EUROPEAN JOURNAL OF CANCER 48 (2012) 586–593

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Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer

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ARTICLE INFO

Article history:
Available online 28 November 2011

Keywords:
Cancer
Cohort study
Pulmonary embolism
Risk
Venous thrombosis

ABSTRACT

Background: In contrast to deep venous thrombosis and pulmonary embolism, superficial venous thrombosis has not been considered to be a marker of occult cancer. However, actual data regarding the association are very limited.

Methods: We identified all patients in Denmark from 1994 to 2009 with a diagnosis of superficial venous thrombosis, deep venous thrombosis in the legs or pulmonary embolism using population-based health registries. The occurrence of cancer in the three venous thromboembolism cohorts was compared with the expected numbers of cases estimated using national incidence rates to compute standardised incidence ratios (SIRs).

Findings: We identified a total of 7663 patients with superficial venous thrombosis, 45,252 with deep venous thrombosis and 24,332 with pulmonary embolism. In the first year of follow-up, very similar proportions of patients in the three cohorts were diagnosed with cancer. The SIR was 2.46 (95% CI, 2.10–2.86) for superficial venous thrombosis, 2.75 (95% CI, 2.60–2.90) for deep venous thrombosis, and 3.27 (95% CI, 3.03–3.52) for pulmonary embolism. After one year, the SIRs declined to 1.05 (95% CI, 0.96–1.16), 1.11 (95% CI 1.07–1.16) and 1.15 (95% CI, 1.09–1.22), respectively. For all three patient cohorts, particularly strong associations were found for cancers of the liver, lung, ovaries and pancreas as well as for non-Hodgkin's lymphoma.

Interpretation: Venous thrombosis, whenever it is seen in the lower limbs, is a preclinical marker of prevalent cancer, particularly during the first year after diagnosis.

1. Introduction

The association between cancer and venous thromboembolism has been recognised since Trousseau reported more than 100 years ago that cancer patients often also had episodic migratory thrombophlebitis.[1] Since then a large body of literature has provided strong evidence that deep venous thrombosis and pulmonary embolism not only are complications of cancer,[2–5] but also may be harbingers of a new cancer diagnosis. Indeed, patients with deep venous thrombosis or pulmonary embolism have a 2–4-fold increased risk of cancer in the first year after the venous thromboembolic event.[6–9]

In contrast, superficial venous thrombosis is generally understood to be a relatively benign condition[10,11] without significant implications for cancer risk, though with substantial uncertainty about the clinical course. However, investigation of the relationship between superficial thrombophlebitis and cancer risk is limited to one study of only

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.10.032

250 patients diagnosed in five primary health care centres in Amsterdam.[12]

To understand better the cancer risks associated with all types of venous thrombosis, we determined the risk of cancer after a diagnosis of superficial venous thrombosis in the legs, deep venous thrombosis and pulmonary embolism using population-based registries in Denmark.

2. Methods

This registry based cohort study was based on the entire Danish population of 5·4 million people.[13] The Danish National Registry of Patients was established in 1977 and 99.4% of all discharges from acute care Danish non-psychiatric hospitals are recorded in it. Since 1995, the Registry has also included all outpatient hospital and emergency room visits, encompassing virtually all specialist care in the country.[14]

Recorded information includes the civil registration number, which is unique to every Danish citizen, dates of admission and discharge, surgical procedures performed, and up to twenty discharge diagnoses, classified according to the International Classification of Diseases, 8th edition until 1994 and the International Classification of Diseases, 10th edition thereafter.

It is possible to obtain the hospital history of a patient back to 1977 by linking records in the registry to the civil registration number. All persons listed in the National Registry of Patients with an inpatient or outpatient diagnosis of superficial venous thrombosis in the lower limb (see Appendix for the ICD codes), deep venous thrombosis in the lower limb or pulmonary embolism between 1st January 1994 and 31st December 2009 were identified.

All cases with a (inpatient) diagnosis of venous thrombosis between 1977 and 1994 were excluded from the study cohort. All members of the study cohort were linked through the civil registration number to the nationwide Danish Cancer Registry[15] and the Danish Civil Registration System.[13] The Cancer Registry has kept records of all reported incident cancer cases in Denmark since 1943, with compulsory registration beginning in 1987. Cancers are reclassified according to the International Classification of Diseases, 10th Revision.

2.1. *Statistical analysis*

Standardised incidence ratios (SIRs) were used as a measure of relative risk, comparing the observed cancer incidence among patients with venous thrombosis or pulmonary embolism with that expected in the entire Danish population. Expected numbers of cancer cases were estimated based on national cancer incidence rates by age (5 year groups), sex, and individual calendar year. Confidence intervals (CI) for the standardised incidence ratio were computed based on 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.

Each patient was followed for the occurrence of cancer from the date of the first record with a diagnosis of venous thrombosis or pulmonary embolism until the date of death or 31st December 2009, whichever came first.

3. Role of funding source

The sponsor had no role in the study design; in the collection, analysis and interpretation of the data, in the writing of this report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. No ethics approval was required because no primary data collection was done.

4. Results

We identified 77,247 patients with lower limb superficial or deep venous thrombosis and/or pulmonary embolism (Table 1). The largest group of patients consisted of those with deep venous thrombosis (45,252), followed by pulmonary embolism (24,332) and 7663 patients with superficial venous thrombosis. 168 patients had diagnoses of both superficial and deep venous thrombosis and 97 patients had both superficial venous thrombosis and pulmonary embolism. These patients were classified as deep venous thrombosis and pulmonary embolism, respectively. Thus, 2.1% of patients with superficial venous thrombosis (168/7831) had a concurrent deep venous thrombosis.

36,620 patients (47%) were more than 65 years old. There were slightly more women (41,507, 54%) than men (35,740, 46%). On average the patients were followed for 5.0 years. During follow-up of patients with superficial thrombosis, 869 (11%) developed deep venous thrombosis, 114 (1.5%) had pulmonary embolism and 97 (1.3%) had both. Within 3 months after superficial venous thrombosis, 382 (5.0%) had a deep venous thrombosis, 26 (0.3%) had a pulmonary embolism, while 18 (0.2%) had both.

2124 patients (2.7%) had a cancer diagnosis within the first year of follow-up, and 4205 (7.0%) during the subsequent follow-up of up to 15 years. All forms of venous thrombosis and embolism were clearly associated with cancer risk. The risk of cancer during the first year of follow-up was 2.2% for superficial venous thrombosis, 2.7% for deep venous thrombosis and 2.9% for pulmonary embolism. The corresponding SIRs were 2.46 (95% CI, 2.10–2.86) for superficial venous thrombosis, 2.75 (95% CI, 2.60–2.90) for deep venous thrombosis and 3.27 (95% CI, 3.03–3.52) for pulmonary embolism. The relative risk was slightly lower for patients older than 65 years than for those younger (Table 1).

For 6507 (14%) patients with lower limb deep venous thrombosis there was information in the hospital registry regarding the exact location of the thrombosis. The SIR for cancer was similar for distal (SIR = 2.87, 95% CI 2.38–3.42) and femoral venous thrombosis (SIR = 3.10, 95% CI 2.39–3.95)(Tables 2–4).

For superficial thrombophlebitis, lower limb deep venous thrombosis and pulmonary embolism, particularly strong associations were found for cancers of the liver, lung, pancreas and ovaries, as well as for non-Hodgkin's lymphoma.

Table 1 – Standardised cancer incidence ratios (SIRs) for all cancers for patients with venous thromboembolism during the first year of follow-up.

	Superficial thrombosis			Deep venous thrombosis			Pulmonary embolism			All venous thromboembolism		
	N	Observed no. of cancers	SIR (95%CI)	*N*	Observed no. of cancers	SIR (95%CI)	*N*	Observed no. of cancers	SIR (95% CI)	*N*	Observed no. of cancers	SIR (95% CI)
Total	7663	171	2.5 (2.1–2.9)	45,252	1236	2.7 (2.6–2.9)	24,332	717	3.3 (3.0–3.5)	77,247	2124	2.9 (2.8–3.0)
Female	4404	87	2.3 (1.8–2.8)	23,647	581	2.7 (2.5–2.9)	13,456	382	3.5 (3.1–3.8)	41,507	1050	2.9 (2.7–3.0)
Male	3259	84	2.7 (2.2–3.3)	21,605	655	2.8 (2.6–3.0)	10,876	335	3.1 (2.8–3.4)	35,740	1074	2.9 (2.7–3.1)
Age at thrombosis: <65	4905	66	3.0 (2.3–3.8)	25,322	399	3.5 (3.2–3.9)	10,400	258	5.5 (4.8–6.2)	40,627	704	3.9 (3.7–4.3)
Age at thrombosis: 65+	2758	105	2.2 (1.8–2.7)	19,930	837	2.5 (2.3–2.7)	13,932	459	2.7 (2.5–3.0)	36,620	1420	2.5 (2.4–2.7)
1994–1999	2414	47	2.2 (1.6–2.9)	13,709	373	2.8 (2.5–3.1)	7541	189	3.3 (2.8–3.8)	23,664	609	2.9 (2.7–3.1)
2000–2004	2649	68	2.7 (2.1–3.5)	14,496	408	2.8 (2.5–3.0)	7706	227	3.1 (2.7–3.5)	24,851	703	2.8 (2.6–3.1)
2005–2009	2600	56	2.4 (1.8–3.1)	17,047	455	2.7 (2.5–2.9)	9085	301	3.4 (3.0–3.8)	28,732	812	2.9 (2.7–3.1)
Unprovoked venous thromboembolism	6199	129	2.3 (1.9–2.7)	34,152	959	2.8– (2.6–3.0)	18,215	559	3.3 (3.0–3.6)	58,568	1647	2.9 (2.7–3.0)
Provoked venous thromboembolism	7116	42	3.4 (2.5–4.6)	40,176	277	2.6 (2.3–3.0)	21,950	158	3.1 (2.6–3.6)	69,241	477	2.8 (2.6–3.1)
No fractures in previous 3 months	6509	164	2.5 (2.1–2.9)	37,025	1169	2.9 (2.7–3.0)	19,376	685	3.4 (3.1–3.6)	62,913	2018	3.0 (2.9–3.1)
Fractures in previous 3 months	1464	7	1.6 (0.6–3.2)	11,100	67	1.6 (1.2–2.0)	6117	32	1.9 (1.3–2.7)	18,679	106	1.7 (1.4–2.0)
No surgical procedure in past 3 months	547	132	2.2 (1.9–2.6)	5,076	1000	2.7 (2.5–2.9)	2382	574	3.2 (3.0–3.5)	8006	1706	2.8 (2.7–3.0)
Surgical procedure within 3 months	1154	39	3.9 (2.8–5.3)	8227	236	2.9 (2.5–3.3)	4956	143	3.4 (2.9–4.0)	14,334	418	3.1 (2.8–3.4)

Table 2 – Standardised cancer incidence ratios (SIRs) for patients with venous thromboembolism during the second and subsequent years of follow-up.

	Superficial thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolism	
	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)	Observed no. of cancers	SIR (O/E)
Total	457	1.1 (1.0–1.2)	2605	1.1 (1.1–1.2)	1143	1.2 (1.1–1.2)	4205	1.1 (1.1–1.2)
Female	253	1.1 (0.9–1.2)	1212	1.1 (1.1–1.2)	601	1.2 (1.1–1.3)	2066	1.1 (1.1–1.2)
Male	204	1.1 (0.9–1.2)	1393	1.1 (1.0–1.2)	542	1.1 (1.0–1.2)	2139	1.1 (1.0–1.1)
Age at thrombosis: 0–65	222	1.1 (1.0–1.3)	1120	1.2 (1.1–1.3)	445	1.3 (1.2–1.4)	1787	1.2 (1.2–1.3)
Age at thrombosis: 65+	235	1.0 (0.9–1.1)	1485	1.1 (1.0–1.1)	698	1.1 (1.0–1.2)	2418	1.0 (1.0–1.1)
1994–1999	250	1.1 (0.9–1.2)	1347	1.1 (1.0–1.1)	572	1.1 (1.1–1.2)	2169	1.1 (1.0–1.1)
2000–2004	169	1.1 (0.9–1.3)	936	1.1 (1.1–1.2)	424	1.2 (1.1–1.3)	1529	1.1 (1.1–1.2)
2005–2009	38	0.9 (0.7–1.3)	322	1.2 (1.0–1.3)	147	1.1 (1.0–1.3)	507	1.1 (1.0–1.2)
Unprovoked venous thromboembolism	379	1.0 (0.9–1.2)	1994	1.1 (1.0–1.1)	887	1.2 (1.1–1.2)	3260	1.1 (1.1–1.1)
Provoked venous thromboembolism	78	1.1 (0.9–1.4)	611	1.2 (1.1–1.3)	256	1.1 (1.0–1.3)	945	1.2 (1.1–2.0)
No fractures in previous 3 months	431	1.1 (1.0–1.2)	2364	1.1 (1.1–1.2)	1076	1.2 (1.1–1.2)	3871	1.1 (1.1–1.2)
Fractures within 3 month	26	1.0 (0.7–1.5)	241	1.1 (1.0–1.3)	67	0.9 (0.7–1.2)	334	1.1 (1.0–1.2)
No surgical procedure	396	1.1 (1.0–1.2)	2134	1.1 (1.0–1.1)	922	1.2 (1.1–1.2)	3452	1.1 (1.1–1.1)
Surgical procedure within 3 months	61	1.0 (0.8–1.3)	471	1.2 (1.1–1.3)	221	1.1 (1.0–1.3)	753	1.2 (1.1–1.2)

From the second through the 15th year of follow-up, the relative risks for most cancers were only slightly increased, and to a similar extent for all three patient cohorts. For all invasive cancers, the SIR during the later follow-up for superficial venous thrombosis was 1.05 (95% CI, 0.96–1.16), 1.11 (95% CI 1.07–1.16) for deep venous thrombosis and 1.15 (95% CI, 1.09–1.22) for pulmonary embolism (Fig. 1). In general the cancer site specific risk estimates were broadly similar. The risk was similar for men and women but slightly higher for persons younger than 65 years of age compared with older patients.

In an additional analysis, patients with superficial thrombophlebitis were censored at the time of other venous thromboembolism. This left the standardised incidence rate (SIR) for the first year of follow-up virtually unchanged (SIR = 2.31, 95% CI, 1.95–2.71).

5. Discussion

We found that patients with a diagnosis of superficial venous thrombosis—like those with deep venous thrombosis and pulmonary embolism[6–9]—had a clearly higher occurrence of cancer than expected, particularly during the first year after diagnosis. The excess occurrence subsequently decreased markedly, though venous thrombosis or embolism, wherever its location, remained a marker of slightly increased long-term cancer risk.[6,7] The increased risks of cancer diagnosis were similar in magnitude for each of the thrombotic manifestations, and each showed particularly strong associations with cancers of the liver, lung, ovaries and pancreas, as well as non-Hodgkin's lymphoma. We also found that distal deep venous thrombosis was associated with cancer relative risks similar to those for femoral thrombosis and pulmonary embolism.

Several clinical studies have reported cancer associations similar to ours for the first year of follow-up after deep venous thrombosis,[9] and our findings were also broadly similar to former reports associated with specific types of cancer.[6–8] However, our results for superficial thrombosis differ from the one previous report on the topic. In this small study from Holland, five out of 25 (2%) patients developed cancer within two years compared with 2% in the control group.[12] The study was only able to control for family physician, but did not exclude persons with a cancer diagnosis before their superficial venous thrombosis diagnosis and had incomplete follow-up. The standardised mortality ratio was 1.1 (95% CI, 0.5–2.7) after 2 years of follow-up based on five cases of cancer.

Our study has limitations. No acute private care exists in Denmark and so our study is virtually population based. Nonetheless, we likely included only a sub-group of patients with superficial venous thromboembolism, namely those diagnosed in the hospital service rather than in the general practitioners' clinics. Data on the incidence of this disorder are very limited, but it seems to be fairly common in the general population,[16,17] and selection factors might partly explain the different results from the previous study.[12] Also, the recorded diagnosis in the Patient Registry may have been erroneous. However, such potential misclassification would tend to result in underestimation of the overall associations.[17]

Table 3 – Standardised cancer incidence ratios (SIRs) for major cancer sites in patients with venous thromboembolism during the first year of follow-up.

Cancer site	Superficial venous thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolism	
	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR(95% CI)	Observed no. of cancers	SIR(95% CI)	Observed no. of cancers	SIR(95% CI)
All	171	2.5 (2.1–2.9)	1236	2.7 (2.6–2.9)	717	3.3 (3.0–3.5)	2124	2.9 (2.8–3.0)
Oesophagus	4	4.2 (1.1–10.7)	13	1.9 (1.0–3.3)	14	4.4 (2.4–7.3)	31	2.8 (1.9–4.0)
Stomach	5	3.5 (1.1–8.2)	28	2.9 (1.9–4.2)	19	4.1 (2.5–6.4)	52	3.3 (2.5–4.3)
Large intestine incl. Colon rectosigmoid	9	1.3 (0.6–2.4)	102	2.1 (1.7–2.6)	65	2.7 (2.1–3.5)	176	2.2 (1.9–2.6)
Rectum	6	1.8 (0.7–3.9)	41	1.8 (1.3–2.4)	14	1.3 (0.7–2.1)	61	1.6 (1.3–2.1)
Liver	6	8.2 (3.0–17.9)	14	2.8 (1.5–4.8)	10	4.2 (2.0–7.7)	30	3.7 (2.5–5.3)
Gallbladder and biliary tract4	0	–	13	3.8 (2.0–6.5)	10	5.9 (2.8–10.8)	23	4.1 (2.6–6.1)
Pancreas	10	4.6 (2.2–8.5)	79	5.4 (4.3–6.8)	50	6.9 (5.2–9.2)	139	5.8 (4.9–6.9)
Larynx	0	–	2	0.5 (0.1–1.8)	1	0.6 (0.0–3.1)	3	0.5 (0.1–1.4)
Lung, bronchi and trachea	31	3.1 (2.1–4.4)	194	3.0 (2.6–3.4)	183	5.7 (4.9–6.6)	408	3.8 (3.4–4.2)
Malignant melanoma	4	1.6 (0.4–4.0)	22	1.4 (0.9–2.2)	8	1.1 (0.5–2.2)	34	1.4 (0.9–1.9)
Breast	15	1.4 (0.8–2.4)	66	1.2 (0.9–1.5)	40	1.5 (1.0–2.0)	121	1.3 (1.1–1.5)
Cervix of uterus	1	1.2 (0.0–6.4)	15	3.4 (1.9–5.6)	6	2.9 (1.1–6.3)	22	3.0 (1.9–4.6)
Uterus	4	2.1 (0.6–5.4)	30	2.9 (1.9–4.1)	16	3.0 (1.7–4.9)	50	2.8 (2.1–3.7)
Ovary	4	2.6 (0.7–6.6)	43	5.2 (3.8–7.0)	44	10.5 (7.6–14.1)	91	6.5 (5.2–8.0)
Prostate	14	2.1 (1.1–3.5)	164	3.1 (2.7–3.7)	57	2.2 (1.7–2.9)	235	2.8 (2.4–3.2)
Testicle	0	–	9	5.5 (2.5–10.4)	0	–	9	3.6 (1.6–6.8)
Kidney	0	–	15	1.7 (0.9–2.8)	21	4.9 (3.0–7.5)	36	2.5 (1.7–3.4)
Urinary bladder	8	3.6 (1.5–7.0)	38	2.3 (1.7–3.2)	17	2.1 (1.2–3.4)	63	2.4 (1.8–3.1)
Brain	6	3.5 (1.3–7.7)	20	1.9 (1.2–3.0)	8	1.7 (0.7–3.3)	34	2.0 (1.4–2.8)
Hodgkin lymphoma	1	5.4 (0.1–30.3)	2	1.8 (0.2–6.6)	3	6.3 (1.3–18.4)	6	3.4 (1.3–7.5)
Non-Hodgkin lymphoma	7	3.4 (1.3–6.9)	57	4.2 (3.2–5.5)	19	2.9 (1.7–4.5)	83	3.7 (3.0–4.6)
Leukaemia	8	4.4 (1.9–8.6)	46	3.7 (2.7–4.9)	9	1.5 (0.7–2.8)	63	3.1 (2.4–4.0)
Metastases and non-specified cancer in lymph nodes	12	5.5 (2.8–9.6)	84	5.6 (4.5–6.9)	30	4.0 (2.7–5.7)	126	5.1 (4.3–6.1)
Multiple myeloma	4	5.1 (1.4–12.9)	16	3.0 (1.7–4.9)	11	4.2 (2.1–7.5)	31	3.5 (2.4–5.0)

Table 4 – Standardised cancer incidence ratios (SIRs) for major cancer sites in patients with venous thromboembolism during the second and subsequent years of follow-up.

Cancer site	Superficial venous thrombosis		Deep venous thrombosis		Pulmonary embolism		All venous thromboembolisms	
	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)	Observed no. of cancers	SIR (95% CI)
All	457	1.1 (1.0–1.2)	2605	1.1 (1.1–1.2)	1143	1.2 (1.1–1.2)	4205	1.1 (1.1–1.2)
Oesophagus	6	1.0 (0.4–2.2)	37	1.1 (0.7–1.5)	22	1.5 (1.0–2.3)	65	1.2 (0.9–1.5)
Stomach	10	1.2 (0.6–2.2)	51	1.1 (0.8–1.4)	17	0.8 (0.5–1.3)	78	1.0 (0.8–1.3)
Large intestine incl. colon rectosigmoid	46	1.1 (0.8–1.4)	272	1.1 (1.0–1.3)	145	1.4 (1.2–1.6)	463	1.2 (1.1–1.3)
Rectum	22	1.0 (0.7–1.6)	125	1.1 (0.9–1.3)	42	0.8 (0.6–1.1)	189	1.0 (0.9–1.2)
Liver	3	0.7 (1.1–2.0)	36	1.4 (1.0–2.0)	21	2.0 (1.2–3.1)	60	1.5 (1.1–1.9)
Gallbladder and biliary tract	3	1.0 (0.2–2.8)	25	1.5 (1.0–2.2)	6	0.8 (0.3–1.8)	34	1.3 (0.9–1.8)
Pancreas	25	1.8 (1.2–2.7)	94	1.3 (1.0–1.5)	40	1.2 (0.9–1.7)	159	1.3 (1.1–1.5)
Larynx	5	1.4 (0.5–3.3)	20	1.0 (0.6–1.5)	7	0.9 (0.4–1.8)	32	1.0 (0.7–1.4)
Lung, bronchi and trachea	53	0.9 (0.6–1.1)	359	1.1 (1.0–1.2)	163	1.1 (1.0–1.3)	575	1.1 (1.0–1.1)
Malignant melanoma	13	0.8 (0.4–1.4)	79	0.9 (0.7–1.2)	41	1.2 (0.8–1.6)	133	1.0 (0.8–1.2)
Breast	70	1.1 (0.8–1.3)	320	1.1 (1.0–1.2)	170	1.3 (1.1–1.5)	560	1.2 (1.1–1.3)
Cervix of uterus	2	0.4 (0.1–1.5)	30	1.5 (1.0–2.1)	12	1.4 (0.7–2.4)	44	1.3 (0.9–1.7)
Uterus	19	1.6 (1.0–2.6)	53	1.1 (0.8–1.4)	15	0.6 (0.4–1.1)	87	1.0 (0.8–1.3)
Ovary	6	0.7 (0.2–1.4)	39	1.0 (0.7–1.4)	18	1.0 (0.6–1.6)	63	0.9 (0.7–1.2)
Prostate	37	0.8 (0.6–1.1)	333	1.1 (1.0–1.2)	97	0.8 (0.6–1.0)	467	1.0 (0.9–1.1)
Testicle	3	2.1 (0.4–6.1)	9	1.1 (0.5–2.1)	6	2.1 (0.8–4.7)	18	1.5 (0.9–2.3)
Kidney	11	1.3 (0.7–2.4)	55	1.2 (0.9–1.6)	26	1.4 (0.9–2.0)	92	1.3 (1.0–1.5)
Urinary bladder	17	1.2 (0.7–2.0)	75	0.9 (0.7–1.1)	44	1.3 (0.9–1.7)	136	1.0 (0.9–1.2)
Brain	9	0.9 (0.4–1.7)	65	1.2 (0.9–1.6)	24	1.1 (0.7–1.6)	98	1.1 (0.9–1.4)
Hodgkin lymphoma	2	2.0 (0.2–7.1)	6	1.1 (0.4–2.4)	0	–	8	0.9 (0.4–1.8)
Non-Hodgkin lymphoma	15	1.1 (0.6–1.9)	70	1.0 (0.8–1.2)	32	1.1 (0.7–1.5)	117	1.0 (0.8–1.2)
Leukaemia	16	1.4 (0.8–2.3)	89	1.4 (1.1–1.7)	43	1.6 (1.2–2.2)	148	1.5 (1.2–1.7)
Metastases and non-specified cancer in lymph nodes	16	1.2 (0.7–2.0)	83	1.1 (0.9–1.4)	43	1.3 (1.0–1.8)	142	1.2 (1.0–1.4)
Multiple myeloma	9	1.8 (0.8–3.4)	37	1.3 (0.9–1.9)	16	1.4 (0.8–2.2)	62	1.4 (1.1–1.8)

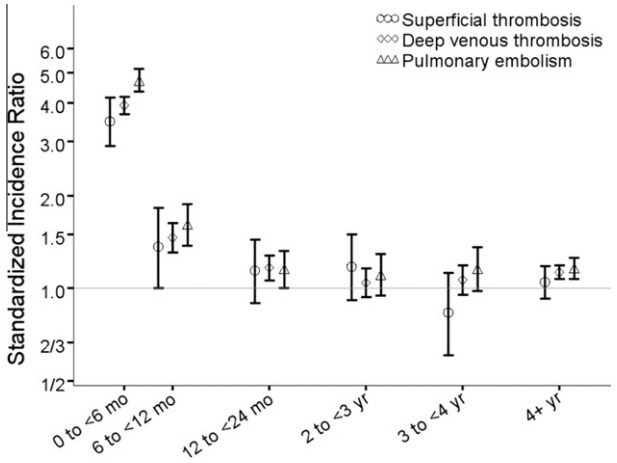

Fig. 1 – Relative risk (Standardised Incidence Ratio) of cancer in relation to length of the follow-up period in patients with superficial venous thrombosis, deep venous thrombosis or pulmonary embolism. The I bars represent 95% confidence intervals.

Our cancer data have high quality and completeness and comprehensive validation has shown that the Cancer Registry is 95–98% complete and valid.[15]

It is possible that unrecognised concomitant deep vein thrombosis, reported to occur in up to 25% of patients with superficial vein thrombosis,[18] might have contributed to the increased risk. Thus we cannot exclude the possibility that in patients with isolated superficial vein thrombosis the incidence of occult or subsequent cancer is lower than that observed in our population. Nonetheless, our findings remained unchanged after omission of patients who subsequently developed deep venous thrombosis or pulmonary embolism.

There may be several explanations for an association between venous thrombosis and cancer risk. Heightened diagnostic activities likely explain some of the associations during the first year of follow-up. Our finding of increased risk of virtually all cancers during that period is consistent with such diagnostic surveillance. However, the persistent increased risk after one year of venous thromboembolism speaks against the prominent diagnostic bias. Likewise, we did not see a compensatory deficit in the cancer risk in the data in the follow-up period more than 1 year later.

Our data are consistent with two other options: on the one hand, common factors may predispose individuals to both thrombosis and cancer[19–22]; on the other hand, occult malignant changes can promote venous thromboembolism. Smoking, obesity and use of oestrogens are indeed risk factors for both deep venous thrombosis and cancer, although obesity and oestrogen use each predisposes only to a limited range of cancers.[21,22] The increased risk of upper gastrointestinal neoplasm and lung cancer after venous thromboembolism is consistent with the smoking exposure.

The manner in which cancer can lead to thrombosis has been studied in detail over the last decades, but the mechanisms are complex and multifactorial.[2,3,23] Cancer growth is associated with the development of a hypercoagulable state. Malignant cells can activate blood coagulation in several ways: by producing fibrinolytic, and proaggregating activities though release of pro-inflammatory and proangiogenetic cytokines, and by interacting directly with host vascular and blood cells, such as endothelial cells, leucocytes and platelets, by means of adhesion molecules.[2]

The practical implications of our findings are unclear. In general a venous thrombotic event within a year of a diagnosis of cancer is a marker of an aggressive malignancy: only 12% of affected patients are alive after one year.[24] However, the implications for screening seem remote. In our study 45,981 persons with venous thrombosis/embolism would have to be investigated for the 304 excess cancers to be found during the first year of follow-up. One cohort study[25] of 830 patients and a clinical trial of 201 patients[26] investigated whether early detection of an occult cancer in patients with venous thromboembolism would yield a more favourable outcome.[25,26] Unfortunately the two studies were not definitive enough to establish whether an early cancer diagnosis ultimately prolongs life in venous thromboembolism patients.

6. Contributors

HTS was the principal investigator and lead author in the conception and design of the study, supervision of the analysis of the data and drafting of the manuscript. CS, DKF and LP coordinated the data collection and did the statistical analysis. JAB, TLL and CFC participated in the study design, provided statistical suggestions and participated in the interpretation of the results. PP participated in the conception and design of the study and the interpretation of the data. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement

None declared.

Acknowledgement

The study obtained support from the Danish Medical Research Council Grant No. 10-084581 and the Karen Elise Jensen Foundation.

Appendix

International Classification of Diseases (ICD) codes defining venous thromboembolism

Superficial thrombophlebitis: ICD-8: 451.01; ICD-10: I80.0
Deep venous thrombosis: ICD-8: 451.00; ICD-10: I80.1–3
Pulmonary embolism: ICD-8: 450.99; ICD-10: I26, I26.98

ICD codes defining cancer

Oesophagus ICD-10: C15
Stomach ICD-10: C16
Large intestine incl. colon rectosigmoid ICD-10: C18-C19

Rectum ICD-10: C20
Liver ICD-10: C22
Gallbladder and biliary tract ICD-10: C23–C24
Pancreas ICD-10: C25
Larynx ICD-10: C32
Lung, bronchi and trachea ICD-10: C33–C34
Malignant melanoma ICD-10: C43
Breast ICD-10: C50
Cervix of uterus ICD-10: C53
Uterus ICD-10: C54–C55
Ovary ICD-10: C56, C570–C574
Prostate ICD-10: C61
Testicle ICD-10: C62
Kidney ICD-10: C64
Urinary bladder ICD-10: C67, D303, D413
Brain ICD-10: C71, D33, D352–D354, D43, D443–D445
Hodgkin malignant lymphoma ICD-10: C81 or pathological morphology codes M965, M966
Non-Hodgkin malignant lymphoma ICD-10: C82–C85, C901–C902 or pathological morphology codes M967, M972
Leukaemia ICD-10: C91–C95
Metastases and non-specified cancer in lymph nodes ICD-10: C77–C79
Multiple myeloma ICD-10: C900

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