

Articles

Venous thromboembolism and cancer

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Summary

Background Although cancer has been clearly associated with venous thromboembolism (VTE), many aspects of this relation are poorly understood, including the cancer sites most affected and the cancer risk during long-term follow-up. To clarify these relations, we carried out a large, population-based analysis of VTE and cancer risk.

Methods Using the Swedish Inpatient Register and linkage to the nationwide Cancer Registry, we assessed cancer incidence during 1989 among 61 998 patients without a previous cancer diagnosis admitted to hospital between 1965 and 1983 for VTE. To measure possible increases in cancer risk, we computed standardised incidence ratios (SIRs) using Swedish national cancer rates for the period of the study.

Findings At the time of thromboembolic admission or during the first year of follow-up, 2509 cancers were diagnosed (SIR 3.2, 95% CI 3.1–3.4). The SIR for polycythaemia vera was 12.9 (8.6–18.7), and the SIRs for cancers of the liver, pancreas, ovary, and brain, and for Hodgkin lymphoma also exceeded 5.0. Patients aged less than 65 years had higher SIRs than those who were older. In subsequent years, 6081 cancers were diagnosed (1.3, 1.3–1.3). Even 10 years or more after admission to hospital with VTE, cancer incidence had measured (1.3, 1.3–1.4).

Interpretation At the time of VTE or in the first year afterwards, we found a large increase in the risk for diagnosis of virtually all cancers. In subsequent years, a persistent 30% increase in risk remains. Either premalignant change promotes thrombosis, or cancer and thrombosis share common risk factors.

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Introduction

An association between cancer and venous thromboembolism (VTE) has been recognised since at least 1865.¹ Patients with clinically evident malignant disease or occult cancer have an increased risk of VTE, and necropsy studies document an increased prevalence of thrombosis among patients with visceral cancers.^{2,3}

Thromboembolic events may be presenting symptoms of cancer, and seem also to be a marker of increased cancer risk in the few years afterwards.^{2,4} However, the longer-term association between cancer and VTE has not been investigated, and limited sample sizes have prevented identification of the cancer sites most associated with thrombosis. Most studies of cancer and VTE, moreover, have been done at referral centres, leaving unanswered questions about the general validity of the findings. To examine these issues in detail, we carried out a large population-based analysis of the association of venous thrombosis and pulmonary embolism with cancer.

Methods

Cohort

Since almost no private inpatient treatment exists in Sweden, hospital medical services are basically population based. In 1964–65, the Swedish National Board of Health and Welfare began an Inpatient Register; in addition to a unique personal national registration number, each record included up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) during 1968, and according to the eighth revision thereafter. The register grew steadily: in 1969 it covered 60% of the Swedish population; in 1978, 75%; and by the end of 1983, 85%.⁵

We searched the inpatient register for records with discharge diagnoses of VTE (venous thrombosis, thrombophlebitis of lower extremity, thrombophlebitis migrans, and pulmonary embolism: ICD-7 466.2, 463.99, 466.2, 465–465.02; ICD-8 450–450.09, 451.00, 453.00, 453.09) between 1965 and 1983. A total of 112 861 unique national registration numbers with at least one such hospital record were identified. Linkage to nationwide registers of the total population, causes of death, and population migration, enabled us to remove 10 577 records with incorrect or incomplete registration information, and those not corresponding to any living, deceased, or emigrated person. These records would otherwise contribute to the analysis person-years with no possible risk of a cancer diagnosis. A further 3679 national registration numbers were excluded because of date discrepancies revealed during record linkage. Of the remaining 98 606 individuals 17 222 (17.5%) were excluded because of prevalent cancer, and 19 385 (19.7%) because the date of the first recorded VTE was identical to the date of death or emigration. The remaining 61 998 patients comprised the cohort for analysis. At entry into the cohort, the patients had a mean age of 63.9 years, and 51% were male. The mean year of admission for thromboembolism was 1978. One admission for VTE was recorded for 75% of the cohort; 7.8% had three admissions or more.

Recent surgery was ascertained by a search of the Inpatient

	First year of follow-up			Second year of follow-up and subsequent years		
	Number of cancers/number of patients in VTE cohort	SIR (95% CI)	p*	Number of cancers/number of patients in VTE cohort	SIR (95% CI)	p*
All patients	2509/61 998	4.4 (4.2–4.6)		6081/54 664	1.3 (1.3–1.3)	..
Patients ≤65 years old	743/27 962	6.7 (6.2–7.2)		2242/26 296	1.3 (1.2–1.3)	
Patients >65 years old	1766/34 036	3.9 (3.7–4.0)	<0.0001	3839/28 368	1.3 (1.3–1.4)	0.23
Men	1356/31 493	4.2 (4.0–4.4)		3459/27 648	1.3 (1.2–1.3)	
Women	1153/31 500	4.7 (4.5–5.0)	0.002	2622/27 016	1.3 (1.3–1.4)	0.48
Surgical procedure in preceding month	433/10 672	4.8 (4.4–5.3)		1044/9778	1.2 (1.2–1.3)	
No surgical procedure	2076/51 326	4.3 (4.2–4.5)	0.049	5037/44 886	1.3 (1.3–1.3)	0.04
VTE discharge diagnosis only	1128/28 312	4.8 (4.5–5.1)		2886/26 085	1.3 (1.2–1.3)	
Other discharge diagnoses	1381/33 686	4.1 (3.9–4.4)	0.0003	3195/28 579	1.3 (1.3–1.4)	0.06
Two or more VTE admissions	1120/14 167	8.2 (7.7–8.6)		1420/12 531	1.4 (1.3–1.5)	

*p for χ^2 test of heterogeneity of two SIRs.

Table 1: Standardised incidence ratios (SIRs) for all cancers

Register for surgical procedures in the 30 days before index admission. Patients were also categorised according to the presence or absence of diagnoses other than VTE or cancer on the index hospitalisation.

Follow-up

We obtained dates of death and emigration from the Swedish Registries of Causes of Death and Population Migration. The national Swedish Cancer Registry, founded in 1958 and almost 98% complete,⁶ was used to ascertain individuals with cancer diagnosed before VTE, as well as those with a subsequent cancer diagnosis. Follow-up was from discharge from the first VTE hospital admission during the study period until the first of cancer diagnosis, emigration, death, or the end of the observation period (Dec 31, 1989). Among patients with two or more VTE admissions, follow-up was also studied by use of the date of the second admission as the start of observation. In the cohort as a whole, follow-up was for a mean 7.7 years, generating 474 422 person-years of observation. The ethics committees of Uppsala University and the Swedish Data Inspection Board approved the registry linkages necessary for this study.

Analyses

The Cancer Registry coded malignant disease according to the ICD-7 classification during the entire study period. For each calendar year, expected numbers of cancers were calculated by multiplication of the person-years of observation by the appropriate nationwide age-specific and gender-specific

incidence rates, with 5-year age groups.

Standardised incidence ratios (SIRs)—the ratio of observed numbers of incident cancers to those expected—were used as measures of relative risk. Only first primary cancer cases were included. We calculated 95% CIs for the SIRs on the assumption that the observed number of events followed a Poisson distribution.⁷ Differences in SIRs were investigated by means of standard χ^2 tests.⁷

Results

Venous thromboembolism was a clear marker of cancer risk. At the time of the first VTE admission, or within the first year afterwards, 2509 (4.0%) cohort patients received a new cancer diagnosis. This risk was much higher than expected: the SIR for all cancers was 4.4 (95% CI 4.2–4.9). The SIRs were 6.7 (6.2–7.2) for patients aged 65 years or younger, and 3.9 (3.7–4.0) for those aged over 65 (p for interaction <0.0001; table 1). The increased relative risks were similar in men and women, and in thromboembolism patients with and without surgery in the month before admission. The excess risk was modestly lower in patients with a discharge diagnosis of VTE only than in those with other diagnoses as well (table 1). Patients with two or more VTE admissions had particularly high risks in the year after the second episode (SIR=8.2, 95% CI 7.7–8.6).

We found a high SIR for polycythaemia vera (12.9, 8.6–18.7), and SIRs exceeded 6.0 also for cancers of the liver, pancreas, ovary, and brain, and for Hodgkin lymphoma (table 2). The SIR for breast cancer was 1.8 (1.5–2.2), lower than that for other sites, but still distinguishable from 1.0. Thrombophlebitis migrans conferred a particularly high relative risk during early follow-up, with an SIR for all cancers of 6.6 (4.5–8.6). Otherwise, we found no substantial differences in cancer risk between thromboembolic diagnoses (data not shown).

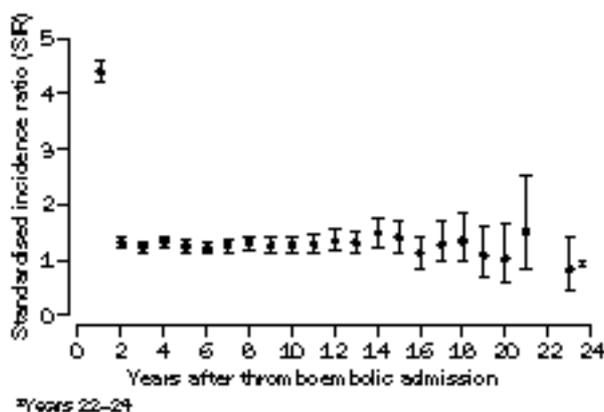
For the 2nd through to the 25th year of follow-up, the excess relative risk for all cancers was roughly 30% overall, and 40% among patients with two or more VTE admissions (table 1). The increases in risks were almost identical in men and women, similar in those with and without recent surgery, and—in contrast to the first years—virtually the same among younger and older individuals (table 1). During this longer follow-up we found no differences in cancer risk between patients with different thromboembolic diagnoses (data not shown). After the first post-thrombosis year, the SIRs for the different cancer sites generally ranged from 1.1 to 1.5 (table 2). As during early follow-up, polycythaemia vera had the highest SIR (3.2, 2.4–4.2).

The SIRs for cancer of all sites by year after admission for thromboembolism are summarised in the figure. In

	At time of VTE admission or in first year afterwards		2 years or more after VTE admission	
	n	SIR (95% CI)	n	SIR (95% CI)
All cancers	2509	4.4 (4.2–4.6)	6081	1.3 (1.3–1.3)
Oesophagus	12	2.0 (1.1–3.6)	68	1.4 (1.1–1.8)
Stomach	160	4.1 (3.5–4.8)	300	1.1 (1.0–1.2)
Large intestine	225	4.7 (4.1–5.4)	529	1.3 (1.2–1.5)
Rectum	69	1.8 (2.0–3.2)	251	1.1 (1.0–1.3)
Primary liver	143	6.6 (5.5–7.7)	256	1.5 (1.3–1.6)
Pancreas	180	7.8 (6.7–9.0)	244	1.2 (1.1–1.4)
Primary lung	237	5.5 (4.8–6.3)	488	1.4 (1.3–1.5)
Melanoma	24	2.6 (1.6–3.8)	111	1.2 (1.0–1.5)
Breast	99	1.8 (1.5–2.2)	525	1.2 (1.1–1.3)
Cervix	26	4.3 (2.8–6.3)	46	1.1 (0.8–1.4)
Endometrium	51	4.4 (3.2–5.7)	109	1.2 (1.0–1.4)
Ovary	144	11.4 (9.6–13.4)	118	1.2 (1.0–1.5)
Prostate	349	4.2 (3.8–4.7)	941	1.3 (1.2–1.4)
Bladder	67	2.5 (1.9–3.1)	294	1.2 (1.1–1.4)
Kidney	99	5.0 (4.1–6.1)	207	1.4 (1.2–1.6)
Brain	96	7.6 (6.1–9.2)	143	1.4 (1.2–1.6)
Non-Hodgkin lymphoma	55	4.2 (3.2–5.5)	165	1.4 (1.2–1.6)
Hodgkin lymphoma	20	7.4 (4.5–11.4)	26	1.5 (1.0–2.2)
Multiple myeloma	27	3.0 (2.0–4.4)	104	1.4 (1.2–1.7)
Lymphocytic leukaemia	31	4.6 (3.3–6.5)	72	1.3 (1.0–1.7)
Non-lymphocytic leukaemia	30	5.6 (3.8–8.0)	60	1.4 (1.1–1.8)
Polycythaemia vera	28	12.9 (8.6–18.7)	54	3.2 (2.4–4.2)

*SIRs based on Swedish national cancer rates.

Table 2: Standardised cancer incidence ratios (SIRs) for patients admitted to hospital for VTE*



Standardised incidence ratios (SIRs) for cancer among patients admitted to hospital for VTE, by years after admission

the 2nd year after VTE, the SIR, at 1.4 (1.3–1.5), was much lower than in the 1st. Little subsequent change occurred in the SIRs over the next 20 years of follow-up. All findings were broadly similar for patients who entered the cohort before 1975 and those who entered later (data not shown).

Discussion

Cancer risk was clearly higher in patients with venous thromboembolism. We found a dichotomous pattern of risk with time. In the first year after admission for VTE, the increase over general population rates was greater than 4-fold, with particularly high relative risks for cancers of the liver, pancreas, ovary, and brain, and for Hodgkin lymphoma, and polycythaemia vera. Thromboembolism was also a marker of long-term cancer risk: even 10 years on or more there was a 30% increase in overall cancer incidence.

Previous investigations have reported that patients with VTE have increases in cancer prevalence and in the risk of subsequent cancer diagnosis, particularly within the first year.^{2,4,8,9} The findings of these studies are similar to those of our early follow-up—overall cancer relative risks of 2–3 during the first few years after the thromboembolic episode. Relative risks were higher in younger than in older patients as in our study.^{4,10}

Previous investigations, however, have not been entirely consistent. One study reported an increased risk of prevalent cancers but not of subsequent cancer,⁸ another reported an increased risk only in the first 6 months after the thromboembolic episode.⁹ These studies involved relatively few patients, and chance variation is a plausible explanation for the differences between their findings and ours. Variable intensity of work-up for cancer at the time of VTE might also have played a part.

Several issues complicate the interpretation of these studies. Investigators who carried out studies at referral centres^{2,4,10} may have researched unusual VTE cases with an increased risk of occult cancer. Also, individuals free of cancer may have been preferentially lost to follow-up. In the short term, both these tendencies would have inflated the observed association between VTE and cancer risk.

There are several reasons why cancer might be associated with VTE. Heightened diagnostic effort and the effects of occult cancer probably explain the association in the short term. Our finding of increased risks of virtually all cancers at the time of VTE and in the

first year afterwards is consistent with this explanation. However, the increased risk was remarkably persistent and generalised; many years after a thromboembolic episode, diagnostic bias should not be prominent, especially for a wide range of malignant diseases. Even in the few years immediately after VTE, diagnostic bias seems unlikely. The period of increased cancer diagnosis would be followed by a compensatory deficit—a pattern that was not seen. Other explanations are required for the persistent association. Small, slow-growing tumours may conceivably remain subclinical for extended periods¹¹ and cause thrombosis, possibly through elaboration of cytokines.³ This process seems unlikely to explain our findings, however, since most cancers are not thought to have such a prolonged subclinical course, and since the associations we found did not wane with time after the first year.

Another possible explanation for our findings is that physiological factors associated with thrombosis might also promote carcinogenesis. For example, prostaglandins are involved in thrombosis, and may be important in cancer aetiology.¹² Activation of fibrinolysis has been associated with malignant disease.^{3,13} The relations we observed could also have developed if both cancer and VTE share risk factors—which is a possibility, though thrombosis and cancer have distinct risk profiles. Several VTE risk factors—recent immobilisation, surgery, and pregnancy—are not strongly related to cancer in general, if at all. Oral-contraceptive use increases the risk of VTE,¹⁴ but not of most cancers, except possibly those of the breast and cervix.^{15,16} On the contrary, oral-contraceptive use decreases the risk of cancers of the ovary and endometrium.^{17,18} Cigarette smoking is a strong risk factor for cancer at many sites,¹⁹ and also confers a modestly increased risk of pulmonary embolism,^{20–23} but seems not to be related to deep venous thrombosis in general.²⁴ Obesity is a risk factor for several cancers (eg, of the breast [postmenopausal], endometrium, colorectum, and kidney),²⁵ and probably for pulmonary embolism,^{22,23} though obesity may not be associated with venous thrombosis.²⁶

Why younger patients with thromboembolic diagnoses should have a particularly high relative risk of cancer in the year after the VTE is not clear. The malignant disease in younger patients could be particularly thrombogenic, or the thromboembolic diagnosis may particularly increase cancer surveillance for them. For other diagnoses at the time of VTE to be associated with a higher relative risk of cancer in the first year after thrombosis is understandable; these diagnoses may have presaged the later cancer.

Although our analysis had the strength of being a large, population-based case series with virtually no losses to long-term follow-up, our data lacked clinical detail—in particular, about risk factors for thromboembolism and haemostatic defects that predispose individuals to thrombosis. Diagnosis of VTE can be difficult, and the recorded diagnoses we relied on may have been erroneous; if non-differential, such misclassification would tend to minimise the strength of the associations we recorded.²⁷ Also, we had no information on whether the cancers that occurred in the cases were occult (and so might have benefited from intensive work-up). These limitations prevent us from suggesting guidelines for the clinical care of patients with VTE.

Our data clearly confirm the association of VTE with

cancer, and extend previous research by showing the association even 10 years or more after the thromboembolic event. The risk of cancers in the lung and brain, and of certain abdominal and haematological malignant diseases, was especially increased soon after a thrombotic admission. The reasons for the long-term increase in risk are not clear, but these data are consistent with the hypotheses that premalignant changes promote thrombosis, or that common factors predispose individuals to both thrombosis and malignant disease. Further research on the underlying mechanisms are likely to clarify the pathophysiology of both VTE and neoplasia.

Contributors

All investigators participated in the design of the study and the writing of the paper. John Baron, Elisabete Weiderpass, and Gloria Gridley analysed the data. John Baron organised and directed the analysis and writing. Gloria Gridley directed database management. Olof Nyrén organised the database-research effort.

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