Deep vein thrombosis in primary care:
possible malignancy?

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ABSTRACT

Background
The increased prevalence of unrecognised malignancy in patients with deep vein thrombosis (DVT) has been well established in secondary care settings. However, data from primary care settings, needed to tailor the diagnostic workup, are lacking.

Aim
To quantify the prevalence of unrecognised malignancy in primary care patients who have been diagnosed with DVT.

Design
Prospective follow-up study.

Setting
All primary care physicians affiliated/associated with a non-teaching hospital in a geographically circumscribed region participated in the study.

Method
A total of 430 consecutive patients without known malignancy, but with proven DVT were included in the study and compared with a control group of 442 primary care patients, matched according to age and sex. Previously unrecognised, occult malignancy was considered present if a new malignancy was diagnosed within 2 years following DVT diagnosis (DVT group) or inclusion in the control group. Patients with DVT were categorised in to those with unprovoked idiopathic DVT and those with risk factors for DVT (that is, secondary DVT).

Results
During the 2-year follow-up period, a new malignancy was diagnosed 3.6 times more often in patients with idiopathic DVT than in the control group (2-year incidence: 7.4% and 2.0%, respectively). The incidence in patients with secondary DVT was 2.6%; only slightly higher than in control patients.

Conclusion
Unrecognised malignancies are more common in both primary and secondary care patients with DVT than in the general population. In particular, patients with idiopathic DVT are at risk and they could benefit from individualised case-finding to detect malignancy.

Keywords
deep vein thrombosis; idiopathic; neoplasms; primary health care.

INTRODUCTION

A relationship between thrombosis and malignancy has been suspected since the times of Virchow and Trousseau. Based on a substantial number of epidemiological studies,[1–13] proof of this relationship has strengthened over the last two decades. Post-mortem studies and studies in surgical patients with a malignancy have shown that malignancy is often accompanied by thromboembolism.[14,15] Other studies have reported that approximately 10–20% of patients with deep vein thrombosis (DVT) are diagnosed with a malignancy before or at the time of the thrombotic event.[3,6,12,13] Several recent studies addressed the question whether thromboembolism is a marker for an unrecognised (occult) or subsequent malignancy, reporting a 4–10% prevalence of unrecognised malignancy in patients with idiopathic (unprovoked) DVT[13] and a lower prevalence in patients with secondary DVT (with known risk factors).[16,17] The prevalence of unrecognised malignancy varied considerably between studies, and was at least partly attributable to the number and type of routine examinations performed to detect malignancies and the characteristics of the included patients.

It should be emphasised that most studies quantifying the association between DVT and the presence of unrecognised malignancy were

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How this fits in

Patients with idiopathic (unprovoked) DVT have an elevated risk of malignancy. The risk in patients with known risk factors (secondary DVT), is nearly the same as in the population at large. These findings in primary care are the same as those known from secondary care.

performed at referral centres, while most patients with DVT are presented in primary care.[1,3,5–7] Knowledge of the prevalence of unknown malignancy after DVT diagnosis in primary care patients is, therefore, important in order to tailor possible screening strategies to this large patient group.[18,19]

In the present study, we compared the frequency of a newly diagnosed malignancy in primary care DVT patients with that in a matched sample from the general population. To our knowledge, studies establishing the prevalence of unrecognised malignancy in patients with DVT in a primary care setting are lacking.

METHOD

Patients

This study was part of a large ongoing investigation aimed at optimising the diagnostic management of DVT in primary care. Details of that study have been published elsewhere.[20,21] Briefly, 1829 consecutive adult patients with clinically suspected DVT, who consulted their primary care physician between 1 January 1996 and 31 July 2002, were evaluated. The suspicion of DVT was based on the presence of a painful, swollen leg that existed no longer than 30 days. The study was conducted in a circumscribed geographic region of the Netherlands that includes a non-teaching hospital with a catchment area of 50 primary care physicians and about 130 000 inhabitants. All 50 primary care physicians in the catchment area participated in our study and used the diagnostic facilities of the participating hospital, without referring the patient to a hospital specialist. During the study period free access to the ultrasound diagnostic facilities participating in our study was the first step in the diagnostic management for all patients suspected of having DVT in the region. Our study protocol was integrated in the regular work-up of primary care patients suspected of having DVT. All 50 primary care physicians contributed to the study and each included on average 9–10 patients suspected of having DVT per year. They all received detailed instructions immediately before the start of the project during a specially organised conference that included workshops dedicated to the logistics of the study.

When a patient was suspected of having DVT, the primary care physician filled in a case record form comprising standardised information with regard to history taking (risk factors for DVT), physical examination, and D-dimer testing. The final diagnosis of DVT was established by real-time B-mode compression ultrasonography (CUS) of the lower extremities with a standard 5-12-MHz linear-array transducer. After 7 days this test was repeated in patients with a normal CUS measurement.[22,23] There was no protocol for the systematic detection of concomitant cancer. Patients with an established DVT were treated initially by their primary care physician with weight-adjusted low molecular-weight (LMW)-heparin concomitant treatment with vitamin K antagonists until an international normalised ratio (INR) of 2–3 was achieved. The vitamin K antagonist therapy was then continued for 3–6 months.

Patients were classified as having secondary DVT if at least one of the following risk factors for DVT was present: recent surgery, prolonged immobilisation; use of oral contraceptives or hormonal replacement therapy; history of previous DVT; trauma of the leg, and; known coagulation disorders.[12,16,17] If no risk factors for DVT were present, the patients were classified as having idiopathic DVT. Controls were recruited from the same primary care practice as the patients. The GP enlisted a control subject without a known diagnosis of malignancy for each DVT patient, matching sex and age (within the same 5-year age category).

The study protocol was approved by the Medical Ethical Committee of the University Medical Center, Utrecht. The GP provided anonymous data for each control patient.

Assessment of unrecognised malignancy

Patients with a known history of malignancy as well as patients in whom a malignancy was detected

Table 1. Characteristics of the study population and results of the study.

	DVT patients			
	All *n* = 430	Idiopathic *n* = 162	Secondary *n* = 268	Control group *n* = 442
Mean age (SD), years	60.7 (18.2)	61.5 (17.8)	60.0 (18.4)	61.1 (17.3)
Male sex *n* (%)	162 (37.7)	66 (40.7)	96 (35.8)	159 (36.0)
Patients with malignancy	19	12	7	9
Malignancy first year	8	7	0	1
Malignancy second year	11	5	7	8
Two-year incidence of malignancy (%) (95% CI)	4.4 (2.5 to 6.3)	7.4 (3.4 to 11.4)	2.6 (0.7 to 4.5)	2.0 (0.1 to 3.9)
RR (95% CI)	2.2 (1.0 to 4.7)	3.6 (1.6 to 8.4)	1.3 (0.5 to 3.4)	1
P value	0.071	0.004	0.842	[a]

[a]*Reference category. DVT = deep vein thrombosis;* n = *number of patients. RR = relative risk = cumulative incidence ratio.*

within 14 days after DVT diagnosis were excluded from the analysis.[2–4] The prevalence of unrecognised malignancy was then estimated in the remaining patients. A 2-year cumulative incidence of a newly diagnosed malignancy was used as a proxy to determine the prevalence of unrecognised malignancy in patients with DVT. This time frame was based on the results of studies showing that a period of 2 years after DVT diagnosis is sufficient to ensure that all cases of DVT with hitherto unrecognised malignancy are found.[1,2,10] In fact, most unrecognised malignancies become apparent within the first 6–12 months after the onset of DVT and, after 2 years, the incidence of malignancy in DVT patients is comparable to that in the population at large.[5,7] Primary care physicians were thus requested to report whether a malignancy was diagnosed within the 2-year period following DVT diagnosis.

In order to compare the prevalence of unrecognised malignancy in DVT patients with that in the control group, the same methods were used to establish the 2-year cumulative incidence in the control patients.

Data analysis

Data were entered in a computerised database and analyses were performed with SPSS software, version 12.0 for Windows (SPSS, Inc., Chicago, IL, US). Proportions and relative risks were calculated with corresponding *P*-values where appropriate.

RESULTS

The diagnosis of DVT was confirmed in 550 patients, 94 (17.1%) of whom were excluded because a malignancy was diagnosed before or within 2 weeks of the DVT diagnosis. In addition, 26 patients were excluded because they were lost to follow-up. Of the remaining 430 DVT patients, 162 were categorised as having idiopathic DVT and 268 as having secondary DVT. The ages of the idiopathic DVT and secondary DVT patients were similar, but there were more men in the idiopathic DVT group (Table 1).

The 2-year incidence of malignancy was 4.4% for all DVT patients combined, 2.6% for the patients with secondary DVT, and 7.4% for those with idiopathic DVT. The 2-year incidence of malignancy in the control group was 2.0%. Using the control group as the reference, the relative risk (RR) of newly diagnosed malignancy was 2.2 (95% CI = 1.0 to 4.7; $P = 0.071$) for all DVT patients, 1.3 (95% CI = 0.5 to 3.4; $P = 0.842$) for the secondary DVT patients, and 3.6 (95% CI = 1.6 to 8.4; $P = 0.004$) for those with idiopathic DVT. This risk was 2.8 (95% CI = 1.1 to 6.9; $P = 0.036$) for idiopathic versus secondary DVT patients.

Malignancy became apparent within the first year after DVT diagnosis in more than half the cases (7 of 12) in the idiopathic DVT group, in none in the secondary DVT group, and in only one of nine patients in the control group (Table 1). The types of malignancy (that is, primary sites) observed is shown in Table 2.

Table 2. Distribution of different types of malignancies among the DVT patient and control patients.

	DVT patients *n* = 430 *n* (%)	Control patients *n* = 442 *n* (%)
All types of malignancy combined	19 (4.4)	9 (2.0)
Colorectal	3 (16)	0 (0)
Urogenital	5 (26)	4 (44)
Breast	4 (21)	4 (44)
Lung	3 (16)	1 (11)
Other	4 (21)	0 (0)

DVT = deep vein thrombosis.

DISCUSSION

Summary of main findings

Our results indicate a relationship between the presence of idiopathic (unprovoked) DVT and hitherto unrecognised malignancy in primary care patients. The short-term risk of a malignancy in patients diagnosed with secondary DVT (with known risk factors) was only slightly higher than that in the population at large. The elevated risk of malignancy usually appeared during the first year after the diagnosis of DVT.

Comparison with existing literature and strengths and limitations of the study

To our knowledge, this is the first large study in primary care to determine the prevalence of unrecognised malignancy in patients with DVT. Despite the difference in setting, our findings are consistent with those of recent studies performed in secondary care.[1,5–7,12] We observed a 2-year incidence of 4.4% for all patients with DVT. This is comparable to the 4.7% found in the secondary care studies summarised by Hettiarachchi *et al*[6] and the 4% reported in two studies based on data from general populations.[5,7] In our study, the 2-year incidence of a newly diagnosed malignancy in patients with idiopathic DVT was 7.4%. This figure was 7.3% in the study by Hettiarachchi *et al*,[6] 7.2% in the study by Prandoni *et al*,[1] and 7.8% in the recent study by Ronsdorf *et al.*[12] A study by Piccioli *et al*[17] showed that the incidence of a newly diagnosed malignancy was higher (13.1%) in patients with idiopathic DVT when an extensive screening was used at the time of DVT diagnosis with an additional incidence of 1% in the 2-year follow-up, than when the patients were not screened (9.8%). Several relatively small secondary care studies also reported a higher incidence, but this

seems attributable to the imprecision of the estimates due to the limited sample sizes.[24–25]

Although our study did not have sufficient power to exclude an increased risk of occult malignancy in patients with secondary DVT compared to the population at large (RR = 1.3; 95% CI = 0.5 to 3.4; *P* = 0.842), the elevated risk of a newly diagnosed malignancy in DVT patients in our study can be attributed to the patients with idiopathic DVT.

In accordance with earlier studies, most of the extra malignancy cases became apparent during the first year after DVT.[5,7,10,13] In addition, the types of malignancies observed in our study were similar to those reported in other studies.[3,5–7] Our numbers were too small to draw any in-depth conclusions regarding the type of malignancy most often implicated in DVT.

Implications for future research and clinical practice

We conclude that the prevalence of a hitherto unknown malignancy in primary care patients with idiopathic DVT is comparable to that known from secondary care studies and is more than three times the prevalence in the population at large. The primary care physician should, therefore, be aware of the possibility of an occult malignancy in these patients, especially during the first year after DVT diagnosis.

A relatively high prevalence of malignancy does not, however, automatically imply that screening for malignancy is indicated in DVT patients since it is unknown whether a substantial proportion of these malignancies can be diagnosed at such an early stage and whether earlier detection will ultimately prolong life rather than merely advance the date of diagnosis. The debate on screening for malignancy when DVT is diagnosed is thus ongoing and there is as yet no consensus.[4,8,9,11,12,19] Definitive evidence of a positive effect of a screening programme for occult malignancy on the prognosis of patients with DVT can only be obtained by means of a large randomised clinical trial. A study that was designed to solve this problem (SOMIT study) was started in 1992, but terminated prematurely because of logistic problems, without conclusive results.[17] As there is as yet no evidence to advise routine screening for malignancy in DVT patients, a strategy of patient-based evaluation (case-finding), particularly in idiopathic DVT patients, should be further explored.

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Ethics committee

The study protocol was approved by the Medical Ethical Committee of the University Medical Center, Utrecht (00-202)

Competing interests

The authors have stated that there are none

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