

PROGNOSIS OF CANCERS ASSOCIATED WITH VENOUS THROMBOEMBOLISM

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ABSTRACT

Background Little is known about the prognosis of cancer discovered during or after an episode of venous thromboembolism.

Methods We linked the Danish National Registry of Patients, the Danish Cancer Registry, and the Danish Mortality Files to obtain data on the survival of patients who received a diagnosis of cancer at the same time as or after an episode of venous thromboembolism. Their survival was compared with that of patients with cancer who did not have venous thromboembolism (control patients), who were matched in terms of type of cancer, age, sex, and year of diagnosis.

Results Of 668 patients who had cancer at the time of an episode of deep venous thromboembolism, 44.0 percent of those with data on the spread of disease (563 patients) had distant metastasis, as compared with 35.1 percent of 5371 control patients with data on spread (prevalence ratio, 1.26; 95 percent confidence interval, 1.13 to 1.40). In the group with cancer at the time of venous thromboembolism, the one-year survival rate was 12 percent, as compared with 36 percent in the control group ($P < 0.001$), and the mortality ratio for the entire follow-up period was 2.20 (95 percent confidence interval, 2.05 to 2.40). Patients in whom cancer was diagnosed within one year after an episode of venous thromboembolism had a slightly increased risk of distant metastasis at the time of the diagnosis (prevalence ratio, 1.23 [95 percent confidence interval, 1.08 to 1.40]) and a relatively low rate of survival at one year (38 percent, vs. 47 percent in the control group; $P < 0.001$).

Conclusions Cancer diagnosed at the same time as or within one year after an episode of venous thromboembolism is associated with an advanced stage of cancer and a poor prognosis. (N Engl J Med 2000;343:1846-50.)

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THE association between cancer and venous thrombosis was first recognized more than 100 years ago¹ by Trousseau.² Modern studies have consistently found a significantly increased risk of a diagnosis of cancer after an episode of venous thromboembolism, particularly within the first six months after the episode.³⁻¹¹ However, it is not clear whether this relation has implications for the clinical course of cancer in patients with venous thromboembolism. In addition, except for a case series of 84 patients and a secondary analysis of one diagnostic trial,^{12,13} little is known about the prognosis of patients with cancer discovered at the time of or after a thromboembolic event.

To investigate this question, we conducted a follow-up study, using population-based data from the Danish National Registry of Patients, the Danish Cancer Registry, and the Danish Mortality Files. We examined the association between a history of venous thromboembolism and the extent of disease at the time of the diagnosis of cancer. We also compared the survival of patients with cancer and venous thromboembolism with the survival of patients with cancer who did not have venous thromboembolism.

METHODS

Study Design

The study was approved by the Danish data-protection board. The Danish National Registry of Patients¹⁴ includes information about all patients admitted to nonpsychiatric hospitals in Denmark. We searched this registry for the period from January 1, 1977, to December 31, 1992, for patients who had either deep venous thrombosis in the leg or pulmonary embolism (codes 451.00 and 450.99, respectively, in the *International Classification of Diseases, 8th revision*)¹⁵ during at least one hospitalization (63,196 patients). By linking this information with data from the Danish Cancer Registry, we excluded patients thought not to have primary (idiopathic) thrombosis or pulmonary embolism¹⁰ — namely, those who had received a diagnosis of cancer (other than nonmelanoma skin cancer) before the thromboembolic event (11,313 patients), had undergone surgery within six months before the thromboembolic event (13,735), had been pregnant or had given birth within nine months before or three months after the thromboembolic event (242), or had received a secondary diagnosis of venous thromboembolism in the discharge record (10,585). After these exclusions, 27,321 patients with a record of primary venous thromboembolism (43.2 percent of the initial 63,196) remained in the study.

Since 1943 the Danish Cancer Registry¹⁶ has kept records of all patients in Denmark with malignant neoplasms, as well as benign tumors of the central nervous system and papillomas of the urinary system. In this registry, the extent of spread of the tumor at the time of diagnosis is classified as localized, regional, metastatic to distant sites, or unknown. All the records of the 27,321 patients identified as having primary venous thromboembolism were linked to the Danish Cancer Registry to identify those who, before December 31, 1993, had received a diagnosis of cancer at the time of or after the thromboembolic event (3135 patients). Three cohorts were established according to the interval between the diagnosis of venous thromboembolism and the diagnosis of cancer: patients in whom cancer was diagnosed while they were hospitalized for primary venous thromboembolism (668), patients in whom cancer was diagnosed within the first year after hospitalization for venous thromboembolism (560), and patients in whom cancer was diagnosed 1 to 17 years after hospitalization for venous thrombo-

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embolism (1907). The patients in the second and third groups were described in an earlier report on the risk of cancer after venous thromboembolism.¹⁰

For each of the three cohorts of patients with venous thromboembolism, a group of patients who had not been hospitalized for venous thromboembolism was randomly selected from the Danish Cancer Registry and served as a control group. For each patient with cancer and venous thromboembolism, 10 control patients were matched according to the type of cancer (at the three-digit coding level of the *International Classification of Diseases, 7th revision*),¹⁷ sex, age at the time of the diagnosis of cancer (in 10-year age groups), and the year of the diagnosis of cancer (5-year calendar periods). One patient in the cohort with a diagnosis of cancer 1 to 17 years after venous thromboembolism was excluded because it was not possible to find any matched control subjects. For 9 other patients, fewer than 10 controls were found. Thus, for the patients with a diagnosis of cancer at the time of a thromboembolic event, 6668 controls were found; for those with a diagnosis of cancer within 1 year after a thromboembolic event, 5586 controls were found; and for those with a diagnosis of cancer 1 to 17 years after a thromboembolic event, 19,042 controls were found. All the patients, both those with venous thromboembolism and those without it, were linked through the patient's civil registration number (which is unique to each resident of Denmark) to the Danish Mortality Files, which have been in operation since 1943.

Statistical Analysis

The proportion of patients with cancer and venous thromboembolism who had distant metastasis was compared with the proportion of the controls who had distant metastasis by calculating the prevalence ratio (the proportion of patients with distant metastasis and venous thromboembolism divided by the proportion of patients with distant metastasis but without venous thromboembolism) and associated 95 percent confidence interval. All the patients, both those with and those without venous thromboembolism, were followed from the date of the diagnosis of cancer until death or December 31, 1995, whichever came first. To summarize the survival of the patients with cancer over time, we used Kaplan-Meier analysis to construct survival curves, which were then compared with the results of log-rank tests. We used standard chi-square tests to assess the probability of survival at one year among the patients with venous thromboembolism as compared with the control patients. Finally, proportional-hazards regression analyses were used to compare the risk of death among the patients with venous thromboembolism with that among the controls, with calculation of the hazard ratios (mortality ratios) and associated 95 percent confidence intervals. Statistical tests were performed with use of SAS software (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Table 1 summarizes the demographic characteristics and types of cancer in the three cohorts of patients with cancer and venous thromboembolism. Overall, the most common sites of cancer were the lung, the prostate, the colon and rectum, the breast, and the pancreas. The proportion of patients with cancer and venous thromboembolism for whom information on the spread of tumor was available was similar to that of the control patients (Table 2). Among the patients in whom cancer was diagnosed at the time of an episode of venous thromboembolism, 44.0 percent had distant metastases, as compared with 35.1 percent of the matched control patients (prevalence ratio, 1.26; 95 percent confidence interval, 1.13 to 1.40) (Table 2). Among the patients in whom cancer was diagnosed within the first year after a thromboembolic event,

TABLE 1. CHARACTERISTICS AND CANCER SITES AMONG THE PATIENTS IN WHOM CANCER WAS DIAGNOSED AT THE TIME OF OR AFTER AN EPISODE OF VENOUS THROMBOEMBOLISM.*

CHARACTERISTIC	TIME OF DIAGNOSIS OF CANCER		
	AT THE TIME OF VENOUS THROMBOEMBOLISM	<1 YR AFTER VENOUS THROMBOEMBOLISM	1-17 YR AFTER VENOUS THROMBOEMBOLISM
No. of patients	668	560	1906†
Sex — M/F	305/363	317/243	1109/797
Age at cancer diagnosis — yr			
Mean	72	69	72
Range	15-100	19-94	22-97
Cancer type — no. (%)			
Lung	114 (17.1)	84 (15.0)	258 (13.5)
Prostate	46 (6.9)	64 (11.4)	144 (7.6)
Colon and rectum	54 (8.1)	39 (7.0)	158 (8.3)
Breast	24 (3.6)	24 (4.3)	150 (7.9)
Pancreas	64 (9.6)	44 (7.9)	68 (3.6)
Bladder	14 (2.1)	19 (3.4)	120 (6.3)
Stomach	35 (5.2)	20 (3.6)	71 (3.7)
Kidney	53 (7.9)	17 (3.0)	47 (2.5)
Leukemia	22 (3.3)	14 (2.5)	58 (3.0)
Ovary	35 (5.2)	27 (4.8)	28 (1.5)
Brain	30 (4.5)	17 (3.0)	36 (1.9)
Non-Hodgkin's lymphoma	14 (2.1)	14 (2.5)	34 (1.8)
Uterus	13 (1.9)	11 (2.0)	33 (1.7)
Liver	19 (2.8)	11 (2.0)	15 (0.8)
Cervix	13 (1.9)	10 (1.8)	18 (0.9)
Multiple myeloma	11 (1.6)	3 (0.5)	26 (1.4)
Esophagus	2 (0.3)	7 (1.2)	29 (1.5)
Other	105 (15.7)	135 (24.1)	613 (32.2)

*Because of rounding, not all percentages total 100.

†One patient in this group was excluded because no matched controls could be found.

39.6 percent had distant metastases, as compared with 32.1 percent of the matched controls (prevalence ratio, 1.23; 95 percent confidence interval, 1.08 to 1.40). In contrast, the proportion of patients with distant metastasis among those in whom cancer was diagnosed more than one year after a thromboembolic event was similar to that of the controls (prevalence ratio, 1.04; 95 percent confidence interval, 0.94 to 1.14).

Figure 1 shows the survival curves for patients in whom cancer was diagnosed at the time of an episode of primary venous thromboembolism and the matched control patients. Of the former, only 12 percent were alive at one year, in contrast to 36 percent of the control group (P<0.001). The mortality ratio was 2.46 (95 percent confidence interval, 2.25 to 2.68) for the first year of follow-up and 2.20 (95 percent confidence interval, 2.05 to 2.40) for the entire follow-up period.

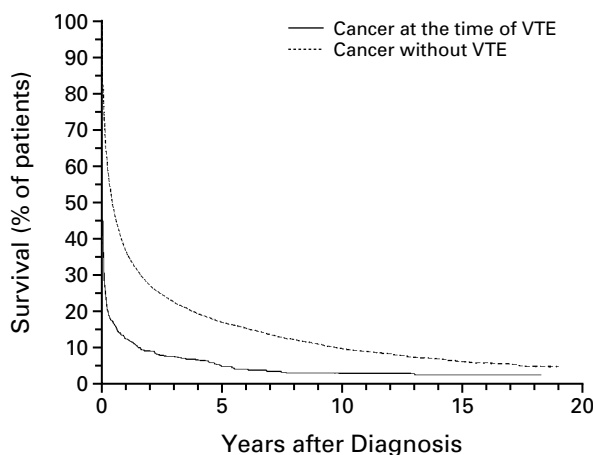
Patients in whom cancer was diagnosed within one year after an episode of primary venous thromboembolism also had a relatively poor prognosis (Fig. 2); 38 percent of them were alive at one year, as compared with 47 percent of the controls (P<0.001). The mortality ratio was 1.35 (95 percent confidence interval, 1.20 to 1.50) for the first year of follow-up and 1.30 (95 percent confidence interval, 1.18 to 1.42) for the entire follow-up period.

TABLE 2. EXTENT OF THE SPREAD OF CANCER, ACCORDING TO THE PRESENCE OR ABSENCE OF VENOUS THROMBOEMBOLISM.*

EXTENT OF SPREAD	CANCER AT SAME TIME AS VENOUS THROMBOEMBOLISM			CANCER <1 Yr AFTER VENOUS THROMBOEMBOLISM			CANCER 1–17 Yr AFTER VENOUS THROMBOEMBOLISM		
	PATIENTS (N=668)	CONTROLS (N=6668)	PREVALENCE RATIO (95% CI)	PATIENTS (N=560)	CONTROLS (N=5586)	PREVALENCE RATIO (95% CI)	PATIENTS (N=1906)†	CONTROLS (N=19,042)	PREVALENCE RATIO (95% CI)
	no. (%)			no. (%)			no. (%)		
Patients with data on spread	563 (84.3)	5371 (80.5)		465 (83.0)	4681 (83.8)		1516 (79.5)	15,712 (82.5)	
No spread	183 (32.5)	1835 (34.2)		166 (35.7)	2008 (42.9)		785 (51.8)	8,130 (51.7)	
Regional spread	132 (23.4)	1652 (30.8)		115 (24.7)	1171 (25.0)		371 (24.5)	3,982 (25.3)	
Distant metastasis	248 (44.0)	1884 (35.1)	1.26 (1.13–1.40)	184 (39.6)	1502 (32.1)	1.23 (1.08–1.40)	360 (23.7)	3,600 (22.9)	1.04 (0.94–1.14)

*The prevalence ratio is the proportion of patients with distant metastasis and venous thromboembolism divided by the proportion of patients with distant metastasis and no venous thromboembolism (i.e., control patients with distant metastasis). Because of rounding, not all percentages total 100. CI denotes confidence interval. Percentages for patients with data are of the entire group of patients. Percentages for patients in the extent-of-spread categories are of patients with data.

†One patient in this group was excluded because no matched controls could be found.



NO. AT RISK				
Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

Figure 1. Survival Curves for Patients with a Diagnosis of Cancer at the Time of Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.

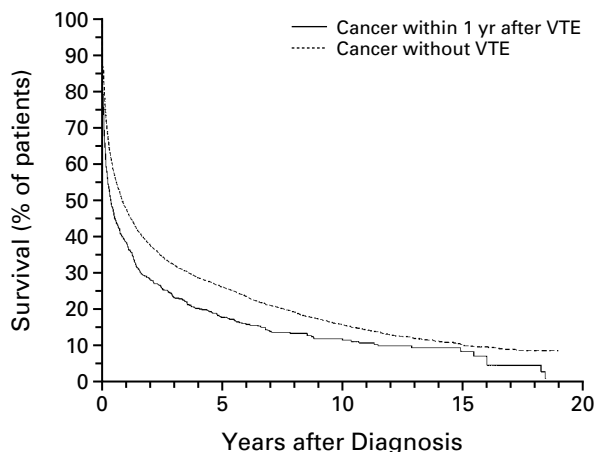
The control patients, who did not have venous thromboembolism, were matched with the patients who had venous thromboembolism according to cancer type, sex, age, and year of diagnosis. $P < 0.001$ for the overall curves, by the log-rank test.

The survival curves for the entire follow-up period for the patients in whom cancer was diagnosed more than one year after an episode of venous thromboembolism were only slightly (though significantly) different from those of the matched control patients (data not shown). In the former group, the rate of survival at one year was 53 percent, as compared with 55 percent in the control group ($P = 0.10$), and the mortality ratio was 1.08 (95 percent confidence interval, 1.00

to 1.15) for the first year. The mortality ratio for the entire follow-up period was 1.10 (95 percent confidence interval, 1.04 to 1.16).

DISCUSSION

In this analysis of more than 34,000 patients with cancer, those in whom cancer was diagnosed within one year after an episode of venous thromboembolism were more likely to have advanced disease and a



NO. AT RISK					
Cancer within 1 yr after VTE	560	72	37	7	
Cancer without VTE	5586	1181	419	106	

Figure 2. Survival Curves for Patients with a Diagnosis of Cancer within One Year after Venous Thromboembolism (VTE) and Matched Control Patients with Cancer.

The control patients, who did not have venous thromboembolism, were matched with the patients who had venous thromboembolism according to cancer type, sex, age, and year of diagnosis. $P < 0.001$ for the overall curves, by the log-rank test.

poor prognosis than patients with cancer who did not have venous thromboembolism. Survival was particularly poor when the diagnosis of cancer was concurrent with the thromboembolic event. These findings, which could not be explained by the type or extent of cancer or by age or sex, indicate that venous thromboembolism in a patient with cancer suggests the presence of advanced and aggressive disease.

Our findings agree with the very limited data available on the prognosis of patients who have both cancer and venous thromboembolism. In a case series without controls, Prandoni et al. found that 54 of 84 patients in whom cancer was diagnosed at the time of or after an episode of venous thromboembolism died within an eight-year follow-up period.¹² In a secondary analysis of a diagnostic trial involving 399 patients with pulmonary embolism (73 of whom had cancer), the most frequent cause of death in the year after the embolic event was cancer (35 percent).¹³

It seems unlikely that complications of venous thromboembolism can account entirely for the increased mortality among the patients in our study who had thromboembolic events. There are indications that the pathways of coagulation and fibrinolysis intersect with those of tumor growth.^{18,19} There is also evidence that anticoagulant therapy can reduce the incidence of cancer and the rate of death due to cancer. In a recent trial in patients with recurrent venous thromboembolism, the incidence of cancer, over a mean fol-

low-up period of 8.1 years, was lower among subjects randomly assigned to 6 months of anticoagulation with warfarin than among those randomly assigned to only 6 weeks of anticoagulation.¹¹ An earlier trial found that anticoagulant therapy may delay the progression of disease and improve survival in patients with small-cell lung cancer,²⁰ and another found that the rate of death due to cancer among patients with cancer who received low-molecular-weight heparin was 65 percent lower than among patients given standard heparin treatment.²¹ However, another trial failed to show a similar effect.²²

These findings raise the question of whether patients with venous thromboembolism and cancer should receive more aggressive anticoagulation than other patients with thrombosis. Our data do not answer this question but may provide an impetus for further study. The relatively poor prognosis of cancer diagnosed soon after venous thromboembolism also suggests that more aggressive therapy would be appropriate in such patients.

Our study has both strengths and limitations. We used nationwide, population-based registries with complete follow-up data. Clinicians caring for patients with venous thromboembolism could have increased their surveillance for cancer in these patients because of the known association with cancer. However, if anything, this should have resulted in earlier diagnosis in the patients with venous thromboembolism

and hence better survival. The survival curve for the patients in whom cancer was diagnosed more than one year after venous thromboembolism was similar to that for the matched patients without venous thromboembolism; this finding speaks against such a bias, which would have resulted in lower mortality in the former group.

A limitation of our data is the lack of clinical detail other than the relatively broad classification according to the extent of spread of disease, which was missing in 15 to 20 percent of the patients. In addition, it is well known that diagnoses at discharge are not entirely accurate; venous thromboembolism may have been misclassified in 10 to 20 percent of the cases listed in Scandinavian hospital discharge registries.¹¹ This lack of specificity may have led us to underestimate the differences between the patients with venous thromboembolism and those without it.

In conclusion, our data show that cancer discovered at the same time as or shortly after venous thromboembolism tends to be advanced, and the prognosis tends to be poor. These findings may have implications for the clinical care of patients with cancer.

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