ORIGINAL INVESTIGATION

Incidence of Venous Thromboembolism in the Year Before the Diagnosis of Cancer in 528 693 Adults

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Background: It is unclear how frequently unprovoked venous thromboembolism (VTE) reflects the presence of an occult cancer.

Methods: The California Cancer Registry was used to identify diagnosed cases of 19 common malignancies during a 6-year period. Cases were linked to a hospital discharge database to identify incident VTE events in the year before the cancer diagnosis date. The standardized incidence ratio (SIR) of unprovoked VTE was determined by using the age-, race-, and sex-specific incidence rates in California.

Results: Among 528 693 cancer cases, 596 (0.11%) were associated with a diagnosis of unprovoked VTE within 1 year of the cancer diagnosis, compared with 443.0 expected cases (SIR, 1.3; 95% confidence interval, 1.2-1.5; $P<.001$). Among cases with metastatic-stage cancer, the SIR was 2.3 (95% confidence interval, 2.0-2.6; $P<.001$), whereas for all other stages, the SIR was 1.07 (95% confidence interval, 0.97-1.18; $P=.09$). The incidence of preceding VTE was increased over that expected only during the 4-month period immediately preceding the cancer diagnosis date ($P<.001$). Only 7 cancer types were associated with a significantly elevated SIR: acute myelogenous leukemia; non-Hodgkin lymphoma; and renal cell, ovarian, pancreatic, stomach, and lung cancer (SIR range, 1.8-4.2).

Conclusions: In the year preceding the diagnosis of cancer, the number of cases with unprovoked VTE was modestly higher than expected, and almost all of the unexpected VTE cases were associated with a diagnosis of metastatic-stage cancer within 4 months. Given the timing and advanced stage of the unexpected cases, it is unlikely that earlier diagnosis of these cancers would have significantly improved long-term survival.

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When a patient develops acute venous thromboembolism (VTE), physicians commonly try to determine whether there is an underlying condition or risk factor associated with the thrombotic event. Patients with a provoking risk factor, such as recent trauma, major surgery, or immobility, have a better long-term prognosis with a lower incidence of recurrent VTE than patients who present with unprovoked VTE.[1] In the absence of an obvious provoking risk factor, the presence of an underlying malignancy is often considered.[2,3] This is because some types of cancer appear to be able to initiate or trigger a thrombotic diathesis through a number of mechanisms, which have been recently reviewed.[4,5] Several cohort studies have suggested that the incidence of cancer among patients who present with unprovoked VTE is more than 3 times higher than among patients with a provoked VTE,[6-12] and there is evidence that more than 40% of these cancers are metastatic at the time of diagnosis.[13]

It is not clear what percentage of patients with unprovoked VTE harbor an asymptomatic occult malignancy. Several studies have shown that approximately 8% to 12% of patients who presented with acute VTE were diagnosed as having cancer after a relatively simple medical evaluation based on symptoms and routine laboratory testing.[6,14] However, these patients did not have truly occult cancers because the malignancies were readily diagnosed. Some recent studies suggest that intensive cancer screening in patients with VTE does lead to the detection of more difficult-to-diagnose cancers,[15,16] but it is still not clear whether the incidence of cancer in these patients is higher than expected, nor whether the

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detection of these occult cancers improves morbidity or survival.[17-19]

If patients with unprovoked VTE have a higher-than-expected standardized incidence of cancer in the ensuing year, then patients with cancer would be expected to have a corresponding increase in the standardized incidence of unprovoked VTE in the year before the cancer diagnosis. Using a large cancer registry linked to a comprehensive hospital discharge database, we determined the incidence of unprovoked VTE during the 1-year period immediately preceding the diagnosis of 19 common types of cancer and compared this with the expected incidence of unprovoked VTE in the general population.

METHODS

DATABASES

Two comprehensive databases were linked together by means of patient-specific identifiers: (1) the California Cancer Registry,[20] which contains information about 99% of all cancer cases (excepting nonmelanoma skin cancer and carcinoma in situ of the cervix) diagnosed in California by pathological examination (95%), radiologic studies (4%), or autopsy (1%); and (2) the California Patient Discharge Data Set, which contains the discharge diagnoses and procedures for all patients hospitalized in all nonfederal acute care facilities in the state, starting in July 1990.[21] Coding uses the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) nomenclature. Approximately 5% of registry cases could not be linked to the hospital discharge data set because of the absence of a Social Security number.

CANCER COHORT

The cancer cohort that was analyzed included all patients 18 years and older who received a first-time diagnosis of common histologic forms of any of the 19 most common malignant cancers during two 3-year periods: January 1, 1993, through December 31, 1995, and January 1, 1997, through December 31, 1999.[20] Cancer cases diagnosed in federal hospitals were excluded because the state's database of hospital discharge dates does not include these hospitals. Information in the registry database included basic demographic information, the cancer stage (classified by Surveillance, Epidemiology, and End Results criteria), the date of diagnosis, and the histologic type.[22]

VTE COHORTS

Deep vein thrombosis and pulmonary embolism were defined by means of previously validated *ICD-9-CM* codes (451.1x, 451.2, 451.81, 453.1, 453.2, 453.8, 453.9, 415.1x) in the principal or a secondary position together with a hospital stay of 3 or more days, unless the patient died.[23-25] Cases coded as having superficial venous thrombosis or upper extremity thrombosis were not included because these patients are not consistently admitted for treatment. Cases coded as having VTE earlier than the specified 1-year period analyzed were excluded. Each record was searched for the first hospital admission with a diagnosis of VTE during the 365-day period immediately preceding the cancer diagnosis date, which was defined as the earliest of (1) the cancer registry diagnosis date or (2) the date of a hospital admission that included a cancer diagnosis code (*ICD-9-CM*) compatible with the cancer type in the registry. Venous thromboembolism events diagnosed before the cancer diagnosis date were categorized as *preceding* or *prior* VTE events, whereas VTE events diagnosed during the same hospitalization when cancer was diagnosed were categorized as *concurrent*.

POPULATION INCIDENCE RATIO OF VTE

The crude age-, race-, and sex-specific VTE incidence rates in California for 1995, 1996, and 1997 were calculated by means of the California Patient Discharge Data Base and the same *ICD-9-CM* codes and the same inclusion criteria that were used to define VTE events in the cancer cohort.[26] The age, race or ethnicity, and sex distribution of the population between 1995 and 1997 was assumed to be the same as in the 2000 census, but the total number of residents in these years used published census estimates for 1995, 1996, and 1997. The average yearly VTE incidence rate during the 3-year reference period was used to calculate the expected number of VTE events.[27]

CLASSIFICATION OF THROMBOEMBOLIC EVENTS

All first-time VTE events in both the general population and the cancer cohorts were classified in a hierarchical fashion into 7 groups based on the presence or absence of a specific risk factor(s) defined by means of specific *ICD-9-CM* codes: (1) malignancy-associated VTE (a code for malignancy at the time of the VTE or in the preceding 6 months in the population cohort only), (2) pregnancy-associated VTE, (3) trauma-associated VTE (1 major or 2 minor trauma codes in the preceding 3 months), (4) surgery-associated VTE (surgery diagnosis related group code in the preceding 3 months), (5) VTE during a medical hospitalization (except for admission with a principal diagnosis of VTE), and (6) VTE after a medical hospitalization ($<$2 months after a medical hospitalization of $\geq$4 days). All remaining cases were classified as unprovoked VTE.

STUDY OUTCOMES

The primary outcomes were the standardized incidence ratio (SIR) of unprovoked VTE diagnosed during the 1 year immediately preceding the diagnosis of cancer and the date of the VTE event relative to the date of the cancer diagnosis.

STATISTICAL ANALYSIS

Exact 95% confidence intervals (CIs) for standardized incidence ratios were obtained by means of the Poisson distribution. The χ^2 goodness-of-fit test was used to test for equal distribution of unprovoked VTE events during the six 2-month periods preceding the cancer diagnosis. Differences in proportions were assessed by means of the normal approximation to the binomial distribution. Analyses were performed with SAS (SAS Institute Inc, Cary, NC), S-plus (Insightful Corporation, Seattle, Wash), or SISA (http://home.clara.net/sisa/smr.htm), and a 2-sided *P* value less than .05 was considered statistically significant. This study was approved by the State of California Committee for the Protection of Human Subjects and the University of California, Davis, Human Subjects Committee.

RESULTS

During the 6-year period that was analyzed, 528 693 cases included in the cancer registry were diagnosed as having 1 of the 19 specified types of cancer and met the other

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Table 1. Distribution of SEER Cancer Stage in the VTE Cohorts

SEER Stage at Time of Cancer Diagnosis	No. (%)		
	Cases With VTE		
	Unprovoked, Diagnosed in Year Preceding a Cancer (n = 596)	Diagnosed Concurrently With Cancer (n = 2246)	Entire Cancer Cohort (n = 528 693)
Local	199 (33)	354 (16)	250 202 (47)
Regional	94 (16)	387 (17)	108 156 (20)
Metastatic	229 (38)	1297 (58)	120 516 (23)
Unknown	74 (12)	208 (9)	49 819 (9)

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; VTE, venous thromboembolism.

study inclusion criteria. The mean ± SD age was 66 ± 17 years, and 49% were women. During the year preceding the diagnosis of cancer, 1113 (0.21%) of these patients were diagnosed as having VTE. Of this total, 596 (54%) had an unprovoked VTE event: 367 (62%) with venous thrombosis and 229 (38%) with pulmonary embolism.

Table 1 shows the distribution of initial cancer stages for (1) all cases with cancer, (2) cases diagnosed concurrently as having VTE and cancer, and (3) cases diagnosed as having unprovoked VTE in the preceding year. Metastatic disease was present initially in 23% of the entire cohort, 38% of the cases that had preceding unprovoked VTE ($P<.001$), and 58% of the cases with concurrently diagnosed VTE and cancer ($P<.001$ vs entire cohort and the preceding VTE cohorts).

For the entire study cohort, the age-, race-, and sex-specific expected 1-year incidence of unprovoked VTE was 443.0 cases, compared with 596 observed cases (SIR, 1.3; 95% CI, 1.2-1.5; $P<.001$). The SIRs for each of the 19 specific cancer types are shown in **Table 2**. Cases with acute myelogenous leukemia (SIR, 4.2; 95% CI, 2.4-6.8), ovarian cancer (SIR, 2.8; 95% CI, 1.9-4.1), non-Hodgkin lymphoma (SIR, 2.7; 95% CI, 1.9-3.7), pancreatic cancer (SIR, 2.6; 95% CI, 1.8-3.6), renal cell cancer (SIR, 2.5; 95% CI, 1.5-3.9), stomach cancer (SIR, 1.8; 95% CI, 1.1-2.8), and lung cancer (SIR, 1.8; 95% CI, 1.5-2.1) had SIR values significantly greater than 1.0. For these 7 specific types of cancer combined, there were 158.7 more cases of VTE observed than expected, and in the remaining cancer types there were 6 fewer cases than expected.

Among the 120 516 cancer cases with metastatic-stage disease, there were 229 observed cases with preceding unprovoked VTE compared with 101.0 expected cases (SIR, 2.3; 95% CI, 2.0-2.6; $P<.001$) (128 unexpected cases). Among the remaining 408 177 cases with localized, regional, or unknown-stage cancer, there were 367 observed cases of preceding unprovoked VTE compared with 342.0 expected cases (SIR, 1.07; 95% CI, 0.97-1.18; $P=.09$) (25 unexpected cases). For the 15 types of solid cancer, the correlation between the magnitude of the SIR for unprovoked VTE and the prevalence of metastatic disease at the time of diagnosis was significant ($R^2=0.73$; $P<.001$).

Figure 1 shows when unprovoked VTE events were diagnosed relative to the cancer diagnosis date, using 2-month (61-day) increments. The unprovoked events were unevenly distributed across the 6 time intervals, with a higher incidence in the two 61-day intervals immediately preceding the diagnosis of cancer ($P<.001$). To further explore this finding, the time of the prior VTE event was divided into 2 time intervals: 12 months to 4 months and 4 months to 1 day before the cancer diagnosis date. The observed incidence of unprovoked VTE in the interval from 12 months to 4 months was 302 cases compared with 296 expected (SIR, 1.02; 95% CI, 0.91-1.14; $P=.34$) (6 unexpected cases), whereas the observed incidence in the interval from 4 months to 1 day was 294 cases compared with 147 expected cases (SIR, 2.0; 95% CI, 1.8-2.2; $P<.001$), an excess of 147 cases.

Figure 2 shows when unprovoked VTE events were diagnosed relative to the cancer diagnosis date using 1-day increments and stratified by the initial cancer stage. Among the unprovoked VTE cases that were subsequently diagnosed as having local-stage cancer (199 cases) or regional-stage cancer (94 cases), there was no significant variation in the incidence rate over time ($P>0.1$). However, there was a nonequal distribution of events during the 1-year period among cases with unknown-stage ($P=.002$) and metastatic-stage ($P<.001$) cancer, with a greater number of events occurring just before diagnosis of cancer (more apparent for metastatic cancer). The data for cases with metastatic cancer were divided into 2 time intervals, 12 months to 4 months and 4 months to 1 day before diagnosis. There were 82 observed cases of unprovoked VTE diagnosed between 12 months and 4 months before the cancer diagnosis date compared with 67.5 expected cases (SIR, 1.2; 95% CI, 1.0-1.5; $P=.04$) (14.5 unexpected cases). However, between 4 months and 1 day before the diagnosis of metastatic cancer, there were 147 observed cases of unprovoked VTE compared with 33.5 expected cases (SIR, 4.4; 95% CI, 3.7-5.2; $P<.001$) (113.5 unexpected cases).

There were 2246 cases that were concurrently diagnosed as having cancer and VTE. Of these, 412 (18%) had an admission for a principal diagnosis of acute VTE ("condition occasioning admission to the hospital").

COMMENT

There are several major findings of this study. First, the standardized incidence ratio of unprovoked VTE during the year preceding a diagnosis of cancer was increased by 30% (153 excess cases) over expected, and this increase was significant only among patients who had one of 7 types of cancer (159 excess cases): acute myelogenous leukemia; non-Hodgkin lymphoma; and pancreatic, ovarian, stomach, renal cell, and lung cancer, all strongly associated with a high prevalence of metastatic-stage disease at the time of diagnosis. Conversely, the incidence of prior unprovoked VTE was not significantly increased among the patients diagnosed as having any of the 12 other common cancers that were analyzed. Second, the excess or unexpected cases with prior VTE were largely confined to cases with metastatic disease at the

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Table 2. SIRs of Unprovoked VTE During the 1-Year Period Immediately Preceding the Diagnosis of Cancer

Type	No.	VTE Cases Observed	VTE Cases Expected	SIR	95% CI
Total	**528 693**	**596**	**443.0**	1.3	1.2-1.5*
Prostate	104 532	84	89.7	0.9	0.7-1.2
Lung	92 359	151	86.0	1.8	1.5-2.1*
Breast	96 570	60	71.4	0.8	0.6-1.1
Colon	68 109	75	65.5	1.1	0.9-1.4
Melanoma	22 721	8	13.9	0.6	0.2-1.1
Bladder	23 174	20	21.9	0.9	0.6-1.4
Non-Hodgkin lymphoma	18 874	37	13.6	2.7	1.9-3.7*
Uterine	18 238	18	15.4	1.2	0.7-1.8
Pancreatic	13 731	34	13.3	2.6	1.8-3.6*
Stomach	12 776	18	10.1	1.8	1.1-2.8*
Ovarian	12 051	27	9.5	2.8	1.9-4.1*
Renal cell	11 255	20	8.0	2.5	1.5-3.9*
Brain	8567	4	5.3	0.8	0.2-1.9
Esophageal	6185	7	5.4	1.3	0.5-2.7
Liver	6486	5	3.6	1.4	0.5-3.2
Chronic lymphocytic anemia	4934	7	4.9	1.4	0.6-2.9
Acute myelogenous leukemia	4838	16	3.8	4.2	2.4-6.8*
Chronic granulocytic leukemia	2228	3	1.5	2.0	0.4-5.8
Acute lymphocytic anemia	1065	2	0.5	4.0	0.5-14

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio; VTE, venous thromboembolism.
*$P<.001$.

time of diagnosis (128 excess cases; SIR, 2.3). Third, essentially all of the unexpected prior VTE events were diagnosed in the 4-month period immediately preceding the date of the cancer diagnosis (147 excess cases).

The association of acute myelogenous leukemia with thrombosis was not expected, but an association has been recently reported.[28] It is certainly plausible that non-Hodgkin lymphoma, renal cell cancer, stomach cancer, and pancreatic cancer might be clinically occult and therefore more difficult to diagnose in some patients presenting with VTE. Lung cancer may have been suspected in some of the VTE cases, but a diagnostic procedure such as needle biopsy or bronchoscopic biopsy may have been delayed for several weeks because of anticoagulant therapy.

There were 2246 cases of VTE diagnosed during the same hospitalization when cancer was diagnosed, a figure much higher than all of the 1113 VTE cases diagnosed during the entire preceding year. A large number of these patients with concurrently diagnosed VTE underwent a surgical procedure during the hospitalization, making it likely that many developed VTE after surgery. Although there is no way of knowing how many of these patients presented with VTE and no suspicion of cancer, 412 of these patients were admitted with a principal diagnosis of VTE, and it is likely that a significant proportion of them had cancer diagnosed during the evaluation and treatment of the VTE. Retrospective studies have shown that about 7% of patients who present with unprovoked VTE are found to have cancer after a "routine evaluation" during the hospitalization.[14]

On the basis of the findings of this study, it appears that patients who develop VTE in the year before being diagnosed as having cancer can be divided into 3 subgroups. The first is made up of patients with "background" or expected cases of VTE, with no biological link between the thromboembolic event and the cancer (443 of the 596 cases [74%]). The second group is composed of the extra or unexpected patients with unprovoked VTE. In the current study, this group had 2 characteristics suggesting a biological link to the cancer: metastatic disease at the time of diagnosis and the occurrence of the VTE event shortly before diagnosis of cancer. One hundred forty-seven (25%) of the 596 VTE cases, or approximately 25 cases each year, met both of these criteria. The final group is made up of patients diagnosed as having both VTE and cancer during the same hospitalization.

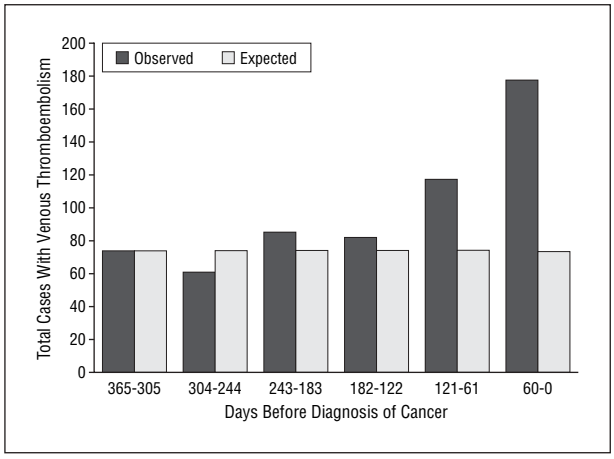

Figure 1. Timing of diagnosis of unprovoked venous thromboembolism events relative to the cancer diagnosis date, using 2-month (61-day) increments.

On the basis of previous studies, approximately 10% of all patients with unprovoked VTE and no evidence of cancer are subsequently diagnosed as having cancer within 1 year.[6-12,17] Because 25% of the VTE cases in the current study had epidemiologic features suggesting a causal link

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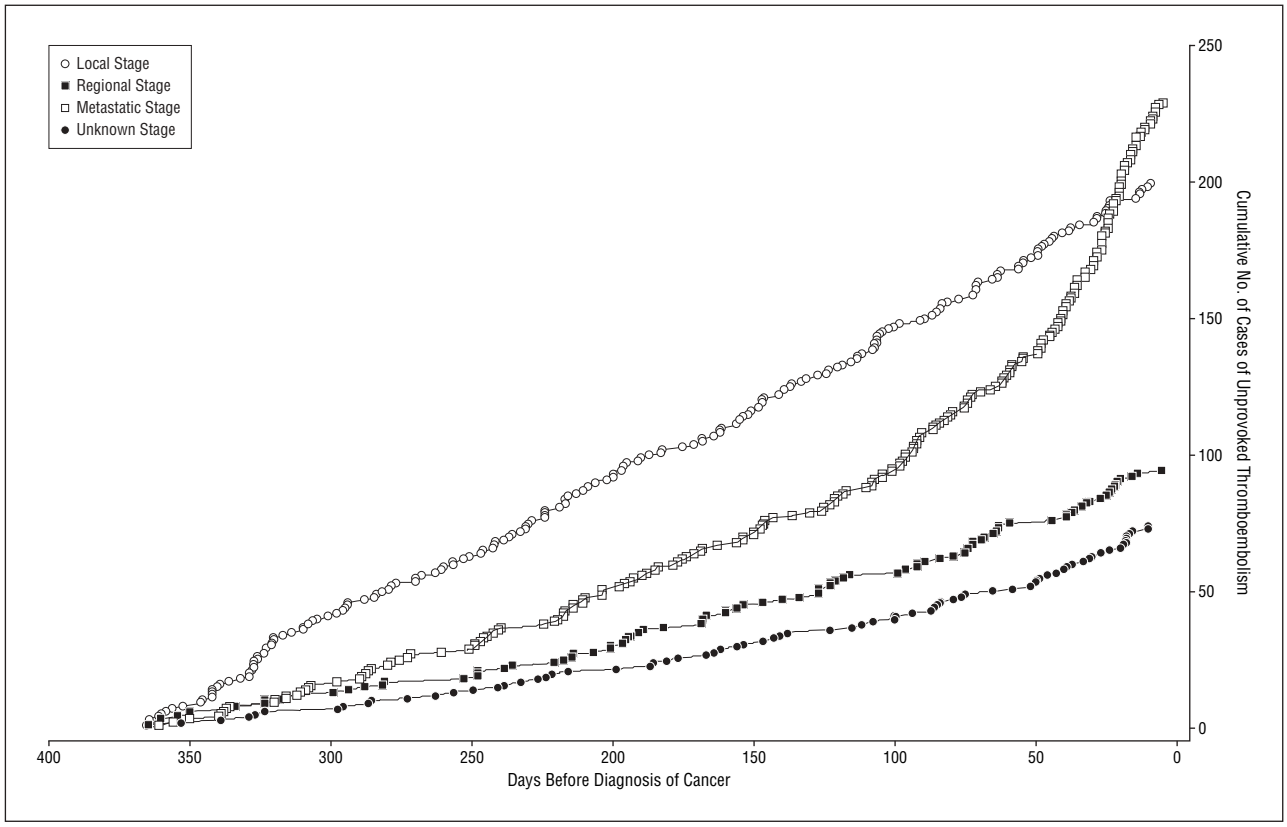

Figure 2. Timing of diagnosis of unprovoked venous thromboembolism events relative to the cancer diagnosis date, using 1-day increments and stratified by the initial cancer stage.

between the cancer and the VTE event, we estimate that about 2.5% of all patients with unprovoked VTE harbor an occult malignancy responsible for triggering thrombosis. However, detection of these cancers at the time of the VTE event would probably not improve long-term survival because, in the current study, almost all of these patients were diagnosed as having metastatic cancer within a few months. The findings of this study support the view that a workup for cancer in a patient with unprovoked VTE should be undertaken on the basis of clinical symptoms and the results of routine laboratory testing.

The current analysis had certain advantages compared with other population-based studies. First, it was possible to select a large number of cases diagnosed as having common types of cancer that had typical histologic features. Second, the date of the diagnosis of cancer could be accurately determined by using both the cancer registry diagnosis date and the hospital discharge data. Reliance on the registry date alone would have significantly increased the number of patients classified as having VTE before a diagnosis of cancer. Third, criteria that were used to quantify and classify VTE events in both the general population (expected cases) and the cancer cohort (observed cases) were applied to the same hospital discharge data set in an identical fashion.

Limitations of this study include the fact that some of the patients with cancer may have had an unprovoked VTE that was not detected because it was diagnosed either in another state or in a federal hospital. Also, no information was available about how intensely physicians evaluated or screened the patients with VTE for cancer. It is possible some cases were worked up very extensively for cancer and some not at all. Regardless, a major strength of this population-based study is that the results reflect the practice of physicians in their communities.

In conclusion, in a large cohort of patients with 19 common types of cancer, most of the patients who were diagnosed as having unprovoked VTE in the preceding year represented "expected" cases, on the basis of age-, race-, and sex-adjusted incidence rates in California. However, a modest percentage (25%) of the cases with preceding VTE did have epidemiologic evidence linking the VTE event and the cancer, and most of these patients were diagnosed as having metastatic-stage cancer within a few months. These finding do not support the view that patients with unprovoked VTE should undergo an exhaustive diagnostic workup for cancer to effect a cure by detecting a cancer at an early stage. However, because only patients with myelogenous leukemia, non-Hodgkin lymphoma, and renal cell, pancreatic, ovarian, stomach, and lung cancer had a higher-than-expected incidence of preceding VTE, knowledge of these associations may benefit clinicians caring for patients with an unprovoked VTE who have nonspecific symptoms or findings suggesting the presence of an underlying malignancy.

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