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Deep venous thrombosis and occult malignancy: an epidemiological study

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Abstract

***Objective*—To determine the risk of subsequent cancer in patients with deep venous thrombosis confirmed by venography.**

***Design*—Follow up of all patients who had venography for suspected deep venous thrombosis during 1984-88. Patients were traced through a cancer registry up to 1 January 1991.**

***Subjects*—4399 patients who had phlebography in one hospital.**

***Setting*—General hospital in Malmö, Sweden, serving a population of 230 000.**

***Main outcome measure*—Number of cancers recorded.**

***Results*—4399 patients had venography for suspected deep venous thrombosis; 604 were known to have a malignancy at the time of venography and were excluded from further analysis. 1383 had deep venous thrombosis, 150 of whom subsequently developed cancer. 182 of the 2412 patients without thrombosis developed cancer.**

During the first six months after venography 66 patients with thrombosis developed malignancy compared with 37 patients without thrombosis ($P < 0{\cdot}0001$). 38 of the cancers in the deep venous thrombosis group were detected by history, physical examination, and laboratory tests. Three patients had postoperative or post-traumatic deep venous thromboses. Only two of the remaining patients would have benefited from early detection by extensive screening. After six months the incidence of cancer was identical in patients with and without thrombosis.

***Conclusion*—Deep venous thrombosis is associated with a significantly higher frequency of malignancy during the first six months after diagnosis. Malignancies can be found with simple clinical and diagnostic methods and extensive screening is not required.**

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Introduction

Although a large number of studies have investigated venous thromboembolism, information about its epidemiology is scarce. A prospective study of 366 patients in Malmö, Sweden, who had treatment after positive results on venography reported an overall incidence of deep venous thrombosis of 159 per 100 000 inhabitants per year.[1] At the time of diagnosis of deep venous thrombosis 71 patients (19%) had a known cancer and a further 19 (5%) developed cancer within the following year. Eight of the cancers were obvious at the time of diagnosis of the deep venous thrombosis and 11 were occult. In 1865 Trousseau described an association between deep venous thrombosis and malignancy,[2] but the relation remains controversial. It is generally accepted that cancer can cause deep venous thrombosis by compressing the veins as well as prothrombotic haematological changes. It is still unclear, however, whether deep venous thrombosis that is not associated with any obvious risk factor, so-called kryptogenic thrombosis, may be an early sign of occult cancer.

Only a few studies have looked at the frequency of occult malignancy in patients with deep venous thrombosis. We analysed the relation between deep venous thrombosis and subsequent malignancy in all patients who had venography for suspected deep venous thrombosis during 1984 to 1988 in Malmö. We wanted to know if patients with deep venous thrombosis had a higher risk of cancer and if so to determine the time elapsing between venography and diagnosis of cancer. We also studied the diagnostic methods used to detect the cancers.

Subjects and methods

All patients with suspected deep venous thrombosis in Malmö are referred to one hospital, where venography is done and treatment given. Venography was the only method used for diagnosing the deep venous thrombosis. The hospital serves a population of about 230 000.

We used the southern Swedish tumour registry to follow up all patients who had venography for suspected deep venous thrombosis (n=4399) during 1984 to 1988. The registry is population based and 95% to 99% of all cancer cases are reported depending on diagnosis.[3,4] Follow up was continued up to 1 January 1991. After the 604 (14%) patients who had cancer diagnosis before venography were excluded, 3795 patients remained. They consisted of 1383 patients with positive results and 2412 patients with negative results on venography according to the radiology department report.

We compared the observed number of cancers in patients with and without deep venous thrombosis with the expected number of cases, determined from the age, sex, and calendar year specific incidences for Malmö and person years at risk. Only the first cancer diagnosis for each person was considered, and the analysis was performed for all cancers as well as for specific types of cancer.

To investigate the relation between incidence of cancer and time from venography we divided the follow up period into two intervals: up to six months and more than six months. The groups were compared regarding some of the main diagnoses as well as the overall number of malignancies. We used routine hospital records to obtain data on the time elapsing between the deep venous thrombosis and the diagnosis of cancer, the extension of the deep venous thrombosis, how the cancer was detected, and the cancer type.

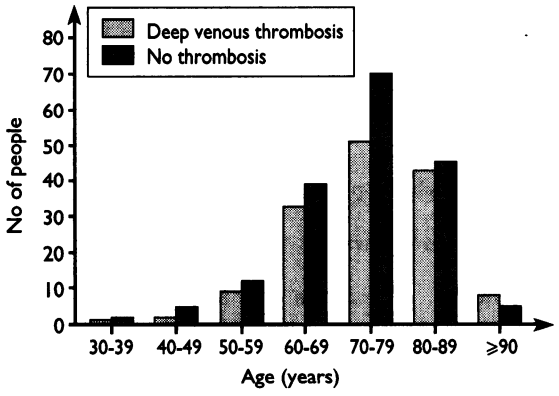

FIG 1—*Age distribution of patients with positive and negative results on venography who subsequently developed cancer*

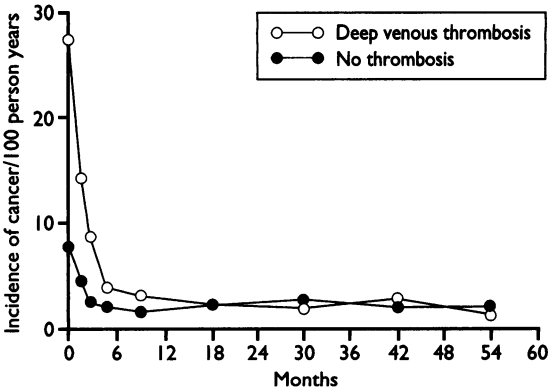

FIG 2—*Incidence of cancer per 100 person years by time after venography in patients with deep vein thrombosis and no thrombosis*

The standardised morbidity ratio was used to compare the cancer incidence in the study cohorts with that of the population of Malmö. Confidence intervals and hypothesis testing were based on the Poisson distribution. A stratified Mantel-Haenszel test was used to compare the incidence of cancer in patients with and without deep venous thrombosis according to person years and age.[5] We constructed 95% confidence intervals for the incidence rate ratio using the methods of Greenland and Robbins.[6]

Results

A total of 150 (11%) patients with deep venous thrombosis subsequently developed cancer. There were 79 men (mean age 73 (range 46-94) years) and 71 women (76 (30-97) years). Twenty one (14%) had postoperative or post-traumatic deep venous thromboses; the other cases were kryptogenic. Figure 1 shows the age distribution. One hundred and eighty two patients (7%), 86 men and 96 women, with negative results on venography developed cancer. The mean age was 72 years for both men (range 53-98 years) and women (33-97 years).

Figure 2 shows the crude incidence rate for malignant disease (cases per 100 person years) for patients with and without deep venous thrombosis. The incidence was high in the deep venous thrombosis group during the first six months, but fell later, becoming roughly equal to the incidence in the group without thrombosis. Cancer was detected within the first six months after phlebography in 66 (44%) patients with thrombosis and 37 (20%) patients without thrombosis. Seven of the 66 patients had postoperative or post-traumatic deep venous thrombosis.

Tables I and II show the observed and expected numbers of primary cancers after venography. For all

TABLE I—*Observed and expected number of all cancers and some of main primary cancers developing after positive results on venography (≤six months or > six months) compared with age and sex matched population from Malmö*

	0–6 Months				>6 Months			
Cancer	No of observed cases	No expected	Standardised morbidity ratio	(95% confidence interval)	No of observed cases	No expected	Standardised morbidity ratio	(95% confidence interval)
All cancer	66	12·52	5·27	(4·10 to 6·74)	84	83·07	1·01	(0·81 to 1·26)
Mouth and throat	0	0·23	0	(0 to 16·04)	2	1·64	1·22	(0·15 to 4·41)
Oesophageal and stomach	3	0·65	4·62	(0·95 to 13·49)	4	4·16	0·96	(0·26 to 2·46)
Intestinal	7	1·74	4·02	(1·62 to 8·29)	10	11·04	0·91	(0·43 to 1·67)
Liver	5	0·24	20·73	(6·73 to 48·36)	3	1·30	2·30	(0·48 to 6·73)
Gall bladder	5	0·29	17·09	(5·55 to 39·88)	1	1·81	0·55	(0·01 to 3·08)
Pancreas	6	0·47	12.73	(4·67 to 27·71)	2	3·37	0·59	(0·07 to 2·15)
Lung	5	1·25	4·0	(1·30 to 9·33)	8	7·82	1·02	(0·44 to 2·02)
Breast	4	1·02	3·92	(1·07 to 10·03)	9	6·66	1·35	(0·62 to 2·57)
Ovarian	5	1·56	3·21	(1·04 to 7·48)	3	4·11	0·73	(0·15 to 2·13)
Prostate	7	1·83	3·83	(1·54 to 7·89)	13	12·85	1·01	(0·54 to 1·73)
Kidney	1	0·41	2·41	(0·06 to 13·45)	4	2·44	1·64	(0·45 to 4·19)
Urinary bladder	0	0·66	0	(0 to 5·60)	7	4·65	1·50	(0·60 to 3·10)
Skin	3	0·82	3·66	(0·75 to 10·69)	8	6·28	1·27	(0·55 to 2·51)
Blood and lymphomas	6	0·78	7·69	(2·82 to 16·74)	4	5·11	0·78	(0·21 to 2·00)
Brain	3	0·49	6·07	(1·25 to 17·75)	1	2·60	0·38	(0·01 to 2·14)
	60	12·44			79	75·84		

TABLE II—*Observed and expected number of all cancers and some of main primary cancers developing after negative results of venography (≤six months or > six months) compared with age and sex matched population from Malmö*

Cancer	0–6 Months				>6 Months			
	No of observed cases	No expected	Standardised morbidity ratio	(95% confidence interval)	No of observed cases	No expected	Standardised morbidity ratio	(95% confidence interval)
All cancer	37	17·98	2·06	(1·46 to 2·86)	145	128·93	1·12	(0·95 to 1·33)
Mouth and throat	2	0·32	6·25	(0·76 to 22·58)	2	2·5	0·80	(0·10 to 2·89)
Oesophageal and stomach	1	0·90	1·11	(0·03 to 6·19)	10	6·1	1·64	(0·79 to 3·01)
Intestinal	4	2·42	1·65	(0·45 to 4·23)	18	16·99	1·06	(0·64 to 1·70)
Liver	0	0·33	0	(0 to 11·05)	6	1·80	3·33	(1·22 to 7·24)
Gall bladder	0	0·42	0	(0 to 8·72)	3	2·93	1·02	(0·21 to 2·99)
Pancreas	1	0·68	1.47	(0·04 to 8·21)	2	5·30	0·38	(0·05 to 1·36)
Lung	5	1·72	2·91	(0·94 to 6·78)	16	11·59	1·38	(0·81 to 2·28)
Breast	3	1·85	1·62	(0·33 to 4·74)	16	13·53	1·18	(0·69 to 1·95)
Ovarian	3	1·06	2·83	(0·58 to 8·27)	10	8·44	1·18	(0·57 to 2·18)
Prostate	4	2·12	1·88	(0·51 to 4·83)	18	15·92	1·13	(0·68 to 1·81)
Kidney	1	0·59	1·70	(0·04 to 9·46)	1	3·67	0·27	(0·01 to 1·52)
Urinary bladder	3	0·90	3·34	(0·69 to 9·77)	9	6·78	1·33	(0·61 to 2·52)
Skin	2	1·20	1·67	(0·20 to 6·02)	14	9·69	1·44	(0·79 to 2·42)
Blood and lymphomas	5	1·10	4·55	(1·48 to 10·61)	8	8·05	0·99	(0·43 to 1·96)
Brain	2	0·73	2·72	(0·33 to 9·84)	2	4·34	0·46	(0·06 to 1·66)

TABLE III—*Methods used for primary diagnosis of cancers by time after phlebography that cancer was detected*

	No (%) with deep venous thrombosis		No (%) with no thrombosis	
	≤6 Months (n=66)	>6 Months (n=84)	≤6 Months (n=37)	≥6 Months (n=145)
Medical history	23 (35)	40 (48)	14 (38)	70 (48)
Physical examination	19 (29)	19 (23)	12 (32)	33 (23)
Blood tests	11 (17)	14 (17)	7 (19)	25 (17)
Surgery	2 (3)	1 (1)	1 (3)	3 (2)
Necropsy	11 (17)	10 (12)	3 (8)	14 (10)

cancers the standardised morbidity ratio in the first six months was 5·3 (95% confidence interval 4·1 to 6·7, P<0·0001) for the deep venous thrombosis group and 2·1 (1·5 to 2·9, P<0·0001) for the group without thrombosis. After six months the standardised morbidity ratio was 1·0 (0·8 to 1·3, P=0·91) in the deep venous thrombosis group and 1·1 (1·0 to 1·3, P=0·15) in the group without thrombosis. Primary cancers in the liver, gall bladder and pancreas were over-represented in the thrombosis group during the first six months.

Comparison of the groups with and without deep venous thrombosis using five age strata gave a cancer incidence rate ratio of 2·5 (95% confidence interval 1·7 to 3·7, P<0·0001) for all cancers during the first six months.

In 84 patients the deep venous thrombosis was located above the knee and in 63 patients below the knee. One patient had a thrombosis of the superior vena cava, and two had a thrombosis in the upper arm. Forty two of the 66 patients who had cancer diagnosed within six months had thrombosis of the ileofemoral vein; thus thrombosis above the knee was not more common in patients with early cancer.

In most patients the cancer was diagnosed through routinely used tests (table III). Of the 66 patients who had cancer diagnosed within six months following the deep venous thrombosis, 38 showed symptoms and signs suggesting cancer when the deep venous thrombosis occurred.

Of the 28 patients who showed no signs of malignancy, 15 had ileofemoral deep venous thrombosis and 13 calf vein thrombosis. Again no relation was seen between larger thrombosis and cancer. Three of the 28 patients had postoperative or post-traumatic deep venous thrombosis but the remainder had no known risk factor. Of the 25 patients with no known risk factor, 14 had metastases (not detected until necropsy in seven), and five were aged over 75 years and had other conditions complicating treatment. Nineteen patients died during the follow up period.

Eleven of the patients with kryptogenic thrombosis had malignancies that could have been detected at an earlier stage if extensive screening procedures such as abdominal ultrasonography, computed tomography, and mammography, had been used. Further analysis of the cancers diagnosed after venography showed that two patients would have benefited from an earlier diagnosis: a 54 year old woman with ovarian cancer diagnosed two and a half months after venography and a 59 year old man with cancer of the kidneys diagnosed five months after venography. Extensive screening of about 1300 patients would thus have led to beneficial early detection of cancer in only two patients. We also studied patients' blood groups but no significant differences were found between the groups.

Discussion

We analysed the relation between deep venous thrombosis and subsequent cancer in all patients who had venography for suspected deep venous thrombosis during 1984-88. As only one department does venography in Malmö, the city is well suited to epidemiological studies.

OTHER STUDIES

In 1952 Wright was among the first to note that venous thrombosis can occur before signs or symptoms of cancer are evident.[7] Goldberg *et al* found an increased risk of occult cancer in the first two years after diagnosis of the deep venous thrombosis by impedance plethysmography,[8] and Naschitz *et al* reported that the incidence of occult cancer among patients with thromboembolism was 11·9%.[9] The thromboembolism preceded the diagnosis of cancer by three to 180 days. Ranft *et al* investigated 200 patients with deep venous thrombosis, confirmed by venography, and found cancer in 11·5%.[10] The number of malignant diseases rose with increasing age and they recommended screening for occult cancer from the age of 50. Our results suggest that the yield of such a programme would be low and hardly cost effective.

Monreal *et al* also suggested that the risk of cancer was increased in patients with idiopathic deep venous thrombosis.[11] Occult cancer was not looked for during the initial admission and as some patients had cancer diagnosed several months after discharge, a new study was done. In this small study the patients with deep venous thrombosis had blood tests, chest radiography, upper gastrointestinal endoscopy, abdominal ultrasonography and computed tomography. A malignancy was found in seven of 31 cases, some at an early stage.

Prandoni *et al* recently followed up 260 patients with symptomatic deep venous thrombosis diagnosed by venography over two years.[12] They found a significant

Clinical implications

- Cancer is often seen in patients with deep venous thrombosis
- This study shows that cancer is five times more commonly diagnosed within six months after deep venous thrombosis than a control group matched for age and sex
- Most of the cancers were easily detected by routinemethods (history, physical examination, and laboratory tests)
- Extensive screening of the 1383 patients with deep venous thrombosis would have resulted in beneficial earlier diagnosis in only two patients
- Extensive screening of patients with deep venous thrombosis does not seem cost effective

association between idiopathic venous thrombosis and subsequent development of cancer, with most cancers becoming clinically apparent within the first year after the diagnosis of the venous thrombosis. In contrast Griffin *et al* found no increased risk of subsequent cancer in patients with objectively documented deep venous thrombosis or pulmonary embolism compared with a control group of patients who did not have thromboembolism.[13]

RECOMMENDATIONS FOR SCREENING

The contradictory results have made it difficult to define suitable recommendations on when to look for an underlying cancer. The selection of patients differs widely in the studies and it is unclear whether detecting an underlying cancer will lower the case fatality rate.[14] Levine *et al* recommended looking for a tumour only if there are signs or symptoms suggesting an underlying cancer or if there is migratory thrombophlebitis or recurrent idiopathic thrombosis.[15] Based on previously published papers, Myrup recommended that patients should be investigated only if they have symptoms suggesting cancer, and that patients under 50 years should be regularly checked for cancer symptoms.[16]

We studied all patients with deep venous thrombosis in one city. Sixty six patients developed cancer within six months after the deep venous thrombosis. Thirty eight of the cancers were easily detected by a combination of a medical history, physical examination, and routine blood tests. Of the remaining 28 (42%) patients with occult cancer, 18 (64%) were older than 75 years. In this study 14% of the deep venous thromboses occurred after surgery or trauma.

Further analysis of the cancers in the patients with delayed diagnosis shows that extensive screening of the 1300 with thrombosis would have identified 11 patients who had cancer without metastasis. Only two, however, would have benefited from earlier diagnosis because of other factors such as age, general health, and tumour type. We therefore suggest that screening all patients with deep venous thrombosis for cancer would not be cost effective and that routine diagnostic tests (including clinical examination and laboratory blood tests) are able to detect cancers if used properly.

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Compliance with recommendations for giving vitamin K to newborn infants

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Newborn infants have low plasma concentrations of vitamin K and are at risk of haemorrhagic disease if not given supplemental vitamin K.[1] In 1992 an association between intramuscular vitamin K and childhood cancer was reported.[2] The British Paediatric Association subsequently recommended that oral vitamin K supplements should be given to newborn infants, with repeat doses for breast fed infants.[3] However, the chief medical officer has stated that there is no licensed preparation of vitamin K for oral use available in the United Kingdom.[4]

The policy regarding vitamin K administration at our hospital was recently changed to follow the British Paediatric Association's recommendations. All infants are given a first oral dose of 0·5 mg of vitamin K within the first 24 hours after birth. A second dose of 0·5 mg vitamin K is dispensed to the mother at discharge from hospital and the community midwife gives it to infants being breast fed at 1 week. The general practitioner is advised by letter to give a further single dose of 0·5 mg oral vitamin K at six weeks to infants who are still breast fed, including those infants receiving supplemental bottle feeds.

This policy was introduced in April 1993, but general practitioners and community midwifes were concerned about giving vitamin K, particularly because the product was not licensed for oral use. We therefore determined compliance with the policy.

Subjects, methods, and results

We attempted to contact by telephone all mothers who delivered live infants at our hospital during June 1993. Mothers whose infants were admitted to the neonatal unit were excluded. We asked mothers about the method of infant feeding, information provided about vitamin K, and administration of vitamin K.

There were 336 deliveries in June 1993 and 348 babies were born. Two of the infants were stillborn and 25 required admission to the neonatal unit; 15 mothers did not have a telephone, four had moved, and a further 95 were not contactable. A total of 207 mothers answered the telephone question-