the 3 months before the VTE were associated with arm or intra-abdominal DVT. Similarly, adjusted for age and gender, the odds of intra-abdominal DVT (analysis 2) were more than 2-fold higher in patients with active cancer (OR, 2.49; 95% CI, 1.48-4.21; *P*=.001), and this association persisted after adjustment for BMI and other VTE risk factors (OR, 2.22; 95% CI, 1.29-3.80; *P*=.004). Although active cancer was not associated with PE with or without DVT (analysis 3; *P*=.59), the odds of bilateral leg DVT were more than 2-fold higher than the odds of unilateral DVT with active cancer (analysis 4; OR, 2.43; 95% CI, 1.33-4.42; *P*=.004), and this association persisted after adjustment for age and gender (OR, 2.26; 95% CI, 1.24-4.14; *P*=.008). After adjustment for BMI and other VTE risk factors, the association between active cancer and bilateral leg DVT was marginally significant (OR, 2.09; 95% CI, 1.12-3.90; *P*=.02). In addition, older age and recent hospitalization for acute medical illness were marginally associated with increased odds of bilateral leg DVT (*P*=.01 and *P*=.05, respectively).

TABLE 2. **Primary Cancer Distribution by Venous Thromboembolism Location Analysis**[a]

Cancer site[b]	Venous thromboembolism location analysis			
	Arm or intra-abdominal DVT (n=36)	Intra-abdominal DVT (n=26)	PE ± DVT (n=154)	Bilateral leg DVT (n=20)
Gastrointestinal	15 (42)	14 (54)	42 (27)	7 (35)
Pancreas	6 (17)	6 (23)	12 (13)	2 (10)
Urogenital	5 (14)	5 (19)	29 (19)	4 (20)
Prostate	4 (11)	4 (15)	15 (10)	2 (10)
Hematologic	6 (17)	2 (8)	24 (16)	2 (10)
Lung	5 (14)	2 (8)	21 (14)	3 (15)
Breast	1 (3)	0 (0)	16 (10)	2 (10)
Renal	1 (3)	1 (4)	4 (3)	0 (0)
Other	3 (8)	2 (8)	18 (12)	2 (10)

[a] Data are provided as number (percentage). DVT = deep venous thrombosis; PE = pulmonary embolism.

[b] Gastrointestinal cancer includes gastric, liver, biliary, pancreas, and colorectal cancers. Urogenital cancer includes bladder, genital, and prostate cancers. Hematologic cancer includes leukemia, lymphoma, and myeloproliferative disorders. Pancreas and prostate subgroups are not included in the total.

DISCUSSION

The principal finding of this population-based study is the association of active cancer with 3 VTE locations. Specifically, active cancer was strongly associated with arm or intra-abdominal DVT and intra-abdominal DVT alone compared with leg DVT or PE, and with bilateral leg DVT compared with unilateral leg DVT. For the most part, this association persisted after adjustment for age and gen-

TABLE 3. **Associations Between VTE Location and Active Cancer**[a]

Characteristic	Analysis 1 (N=1543) Arm or intra-abdominal DVT vs nonarm or intra-abdominal DVT, or PE		Analysis 2 (N=1497) Intra-abdominal DVT vs nonarm or intra-abdominal DVT, or PE		Analysis 3 (N=1428) PE ± DVT vs leg DVT only		Analysis 4 (N=928) Bilateral leg DVT vs unilateral leg DVT	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted	1.49 (0.98-2.25)	.06	1.97 (1.19-3.26)	.008	0.93 (0.73-1.19)	.59	2.43 (1.33-4.42)	.004
Adjusted for age and gender	2.04 (1.32-3.15)	.001	2.49 (1.48-4.21)	.001	0.87 (0.68-1.12)	.29	2.26 (1.24-4.14)	.008
Adjusted for VTE risk factors[b]	1.76 (1.12-2.77)	.01	2.22 (1.29-3.80)	.004	0.84 (0.65-1.09)	.19	2.09 (1.12-3.90)	.02

[a] CI = confidence interval; DVT = deep venous thrombosis; OR = odds ratio; PE = pulmonary embolism; VTE = venous thromboembolism.
[b] Adjusted for age, male gender, body mass index, neurologic disease with leg paresis, and hospitalization with or without surgery within the preceding 3 months, prior superficial thrombosis, varicose veins, and nursing home residency.

der and for BMI and other independent VTE risk factors. However, active cancer was not associated with PE with or without DVT compared with leg DVT only.

Previous publications have suggested that the location of the thrombosis may be indicative of the cancer location.[21,22] Arm DVT unrelated to a central venous catheter or transvenous pacemaker is uncommon. In a systematic review of 47 studies including 2557 patients with VTE, the proportion with arm DVT ranged from only 1% to 4%.[23] Two previous studies lend support to our finding of an association between active cancer and arm DVT (in the absence of a central venous catheter). In a US multicenter DVT registry containing 268 patients with arm DVT unrelated to a central venous catheter, arm DVT was associated with active cancer (OR, 1.30; 95% CI, 0.92-1.83) when compared with catheter-associated arm DVT, although this finding did not reach statistical significance.[24] However, in the Multiple Environmental and Genetic Assessment study, after adjustment for age and gender, arm DVT in the absence of a central venous catheter was associated with an 18-fold increased risk of cancer.[25]

Several previous studies support our finding of an association between active cancer and intra-abdominal DVT.[21,22,26,27] Our study expands on the results of previous studies in that the association between active cancer and intra-abdominal DVT remains after controlling for other VTE risk factors. Our findings further substantiate the need to consider active cancer as an underlying cause of intra-abdominal DVT. The presence of active cancer also influences the overall survival of patients with intra-abdominal DVT. For instance, active cancer is an independent predictor of reduced survival among patients with splanchnic vein thrombosis (hazard ratio, 2.23; 95% CI, 1.78-2.78).[27] Similarly, cancer is the most common underlying cause of renal vein thrombosis, and the presence of malignancy is associated with poor survival (hazard ratio, 2.4; 95% CI, 1.2-4.7).[21]

Our finding of an association between active cancer and bilateral leg DVT is supported by one previous study in which cancer was present in 45% of patients with bilateral DVT; these cancer patients more often had distant metastases and resulting poor prognosis.[15]

Whether more aggressive cancer screening is appropriate among all patients with VTE remains arguable. In a large registry of VTE patients in Spain, a limited diagnostic work-up for occult cancer in patients with VTE identified about half of the prevalent cancers, and these cancers were at an earlier stage compared with those identified during follow-up (61% vs 14%).[28] In a recent systematic review, the period prevalence of previously undiagnosed cancer in patients with idiopathic VTE was 6.1% at baseline and 10.0% from baseline to 12 months.[29] An extensive screening strategy increased the proportion of previously undiagnosed cancers detected from 49% to 70%. Because of the higher risk of recurrent VTE and bleeding among cancer patients treated with a vitamin K antagonist,[30] identifying such patients early was considered important; cancer patients with VTE are best treated with low-molecular-weight heparin.[12,29,31,32] However, an extensive cancer screening strategy has not been shown to improve survival,[29] possibly owing to limited sample size.[10] The survival of patients in a Danish cancer registry was poor if cancer was diagnosed at the same time or within 1 year after VTE.[8,14] Although not specifically tested in our study, cancer screening beyond recommended testing for routine health maintenance may be cost-effective for patients with idiopathic VTE; arm DVT unrelated to a central venous catheter, transvenous pacemaker, or thoracic outlet syndrome; intra-abdominal DVT; or bilateral leg DVT.

CONCLUSION

Active cancer is associated with intra-abdominal and bilateral leg DVT. Patients with DVT in these locations and

no previously diagnosed cancer should be considered for more extensive screening for occult cancer.

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