Venous thromboembolism, coagulation and cancer
van Doormaal, F.F.

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Is there an increased incidence of cancer in primary care patients diagnosed with idiopathic superficial thrombophlebitis?

F.F. van Doormaal, S. Atalay, H. Brouwer, E.F. van der Velde, H.R. Büller, H. van Weert

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ABSTRACT

Purpose
The association of spontaneous venous thromboembolism with occult malignancy is well established. Less clear is the incidence of subsequent cancer in patients with superficial thrombophlebitis. Therefore, we determined the incidence of cancer after an episode of spontaneous superficial thrombophlebitis in a large general practice population.

Methods
The objective of this study was to assess the incidence of newly diagnosed malignancies in patients within two years after presenting with a spontaneous episode of superficial thrombophlebitis and to compare this incidence to non-exposed matched control patients and the Dutch population. The patients and their controls were identified by a search in the electronic patient records of 5 primary health care centers in Amsterdam, The Netherlands. A standardised morbidity ratio was calculated using data of the Dutch cancer registry.

Results
A total number of 277 superficial thrombophlebitis patients were identified, of which 250 patients had no cancer at study entry. In 5 of these 250 patients (2%; 95% CI 1-5%) a new malignancy was diagnosed within two years after their superficial thrombophlebitis compared to 2% (95% CI 1-4%) in the control subjects. The standardised morbidity ratio was 1.1 (95% CI 0.5-2.7). A recurrent episode of superficial thrombophlebitis was observed in 18 of the 250 patients and in one of these patients cancer was diagnosed within 24 months after the first episode of superficial thrombophlebitis.

Discussion
We conclude that a single episode of unprovoked superficial thrombophlebitis diagnosed by a family physician is not associated with an increased risk of subsequent cancer.
INTRODUCTION
In 1865, Armand Trousseau described an association between recurrent superficial thrombophlebitis and occult malignancy, which is now termed the Trousseau syndrome [1]. This entity is characterized by a recurrent and migratory pattern of inflammation of superficial veins, frequently in unusual sites such as the arm or chest. Since then, many studies reported on the association between venous thromboembolism and cancer. A recent study observed a mean 10% (95% CI 8.6-11.3) incidence of malignancy within the first 12 months after the diagnosis of an unprovoked deep vein thrombosis of the leg or pulmonary embolism [2]. The venous thromboembolism is believed to be at least partially provoked by the at that time still occult cancer. The incidence of newly diagnosed cancer is increased until years after presentation with unprovoked venous thromboembolism, however most cancers are diagnosed within the first months after diagnosis of VTE [3;4]. In numerous text books it is stated that not only deep vein thrombosis or pulmonary embolism, but also superficial venous thrombophlebitis (SVTP) is associated with occult malignancy. However, careful analysis of the literature reveals that so far only case reports have described this association.

We, therefore, performed a study to determine the incidence of cancer during a two year follow up period after a first episode of unprovoked SVTP in a large general practice population. The incidence of cancer was compared to a cohort of practice-, age-, and gender matched control patients without SVTP and to the incidence of cancer in the Dutch population.

METHODS
The objective of this study was to determine the incidence of newly diagnosed malignancies in patients presenting with a spontaneous first episode of SVTP and to compare this incidence to the incidence of cancer in non-exposed control patients and the general population. In the Dutch health care system every citizen is enlisted by a family physician, who keeps health records and functions as a gate keeper to secondary care. In case of any health problem, for which medical care is needed this family physician is consulted. Family physicians treat approximately 94% of the health problems themselves and refer if necessary [5].

The electronic patient records of 5 health care centers (28 family physicians) are stored anonymously at the Department of General Practice in the Academic Medical
Center, Amsterdam, the Netherlands and were available for the present analyses. In this register relevant information of all contacts between the physician and patients is recorded. For diagnostic coding the ICPC (International Classification of Primary Care) codes and for medication ATC (Anatomical Therapeutic Chemical) codes are used. For the study reported here, anonymous data of approximately 38,000 adult patients were analyzed. The inception period was from January 1995 until December 2004.

**Identification of cases and controls**
The medical records were searched for episodes of SVTP using diagnostic coding and truncated keywords (t(h)romb*, phleb* and *eb*). Family physicians diagnosed SVTP clinically according to the rules of the ICPC: ‘signs of inflammation along a superficial vein’. The medical records were checked by two investigators independently, to determine if the record did concern a SVTP. In case of a list of more than one possible diagnosis, SVTP should be the first diagnosis in the list to be considered as a case of SVTP. The date of diagnosis of SVTP was taken as the index date. SVTP associated with venous catheters or recent surgery as noted in the medical records were considered as provoked and therefore excluded. We studied all consultations during a month after the event manually to exclude misclassified cases. For each SVTP patient two control patients were selected. These patients had no history of venous thrombosis or SVTP and were matched for family physician, gender and age. No other patient characteristics to control for possible cofounding could be extracted out of the source database.

**Follow-up**
The family physician registers all malignancies with the date of diagnosis in the ‘problem’ lists of the medical records of all patients. Because of the seriousness of the disease it was assumed that all diagnosed malignancies were captured in this database. Additionally, the medical records of both the SVTP group and the control group were searched manually for listing of cancer. The subjects in which cancer was diagnosed before the moment of diagnosis of SVTP were categorized separately. Patients and control subjects were followed up for 24 months.

The cumulative incidence of cancer per gender and age category of the SVTP population was also compared to the incidence of cancer per gender and age of the overall Dutch population using data of the national cancer registration. This registration collects data from cancer patients including tumour type, date of diagnosis and tumour
stage and is linked to the international agency for research on cancer [6]. A standardized morbidity ratio (SMR) was calculated using STATA.

RESULTS
A total number of 880 case records were searched for SVTP. In 27 patients a provoked SVTP was recorded. The total number of patients with a spontaneous episode of SVTP was 277 of whom 26% were men. The mean age was 59 years. The matched control group consisted of 553 subjects of whom also 26% were men whereas the mean age was 58 years. For one female patient born in 1907, only one control of the same age, gender and family physician could be identified. Of all patients with unprovoked SVTP cancer was diagnosed in 27 patients (10%, 95% CI 7-14) before the episode of SVTP, whereas in 49 of the controls (9%, 95% CI 7-12) a malignant process was diagnosed before the index date.

We retrieved complete follow up data during 24 months after the indexdate in 243 (88%) SVTP patients compared to 469 (85%) control subjects. The other subjects were either lost to follow up (n=83) or died within 24 months after the indexdate (n=35) with similar rates in both groups. The mean follow up period of the SVTP patients who did not complete follow up was 12 months compared to a mean follow up of 11 months in the control subjects without complete follow up.

In 5 of the 250 SVTP patients without cancer at study entry (2%, 95% CI 1-5) a new malignancy was diagnosed within 24 months after the diagnosis of spontaneous SVTP compared to 10 new malignancies in the 504 control subjects without cancer at study entry (2%, 95% CI 1-4). The outcomes are summarized in Table 1. Two of the five newly diagnosed cancer patients in the SVTP group died within the 24 months follow up period compared to two of the ten control subjects with a newly diagnosed malignancy. None of the other cancer patients in the SVTP and control group were lost to follow up. The types of cancer are described in Table 2. Compared to the overall Dutch population no difference was observed in the incidence of cancer in two years after the index date, with a SMR of 1.1 (95% CI 0.5-2.7).

Of all 245 SVTP patients without cancer at study entry or during follow-up 5 patients (2%) died before the end of the 24 month follow up period (Table 1). In the control group 11 (2%) of the 494 subjects died within 24 months after the index date. None of those deaths was associated with cancer.
Of the 250 SVTP patients without cancer at study entry, 18 patients (7%, 95% CI; 4-11) experienced at least one recurrent episode of SVTP during the 2 year follow up period. The mean age of these patients was 62 years (range 35-87) and 4 of them were men. The median period between the first SVTP and the recurrence was 12 months (range 0.6-23). In one recurrent SVTP patient (6%, 95% CI 0.1-27) a malignancy was diagnosed during the follow up period. Careful review of his medical records (including hospital records) revealed that a Grawitz tumor already was present (but not diagnosed) when he presented his first episode of SVTP.

Table 1 - Follow-up and Outcomes

<table>
<thead>
<tr>
<th>SVTP patients</th>
<th>Control group</th>
<th>Absolute difference %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%; 95% CI)</td>
<td>N (%; 95% CI)</td>
</tr>
<tr>
<td>Patients with incomplete follow up</td>
<td>34 (12%; 8 to 16)</td>
<td>84 (15%; 12 to 18)</td>
</tr>
<tr>
<td>Deaths within 24 months after index date</td>
<td>16 (6%; 3 to 9)</td>
<td>19 (3%; 2 to 5)</td>
</tr>
<tr>
<td>Subjects with newly diagnosed cancer within 24 months after index date</td>
<td>5 (2%; 1 to 5)</td>
<td>10 (2%; 1 to 4)</td>
</tr>
<tr>
<td>Recurrent SVTP in patients without cancer at study entry</td>
<td>18 (7%; 4 to 11)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2 - Malignancies diagnosed within 2 years after the indexdate

<table>
<thead>
<tr>
<th>SVTP group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic syndrome</td>
<td>Breast carcinoma (N=6)</td>
</tr>
<tr>
<td>Urothelial cell carcinoma, bladder</td>
<td>Bronchial carcinoma</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Urothelial cell carcinoma, bladder</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>Unknown primary origin (N=2)</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
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</table>

**DISCUSSION**
In this case-control study no increased incidence of cancer after the diagnosis of a first episode of unprovoked SVTP was observed. During the two year observation period after SVTP, the cumulative incidence of cancer was 2% (95% CI 1-5). These findings were confirmed comparing the incidence of new cancers in the SVTP patients with the incidence in the overall Dutch population (SMR 1.1, 95% CI; 0.5-2.7). However, two or
more episodes of SVTP might be associated with a higher risk of cancer, but in the present cohort it concerned only one patient.

We acknowledge some strengths and limitations of this work. To our knowledge this is the first empirical study in general practice which determines the possible association of spontaneous SVTP with cancer. A very sensitive search strategy was used within the registry to identify patients with SVTP, which we believe made the identification of patients with SVTP almost complete. Furthermore, missing a diagnosis of cancer is most unlikely because of the importance of this disease for daily practice and the analyzed recording system. Finally, we used the same search strategy in both groups. Matching for family physician reduces the influence of interdoctor variation.

A limitation of the study is the lack of objective assessment of the diagnosis of SVTP. Family physicians diagnose SVTP clinically. An objective assessment of the diagnosis is performed only when (also) deep venous thrombosis is suspected. To diminish the number of misclassifications, we checked the medical records of these patients for four weeks after the date of diagnosis of SVTP with the assumption that family physicians would change their diagnosis when it proved wrong. Another limitation of this study is the relatively high rate of ‘lost to follow up’ of 6% in the SVTP and 12% in the control group. The diagnosis of new malignancies in these subjects can not be excluded, however considering the higher number of patients lost to follow up in the control group it is more likely to bias towards the no-difference observation. Furthermore, the patient groups are quite small. However, 1245 SVTP patients should have been included in the study to detect a difference of 2% between both groups. Assuming a 4% incidence of cancer in the SVTP group compared to 2% incidence of cancer in the control group (one sided α 0.05, β 0.1). Such a small difference however would probably not be of great clinical relevance. Finally, more information on patient characteristics could not be extracted out of the source database, which impairs analyses on potential confounders.

We conclude that a first episode of unprovoked SVTP diagnosed by a family physician is not associated with an increased risk of cancer in the next two years relative to non SVTP patients or the general public. As a result it is unlikely that SVTP patients have more often an occult malignancy at the time of their presentation. However, recurrent SVTP might be associated with cancer and further diagnostic evaluation seems appropriate.
ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest.
REFERENCE LIST


PART

Microparticles and cancer
Microparticle-associated tissue factor activity in cancer patients predicts the risk for developing venous thromboembolism


Submitted for publication
ABSTRACT
Procoagulant microparticles (MP) have been observed in cancer patients with venous thromboembolism (VTE). This study evaluates the predictive value of the MP-associated procoagulant activity for development of VTE in cancer patients. The procoagulant activity was measured by (i) a phospholipid-dependent coagulation test (PPLT), (ii) a factor Xa-generation assay and (iii) a fibrin generation test (FGT). The last two tests were also performed in the presence of anti-tissue factor (TF; factor Xa-generation assay) or anti-factor VII(a) (FGT). Plasma was collected of 43 unselected cancer patients. Five patients (12%) developed VTE within six months. No difference was observed in the PPLT at baseline between patients with and without VTE (p=0.519). Marked differences, however, were present in the FGT in the absence of antibodies (p=0.014), and in TF-dependent factor Xa generation and fibrin generation (p=0.016 and p=0.036, respectively). Receiver operating characteristic analyses showed that the FGT had the highest area under the curve (0.83; 95% CI 0.68-0.98; p=0.017). A cut off level of 909 seconds resulted in a sensitivity of 80% and a specificity of 84%. We conclude that the MP-associated procoagulant activity may identify those cancer patients at high risk for development of VTE.