Peer reviewed article

Search for occult malignancy in patients with deep venous thrombosis

Results of a retrospective cohort study

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Summary

Questions under study: The association of deep vein thrombosis (DVT) and cancer is well established. It is controversial how large the association is and how extensive the evaluation for an underlying cancer should be.

Principles and methods: 485 patients without a known cancer and a proven DVT formed the cohort of a retrospective study. Newly diagnosed (prevalent) cancers in patients with idiopathic (IDVT) and secondary DVT (SDVT) during the index hospitalisation were compared and the contribution of the steps in an institutional tumour search program was analysed. The incidence of cancer in 204 patients with IDVT and 230 patients with SDVT during follow-up was determined.

Results: During the index hospitalisation routine evaluation revealed eleven cancers in 236 patients (4.7% [95%-CI: 2.0–7.3]) with IDVT and five cancers in 249 patients (2.0% [95%-CI: 0.3–3.7]) with SDVT. Combining patient history, clinical examination, routine laboratory tests and chest x-ray showed a sensitivity of 88% and a specificity of 79% for the diagnosis of cancer. Abdominal ultrasound did not significantly increase the yield. 93% of the patients were followed for up to 5 years (mean 32 months). Sixteen cancers occurred in 204 patients (7.8% [95%-CI: 4.0–11.5]) with IDVT and ten in 230 patients (4.35% [95%-CI: 1.7–7.0]) with SDVT ($p < 0.001$).

Conclusion: Prevalence and incidence of cancer were higher in IDVT patients compared to those with SDVT. Combining patient history, clinical examination, simple laboratory tests, and a routine chest x-ray is an appropriate strategy to detect underlying cancer in patients with IDVT. Routine abdominal ultrasound can safely be omitted.

Key words: deep venous thrombosis; occult cancer; safe limited screening; abdominal ultrasound

Introduction

Ever since the description of an association between cancer and deep venous thrombosis (DVT) in 1865 by Trousseau [1], it has been clinical practice to view idiopathic deep venous thrombosis (IDVT), i.e. DVT without a triggering factor, as a marker for occult cancer. However, it is unclear if the search for occult cancer in IDVT is justified by a large enough yield, i.e. the detection of a clinically important number of malignancies in early and potentially curable stages. It is furthermore controversial how extensive the evaluation for occult cancer should be to remain effective both in terms of patients' distress and of cost [2–13]. A randomised trial of screening for occult malignancies with cost and quality of life as outcome measures has been ongoing since 1992 [14]. Preliminary results were recently presented [15, 16].

In our institution it has been clinical practice to routinely perform a work-up including history, physical examination and laboratory tests, a chest x-ray and an abdominal ultrasound in every patient with DVT. We conducted a retrospective cohort study in order to evaluate the clinical effectiveness of this institutional practice. The main goals of the study were: (1) to determine the prevalence of so far undiagnosed malignancies in patients with IDVT and secondary DVT (SDVT); and (2) to compare the incidence of cancer after discharge in patients with IDVT in whom no malignancy was detected during the index hospitalisation with the incidence of cancer in patients with SDVT during follow-up.

All authors are free of any financial interests or conflicts.

Material and Methods

Patient identification

The study is a retrospective cohort study. The exposure is defined as confirmed DVT. The outcome was newly diagnosed cancer. The cohort was assembled by identifying patients with the admission diagnosis of suspected DVT from the emergency room log book during a period of five years (1990 to 1995). Cross-referencing with the medical charts definitely allocated patients to one of two groups: idiopathic DVT (IDVT) or secondary DVT (SDVT). Only patients in whom the diagnosis of DVT of the lower extremities was confirmed by a physician specialized in vascular medicine using compression sonography with Duplex and/or phlebography were included. The cohort was completed by cross-referencing the list obtained from the emergency log with the coded hospital discharge log using the ICD-9 codes 451.X and 454.X. Patients in whom DVT occurred during an in-hospital stay for other reasons were not included.

Data collection

The data collected by structured chart review included demographic characteristics, the main discharge diagnosis, the Charlson Comorbidity Index [17], an assessment of possible risk factors for DVT, the location and extent of the DVT, and the type, number and results of laboratory tests and procedures ordered in the search for an occult cancer. Risk factors for DVT that allowed a classification as secondary DVT included a clinically active malignant disorder, a history of a confirmed prior DVT, prolonged immobilisation, a recent (<3 weeks) surgery or trauma of the limb, hormonal replacement therapy or oral contraception, known coagulation disorders, and severe congestive heart failure.

The usual evaluation for an underlying cancer in patients with DVT consisted of a structured patient history, a physical examination, basic laboratory tests (blood sedimentation rate, red and white blood cell count, serum electrolytes and creatinine, urinanalysis), a chest x-ray and an abdominal ultrasonography. Screening procedures such as mammography, tests for faecal blood, sigmoidoscopy, or measurement of the prostate specific antigen were not part of the routine. The evaluation scheme did not exist as a written protocol or a guideline but it was traditionally taught and endorsed as usual care by the senior physicians.

Findings in the evaluation that were suggestive of underlying cancer were identified by review of the data forms by an experienced physician who was not aware of the follow-up data. In the medical history findings classified as suspicious for cancer included weight loss (>5 kg in 3 months), unusual pain, modification of bladder or bowel habits, or recent onset of cough or hoarseness. In the physical examination abnormal abdominal or breast masses, unusual pigmentation of the skin, irregular digital rectal examination or enlarged lymph nodes were regarded as suspicious for cancer. Abnormalities on chest x-rays defined as suspicious were lung nodules, mediastinal enlargement, pleural effusions, and bilateral interstitial thickening. In addition any unclear organ irregularity or intraabdominal mass in abdominal sonography was regarded as suggestive of underlying cancer.

Follow up

Both groups of patients with IDVT and SDVT were followed up using a mailed questionnaire. In a first mailing they were informed about the purpose of the study and were asked to return a postcard indicating their willingness to participate in the survey. Patients who agreed to participate were then mailed the questionnaire with questions about their present state of health. From patients who were readmitted to our institution during follow-up information regarding incident cancer was obtained from the medical charts. From patients who died during follow-up information about the cause of death was obtained by contacting the family physician or from the state mortality registry.

Data analysis

Data were entered in a computerised database (Epi-Info 5.0) and analysed with the SAS statistical package. Proportions were calculated in percent with 95%-confidence-intervals assuming a binominal distribution. Continuous parameters were compared with the Student's-t-test when normally distributed, otherwise a Mann-Whitney-U test was applied. A p-value <0.05 was defined as statistical significant. The incidence rates for cancer were calculated in person years of follow-up. The sensitivity and specificity of the initial workup were calculated with standard methods. Survival curves were compared with the log-rank-test.

Results

The study profile and the main results are summarized in figure 1. The risk factors in patients with SDVT were a history of prior DVT in 41%, prolonged immobilisation in 19%, trauma or surgery in the lower limb in 16%, hormonal replacement therapy or oral contraception in 13%, and miscellaneous in 10%. Patients with IDVT were older and more often male than those with SDVT (table 1). The recommended cancer workup including abdominal ultrasound was performed in almost all patients with IDVT. In patients with SDVT a chest x-ray was also routinely ordered (98%) and an abdominal ultrasound was carried out in 68%. Findings in the clinical examination, on chest x-rays, and in abdominal sonography suspicious of an underlying malignant disorder were significantly more frequent in patients with IDVT than in those with SDVT (table 1).

During the index hospitalisation a hitherto unknown malignant disorder was detected in sixteen patients: in eleven of the 236 patients with IDVT and in five of the 249 patients with SDVT resulting in a prevalence of 4.7% (95%-CI: 2.0–7.3%) and of 2.0% (95%-CI: 0.3–3.7%), respectively (Odds ratio 2.4 [95%-CI: 0.8–7.0]) (figure 1). There were four patients with lung cancer, three each with pancreas, colorectal or prostate cancer, and one patient with breast cancer, cancer of unknown origin with liver metastasis, and polycythaemia vera, respectively (table 2). Mostly, the

Figure 1

Patient flow and main results in a retrospective cohort study of patients with deep venous thrombosis (DVT) of the lower extremities. Prevalent cancer denotes cancers newly diagnosed during the in-hospital stay for DVT. Incident cancer denotes cancers diagnosed during follow-up. IDVT: Idiopathic deep venous thrombosis; SDVT: Secondary deep venous thrombosis; CI: Confidence interval.

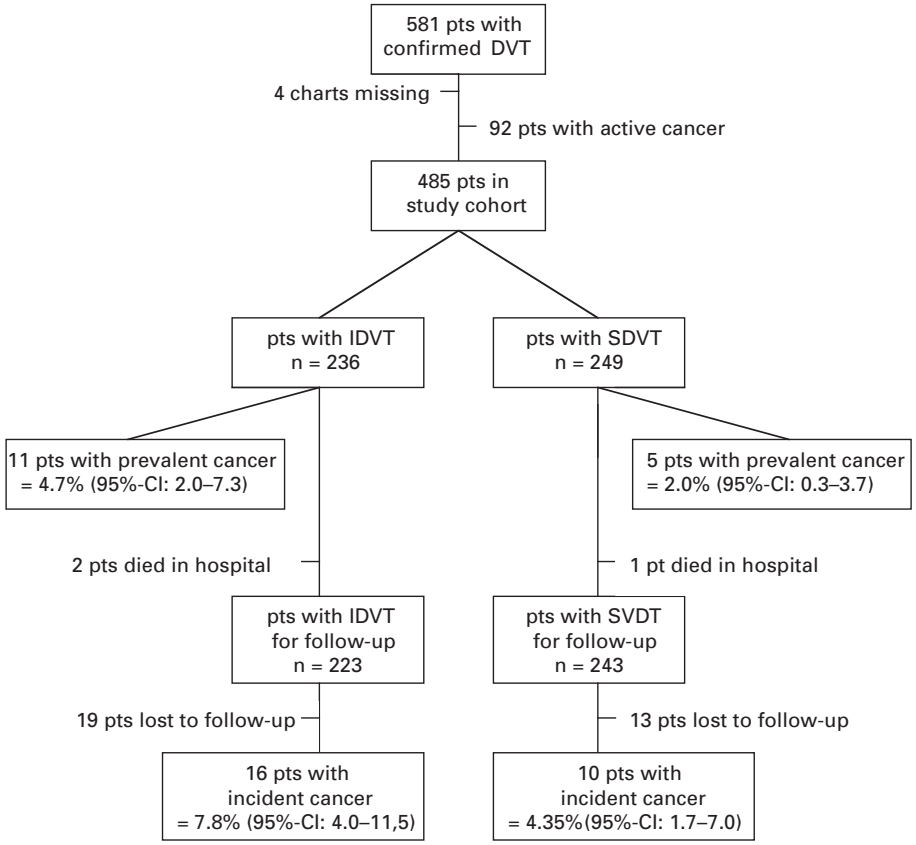


Table 1

Demographics and extent of evaluation for occult cancer in patients with idiopathic and secondary deep venous thrombosis.

	Idiopathic DVT (n = 236)	Secondary DVT (n = 249)	p-value
Age (years)	66 ± 15	59 ± 19	<0.001
Male	149 (63)	112 (45)	<0.001
Charlson Comorbidity Index*	0.96 ± 1.22	0.96 ± 1.28	NS
Proximal DVT	197 (83)	192 (77)	NS
Smoker	117 (50)	133 (53)	NS
History suspicious	35 (15)	20 (8)	0.02
Clinical exam suspicious	41 (17)	9 (4)	<0.001
Chest x-ray performed	235 (100)	244 (98)	NS
Chest x-ray suspicious	28 (12)	9 (4)	<0.005
Abdominal US performed	216 (92)	169 (68)	<0.001
Abdominal US suspicious	21 (10)	7 (3)	0.04

Data are shown as number (%) or mean ± standard deviation;
* see Ref [17]; DVT: deep venous thrombosis; NS: non significant; US: ultrasonography.
Suspicious denotes one or more findings suggesting underlying cancer (for definitions see Methods section).

malignant disorder was advanced and more than half of the patients died within a year of diagnosis.

Eleven of the 16 malignant disorders were detected by an abnormal finding in only one step of the diagnostic evaluation (table 3). Four patients had an abnormal clinical examination only, two patients each had only a suspicious history, chest x-ray or abdominal ultrasound. In one patient the red cell blood count was decisive. In the remaining five patients a combination of pathological findings in more than one of the procedures led to the identification of the cancer. By omitting abdominal ultrasound two cancers would have been missed: a pancreatic cancer in an 88-year old man treated with supportive care and liver metastases of an unknown primary tumour in a 58-year old man also palliatively treated.

In our cohort the further evaluation of a history suspicious of cancer alone resulted in a sensitivity of 56% and a specificity of 90% for the detection of occult cancer. Seven of the 16 cancers detected would have been missed when relying on the history alone. Combining the further evaluation of suspicious findings in history, physical examination and/or chest x-ray resulted in a sensitivity of 88% and a specificity of 79%. By adding abdominal ultrasound to the search strategy two additional cancers were found.

Table 2

Malignant disorders detected in patients with deep venous thrombosis during index hospitalisation (prevalent cancers).

	Age (y)	Sex	DVT	Primary Cancer Site	Stage	Therapy	Survival
1	81	M	I	Prostate	$T_1N_xM_x$	None	>24 m
2	82	M	I	Prostate	$T_3N_xM_x$	None	>12 m
3	84	M	S	Prostate	$T_3N_1M_1$	Hormone	54 m
4	68	M	I	Lung	$T_4N_2M_1$	Palliative	1 m
5	70	M	I	Lung	Extensive disease	Chemotherapy	4 m
6	58	F	I	Lung	$T_3N_2M_x$	Palliative	2 m
7	70	M	I	Lung	$T_3N_2M_1$	Palliative	7 m
8	70	M	I	Pancreas	$T_3N_1M_1$	Palliative	2 w
9	88	F	I	Pancreas	$T_3N_xM_1$	Palliative	2 m
10	84	F	S	Pancreas	$T_3N_xM_x$	Palliative	7 w
11	83	F	S	Colon	$T_3N_2M_o$	Hemicolectomy	17 m
12	85	F	I	Colon	$T_3N_2M_1$	Hemicolectomy	10 m
13	80	M	I	Rectum	$T_2N_oM_o$	Resection	>24 m
14	90	F	S	Breast	$T_2N_xM_x$	Hormone	>54 m
15	86	M	S	MPD	Polycythaemia vera	Phlebotomy	>24 m
16	59	M	I	Unknown	Liver metastasis	Palliative	43 m

DVT: deep venous thrombosis; F: female: I: idiopathic; M: male; m: month; MPD: myeloproliferative disorder; S: secondary; y: years; Survival denotes survival after the diagnosis of cancer in months (m) or weeks (w); patients with an upper limit (e.g. >24 m) were alive at the last point of follow-up.

Table 3

Contribution of diagnostic steps in the evaluation of patients with deep venous thrombosis for occult cancer.

Diagnostic step(s)	Decisive finding(s)	Malignant disorder	Stage
History	Change of bowel habits	Rectum	$T_2N_0M_0$
History	Tar stool	Colon	$T_3N_2M_0$
Physical exam	Breast lump	Breast	$T_2N_xM_x$
Physical exam	DRE	Prostate	$T_1N_xM_x$
Physical exam	DRE	Prostate	$T_3N_xM_x$
Physical exam	DRE	Prostate	$T_3N_1M_1$
Chest x-ray	Rib osteolysis	Pancreas	$T_3N_1M_1$
Chest x-ray	Hilus enlargement	Lung	$T_3N_2M_1$
Abdominal US	Retroperitoneal mass	Pancreas	$T_3N_xM_x$
Abdominal US	Liver metastases	Unknown origin	Liver metastasis
Laboratory tests	Haemoglobin elevated	Polycythaemia vera	–
History + chest-x-ray	Haemoptysis / pulmonary mass	Lung	$T_4N_2M_1$
Physical exam + chest-x-ray	Lymphadenopathy / pulmonary mass	Lung	Extensive disease
Physical exam + chest-x-ray	Lymphadenopathy / pulmonary nodule	Lung	$T_3N_2M_1$
History + abdominal US	Weight loss / Pancreatic mass	Pancreas	$T_3N_xM_x$
History + abdominal US	Weight loss / hydronephrosis	Colon	$T_3N_2M_1$

DRE: digital rectal examination suspicious; US: ultrasonography

For 434 (94%) patients follow-up data were complete (figure 1). They were followed for 33 ± 19 months [range 3–84]. In these patients 26 cancers occurred, sixteen (7.8% [95%-CI: 4.0–11.5]) in patients with IDVT and ten (4.35% [95%-CI: 1.7–7.0]) in those with SDVT, representing an incidence rate of 1.36 per 100 patient-years in the IDVT group and 0.85 per 100 patient-years in the SDVT group.

Five of the 26 (19%) incident malignomas were lymphoproliferative disorders, four each (15%) colorectal or lung cancers, and two each (8%) were thyroid, breast, prostate or renal cancer (table 4). In the first year after the diagnosis of cancer seventeen of the 26 patients died, only one of them from a cause other than the cancer. Less than 50% (12/26) survived the first six months after the diagnosis of cancer was made.

The difference in the incidence rates for cancer over time in patients with IDVT and those with SDVT did not reach statistical significance, but there was a trend towards an higher incidence of cancer in the IDVT group (hazard ratio 1.9 [95%-CI: 0.86–4.1]: figure 2). In the first six months six of the 26 cancers were diagnosed – five of 16 (31%) in patients with IDVT and one of 10 (10%) in those with SDVT.

Table 4

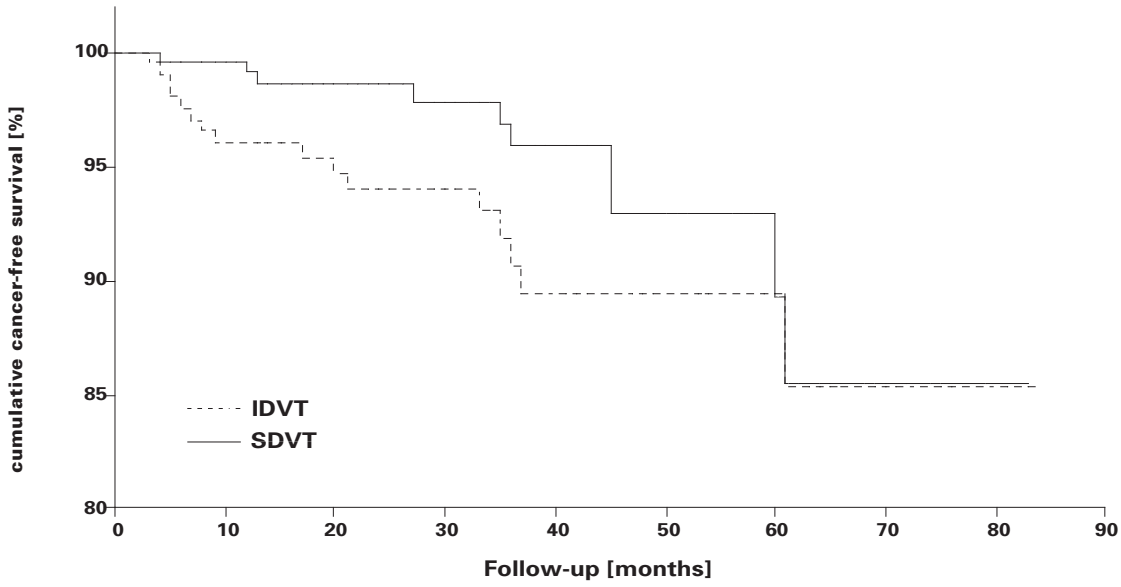
Incident cancers during follow up after an episode of idiopathic or secondary deep venous thrombosis.

	Age (y)	Sex	DVT	Primary cancer site	Stage	Time after DVT	Survival* after diagnosis
1	78	M	I	Unknown	Lymphangiosis	3 m	In-hospital death
2	65	M	S	Colon	$T_3N_1M_1$	4 m	4 m
3	50	M	I	Lung	$T_3N_1M_1$	4 m	8 m
4	76	M	I	Lung	$T_4N_2M_1$	5 m	In-hospital death
5	66	M	I	Kidney	$T_2N_0M_0$	5 m	In-hospital death**
6	77	M	I	Prostate	$T_3N_0M_0$	6 m	>65 m
7	71	M	I	Lung	$T_3N_xM_x$	7 m	In-hospital death
8	73	M	I	Cerebral lymphoma	–	8 m	In-hospital death
9	82	M	I	Prostate	$T_4N_1M_1$	9 m	29 m
10	79	F	S	Colon	$T_4N_2M_1$	12 m	>8 m
11	57	M	S	Stomach	$T_2N_1M_x$	13 m	4 m
12	74	M	I	Osteomyelofibrosis	–	17 m	>22 m
13	73	F	I	Breast	$T_2N_0M_0$	20 m	>8 m
14	52	M	I	Pharynx	$T_3N_1M_x$	21 m	>3 m
15	80	F	S	Melanoma	$C_5T_xN_xM_1$	27 m	2 m
16	81	F	I	Colon	$T_2N_2M_x$	33 m	11 m
17	73	M	I	Rectum	$T_2N_0M_0$	35 m	37 m
18	72	F	S	AML	–	35 m	In-hospital death
19	72	M	S	Thyroid	$T_2N_xM_1$	36 m	1 m
20	83	F	I	Kidney	$T_2N_xM_2$	36	2 m
21	82	M	I	Lung	$T_2N_1M_1$	37	In-hospital death
22	30	M	S	NHL	IIIB	45	3 m
23	64	F	S	Breast	Recurrent	45	>3 m
24	76	F	S	Thyroid	$T_2N_xM_1$	60	11 m
25	49	M	I	NHL	Cutaneous	61	>61 m
26	80	F	S	Ovary	$T_3N_xM_1$	61	2 m

AML: acute myeloid leukaemia; DVT: deep venous thrombosis; F: female; I: idiopathic; m: months; NHL: Non-Hodgkin-lymphoma; S: secondary; y: years.*Survival denotes survival after the diagnosis of the incident cancer; patients with an upper limit (e.g. >65 m) were alive at the last point of follow-up. In-hospital death means the patient died during the hospital stay during which the cancer was diagnosed. ** Patient died of heart failure, the cancer was an autopsy finding.

Figure 2

Kaplan-Meier event-free survival curves comparing the cumulative percentages of patients with idiopathic deep venous thrombosis (IDVT) and secondary deep venous thrombosis (SDVT) who remained free of cancer. There is a trend towards a higher incidence of cancer in patients with IDVT compared to those with SDVT (p = 0.1090).



Discussion

In a large cohort of 485 consecutive patients admitted primarily with a confirmed DVT who were evaluated for an underlying cancer 16 (3.3%) patients with a hitherto unknown malignant disorder were identified. The prevalence of cancer was more than twofold higher in patients with idiopathic DVT (4.7%) i.e. in patients without a risk factor for DVT than in patients having at least one of several conditions generally accepted to predispose for DVT (2.0%). Our study confirms the clinical wisdom that an idiopathic DVT can in fact be a marker for undiagnosed cancer [11, 18–26]. In studies that found no clinically relevant association of DVT with cancer the diagnosis of DVT was often based either on clinical findings alone or patients with IDVT and SDVT were analysed together which may have diluted the real magnitude of the association [27, 28].

Nearly all patients with IDVT were evaluated for cancer following the scheme endorsed as usual care in our hospital (patient history, clinical examination, basic laboratory tests, routine chest x-ray, and abdominal ultrasound). In more than two thirds of the patients with SDVT an abdominal sonography was ordered. The yield of this search strategy in terms of prevalent cancer is comparable to that reported in similar studies [20, 24, 26, 29]. In earlier series reporting cancer rates of more than 20% the number of patients was small [30], patients with already known malignant disorders were included [31], a far more aggressive tumour search program was used [21, 23, 31, 32], or investigators were instructed to pay special attention to symptoms suggestive of cancer allowing for a positive observation bias [21].

We believe our experience justifies a search for an underlying cancer especially in patients with IDVT although only few patients were treatable with a curative intention in our series. However, the evaluation can be restricted to a systematic patient history, a clinical examination,a few basic laboratory tests, and a chest x-ray. Almost all patients with cancer were identified by abnormal findings in one or more of these components. The incremental yield of routine abdominal ultrasound was small. In only two patients – one patient with advanced pancreatic cancer and another with liver metastases of an unknown primary tumour – abdominal sonography was decisive for the detection of a cancer. Screening for cancer with abdominal sonography generates costs by itself and through follow-up tests ordered for false-positive results. Furthermore, it may result in additional procedural morbidity and psychological distress for the patients. Although the detection of only two cancers in our series solely by abdominal ultrasound may represent a chance finding, we think, in accordance with most former reports, abdominal ultrasound can safely be omitted when evaluating patients with DVT for occult cancer [26, 29, 33–39]. In one of our institutions (Buergerspital Solothurn) this approach has become the standard procedure.

In the absence of a randomised, prospective study one next best way to evaluate the value of a tumour search programme is to follow a cohort of patients with DVT for the occurrence of cancer after the index hospital stay. We achieved an excellent follow up of 94% with a mean duration of 32 months and observed a probability of cancer in patients with IDVT of 7.8% (95%-CI: 4.0–11.5) and of 4.5% (95%-CI: 1.7–7.0) in those with SDVT. These figures compare well to those of similar cohort studies [20, 21, 33, 34, 40]. The higher incidence rate of cancer in patients with IDVT than in those with SDVT adds weight to the hypothesis that an otherwise unexplained DVT is a marker for an occult cancer.

Why the difference in cancer incidence rates between patients with IDVT and SDVT did not reach statistical significance in our study as it did in others remains unclear [20]. The allocation of patients with a prior DVT to the SDVT group rather than treating them as IDVT patients does not explain this observation. When patients with prior DVT were handled as IDVT cases, the incidence of cancer in IDVT was 7.0% (95%-CI: 4.1–9.9), in SVDT 3.7% (95%-CI: 2.1–5.4) (p = ns). Our comparison group of SDVT patients probably does not accurately reflect the baseline population risk of cancer. Alternatively, the follow-up may have been too long resulting in a dilution of a probable difference in cancer incidence. Confirming reports that cancer in patients after IDVT becomes clinically symptomatic predominantly in the first six months after the thrombotic episode we found that six of 26 (31%) incident cancers were diagnosed within the first half year after the DVT [20, 22, 41–43]. Five of these six tumours were diagnosed in an advanced stage – a relationship well described in a recent population based analysis [44]. Whether they might have been diagnosed in an earlier stage if a more aggressive evaluation had been done while hospitalised for DVT must remain speculative. A critical review of the charts, chest x-rays and ultrasound reports of the six patients showed that no diagnostic clue for cancer was obviously missed. Computed tomography of the thorax in two patients with lung cancer and colonoscopy in one patient with colon cancer might have revealed the diagnosis several months earlier. However, we believe that introducing these two methods into the routine evaluation of patients with IDVT cannot be justified by a large enough yield and would generate unacceptable costs.

The identification of additional risk factors for cancer in patients with IDVT would help to focus an in-depth evaluation for malignant disorders on those with a higher chance to profit from it. In ear-

lier studies a larger risk for cancer was reported in patients younger than 60 years [22, 42]. The fact that we could not reproduce this finding may be due to the smaller number of patients in our cohort. If certain types of undiagnosed cancer were associated more often with DVT than others an aggressive tumour search could be directed towards such specific sites. Former studies have emphasised the occurrence of gastrointestinal and urogenital tumours with DVT and have stated that unknown lung, breast, and brain tumours are almost never found while evaluating a thrombotic episode [20, 32]. However, we found a mixed composition of incident cancers in patients after IDVT including lung, prostate, and intestinal tumours. Probably the predominance of gastrointestinal and urogenital tumours in older reports represents an observation bias as technologies such as computed tomography or colonoscopy were not or only rarely available when these studies were done.

In conclusion patients with IDVT have a prevalence and incidence of cancer large enough to justify an evaluation for an underlying malignant disorder. A search consisting of history, physical examination, basic laboratory tests and a chest x-ray detects occult cancers with a sufficient sensitivity and specificity. An abdominal ultrasonography is not a compulsory part of the work-up.

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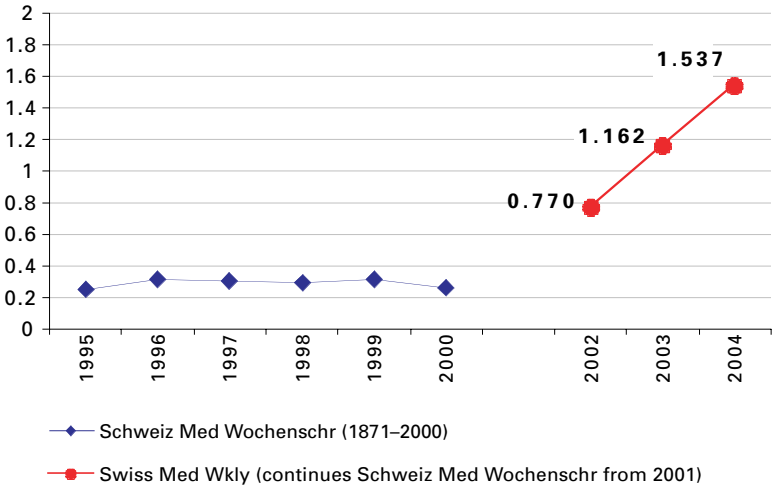

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