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Cancer before and after venous thrombosis and the risk of recurrent venous thrombosis: Results from the MEGA follow-up study

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Abstract

Background
The magnitude of the risk of recurrent venous thrombosis (VT) in patients with cancer is not well described and results for different types of cancer are not consistent. We aimed to evaluate the risk of recurrent VT in relation to time of diagnosis and for several types of cancer.

Patients and methods
Patients with a first deep vein thrombosis of the leg or pulmonary embolism were followed for recurrence from time of VT-diagnosis (MEGA follow-up study). Incidence rates (IR) of recurrence per 1000 person-years (py) were estimated for patients with cancer as well as (time-dependent) hazard ratios (HR) adjusted for sex and age comparing recurrence in patients with cancer with those without. Cancer diagnoses were self-reported and complemented with data from the Dutch Hospital Data Register.

Results
4643 Patients were included with a median follow-up of 5.9 years (IQR 1.7-7.8). Participants with a history of cancer within five years before first VT (n=423) did not have an increased risk of recurrence (HR 1.1; 95%CI,0.8-1.6), except for patients with a malignancy that was still active during follow-up. Their recurrence-risk was about two-fold increased (HR 2.3; 95%CI,1.5-3.6). Participants who developed cancer after the first thrombosis (n=161) also had an increased recurrence-risk (HR 2.2; 95%CI,1.5-3.4), which was especially high in the first three months after cancer diagnosis (HR 5.2; 95%CI,2.3-11.6; cumulative incidence 4%). Risk of recurrence was high for patients who developed non-Hodgkin lymphoma, cancer of the gastro-intestinal tract, prostate or testis.

Conclusion
VT patients with a history of cancer do not have an increased risk of recurrent VT compared with patients without cancer, except when their cancer is still active during the first VT. Patients who develop cancer after a first VT also have an increased recurrence-risk, which varies for different types of cancer and for different time periods after cancer diagnosis.

Introduction
A strong relation between cancer and venous thrombosis has been known for a long time, since its first notion in the early 19th century.[1,2] Venous thrombosis, encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a multicausal disease which affects about 1-2 per 1000 persons per year.[3] A long list of risk factors, both genetic and acquired has arisen over the past decades, of which the presence of active cancer is reported to be one of the strongest.[4] About 20-30% of all first venous thrombotic events are related to cancer and cancer increases the risk of a first thrombosis about 4- to 7-fold.[5-11]

After a first venous thrombotic event recurrence is common. The five-year cumulative incidence is reported to range from 12 to 25%.[12-14] Few studies have investigated the risk of recurrent venous thrombosis in patients with cancer.[9,13-19] Furthermore, most of these previous studies were small and heterogeneous with regard to duration of follow-up (either during anticoagulant treatment or after discontinuation), selection of patients (either DVT and PE or DVT only) and definition of recurrent venous thrombosis.[9,13-19]

The risk of a first event depends strongly on type and stage of cancer and the time point after cancer diagnosis.[5,20-22] Furthermore, certain cancer treatment modalities, such as chemotherapy, substantially increase the thrombotic potential.[9,23,24] It is likely that the risk of recurrent venous thrombosis also varies between patients with different types and stages of cancer, different treatment strategies and for different time periods after diagnosis. However, results of previous studies are contradictory with regard to recurrence risk for different types of cancer.[19,25-27] Prandoni and colleagues reported increased risks of recurrence of similar magnitude for patients with cancer at various sites as compared with patients without cancer.[19] The exception was with patients with breast cancer, for whom a much lower recurrence risk was found than for other cancer patients. Findings from the RIETE register showed that only age and time since cancer diagnosis were associated with recurrent DVT and only age, time since cancer diagnosis and type of first event with recurrent PE.[27] Although patients with either recurrent PE or DVT more often had lung or pancreatic cancer than patients who did not develop recurrent thrombosis, on multivariate analyses no association was found between type of cancer and risk of recurrence. Two other studies, however, showed considerable variation in recurrence risk for patients with different types of cancer, with high recurrence rates seen in patients with lung, brain and ovarian cancer.[25,26]

Although cancer is a heterogeneous disease all patients with cancer and a venous thrombotic event are currently treated the same way and for the same duration of time.[28,29] Knowledge on characteristics that influence risk of recurrent venous
thrombosis in these patients is needed, so that targeted and prolonged therapy may be offered only to patients with a high recurrence risk and that such prolonged therapy is withheld in patients with a low recurrence risk to prevent them being exposed to an unnecessary risk of bleeding.

We aimed to evaluate the risk of recurrent venous thrombosis in relation to the presence of cancer in a large prospective cohort of venous thrombosis patients (MEGA follow-up study) with a strict definition of objectively identified recurrent events, both during and for a prolonged period after discontinuation of anticoagulant treatment. Our secondary aim was to study recurrence risk according to different types of cancer and according to different time periods after cancer diagnosis.

Methods

Patients

This study includes patients who took part in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. Details of the MEGA study have been described previously.[5] In brief, between March 1999 and August 2004, 4956 consecutive patients with an objectively diagnosed first DVT of the leg or PE were included. Patients were aged 18-70 years and were enrolled from six anticoagulation clinics in the Netherlands. Anticoagulation clinics monitor all patients taking vitamin K antagonists in a well-defined geographical area. All patients filled in a detailed questionnaire (“Questionnaire CC”) on the presence of possible risk factors for venous thrombosis before their first venous thrombotic event. Of 4956 patients included in the MEGA study, 4731 gave written informed consent for future follow-up on recurrent venous thrombosis (MEGA follow-up study). Between June 2008 and July 2009 these participants were asked whether they had developed a recurrent venous thrombotic event by means of a short answer form with one yes/no question. Furthermore, all participants were asked to complete a second questionnaire on the presence of risk factors for venous thrombosis after their first event (“Questionnaire FU”). Duration of follow-up was estimated as the time at risk from the date of the first thrombotic event to the end of follow-up. The end of follow-up was defined as the date of a recurrent event and in the absence of a recurrence, the date of filling in the short answer form. If a patient did not fill in this form, they were censored at the last date we knew them to be recurrence free. This could be date of death (n=99), date of emigration (n=3), date of the last visit to the anticoagulation clinic (n=489) or the last moment known to be recurrence free from information of the MEGA case-control study (n=411). Details of assessment of end of follow-up have been described previously.[30] Data on anticoagulant treatment during follow-up, both starting dates and dates of discontinuation of treatment, were retrieved for all participants from the anticoagulation clinics where patients were treated for their first event. All participants gave informed consent and gave written permission to obtain information about their medical history. The study was approved by the ethics committee of the Leiden University Medical Center, the Netherlands.

Adjudication of cancer diagnoses

In Questionnaires CC and FU, participants were asked to self-report on the presence of cancer, either before or after the first venous thrombotic event, and if present, on date of diagnosis, type of cancer and presence or absence of metastases. Data from Questionnaire CC, i.e., cancer diagnosed before the first venous thrombosis, have been verified earlier by Blom et al.[5] For Questionnaire FU the response rate was 60% (2827/4731). Our data were linked to the Dutch hospital data register, which allowed us to verify the cancer diagnoses. The Dutch hospital data register covers complete, nationwide data on hospital admissions since 1986. The data from the follow-up were linked to discharge diagnosis data from 1995 up to 2010 from this register by the Dutch Central Bureau of Statistics (CBS). Discharge diagnosis data are collected in practically all general and university hospitals and most specialized clinics, such as cancer clinics. Diagnosis at discharge is determined by the treating physician and subsequently coded by trained hospital staff according to International Classification of diseases, ninth version clinical modification (ICD-9-CM). 92% (4350/4731) of our participants could be individually linked to records of the hospital data register. Furthermore, between 2007 and 2009 the vital status of all follow-up participants was acquired from the Dutch population register, as has been described previously.[31] For the patients who died during follow-up, the cause of death was obtained from the national register of death certificates. The causes of death were encoded according to the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM).

Data on cancer diagnoses from questionnaires CC and FU, the Dutch hospital data register and cause of death statistics were combined. From these 4 different sources, a decision rule regarding certainty of the cancer diagnosis was made using the information collected per patient. Participants were classified as having no cancer, probably no cancer, a probable cancer diagnosis, a certain cancer diagnosis or as having missing data regarding cancer (see Supplement for decision rule).

As date of a certain or probable cancer diagnosis we used the first date reported in either Questionnaire CC or FU, the hospital discharge diagnoses or cause of death statistics. If a date of cancer diagnosis was not available from any source of information, we classified date of diagnosis as the date of the first thrombosis in case of a cancer diagnosis before the first thrombotic event (n=9) and as the date halfway between date of the first thrombotic event and end of follow-up in case of a cancer diagnosis during follow-up (n=1). In case a malignancy was reported in the cause of death statistics only (n=22), the date of cancer diagnosis was set at the date halfway between the first thrombotic event and date of death.
Patients could have a cancer diagnosis before or after the first thrombotic event. See Figure 1 for a timeline of events and overview of cancer exposure categories. We classified participants with a cancer diagnosis before the first thrombotic event as participants with a cancer diagnosis within five years before first venous thrombosis. Participants who reported a cancer diagnosis date of more than five years before the first thrombotic event and for whom no other data on subsequent cancer progression from any of our sources was registered (and who were therefore assumed to be relapse free) (n=66), were excluded from all analyses. Furthermore, we decided to exclude participants with a missing cancer diagnosis (n=22). This left 4643 participants to be included for analyses, out of 4731 participants eligible for follow-up.

Cancer that was diagnosed after the end of follow-up was not taken into account. Types of skin cancer other than melanoma were not registered as a cancer diagnosis.

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During the same period when participants were asked to self-report on any recurrent thrombotic events during follow-up, information about recurrences was additionally retrieved from the anticoagulation clinics where patients were initially included for their first event and in case they moved house, at the clinic nearest to their new address. Death due to venous thrombosis was also included. For recurrent events reported by either the patient or the clinic discharge letters from the treating physician were requested. A decision rule regarding certainty of the diagnosis was made according to the information collected per patient. Possible recurrences were classified into certain recurrences and uncertain recurrences, with as a main purpose to distinguish extensions of a first event from truly new thromboses. Details of this decision rule have been described previously.[30] For this study, we considered certain recurrences as outcome event only (n=664). In short, reported recurrences were classified into certain recurrences when 1) there was a discharge letter stating a diagnosis of a recurrent event based on clinical and radiological data, or when 2) both the anticoagulation clinic and the patient reported a recurrent event at either a clearly different location than the first event or that occurred more than one year since the first event, or when 3) a registered death from a recurrent event at least six months after the first event was found. Participants with uncertain recurrent events (n=212) were censored from this uncertain recurrent event onward.

**Statistical analyses**

All statistical analyses were performed separately for: 1) patients with cancer diagnosed before the first thrombotic event and 2) patients with cancer diagnosed after the first thrombotic event. This was done since selection into the study was different for both patient groups. Patients with a cancer diagnosis before first venous thrombosis only represent subjects who survived long enough to develop venous thrombosis, while we identified all participants with a cancer diagnosis after the first thrombosis.

Incidence rates of recurrent venous thrombosis were first estimated separately for participants without cancer, with probably no cancer, with probable cancer and with certain cancer. Next, we further classified the probable groups based on the recurrence rates we found in these groups (Supplementary Table 1). For analyses on cancer diagnosed before the first thrombotic event, patients with a probable diagnosis of cancer were further excluded, considering their low recurrence rate. For analyses on cancer diagnosed after the first thrombotic event participants with a probable cancer diagnosis were grouped with the certain cancers. Participants with probably no cancer were reclassified in the group without cancer.

After these classifications, incidence rates of recurrent venous thrombosis were estimated as the number of events over the accumulated follow-up time with person time split and divided over persons with and without cancer. The Cox-proportional hazards model was used to evaluate risks of recurrent venous thrombosis between groups. Hazard ratios and corresponding 95% confidence intervals were estimated by means of a time-dependent Cox regression analysis using anticoagulant treatment and cancer diagnosis as time-dependent variables. Hazard ratios were adjusted for age, sex and anticoagulant treatment.

**Analyses for cancer before the first thrombotic event**

Incidence rates of recurrence for patients with a diagnosis of cancer before the first thrombotic event and for participants without cancer were estimated. Incidences were further split for participants with and without cancer during and after the initial anticoagulant treatment period. Participants with a cancer diagnosis within five years before the first thrombosis probably represent a mix of patients who have gone into remission and patients whose cancer continued to be active after the first event. For this reason, in a subgroup analysis, we classified patients separately as active during follow-up and not active. In the ‘active’ group we entered subjects with metastases at time of the first venous thrombosis or during follow-up and those who died of cancer.
Malignancies and recurrent venous thrombosis

Clinical characteristics

463 patients with a first episode of venous thrombosis were followed for recurrent events. Mean age of participants was 48 years and 46% were men. Most of the initial thrombotic events were deep vein thrombosis (67%). Median duration of follow-up was 5.9 years (IQR 1.7-7.8). During 23 650 person-years of follow-up, 664 certain recurrent venous thrombotic events were identified for a total incidence rate of 28.1 per 1000 person-years (95% CI 26.0-30.3). We identified 575 patients with certain cancer and 81 patients with probable cancer.

Analyses for cancer diagnosed BEFORE the first thrombotic event:

423 patients with a cancer diagnosis before the first thrombotic event were identified. The mean time between cancer diagnosis and thrombosis diagnosis was 2.8 years and most of the diagnoses were cancer of the colon (15%), breast (16%), lung (12%), prostate (9%) or a gynaecological type of cancer (8%). 25 Patients were identified with both a cancer diagnosis before and after the first thrombotic event, at different sites.

Analyses for cancer after the first thrombotic event:

Incidence rates of recurrence and corresponding hazard ratios for patients with a cancer diagnosis after the first thrombotic event and for participants without cancer were estimated. This was additionally done for different time periods after cancer diagnosis: three months, one year, two years and five years. Furthermore, cumulative incidences were estimated for the different time frames. These were corrected for competing events, since cumulative incidences derived from standard life-table methods are biased in studies on cancer-associated venous thrombosis. For this competing risk approach, cumulative incidence functions were generated using Stata's user-contributed stcompet suite. Risks of recurrence were additionally estimated for different types of cancer.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, NY) and Stata version 12 (Stata Corp., College Station, Texas).

Results

Table 1. Risk of recurrent venous thrombosis for patients without or with cancer, diagnosed before the 1st event

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation years</th>
<th>Recurrent events</th>
<th>IR/1000 yrs (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>3987</td>
<td>21336</td>
<td>588</td>
<td>27.6 (25.4-29.9)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cancer before 1st event</td>
<td>423</td>
<td>1176</td>
<td>42</td>
<td>35.7 (26.4-48.3)</td>
<td>1.3 (0.9-1.7)</td>
</tr>
<tr>
<td>Two cancer types before 1st event</td>
<td>12</td>
<td>14</td>
<td>1</td>
<td>72.0 (10.1-511.3)</td>
<td>2.7 (0.4-18.9)</td>
</tr>
<tr>
<td>Cancer before and after 1st event</td>
<td>25</td>
<td>84</td>
<td>5</td>
<td>59.7 (24.8-143.3)</td>
<td>2.1 (0.9-5.0)</td>
</tr>
</tbody>
</table>

IR denotes incidence rate; yrs, person-years; CI, confidence interval; HR, hazard ratio.

*Hazard ratio adjusted for age and sex.

Table 2. Risk of recurrent venous thrombosis for patients without or with cancer, diagnosed before 1st event, according to anticoagulant treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation years</th>
<th>Recurrent events</th>
<th>IR/1000 yrs (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During anticoagulant treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>3987</td>
<td>3331</td>
<td>23</td>
<td>6.9 (4.6-10.4)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cancer before 1st event</td>
<td>423</td>
<td>343</td>
<td>9</td>
<td>26.2 (13.6-50.4)</td>
<td>4.6 (2.1-10.2)</td>
</tr>
<tr>
<td>After discontinuation treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>3350</td>
<td>18194</td>
<td>565</td>
<td>31.1 (28.6-33.7)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cancer before 1st event</td>
<td>217</td>
<td>857</td>
<td>33</td>
<td>38.5 (27.4-54.2)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
</tbody>
</table>

IR denotes incidence rate; yrs, person-years; CI, confidence interval; HR, hazard ratio.

*Hazard ratio adjusted for age and sex.
Malignancies and recurrent venous thrombosis

(95%CI; 0.8-1.6) after correction for age and sex. Participants with a diagnosis of cancer before and after the first thrombotic event had a recurrence rate of 28.1 per 1000 person-years (95%CI; 24.8-31.3). Additional correction for anticoagulant treatment (as a time-dependent variable) in the abovementioned analyses did not materially affect results (data not shown).

Overall, in the current study population 33 recurrent thrombotic events were identified during anticoagulant treatment, for an incidence rate of 8.8 per 1000 person-years (95%CI; 6.3-12.4). Recurrence rate after discontinuation of anticoagulant treatment was much higher (31.3 per 1000 person-years (95%CI; 28.9-33.9)). During anticoagulant treatment participants with a cancer diagnosis before the first thrombotic event had an approximately four-fold higher recurrence risk than patients without cancer (HR 4.2 (95%CI; 1.8-9.7)) (Table 2). However, after discontinuation of anticoagulant treatment recurrence risk in this group of patients with cancer was not increased compared with patients without cancer (HR 1.0 (95%CI; 0.7-1.5)).

Table 3. Risk of recurrent venous thrombosis for patients with cancer diagnosis before 1st event, according to cancer severity

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Observation years</th>
<th>Recurrent events</th>
<th>IR/1000 pyrs (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>3987</td>
<td>21336</td>
<td>588</td>
<td>27.6 (25.4-29.9)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cancer before 1st event, without metastasis</td>
<td>187</td>
<td>718</td>
<td>18</td>
<td>25.0 (15.9-39.8)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>Cancer before 1st event, with metastasis</td>
<td>189</td>
<td>351</td>
<td>17</td>
<td>48.5 (32.0-80.6)</td>
<td>1.7 (1.1-2.8)</td>
<td>1.7 (1.0-2.7)</td>
</tr>
<tr>
<td>Cancer before 1st event, who died from cancer during follow-up</td>
<td>266</td>
<td>287</td>
<td>21</td>
<td>73.2 (47.8-112.3)</td>
<td>2.5 (1.6-3.9)</td>
<td>2.3 (1.5-3.6)</td>
</tr>
</tbody>
</table>

IR denotes incidence rate; pyrs, person-years; CI, confidence interval; HR, hazard ratio.
*Groups are not mutually exclusive.
†Hazard ratio adjusted for age and sex.

Table 4. Risk of recurrent venous thrombosis for patients with or without cancer, diagnosed after the 1st event

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Observation years</th>
<th>Recurrent events</th>
<th>IR/1000 pyrs (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>3987</td>
<td>21797</td>
<td>588</td>
<td>27.0 (24.9-29.2)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Cancer after 1st event</td>
<td>161</td>
<td>403</td>
<td>26</td>
<td>64.5 (43.9-94.7)</td>
<td>2.6 (1.8-3.9)</td>
<td>2.2 (1.5-3.4)</td>
</tr>
<tr>
<td>Two cancer types after 1st event</td>
<td>&lt;10</td>
<td>15</td>
<td>0</td>
<td>0 (0-245.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

IR denotes incidence rate; pyrs, person-years; CI, confidence interval; HR, hazard ratio.
*Hazard ratio adjusted for age and sex.
Malignancies and recurrent venous thrombosis

For participants with a cancer diagnosis during follow-up, i.e. after their first thrombosis, recurrence rates and corresponding hazard ratios were estimated for different time periods after their cancer diagnosis (Table 5). The risk of recurrent venous thrombosis was especially high in the first three months after cancer diagnosis, with an incidence rate of 164.5 per 1000 person-years (95%CI; 74.0-366.5), and a five-fold increased risk of recurrence compared with participants without cancer (HR 5.2 (95%CI; 2.3-11.6)). Recurrence risks steadily decreased after the first three months up until the first year after diagnosis, and was about 40 per 1000 person-years in the years thereafter. Following correction for anticoagulant treatment results remained similar (data not shown).

Cumulative incidences of recurrence, corrected for the competing risk of death, were 4% (95%CI; 2-8) in the first three months after diagnosis, 10% (95%CI; 4-15) in the first year, 13% (95%CI; 8-19) in the first two years and 20% (95%CI; 13-28) in the five years following cancer diagnosis.

Incidence of recurrent venous thrombosis for different types of cancer

Table 6 shows incidence rates and corresponding hazard ratios of recurrent venous thrombosis for participants with different types of cancer diagnosed during follow-up. High recurrence risks were seen for patients with lung cancer, certain types of gastrointestinal cancer, prostate cancer, urinary tract cancer, non-Hodgkin lymphoma and testicular cancer.

Discussion

In this follow-up study with over 4500 participants with a first venous thrombosis we studied risk of recurrent thrombosis for participants with and without cancer. In a time-dependent analysis we found participants with cancer diagnosed after the first thrombotic event, to have a two-fold increased risk of recurrence (HR 2.2; 95%CI, 1.5-3.4). We found a high rate of recurrence in the first three months after these cancer diagnoses (IR 165 per 1000 pyrs; 95%CI, 74-367 and cumulative incidence 4%), which corresponds with a five-fold increased risk compared with participants without cancer. Recurrence risks were different for different types of cancer, with high rates observed in participants with gastrointestinal cancer, lung cancer, prostate and urinary tract cancer, non-Hodgkin lymphoma and testicular cancer. For participants with a cancer diagnosis before the first venous thrombosis the risk of recurrence was not increased compared with patients without cancer (HR 1.1; 95%CI, 0.8-1.6). However, in a selection of these participants, i.e. with cancer which was active during follow-up, we did find an increased recurrence risk, which was of similar size as in those patients who developed cancer after venous thrombosis (doubled).
The few studies that have so far investigated the risk of recurrent venous thrombosis in patients with cancer described a two- to nine-fold increased risk compared with patients without.[9,13-19] However, these studies differed substantially with regard to patient characteristics, duration of follow-up, type of analysis and data collection. Two studies, which included DVT patients only, with long duration of follow-up (3-9 years), reported similar hazard ratios of 1.97 (95%CI; 1.20-3.3) and 1.72 (95%CI; 1.31-2.25) for recurrence in patients with known cancer at time of the first thrombosis compared with patients without cancer.[13,14] One study, based on data from the Olmsted County population, with a similarly long duration of follow-up, that included both patients with DVT and PE, reported hazard ratios of 2.2 and 4.2 for patients treated with and without chemotherapy, respectively.[9] Another study reported a high relative risk of 9.2 (HR 9.2 (95%CI; 2.0-41.7)).[15] This result might be explained by a small number of recurrent events or the design of the study in which thrombotic events were identified by hospital discharge records only. Four studies reported relative risks of recurrence during anticoagulant treatment.[16-19] They all reported that patients with active cancer at time of thrombosis had an approximately three-fold increased risk of recurrent venous thrombosis as compared with patients without cancer during anticoagulant treatment [OR 2.7; HR 2.6; RR 3.0; HR 3.2]. Some of the abovementioned relative risks were adjusted for potential confounders, while others were not.

In this large follow-up study with long duration of follow-up we were able to study the risk of recurrent venous thrombosis for patients with different cancer characteristics, such as type of cancer or metastasized cancer and to study recurrence risk for different time points after cancer diagnosis. The risk of recurrence in patients who developed cancer after the first thrombotic event has not been studied before, since all of abovementioned previous studies were in patients with cancer known or active at time of the first venous thrombotic event only. We included diagnoses of cancer both before and after the first thrombotic event. Additionally, we were able to study the risk of recurrent venous thrombosis both during and after discontinuation of anticoagulant treatment and to show results with and without adjustments for age and sex. This increases comparability with other studies. Recurrent events reported in this study were objectively defined and only certain recurrent events were taken into account. Diagnoses of cancer were considered based on four different sources of information and we took care to use only those in whom we were certain of a correct diagnosis.

We did not find an increased risk of recurrent venous thrombosis in participants with a cancer diagnosis before the first thrombotic event. This finding is probably explained by participants with a cancer diagnosis within five years before the first thrombosis representing a mix of patients who had gone into remission and patients whose cancer was still active. Additionally, we could have had a selection of patients with cancer with a relatively good prognosis, because patients with a worse prognosis may not have wanted to participate in our MEGA study. When we stratified results for patients

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### Table 6. Risk of recurrent venous thrombosis for patients with cancer diagnosis after 1st event, according to type of cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>N*</th>
<th>Observation years</th>
<th>Recurrent events</th>
<th>IR/ 1000 pyrs (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>3987</td>
<td>21797</td>
<td>588</td>
<td>27.0 (24.9-29.2)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Lung</td>
<td>26</td>
<td>28</td>
<td>2</td>
<td>71.0 (17.8-283.9)</td>
<td>2.8 (0.7-11.3)</td>
<td>2.1 (0.5-8.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>33</td>
<td>94</td>
<td>4</td>
<td>42.3 (15.9-112.8)</td>
<td>1.8 (0.7-4.7)</td>
<td>1.2 (0.4-3.2)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt;10</td>
<td>6</td>
<td>1</td>
<td>180.4 (25.4-1280.5)</td>
<td>8.9 (1.2-63.8)</td>
<td>5.6 (0.8-40.3)</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;10</td>
<td>8</td>
<td>1</td>
<td>132.0 (18.6-937.1)</td>
<td>5.6 (0.8-39.6)</td>
<td>3.6 (0.5-25.4)</td>
</tr>
<tr>
<td>Colon</td>
<td>23</td>
<td>81</td>
<td>1</td>
<td>12.4 (1.7-88.1)</td>
<td>0.5 (0.1-3.7)</td>
<td>0.3 (0.0-2.5)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&lt;10</td>
<td>1</td>
<td>1</td>
<td>1250.9 (176.2-8879.9)</td>
<td>39.7 (5.5-285.3)</td>
<td>25.2 (3.5-181.6)</td>
</tr>
<tr>
<td>Breast</td>
<td>24</td>
<td>72</td>
<td>2</td>
<td>28.0 (7.0-111.8)</td>
<td>1.2 (0.3-4.9)</td>
<td>1.6 (0.4-6.6)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>13</td>
<td>45</td>
<td>1</td>
<td>22.0 (3.1-156.3)</td>
<td>0.9 (0.1-6.2)</td>
<td>1.3 (0.2-9.4)</td>
</tr>
<tr>
<td>Prostate</td>
<td>18</td>
<td>43</td>
<td>6</td>
<td>140.0 (62.9-311.7)</td>
<td>5.4 (2.4-12.0)</td>
<td>3.4 (1.5-7.7)</td>
</tr>
<tr>
<td>Urinary</td>
<td>17</td>
<td>53</td>
<td>4</td>
<td>75.7 (28.4-201.7)</td>
<td>2.9 (1.1-7.7)</td>
<td>2.4 (0.9-6.4)</td>
</tr>
<tr>
<td>Brain</td>
<td>&lt;10</td>
<td>1</td>
<td>0</td>
<td>0 (0-3689.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hematological</td>
<td>10</td>
<td>30</td>
<td>3</td>
<td>100.4 (32.4-311.4)</td>
<td>3.6 (1.1-11.1)</td>
<td>3.0 (1.0-9.3)</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>&lt;10</td>
<td>12</td>
<td>0</td>
<td>0 (0-307.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-hodgkin</td>
<td>&lt;10</td>
<td>16</td>
<td>3</td>
<td>183.3 (59.1-568.3)</td>
<td>6.6 (2.1-20.6)</td>
<td>5.2 (1.7-16.3)</td>
</tr>
<tr>
<td>Kahler</td>
<td>&lt;10</td>
<td>1</td>
<td>0</td>
<td>0 (0-3689.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Testis</td>
<td>&lt;10</td>
<td>2</td>
<td>2</td>
<td>976.6 (244.2-3904.9)</td>
<td>25.3 (6.3-102.0)</td>
<td>18.2 (4.5-73.8)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>&lt;10</td>
<td>12</td>
<td>0</td>
<td>0 (0-307.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Other†</td>
<td>15</td>
<td>31</td>
<td>2</td>
<td>64.3 (16.1-257.0)</td>
<td>2.8 (0.7-11.4)</td>
<td>2.4 (0.6-9.5)</td>
</tr>
</tbody>
</table>

IR denotes incidence rate; pyrs, person-years; CI, confidence interval; HR, hazard ratio; NA, not applicable.
*Number of patients per type of cancer do not add up to 161, since patients with several types of cancer were counted more than once.
†Patients diagnosed with metastasized cancer, without information on primary tumor site, were included in this group.
‡ Patients diagnosed with metastasized cancer, without information on primary tumor site, were included in this group.
Chapter 4

Malignancies and recurrent venous thrombosis

During anticoagulant treatment of the first venous thrombosis we found participants with a cancer diagnosis before this event to have an almost four-fold increased recurrence risk compared with participants without cancer. After discontinuation of anticoagulant treatment, however, recurrence risk was similar between participants with and without cancer. This finding is largely explained by the much increased recurrence rate in participants without cancer after discontinuation of treatment (31.1 vs 6.9 per 1000 person-years during treatment). Patients with cancer had a less strong increase in absolute risk (38.5 vs 26.2 per 1000 py after discontinuation of anticoagulant treatment). Possibly, the risk of recurrent venous thrombosis in patients with cancer is increased to such an extent that it outweighs the anticoagulant effect of treatment. An additional explanation might be that anticoagulant treatment in patients with cancer is usually provided as long as the cancer is active or as long as patients receive antineoplastic treatment. If a patient is in remission, and anticoagulant treatment is discontinued, these patients may not have an increased risk of recurrent venous thrombosis anymore as compared with participants without cancer.

Currently, guidelines provide treatment recommendations for the group of patients with cancer-associated venous thrombosis as a whole and recommend long-term treatment with low molecular weight heparins (LMWHs) for as long as cancer is active.[28,29] However, the risk of recurrent venous thrombosis in these patients may well vary and be influenced by tumour characteristics, such as tumour site, histology and stage. If this is the case it might be worthwhile to adjust treatment regimens accordingly. Obviously, risk of bleeding should additionally be taken into account.

It was suggested in a recent meta-analysis that metastatic malignancy, adenocarcinoma or lung malignancy confers a higher risk of recurrence than localized malignancy, non-adenocarcinoma or breast cancer.[33] The main finding according to the authors was, however, that “no definitive conclusions can be drawn from the published literature because reporting of malignancy characteristics in patients with cancer and recurrent venous thrombosis during the anticoagulation period is scarce”. A large register study recently reported on an increased recurrence risk for patients with brain, lung and ovarian cancer, for patients with myeloproliferative or myelodysplastic disorders and for patients with advanced stage of cancer.[25] In the Ottawa prognostic score lung cancer was reported to increase recurrence risk, while patients with breast cancer or localized disease were reported to have lower risks of recurrent venous thrombosis.[26]

Our study supports current thought that risk of recurrent venous thrombosis is not the same for all patients with cancer and that stratification of patients with cancer-associated venous thrombosis according to their recurrence risk is of relevance to offer these patients a better tailored treatment approach. Our results show that patients with advanced cancer have a higher risk than patients with more localized or less active disease. Our results for different types of cancer diagnosed after a first event are based on small numbers, but we could still observe differences in recurrence risk for the different types of cancer. We also show an increased risk of recurrent venous thrombosis in patients diagnosed with cancer after a first thrombotic event. The risk was especially high in the first three months after cancer diagnosis and steadily decreased thereafter. Physicians should be aware of this in case a diagnosis with cancer is made in a patient with a history of venous thrombosis. To give definite answers to which patients would benefit from long-term anticoagulant treatment and which patients should not, larger studies are required. For this, meta-analyses of individual patient data could prove useful.

Some limitations of this study warrant comment. First, 8% of all MEGA study participants could not be individually linked to the Dutch hospital data register. Furthermore some diagnoses of cancer from the hospital data register might have been missed because of incomplete recording. This possible underreporting of cancer diagnoses might have led to a slight underestimation of our incidence rates. However, since data from the hospital data register were combined with two questionnaires filled in by the participants at two points in time and with causes of death, underreporting of cancer diagnoses was probably limited. Second, before a cancer diagnosis is made the malignancy has been present for some time. This implies that person-time may occasionally have been misclassified as unexposed in participants with a malignancy that was present but not yet diagnosed. The recurrence rate for patients without cancer may therefore have been somewhat overestimated and the hazard ratios therefore somewhat underestimated. Third, our classification of patients with a history of cancer within five years before the first thrombotic event into patients whose cancer was still active during follow-up and patients whose cancer had gone into remission, may have been somewhat crude. However, our finding of similarly increased recurrence risks in patients we classified as still active during follow-up, and patients with a cancer diagnosis after venous thrombosis suggests that misclassification has been limited. The same applies to the patients we classified as having cancer that had gone into remission, as we found a similar recurrence risk in this group of patients as in participants without cancer. Fourth, we had information on anticoagulant treatment from the anticoagulation clinics, that register outpatient use only. Participants (with cancer) may have received anticoagulant treatment in the hospital. Data on this use of anticoagulant treatment lack in our study, possibly inducing an additional underestimation of the recurrence risk. However, after adjustment for anticoagulant treatment hazard ratios did not change, which suggests that this did not play a major role. Fifth, we had not enough data to take cancer treatment regimens into account in our study. Cancer treatment regimens affect cancer activity and risk of venous thrombosis and it would have been interesting to study recurrence risks during and after treatment. However, we found increased recurrence rates in patients with a cancer diagnosis after their first thrombotic event,
especially during the first three months after diagnosis. Cancer treatment might have played a role in this highly increased recurrence risk we found shortly after diagnosis.

To conclude, patients with venous thrombosis and cancer had an increased risk of recurrent venous thrombosis compared with patients without cancer. Participants with a cancer diagnosis before the first venous thrombotic event whose malignancy was still active after thrombosis had a two- to three-fold increased risk of recurrence compared with patients without cancer. Participants who developed cancer after the first thrombosis had an increased recurrence risk, which was especially high in the first three months after cancer diagnosis (about five-fold compared with patients without cancer, cumulative incidence 4%). Risk of recurrent venous thrombosis varied for different types, stages and for different time periods after cancer diagnosis. Stratification of patients with cancer-associated venous thrombosis according to their recurrence risk is of relevance to offer these patients a better tailored treatment approach.

**Reference List**


**SUPPLEMENTAL DATA**

**Supplemental Methods**

**Decision rule regarding certainty of cancer diagnosis**

Participants were classified as having a certain cancer diagnosis either when their cause of death listed cancer, when any hospital discharge diagnose contained a cancer diagnosis or when a cancer diagnosis was mentioned at both questionnaires CC and FU (n=575). Participants were classified as having a probable cancer diagnosis when they responded on either questionnaire CC or questionnaire FU that they had cancer and when hospital discharge register data did not report a cancer diagnosis or were missing (n=81). Participants were classified as having no cancer diagnosis when, in questionnaire FU, they responded, “No, I have never had a cancer diagnosis” and when hospital discharge register data did not contain a cancer diagnosis or were missing (n=2504). Participants who responded in questionnaire CC “No, I did not have a cancer diagnosis before my 1st thrombotic event”, who did not fill in questionnaire FU, and for whom hospital discharge registry data did not contain a cancer diagnosis or were missing were classified as ‘probably no cancer diagnosis’ (n=1483). When no information was obtained from either questionnaire regarding cancer and when hospital discharge register and cause of death statistics data did not report a cancer diagnosis, data regarding cancer diagnoses were considered to be missing (n=22).

**Classification of types of cancer**

All cancer diagnoses were classified into one of the following types; lung, gastrointestinal (esophagus, stomach, colon, pancreas), breast, gynaecological, prostate, urinary (bladder, kidney, urinary tract), brain, hematological (leukaemia, Hodgkin, non-hodgkin, Kahler), testis, melanoma, thyroid or other. When patients with a certain or probable cancer diagnosis appeared to have been diagnosed with several types of cancer (n=244) we checked for every patient individually, whether the second diagnosis with cancer was most probably a metastasized tumour of the first cancer type or a new malignancy. When this was the case only the first type of cancer was taken into account. For (n=43) patients we decided that the second reported cancer type was probably a second primary tumour, rather than a metastasis of the first.

**Table 1. Incidence rates of recurrent venous thrombosis in patients with or without cancer**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cancer before 1st event*</th>
<th>Cancer after 1st event†</th>
<th>N</th>
<th>Observation (yr)</th>
<th>Recurrent events</th>
<th>IR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td>2504</td>
<td>1549</td>
<td>429</td>
<td>27.8 (25.2-30.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable cancer</td>
<td>45</td>
<td>173</td>
<td>3</td>
<td>17.4 (5.6-53.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certain cancer</td>
<td>423</td>
<td>1176</td>
<td>42</td>
<td>35.7 (26.4-48.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data with regard to cancer</td>
<td>22</td>
<td>77</td>
<td>1</td>
<td>12.9 (1.8-91.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probably no cancer</td>
<td>1483</td>
<td>5877</td>
<td>159</td>
<td>27.1 (23.2-31.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients with a cancer diagnosis after the first thrombotic event excluded from analyses.
† Patients with a cancer diagnosis before the first thrombotic event excluded from analyses.

IR denotes: incidence rate per 1000 person years; CI: confidence interval.