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## THE RISK OF A DIAGNOSIS OF CANCER AFTER PRIMARY DEEP VEIN THROMBOSIS OR PULMONARY EMBOLISM

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### ABSTRACT

**Background** Several small studies have indicated an association between deep venous thrombosis or pulmonary embolism and a subsequent diagnosis of cancer, but the subject is controversial.

**Methods** We conducted a nationwide study of a cohort of patients with deep venous thrombosis or pulmonary embolism that was drawn from the Danish National Registry of Patients for the years 1977 through 1992. The occurrence of cancer in the cohort was determined by linkage to the Danish Cancer Registry. The expected number of cancer cases was estimated on the basis of national age-, sex-, and site-specific incidence rates.

**Results** A total of 15,348 patients with deep venous thrombosis and 11,305 patients with pulmonary embolism were identified. We observed 1737 cases of cancer in the cohort with deep venous thrombosis, as compared with 1372 expected cases (standardized incidence ratio, 1.3; 95 percent confidence interval, 1.21 to 1.33). Among the patients with pulmonary embolism, the standardized incidence ratio was 1.3, with a 95 percent confidence interval of 1.22 to 1.41. The risk was substantially elevated only during the first six months of follow-up and declined rapidly thereafter to a constant level slightly above 1.0 one year after the thrombotic event. Forty percent of the patients given a diagnosis of cancer within one year after hospitalization for thromboembolism had distant metastases at the time of the diagnosis of cancer. There were strong associations with several cancers, most pronounced for those of the pancreas, ovary, liver (primary hepatic cancer), and brain.

**Conclusions** An aggressive search for a hidden cancer in a patient with a primary deep venous thrombosis or pulmonary embolism is not warranted. (N Engl J Med 1998;338:1169-73.)

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THE association between cancer and venous thromboembolism is well known.<sup>1</sup> Over 100 years ago, Trousseau reported cases of episodic migratory thrombophlebitis in patients with cancer.<sup>2</sup> The pathogenic mechanisms for the association include hypercoagulability due to activation of clotting by tumor cells, vessel-wall injury, and stasis.<sup>1</sup> Occasionally, the thromboembolic event occurs before the diagnosis of cancer, and it has been suggested that deep venous thrombosis may be a predictor of the subsequent diagnosis of cancer; this idea is controversial, however. Several studies have indicated an association,<sup>3-7</sup> but others have not.<sup>8,9</sup>

Two recent studies have shown a significant association between primary venous thrombosis and a subsequent diagnosis of cancer. This link seems particularly strong in patients with recurrent deep venous thrombosis. Prandoni et al. followed 145 patients over a period of two years and found 11 cases of cancer, as compared with 2 cases among 105 patients with secondary venous thrombosis, representing an odds ratio of 2.3.<sup>6</sup> They also found that the incidence of cancer in patients with recurrent idiopathic venous thrombosis was higher than in patients without this condition, with an odds ratio of 4.3.<sup>6</sup> In a hospital-based study of 1183 patients with deep venous thrombosis,<sup>5</sup> Nordström and coworkers found five times the risk of cancer in these patients as compared with the general population during the first six months of follow-up but no increased risk during later follow-up.

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The existing studies are thus limited in size, and few are population-based, which limits the general applicability of the results. To assess whether this association has important clinical implications, we determined the risk of cancer after the diagnosis of primary deep venous thrombosis and pulmonary embolism, using population-based data from the Danish National Registry of Patients and the Danish Cancer Registry.

## METHODS

The Danish National Registry of Patients was established in 1977, and 99.4 percent of all discharges from Danish medical hospitals are recorded there.<sup>10</sup> Recorded information includes the civil registration number, which is unique to every Danish citizen, the dates of admission and discharge, the surgical procedures performed, and up to 20 discharge diagnoses, classified according to the Danish version of the *International Classification of Diseases, 8th Revision* (ICD-8).<sup>11</sup> It is possible to obtain the full discharge history of a patient by linking discharge records to the civil registration number. All persons listed in the National Registry of Patients from January 1, 1977, to December 31, 1992, were included in the study if they had a diagnosis of deep venous thrombosis in the lower limb or pulmonary embolism (ICD-8 codes 451.00 and 450.99) during at least one hospitalization. Deep venous thrombosis and pulmonary embolism were defined as primary in the absence of the following: surgery during the six months before the diagnosis of thromboembolism (determined on the basis of surgical-procedure codes), a diagnosis of venous thrombosis or pulmonary embolism that was not the primary diagnosis in the discharge record, preexisting cancer, or pregnancy (ICD-8 codes 630.00 to 678.00). All cases of venous thrombosis and pulmonary embolism involving any of these circumstances were excluded from the analyses because they were thought to be secondary. Subcohorts were defined according to age at the time of entry (<60, 60 to 74, and >74 years of age) and according to whether there was recurrence of the thromboembolic event. A recurrent episode was defined as two or more diagnoses of deep venous thrombosis or pulmonary embolism separated by at least three months.

All members of the study cohort were linked through their civil registration numbers to the nationwide Cause of Death Registry and the Cancer Registry, which have kept records of all incident cases of cancer in Denmark since 1943, including benign brain tumors and papillomas of the urinary tract. Cancers are classified according to the modified Danish version of the *International Classification of Diseases, 7th Revision*.<sup>12</sup> The registration is based on notification forms that are filled in by hospital departments (including departments of pathology and forensic medicine) and practicing physicians whenever a case of cancer is diagnosed or found at autopsy and whenever there are changes in an initial diagnosis. The cases recorded manually are supplemented by unreported cases revealed by the computerized linkages to the death-certificate file and the National Registry of Patients. The entire process is supervised by medical doctors. Ambiguous or contradictory information, either within a notification form or between forms, leads to queries in approximately 10 percent of the notifications received. Comprehensive evaluation has shown that the Registry is 95 to 98 percent complete and valid.<sup>13</sup>

Each patient was followed for the occurrence of cancer from the date of the first hospitalization with deep venous thrombosis or pulmonary embolism until the date of death or December 31, 1993, whichever came first.

### Statistical Analysis

The expected number of cases of cancer was calculated on the basis of national incidence rates obtained from the Cancer Registry according to sex, age, and calendar period in five-year inter-

vals. Multiplying the number of person-years of observation by the incidence rates yielded the number of cancer cases that would be expected if patients with deep venous thrombosis and pulmonary embolism had the same risk of cancer as the general population. Confidence intervals for the standardized incidence ratio — i.e., the ratio of observed to expected cancers — were computed on the basis of the assumption that the observed number of cases in a specific category follows a Poisson distribution. Exact limits were used when the observed number was less than 10; otherwise, Byar's approximation was used.<sup>14</sup>

## RESULTS

We identified 15,348 patients with deep venous thrombosis and 11,305 patients with pulmonary embolism, each cohort consisting of approximately similar proportions of men and women. In the two cohorts combined, 33 percent were below the age of 60 years at the time of the thromboembolic episode, 37 percent were 60 to 74 years old, and 30 percent were 75 or older. On average, the patients with deep venous thrombosis were followed for longer periods than the patients with pulmonary embolism (6.1 vs. 3.6 years).

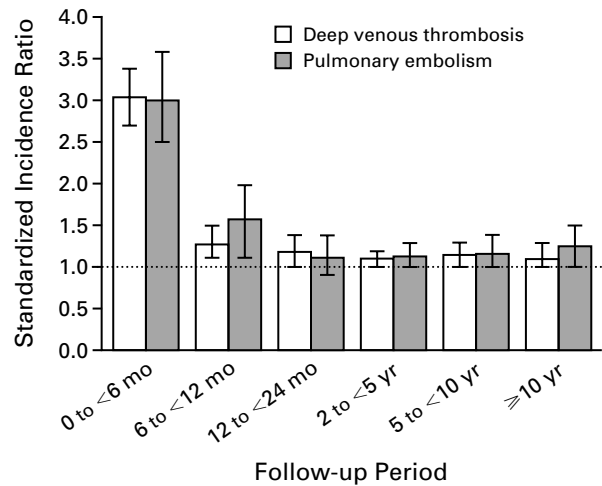
Standardized incidence ratios of 1.3 for all types of cancer were observed in both the cohort with deep venous thrombosis and the cohort with pulmonary embolism, based on 1737 observed and 1372 expected cases among the patients with deep venous thrombosis (95 percent confidence interval for the standardized incidence ratio, 1.21 to 1.33) and 730 observed and 556 expected cases among those with pulmonary embolism (95 percent confidence interval for the standardized incidence ratio, 1.22 to 1.41). There were no particular differences in risks between men and women.

The risk for both cohorts was three times the expected level during the first six months of follow-up, after which the risk declined to a constant level of slightly more than 1.0 one year after the thrombotic event and throughout the study period (Fig. 1).

Table 1 shows the risks of various types of cancer in the two cohorts during the first year of follow-up. The overall risk of the subsequent diagnosis of the neoplasms listed in Table 1 was 2.2 for the group with deep venous thrombosis and 2.3 for the group with pulmonary embolism. For both cohorts there were strong associations with certain types of cancer — in particular, cancer of the pancreas, ovary, liver (primary hepatic cancer), and brain. We found no association in either cohort with a few types — namely, cancer of the breast, urinary bladder, and rectum, and malignant melanoma. Of the 560 cases of cancer that were diagnosed during the first year of follow-up, we had no information about the extent of the disease at the time of diagnosis in 95 cases (17 percent). Of the remaining 465 cases, 184 (40 percent) had distant metastases, 115 (25 percent) had regional spread of the disease, and 166 (36 percent) had no spread.

During the period of follow-up beyond one year, the overall occurrence of cancer was slightly though significantly increased in both cohorts (Table 2). However, this moderate overall excess was evenly distributed among various cancer sites, and no significant excess persisted for the sites (pancreas, ovary, liver, and brain) that showed the strongest association with both types of venous thromboembolism during the first year of follow-up. After one year of follow-up, only for leukemia was the lower confidence limit of the standardized incidence ratio above 1.0 among the patients with deep venous thrombosis. We did not find any substantial differences between smoking-related cancers and those without a known relation to smoking.

In the subcohort of 3762 patients with recurrent episodes of deep venous thrombosis or pulmonary embolism, the risk of all types of cancer combined was 3.2 (95 percent confidence interval, 2.0 to 4.8) during the first year of follow-up and 1.3 (95 percent confidence interval, 1.2 to 1.5) thereafter. Among the remaining 22,891 patients with only one episode



**Figure 1.** Risk of Cancer in Relation to the Length of the Follow-up Period in 26,653 Patients with Primary Deep Venous Thrombosis or Pulmonary Embolism. The I bars represent 95 percent confidence intervals.

**TABLE 1.** STANDARDIZED INCIDENCE RATIOS (SIRs) FOR SELECTED CANCERS AMONG PATIENTS FOLLOWED FOR ONE YEAR AFTER HOSPITALIZATION FOR PRIMARY DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM.

SITE OR TYPE OF CANCER (ICD-7 CODE)*	DEEP VENOUS THROMBOSIS			PULMONARY EMBOLISM		
	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†
All malignant neoplasms (140–205)‡	390	181.5	2.1 (1.9–2.4)	170	74.1	2.3 (2.0–2.7)
Cancers with strong association in both cohorts						
Pancreas (157)	35	5.8	6.0 (4.2–8.4)	9	2.4	3.8 (1.7–7.2)
Ovary (175)	16	3.1	5.2 (2.9–8.3)	11	1.4	7.9 (4.0–14.4)
Liver, primary (155.0)	6	1.9	3.2 (1.2–6.9)	5	0.8	6.3 (2.1–15.3)
Brain (193)	10	3.3	3.0 (1.5–5.6)	7	1.4	5.0 (2.0–10.5)
Non-Hodgkin's lymphoma (200, 202)	10	3.5	2.9 (1.4–5.2)	4	1.4	2.9 (0.8–7.2)
Esophagus (150)	5	1.8	2.8 (0.9–6.6)	2	0.7	2.9 (0.3–10.4)
Kidney (180)	12	5.0	2.4 (1.2–4.1)	5	2.1	2.4 (0.8–5.6)
Leukemia (204)	11	4.4	2.5 (1.2–4.4)	3	1.8	1.7 (0.3–4.9)
Cancers with strong association in one cohort						
Prostate (177)	58	13.7	4.2 (3.2–5.5)	6	5.5	1.1 (0.4–2.4)
Corpus uteri (172)	10	3.4	2.9 (1.4–5.4)	1	1.5	0.7 (0.0–3.6)
Lung (162)	43	24.4	1.8 (1.3–2.4)	41	10.3	4.0 (2.9–5.4)
Cancers with weak or no association						
Stomach (151)	14	7.0	2.0 (0.7–3.3)	6	2.8	2.1 (0.8–4.6)
Colon (153)	26	16.3	1.6 (1.0–2.3)	13	6.5	2.0 (1.1–3.4)
Breast (170)	18	14.3	1.3 (0.7–2.0)	6	6.1	1.0 (0.4–2.2)
Urinary bladder (181)	12	11.9	1.0 (0.5–1.8)	7	4.8	1.5 (0.6–3.0)
Rectum (154)	6	9.1	0.7 (0.2–1.4)	6	3.7	1.6 (0.6–3.5)
Malignant melanoma (190)	1	3.0	0.3 (0.0–1.9)	0	1.2	0.0 (0.0–3.1)

\*The sites and types of cancer are from the modified version of the *International Classification of Diseases, 7th Revision* (ICD-7) found in Storm et al.<sup>12</sup>

†P<0.001 by the test for homogeneity of the standardized incidence ratios for the sites and types of cancer listed. CI denotes confidence interval.

‡Because all cancer sites and types are not shown, the numbers of observed and expected cases for the individual sites and types do not add up to the total numbers.

**TABLE 2.** STANDARDIZED INCIDENCE RATIOS (SIRs) FOR SELECTED CANCERS AMONG PATIENTS FOLLOWED FOR 2 TO 17 YEARS AFTER HOSPITALIZATION FOR PRIMARY DEEP VEIN THROMBOSIS OR PULMONARY EMBOLISM.

SITE OR TYPE OF CANCER (ICD-7 CODE)*	DEEP VEIN THROMBOSIS			PULMONARY EMBOLISM		
	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)†	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)‡
All malignant neoplasms (140–205)§	1347	1190.4	1.1 (1.1–1.2)	560	482.4	1.2 (1.1–1.3)
Pancreas (157)	50	36.1	1.4 (1.0–1.8)	18	14.7	1.2 (0.7–1.9)
Ovary (175)	21	18.6	1.1 (0.7–1.7)	7	7.8	0.9 (0.4–1.8)
Liver, primary (155.0)	11	12.1	0.9 (0.5–1.6)	4	4.9	0.8 (0.2–2.1)
Brain (193)	26	21.6	1.2 (0.8–1.8)	10	8.7	1.1 (0.6–2.1)
Non-Hodgkin's lymphoma (200, 202)	22	24.4	0.9 (0.6–1.4)	12	9.8	1.2 (0.6–2.1)
Esophagus (150)	20	12.4	1.6 (1.0–2.5)	9	4.9	1.8 (0.8–3.5)
Kidney (180)	25	32.5	0.8 (0.5–1.1)	22	13.2	1.7 (1.0–2.5)
Leukemia (204)	45	28.7	1.6 (1.1–2.1)	13	11.6	1.1 (0.6–1.9)
Prostate (177)	102	95.2	1.1 (0.9–1.3)	42	39.0	1.1 (0.8–1.5)
Corpus uteri (172)	26	21.0	1.2 (0.8–1.8)	7	8.9	0.8 (0.3–1.6)
Lung (162)	184	157.5	1.2 (1.0–1.4)	74	64.4	1.1 (0.9–1.4)
Stomach (151)	45	40.3	1.1 (0.8–1.5)	26	16.3	1.6 (1.0–2.3)
Colon (153)	114	106.5	1.1 (0.9–1.3)	44	43.0	1.0 (0.7–1.4)
Breast (170)	105	90.8	1.2 (0.9–1.4)	45	37.6	1.2 (0.9–1.6)
Urinary bladder (181)	82	80.3	1.0 (0.8–1.3)	42	32.4	1.3 (0.9–1.8)
Rectum (154)	53	57.6	0.9 (0.7–1.2)	25	23.3	1.1 (0.7–1.6)
Malignant melanoma (190)	27	20.3	1.3 (0.9–1.9)	8	8.1	1.0 (0.4–2.0)

\*The sites and types of cancer are from the modified version of the *International Classification of Diseases, 7th Revision* (ICD-7) found in Storm et al.<sup>12</sup>

†P=0.22 by the test for homogeneity of the standardized incidence ratios of the sites and types of cancer listed. CI denotes confidence interval.

‡P=0.79 by the test for homogeneity of the standardized incidence ratios of the sites and types of cancer listed. CI denotes confidence interval.

§Because all sites and types of cancer are not shown, the numbers of observed and expected cases for the individual sites and types do not add up to the total numbers.

of deep vein thrombosis or pulmonary embolism, the overall risk of cancer was 2.2 (95 percent confidence interval, 2.0 to 2.4) during the first year and 1.1 (95 percent confidence interval, 1.1 to 1.2) during the subsequent years. The estimated risk of all types of cancer during the first year of follow-up decreased with increasing age at first discharge with venous thromboembolism (<60 years: standardized incidence ratio, 3.6; 95 percent confidence interval, 2.9 to 4.2; 60 to 74 years: standardized incidence ratio, 2.2; 95 percent confidence interval, 1.9 to 2.5; >74 years: standardized incidence ratio, 1.8; 95 percent confidence interval, 1.6 to 2.1).

## DISCUSSION

We evaluated the association between deep vein thrombosis or pulmonary embolism and a subsequent diagnosis of cancer in a large cohort and found an increased risk of several types of cancer, almost entirely during the first year of follow-up. In particular, there was a strong association between thrombosis and cancer of the pancreas, ovary, liver, and brain during the first year. The magnitude of risk was similar to that observed in previous studies.<sup>5,6</sup> However, the rapid fall in the standardized incidence ratio after six months of follow-up strongly suggests that a thromboembolic event in patients later given a diagnosis of cancer is the result rather than the cause of

the cancer. If the thromboembolic event had contributed to causing the cancer, we would have expected an increasing risk with length of follow-up, because of the long latency period for most cancers. If, alternatively, common risk factors for thromboembolism and cancer had been present, we would have expected a constant excess risk over time.

The higher risk of cancer among patients less than 60 years of age and among patients with recurrent episodes of deep vein thrombosis or pulmonary embolism accords with the results of a recent study.<sup>6</sup> These findings indicate that preclinical cancer has a larger role in thromboembolism among middle-aged patients than among older ones.

The large population we studied was well defined, and the follow-up almost complete, because the design relied on computerized registries with almost complete nationwide coverage. This gave us considerably more statistical precision than previous studies.<sup>5-7</sup> It is well known that discharge diagnoses vary in quality,<sup>15</sup> and some registered patients with deep vein thrombosis in their discharge records would not fulfill the criteria for thromboembolism. This would cause bias toward the null hypothesis. Our use of routine data might actually be a strength, since the study itself did not affect the diagnostic process and thus did not introduce bias due to surveillance in follow-up studies.<sup>15</sup>

The benefit of searching for cancer in a patient with a primary thrombotic event is difficult to assess.<sup>16</sup> In our cohort, most of the cancers that were found during the first year of follow-up were probably present at the time of the diagnosis of thromboembolism. The detection of some of these cancers would have required an extensive workup, and it is unclear whether early diagnosis would have changed the outcome. For several of the types of cancer, such as pancreas and liver cancers, early detection does not change the prognosis. Other cancers might be detected by simple methods.<sup>17</sup> In the group we studied, 26,600 persons would have had to be screened for the 304 excess cancers to be found during the first year of follow-up, and at least 40 percent of these patients would probably have had metastases at the time of diagnosis, as compared with 29 percent in a sex- and age-matched population of patients with the same types of cancer. Therefore, extensive cancer screening of patients with thromboembolism does not seem to be cost effective.<sup>5</sup> Extensive screening may cause several other problems, including discomfort and psychological stress.<sup>16</sup> Our results strongly support the pragmatic recommendation to use only simple methods of screening and to look for cancer in patients with signs and symptoms of cancer.<sup>7,18</sup>

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