DEEP-VEIN THROMBOSIS AND THE INCIDENCE OF SUBSEQUENT SYMPTOMATIC CANCER

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Abstract *Background.* In contrast to the established relation between overt cancer and subsequent venous thromboembolism, it is unclear whether symptomatic deep-vein thrombosis is associated with a risk of subsequent overt malignant disease.

Methods. Two hundred sixty consecutive patients with symptomatic, venographically proved deep-vein thrombosis were enrolled in a study, of whom 250 were followed during a two-year period. Among those assessed during follow-up, the incidence of subsequently detected cancer in the 105 patients with secondary venous thrombosis (i.e., thrombosis associated with a well-recognized risk factor other than cancer) was compared with the incidence of cancer in the 145 patients with idiopathic venous thrombosis.

Results. Routine examination at the time of diagnosis of the venous thrombosis revealed cancer in 5 of the 153 enrolled patients with idiopathic venous thrombosis (3.3 percent) and in none of the 107 enrolled patients with secondary venous thrombosis. During follow-up, overt cancer developed in 2 of the 105 patients with secondary venous thrombosis (1.9 percent) and in 11 of the 145 patients with idiopathic venous thrombosis (7.6 percent; odds ratio, 2.3; 95 percent confidence interval, 1.0 to 5.2; P = 0.043). Of the 145 patients with idiopathic venous thrombosis, 35 had confirmed recurrent thromboembolism. Overt cancer subsequently developed in 6 of the 35 (17.1 percent). The incidence of cancer in the patients with recurrent idiopathic venous thrombosis was higher than that in the patients with secondary venous thrombosis (P = 0.008; odds ratio, 9.8; 95 percent confidence interval, 1.8 to 52.2) or in the patients with idiopathic venous thrombosis that did not recur (P = 0.024; odds ratio, 4.3; 95 percent confidence interval, 1.2 to 15.3).

Conclusions. There is a statistically significant and clinically important association between idiopathic venous thrombosis and the subsequent development of clinically overt cancer, especially among patients in whom venous thromboembolism recurs during follow-up. (N Engl J Med 1992;327:1128-33.)

SINCE the initial observation by Trousseau in 1868 relating thrombotic phenomena to cancer,[1] numerous studies have addressed the relation between malignant disease and venous thromboembolism. An increased incidence of venous thromboembolism in patients with known cancers has been convincingly demonstrated. Thus, cohort studies of surgical patients that used mandatory objective tests to confirm the presence of postoperative venous thrombosis showed that the incidence of venous thrombosis was markedly higher in patients with malignant disorders than in patients with other (nonmalignant) diseases.[2,3] Furthermore, an increased risk of venous thromboembolism is suggested by the high incidence of pulmonary embolism and subclinical activation of the coagulation system in nonsurgical patients with cancer.[4-6]

In contrast to the established relation between known cancer and subsequent venous thromboembolism, an association between venous thrombosis and the risk that cancer will become manifest after the thrombotic episode has not been convincingly demonstrated. Thus far, studies have been limited to small or retrospective series of patients.[7-18] Furthermore, in all of these studies the potential for bias was high, either because patients with overt signs of cancer at entry were not excluded or because the search for subsequent cancers was more extensive in the patients than in the controls. The clinical implication of a high risk of subsequent cancer in patients with venous thromboembolic disorders could be an extensive diagnostic workup for an underlying neoplasm at the time of the thrombotic episode. Such a procedure would only be worthwhile, however, if a substantial proportion of the occult cancers could be recognized, if such cancers were treatable, and if their discovery ultimately prolonged life (and did not merely advance the date of diagnosis without improving ultimate survival).

In order to determine whether there is an association between venous thrombosis and a risk of subsequent clinically overt cancer, we performed a prospective, cohort study of consecutive outpatients with a first episode of venographically documented deep-vein thrombosis. The primary aim of this study was to determine the incidence of subsequent symptomatic cancer during a two-year follow-up period in patients with venous thrombosis in whom a routine examination at the time of referral did not identify the presence of a cancer. We compared the incidence in patients whose first episode of venous thrombosis was associated with a well-recognized risk factor other than cancer with the incidence

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in patients whose first episode of venous thrombosis was without apparent cause. We also investigated whether the recurrence of venous thromboembolism was associated with a higher risk of subsequent malignant disease.

Methods

Identification of the Initial Cohort

The Second Department of Internal Medicine of the University of Padua (Padua, Italy) serves as a primary care referral center for patients with clinically suspected venous thromboembolism in a community of approximately 350,000 persons. All consecutive outpatients with a first episode of clinically suspected deep-vein thrombosis who were referred by their general practitioners underwent objective testing.[19,20] Patients were potentially eligible for the study if they had venographically proved deep-vein thrombosis. Patients were excluded from the study if they were referred because of recurrent venous thrombosis, if they presented with a known cancer, or if they refused to give informed consent.

Limited Search for Cancer at the Time of Referral

A routine examination for the presence of malignant disease was carried out in all patients at the time of referral. This search consisted of a thorough history taking, physical examination (including pelvic, rectal, and breast examinations), measurement of the erythrocyte sedimentation rate, complete blood count, liver- and renal-function tests, urinalysis, and chest roentgenography. If there were abnormalities compatible with the presence of cancer, further testing was performed, including histologic examinations if indicated. Patients were excluded from follow-up if the presence of cancer was confirmed at the time of referral or if they were unable because of geographic distance to return to the study center for follow-up visits.

Study Design

The study was a prospective, cohort follow-up study in which the association between deep-vein thrombosis and subsequent malignant disease was assessed among patients with a first episode of deep-vein thrombosis in whom routine examination at the time of entry did not detect cancer. If this association exists, the incidence of subsequent cancer should be higher in patients with idiopathic venous thrombosis than in patients whose venous thrombosis occurred in the presence of well-recognized risk factors. We therefore classified patients as having either secondary or idiopathic venous thrombosis. Secondary venous thrombosis was defined as thrombosis that occurred in patients with a strong family history of proved venous thromboembolism (e.g., first-degree relatives with venous thrombosis or pulmonary embolism); in patients who had a lupus anticoagulant or who were deficient in antithrombin III, protein C, or protein S; and in patients after trauma to the lower limb, after prolonged immobilization due to medical disorders or surgical procedures, and during pregnancy or the puerperium. Deep-vein thrombosis that occurred in the absence of these conditions was defined as idiopathic. Patients were subdivided into those with one or more recurrent episodes of venous thromboembolism during follow-up and those with no recurrent episodes. Recurrent venous thromboembolism was defined as a confirmed thromboembolic event after the initial thrombosis but before a diagnosis of cancer was made. The routine examination for cancer was repeated in the patients who had confirmed recurrent venous thromboembolism during follow-up. All the patients were treated with either continuous adjusted-dose intravenous standard heparin or fixed-dose subcutaneous low-molecular-weight heparin.[21] Treatment with an oral anticoagulant (warfarin) was started in all the patients on the seventh day of heparin therapy. The dose of the oral anticoagulant was adjusted daily to maintain the international normalized ratio between 2.0 and 3.0. Treatment with intravenous standard heparin or low-molecular-weight heparin was discontinued on day 10, or later if the international normalized ratio was less than 2.0.

Follow-up

All the patients were seen three months after their acute episode of venous thrombosis and were asked to return to the study center every six months for follow-up assessments. Follow-up continued for up to 24 months. The minimal period of follow-up was three months. To avoid diagnostic suspicion bias, the general medical history, hospital admission data, and information on the occurrence of signs and symptoms of cancer were obtained on a standardized form by a physician who was unaware of whether the thrombotic episode was idiopathic. If cancer was suspected during follow-up, further testing was performed, and the diagnosis of cancer was established by histologic examinations. Patients who were not able to attend the follow-up sessions were visited at home or were interviewed by telephone. For all patients who died during the follow-up period, the date of death, cause of death, and information on the occurrence of cancer, including tumors found at autopsy, were recorded.

Diagnosis of Recurrent Venous Thrombosis

Contrast venography was performed as previously described.[22,23] The criteria for deep-vein thrombosis were an intraluminal filling defect confirmed in at least two projections or the inability to visualize a vein or venous segment despite repeated injections with contrast material. The presence or absence of venous thrombosis was assessed by a panel of independent observers who were unaware of the clinical condition of the patient or earlier test results. Patients were asked to return immediately to the study center if symptoms suggestive of recurrent venous thromboembolism developed. If a patient presented with clinically suspected leg-vein thrombosis, venography was performed. The criterion for recurrent leg-vein thrombosis was evidence of a new intraluminal filling defect on the venogram.[24,25] If the venogram was not diagnostic, recurrent venous thrombosis was diagnosed on the basis of a positive ^{125}I-fibrinogen leg scan or the results of noninvasive tests that changed from normal to abnormal. Patients with suspected pulmonary embolism underwent venography if they had concurrent leg symptoms, and perfusion lung scanning if they did not. The diagnosis of pulmonary embolism was excluded if the perfusion scan was normal. Since ventilation lung scanning was not available and pulmonary angiography could not routinely be performed, we were unable to make a definitive diagnosis of pulmonary embolism in all patients. If no definitive diagnosis could be made, the patients were classified as not having recurrent venous thromboembolism. Perfusion lung scanning and pulmonary angiography were performed, and the results interpreted according to standard procedures.[26,27]

Statistical Analysis

The incidence of cancer in patients with secondary venous thrombosis was compared with that in patients with idiopathic venous thrombosis. In addition, the incidence was compared in patients with single and recurrent episodes of venous thromboembolism.

The incidence of cancer was compared in six-month periods and for the whole two-year period. We controlled for differences in age and sex among the study patients by using logistic-regression analysis in which sex was represented by a dichotomous variable and age (in years) by a continuous variable. The odds ratios of the risk of clinically overt cancer and the 95 percent confidence intervals were calculated from the logistic-regression coefficients and their standard errors. The cumulative incidence of cancer in the study groups was calculated according to the Kaplan–Meier method, and significance was assessed by the Mantel–

Haenszel method. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

Results

Study Patients

From 1985 to 1991, a total of 1159 consecutive outpatients with clinically suspected deep-vein thrombosis of the leg were referred to the study center by their general practitioners. Venography confirmed the presence of acute venous thrombosis in 342 patients. Of these 342 patients with venous thrombosis, 30 (9 percent) were excluded from the study because the episode at entry was recurrent venous thrombosis. Malignant disease had already been diagnosed in another 49 of the patients (16 percent) before their referral for the acute thrombotic event. These 49 patients were also excluded from the study. Three patients were unwilling to participate. The cohort therefore comprised 260 patients at the study's inception, of whom 107 (41 percent) had secondary venous thrombosis and 153 (59 percent) idiopathic venous thrombosis.

New Cancers Detected at the Time of Referral

In 76 patients (29 percent), the findings of the routine examination at hospital admission were compatible with the presence of cancer. Additional investigations confirmed the presence of malignant disease in 5 of these patients (6.6 percent), but not in the remaining 71. All five patients belonged to the group with idiopathic venous thrombosis; cancer was thus detected at referral in 3.3 percent of the patients in that group. Two of the five patients presented with anorexia, dyspnea, and coughing. In both patients, a mass on the chest roentgenogram suggested the presence of a carcinoma, which was subsequently confirmed by biopsy. In two other patients the findings of the physical examination raised the suspicion of cancer. Bilateral supraclavicular, axillary, and inguinal nodes were found in one patient, and chronic lymphatic leukemia was diagnosed; in the other patient a palpable tumor of the calf was caused by an osteosarcoma. In one patient multiple myeloma was diagnosed after investigations that had been prompted by a high erythrocyte sedimentation rate. These five patients were excluded from follow-up assessments. In addition, another five patients who could not be followed up were excluded. A total of 250 patients were thus included in our follow-up analyses. Of these, 105 (42 percent) had secondary thrombosis and 145 (58 percent) had idiopathic thrombosis. Their clinical characteristics are shown in Table 1.

Table 1. Characteristics of the Follow-up Patients at Study Entry.

Characteristic	Idiopathic Deep-Vein Thrombosis (N = 145)	Secondary Deep-Vein Thrombosis (N = 105)
Mean (±SD) age — yr	62.9±14.3	55.1±18.7
Sex — no.		
Male	87	55
Female	58	50
Tobacco use — no. (%)	51 (35)	29 (28)
Alcohol abuse — no. (%)	5 (3.4)	6 (5.7)
Estrogen use — no. (%)	3 (2.1)	9 (8.6)
Liver disease — no. (%)	4 (2.8)	4 (3.8)
COPD — no. (%)*	12 (8.3)	7 (6.7)

*COPD denotes chronic obstructive pulmonary disease.

Incidence of Cancer and Recurrent Venous Thromboembolism

During follow-up, cancer was diagnosed in a total of 13 of the 250 patients (5.2 percent), whereas recurrent episodes of thromboembolic disease were observed in 40 patients (16.0 percent).

Patients with Secondary Thrombosis

Of the 105 patients with secondary venous thrombosis, 5 (4.8 percent) died of nonmalignant disease during the mean 82.6 weeks of follow-up and 2 were lost to follow-up (after 6 and 15 months, respectively) (Table 2). Two patients (1.9 percent) had cancers diagnosed after 11 and 18 months, respectively. Both were among the 47 patients who were 60 years old or older. Five patients (4.8 percent) had recurrent venous thrombotic disease; none of them subsequently had cancer.

Patients with Idiopathic Thrombosis

Among the 145 patients with idiopathic thrombosis, 13 (9 percent) died of nonmalignant disorders during a mean of 79.8 weeks of follow-up (Table 2). One patient in this group was lost to follow-up after six months. Symptomatic malignant disease developed in 11 patients (7.6 percent). Six of the 11 cancers were in the 98 patients who were 60 or older (incidence, 6.1 percent), and 5 in those who were younger (incidence, 10.6 percent).

A total of 35 patients (24.1 percent) had one or more episodes of recurrent venous thromboembolism. Six of the 11 patients with idiopathic thrombosis in whom symptomatic cancer developed belonged to this group of 35 patients (incidence, 17.1 percent).

Comparisons between Study Groups

The difference between the incidence of cancer in the patients with secondary thrombosis and that in the patients with idiopathic thrombosis was statistically significant (P = 0.043; odds ratio, 2.3; 95 percent confidence interval, 1.0 to 5.2). The cumulative incidence of cancer in the two groups is depicted in Figure 1. Most of the cancers in the patients with idiopathic thrombosis (9 of 11) occurred during the first year of observation. The incidence of cancer in the patients with recurrent idiopathic thrombosis was significantly higher than that in the patients with secondary thrombosis (P = 0.008; odds ratio, 9.8; 95 percent confidence interval, 1.8 to 52.2) and also significantly higher than that in patients with idiopathic venous

Table 2. Incidence of Cancer during Follow-up in Patients with Secondary or Idiopathic Venous Thrombosis.

VARIABLE	MONTHS OF FOLLOW-UP				
	0–6	7–12	13–18	19–24	TOTAL
Secondary thrombosis (n = 105)					
Incidence of cancer (no./no. at risk)	0/105	1/93	1/82	0/72	2/105
Death from nonmalignant causes (no.)	3	1	1	0	5
Lost to follow-up (no.)	0	1	1	0	2
Idiopathic thrombosis (n = 145)*					
Incidence of cancer (no./no. at risk)	6/145	3/121	2/108	0/97	11/145
Death from nonmalignant causes (no.)	7	5	0	1	13
Lost to follow-up (no.)	0	1	0	0	1

*The incidence of cancer in the patients with idiopathic deep-vein thrombosis was significantly higher than that in the patients with secondary thrombosis in the first six months of follow-up (P = 0.048) and the total period (P = 0.043).

thrombosis who did not have recurrent venous thromboembolism (P = 0.024; odds ratio, 4.3; 95 percent confidence interval, 1.2 to 15.3).

The cumulative incidence of cancer in the patients with recurrent idiopathic thromboembolism was calculated as a function of the time elapsed since the recurrent thrombotic episode (Fig. 1). This curve was significantly different from both the curve for patients with secondary venous thrombosis and the curve for all patients with idiopathic venous thrombosis (P<0.001 and P = 0.034, respectively).

Cancers Diagnosed during Follow-up

All the patients in whom cancer became apparent during follow-up went to their general practitioners because of the development of signs and symptoms. None of the cancers were suspected at the time of follow-up visits. The clinical characteristics of the patients given a diagnosis of cancer during follow-up are summarized in Table 3.

DISCUSSION

This study was designed to evaluate a possible association between venous thrombosis and the occurrence of cancer. We excluded patients with cancers detected by routine history taking, physical examination, or limited laboratory screening, since our objective was to determine whether patients with normal findings at routine screening are at increased risk for subsequent cancer.

The results of this prospective study clearly show that a statistically significant and clinically important association exists between idiopathic thrombosis and subsequent clinically overt cancer (cumulative incidence, 7.6 percent). Since the majority of cancers became clinically apparent in the first year after the diagnosis of the venous thrombosis, it is likely that these cancers were present but asymptomatic at that time. In the patients with idiopathic thrombosis who had recurrent venous thromboembolism during the two years of follow-up, the risk of cancer was even more pronounced (cumulative incidence, 17.1 percent). The risk of cancer was low in patients with secondary thrombosis (cumulative incidence, 1.9 percent).

A routine examination for the presence of cancer was performed in all patients at the time of admission to the hospital. A previously undetected cancer was discovered in 3.3 percent of the patients with idiopathic venous thrombosis but in none of those with secondary venous thrombosis. Therefore, in all 153 patients admitted with idiopathic venous thrombosis, 16 (10.5 percent) were recognized as having cancer.

We attempted to avoid selection bias by including consecutive patients with a first episode of venographically proved venous thrombosis who did not have overt cancer at the time of referral. We prevented observation bias by performing a standardized search for cancer in all study groups. Bias due to a more extensive search for cancer in the patients with idiopathic thrombosis than in those with secondary thrombosis can be excluded, since cancers were only detected during follow-up after the patients presented to their family doctors with newly developed symptoms. Because there were important differences in sex and age between the two patient groups, we used logistic-regression analysis to eliminate their confounding effect. Unexpectedly, almost 50 percent of the cancers detected in patients with idiopathic venous thrombosis were in the 30 percent of patients in this group who were younger than 60 years.

The incidence of recurrent venous thromboembolism in our study was high but was similar to figures reported previously.[21,28,29]

In this study, the incidence of subsequent cancer was compared in patients with idiopathic venous thrombosis and patients with secondary venous thrombosis. The use of patients with secondary venous thrombosis as controls, instead of patients who are venographically evaluated for suspected throm-

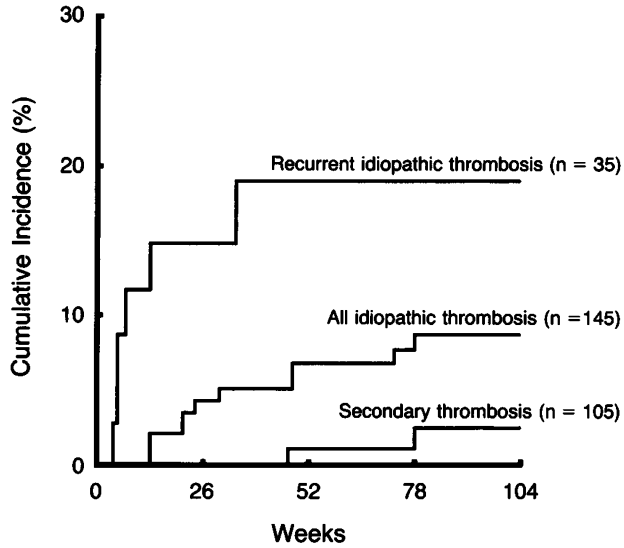

Figure 1. Cumulative Incidence of Cancer in Patients with Secondary Thrombosis, Idiopathic Thrombosis, and Recurrent Idiopathic Thrombosis.

Table 3. Characteristics of the Patients with Cancer and Results of Diagnostic Testing.

Patient No.	Sex/Age	Histologic Diagnosis	Cancer Stage	Time between Diagnosis of Thrombosis and Diagnosis of Cancer*	Clinical Manifestations Leading to Diagnosis of Cancer	Additional Diagnostic Tests Performed When Cancer Suspected
				wk		
Idiopathic thrombosis (first episode)						
1	M/58	Leiomyosarcoma	T1N0M0	8	Local pain, tumor	Surgical biopsy
2	F/59	Glioblastoma of brain		8	Neurologic deficits	CT scan
3	M/63	Adenocarcinoma of colon	T4N4M1	21	Jaundice, weight loss	Colonoscopy, biopsy
4	M/75	Adenocarcinoma of pancreas	T4N2M1	21	Jaundice, anorexia, weight loss	CT scan, surgical biopsy
5	F/58	Adenocarcinoma of breast	T1N1M0	73	Breast node	Mammography, surgical biopsy
Recurrent idiopathic thrombosis						
6	M/73	Adenocarcinoma of pancreas	T4N1M1	13 (5)	Jaundice	CT scan, biopsy
7	F/49	Cystadenocarcinoma of ovary	T1N0M0	24 (7)	Pelvic pain	Laparoscopic biopsy
8	M/54	Adenocarcinoma of lung	T1N1M0	30 (13)	Coughing, weight loss, hemoptysis	Bronchoscopy, biopsy
9	M/65	Adenocarcinoma of prostate	T3N1M1	48 (5)	Lumbar back pain	Bone scan, biopsy
10	M/84	Glioblastoma of brain		48 (4)	Neurologic deficits	CT scan
11	F/72	Adenocarcinoma of stomach	T2N2M0	78 (34)	Abdominal pain, weight loss	Gastroscopy, biopsy
Secondary thrombosis						
12	F/76	Adenocarcinoma of uterus	T1N0M0	47	Postmenopausal blood loss	Colposcopic biopsy
13	M/74	Adenocarcinoma of prostate	T2N0M0	78	Prostatism	Ultrasonography, biopsy

*For the group with recurrent thrombosis, the value in parentheses indicates the number of weeks between the recurrence and the diagnosis of cancer.

botic disease but found to have no abnormalities, has important advantages. Patients with secondary thrombosis, like those with idiopathic thrombosis, are hospitalized for anticoagulant treatment, allowing truly comparable initial screening for cancer and ensuring the same antithrombotic treatment in both groups.[30] Also, all study groups have the same disease, which minimizes other unrecognized potential biases.

Although an increased risk of subsequent cancer among patients with idiopathic venous thrombosis was demonstrated in this study, the precise clinical implications of these findings are not clear. Cancers that became overt during follow-up were mainly adenocarcinomas and involved the gastrointestinal, respiratory, and urogenital tracts, the brain, and the breast. Detecting these tumors at the time of referral for venous thrombosis would have required extensive diagnostic testing. The design of our study does not indicate whether occult cancers could have been detected by such tests. The potential benefit of early detection of such malignant tumors must be weighed against the morbidity, discomfort, and high costs associated with extensive investigations. To produce firm recommendations, randomized clinical trials are needed in which patients with idiopathic thrombosis are assigned to an extensive diagnostic workup for occult cancer or to no extra testing.

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