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Epidemiology of cancer-associated venous thrombosis

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Abstract

Cancer-associated venous thrombosis is a common condition, though the reported incidence varies widely between studies depending on patient population, start and duration of follow-up and the method of detecting and reporting thrombotic events. Furthermore, as cancer is a heterogeneous disease, the risk of venous thrombosis depends on cancer types and stages, treatment measures and patient-related factors. In general, cancer patients with venous thrombosis do not fare well and have an increased mortality compared with cancer patients without. This may be explained by the more aggressive type of malignancies associated with this condition. It is hypothesized that thromboprophylaxis in cancer patients might improve prognosis and quality of life by preventing thrombotic events. However, anticoagulant treatment leads to increased bleeding, particularly in this patient group, so in case of proven benefit of thromboprophylaxis only patients with a high risk of venous thrombosis should be considered. This review describes the literature on incidence of and risk factors for cancer-associated venous thrombosis, with the aim to provide a basis for identification of high-risk patients, and for further development and refinement of prediction models. Furthermore, knowledge on risk factors for cancer-related venous thrombosis may enhance understanding of the pathophysiology of thrombosis in these patients.

Introduction

In 1865, Armand Trousseau, a French physician, was one of the first to describe an association between thrombosis and cancer. Not many know the association had already been reported earlier in 1823 by Jean Baptiste Bouillaud.[1,2] Perhaps because of the irony of Trousseau diagnosing the condition on himself and dying from it in 1867, the condition was later called Trousseau’s syndrome. Since then, many studies have confirmed the association between cancer and venous thrombosis and demonstrated that the incidence of venous thrombosis in cancer patients is high, that it has risen over the past decades and that cancer patients with venous thrombosis do not fare well. It is hypothesized that thromboprophylaxis targeted at cancer patients with a particular high risk of thrombosis might improve their prognosis. Therefore a need exists to identify such patients, which is not easy since cancer is a heterogeneous disease and the risk of venous thrombosis depends on the interaction between tumor cells, the hemostatic system and characteristics of the patient. Furthermore, identification of risk factors for cancer-related venous thrombosis will help to improve understanding of the pathophysiology of thrombosis in cancer patients. Thus, even 150 years after Trousseau died, there is still a need to study the epidemiology of venous thrombosis and cancer in detail.

Incidence of venous thrombosis in cancer patients

It is estimated consistently that about 20 to 30% of all first venous thromboembolic events are cancer-associated (Table 1).[3-9] In a population-based, nested case-control study within the Olmsted County population (Minnesota), 625 residents with an incident deep vein thrombosis (DVT) or pulmonary embolism (PE) were matched on age and sex to 625 unaffected residents. A population attributable risk (PAR; the percentage of all cases of a disease in a population that can be attributed to a risk factor) was calculated and reported to be 18% (95%CI; 13.4-22.6) for an active malignancy.[5] White and coworkers used the California discharge data set to identify a cohort of 21 002 patients hospitalized with incident venous thrombosis in 1996. Of these patients again about 20% (4368) were reported to have cancer-associated venous thrombosis.[9] In a third study, medical records of residents from the Worcester metropolitan area were obtained for a total of 1399 subjects with a confirmed episode of venous thrombosis. Of these patients 29% had a recent or active malignant neoplasm.[8] In a more recent registry, the RIETE registry, which included over 35 000 consecutive symptomatic VT patients from 2001 up to 2011, active cancer was reported in 6075 patients (17%).[4] Lastly, the Tromsø study is a population-based prospective follow-up study of over 26 000 subjects. Participants were followed for venous thrombosis from 1994 to 2007. Of 462 patients with a first-ever VT event, 106 had an active cancer (23%).[3]

Cancer patients have a several fold increased risk of venous thrombosis as compared with the general population or patients without cancer, with relative risks ranging from 4 to 7 (Table 1).[10-13] Frequently cited is the Olmsted County population study. In this
### Table 1: Incidences and risk factors for venous thromboembolism as discussed in the review

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study Design</th>
<th>Number of patients</th>
<th>Effect estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of cancer-associated VT cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmsted county population</td>
<td>Nested case-control</td>
<td>625/625</td>
<td>18% (PAR)</td>
<td>5</td>
</tr>
<tr>
<td>Worcester metropolitan area, outpatient setting</td>
<td>Cohort</td>
<td>1399</td>
<td>29%</td>
<td>8</td>
</tr>
<tr>
<td>RIETE Registry</td>
<td>Cohort</td>
<td>35 539</td>
<td>1%</td>
<td>4</td>
</tr>
<tr>
<td>Tromsø Study</td>
<td>Cohort</td>
<td>462</td>
<td>2.8%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Relative risk of VT for cancer vs no cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEGA study</td>
<td>Case-control</td>
<td>2331/3220</td>
<td>OR 6.7 (95%CI; 5.2-8.6)</td>
<td>10</td>
</tr>
<tr>
<td>Olmsted county population</td>
<td>Nested case-control</td>
<td>625/625</td>
<td>OR 4.1 (95%CI; 1.9-8.5)</td>
<td>12</td>
</tr>
<tr>
<td>Linked United Kingdom databases</td>
<td>Cohort</td>
<td>82 203/77 207</td>
<td>HR 4.7 (95%CI; 4.5-4.9)</td>
<td>13</td>
</tr>
<tr>
<td>Danish population-based registries</td>
<td>Cohort</td>
<td>57 591/287 476</td>
<td>HR 4.7 (95%CI; 4.3-5.1)</td>
<td>11</td>
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<tr>
<td><strong>Absolute risk of VT in cancer patients</strong></td>
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</tr>
<tr>
<td>Linkage of California Cancer Registry and California Discharge Dataset</td>
<td>Cohort</td>
<td>23,149</td>
<td>1.8% within two years</td>
<td>14</td>
</tr>
<tr>
<td>Referred patients with solid tumors</td>
<td>Cohort</td>
<td>1081</td>
<td>7.8% (median follow-up 26 months)</td>
<td>15</td>
</tr>
<tr>
<td>Vienna Cancer and Thrombosis Study (CATS)</td>
<td>Cohort</td>
<td>840</td>
<td>8% within one year</td>
<td>16</td>
</tr>
<tr>
<td>38 Papers on cohorts with cancer patients</td>
<td>Meta-analysis</td>
<td>NA</td>
<td>13/1000 PY (95%CI; 7-23) for average risk patients</td>
<td>17</td>
</tr>
<tr>
<td>Linked United Kingdom databases</td>
<td>Cohort</td>
<td>82 203</td>
<td>14/1000 PY (95%CI; 13-14)</td>
<td>13</td>
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<tr>
<td><strong>Incidence of VT in cancer patients over time</strong></td>
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<tr>
<td>US National Hospital Discharge Survey</td>
<td>Cohort</td>
<td>40 787 000</td>
<td>1.5% in 1989; 3.5% in 1999</td>
<td>19</td>
</tr>
<tr>
<td>Discharge Database from University HealthSystem Consortium</td>
<td>Cohort</td>
<td>1 015 598</td>
<td>~3.5% in 1995; ~4.5% in 2002</td>
<td>18</td>
</tr>
<tr>
<td>Linked United Kingdom databases</td>
<td>Cohort</td>
<td>82 203</td>
<td>10.3/1000 PY in 1997; 19/1000 PY in 2006</td>
<td>13</td>
</tr>
<tr>
<td><strong>Risk factors for VT in cancer patients</strong></td>
<td></td>
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<tr>
<td><strong>Type of cancer</strong></td>
<td></td>
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<tr>
<td>38 Papers on cohorts with cancer patients</td>
<td>Meta-analysis</td>
<td>NA</td>
<td>Pancreatic cancer: ~130/1000 PY</td>
<td>17</td>
</tr>
<tr>
<td>Referred patients with solid tumors</td>
<td></td>
<td></td>
<td>Breast cancer: ~30/1000 PY</td>
<td>15</td>
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<tr>
<td>Linkage of California Cancer Registry and California Discharge Dataset</td>
<td></td>
<td></td>
<td>Lung cancer: ~14/1000 PY</td>
<td>14</td>
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<tr>
<td>Vienna Cancer and Thrombosis Study (CATS)</td>
<td></td>
<td></td>
<td>Hematologic cancer: ~10/1000 PY</td>
<td>16</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Colorectal cancer: ~45/1000 PY</td>
<td>25</td>
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<td></td>
<td></td>
<td></td>
<td>Bone cancer: ~10/1000 PY</td>
<td>35</td>
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<tr>
<td><strong>Stage of cancer</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Danish population-based registries</td>
<td>Cohort</td>
<td>40994/204970</td>
<td>HRs 2.9, 2.9, 7.5 and 17.1 for stage I, II, III and IV cancer patients respectively vs general population</td>
<td>11</td>
</tr>
<tr>
<td>Linkage of California Cancer Registry and California Discharge Dataset</td>
<td>Cohort</td>
<td>233149</td>
<td>HRs ranging from 1.1-21.5 for different types of cancer; metastatic vs localized cancer</td>
<td>14</td>
</tr>
<tr>
<td>Vienna Cancer and Thrombosis Study (CATS)</td>
<td>Cohort</td>
<td>740</td>
<td>HR 2.0 (95%CI; 1.1-3.5) for (solid) tumor grade G3+G4 vs G1+G2</td>
<td>24</td>
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<tr>
<td><strong>Time since cancer diagnosis</strong></td>
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<tr>
<td>MEGA study</td>
<td>Case-control</td>
<td>2331/3220</td>
<td>OR 53.5 (95%CI; 8.6-334.3) in first 3 months after cancer diagnosis</td>
<td>10</td>
</tr>
<tr>
<td>Linkage of California Cancer Registry and California Discharge Dataset, colorectal cancer patients</td>
<td>Cohort</td>
<td>68142</td>
<td>OR 14.3 (95%CI; 5.8-35.2) in 3-12 months after cancer diagnosis</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 2.1 (95%CI; 0.6-2.2) &gt;15 years after cancer diagnosis</td>
<td>25</td>
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<tr>
<td>Linked United Kingdom databases</td>
<td>Cohort</td>
<td>82,20</td>
<td>Median ratio 3.2 for VT risk in first 3 months after diagnosis vs whole follow-up period, for cancer types separately</td>
<td>13</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td>Olmsted county population</td>
<td>Nested case-control</td>
<td>625/625</td>
<td>OR 4.1 vs OR 6.5 for treatment with and without chemotherapy</td>
<td>12</td>
</tr>
<tr>
<td>Node positive primary operable breast cancer patients</td>
<td>RCT</td>
<td>353/352</td>
<td>Cum. inc. of VT: 13.6% vs 2.6% for 2 years tamoxifen with vs without 6 months additional chemotherapy</td>
<td>33</td>
</tr>
<tr>
<td>Advanced gastroesophageal cancer patients</td>
<td>RCT</td>
<td>490/474</td>
<td>Cum. inc. of VT during and 30 days after chemotherapy: 12.4% for cisplatin vs 6.5% for oxaliplatin containing regimens</td>
<td>34</td>
</tr>
<tr>
<td>35 Papers on trials with cancer patients</td>
<td>Meta-analysis</td>
<td>6769</td>
<td>RR 1.7 (95%CI; 1.4-2.1) for VT in cancer patients treated with red blood cell transfusions with vs without ESA</td>
<td>35</td>
</tr>
<tr>
<td>38 Papers on phase 3 trials with cancer patients</td>
<td>Meta-analysis</td>
<td>8172</td>
<td>RR 1.6 (95%CI; 1.3-1.9) for VT in cancer patients treated with red blood cell transfusions with vs without ESA</td>
<td>36</td>
</tr>
</tbody>
</table>
study malignant neoplasm was shown to increase the risk of venous thrombosis fourfold (OR 4.1 (95%CI: 1.9-8.5)).[12] However patients were included between 1976 up to 1990, which might outdate the findings. In a Dutch population-based case-control study (the MEGA study), over 3000 consecutive patients with venous thrombosis were included between 1999 and 2004, together with over 2100 partner controls. [10] The risk of venous thrombosis was increased seven-fold in patients with cancer compared with patients without (OR 6.7 (95%CI: 5.2-8.6)). By linkage of four United Kingdom databases Walker and coworkers estimated the relative risk of VT in cancer versus age-matched non-cancer controls from the general population to be 4.7 (HR 4.7 (95%CI: 4.5-4.9)).[13] Surprisingly similar results were reported from a Danish population-based cohort of 57 591 incident cancer cases that were followed in time for venous thrombosis, together with 287 476 individuals without cancer from the general population. Non-cancer controls were matched on age, sex and county of residence. After adjustment for comorbid conditions the risk of venous thrombosis was also 4.7 times higher in cancer patients compared with the non-cancer participants (RR 4.7 (95%CI: 4.3-5.1)).[11] Although these relative risks demonstrate a strong association between cancer and venous thrombosis, absolute risks are clinically more meaningful, for example to communicate a patient’s risk of venous thrombosis or to decide whether a patient needs prophylactic treatment with anticoagulants or not, for which it needs to be balanced with the risk of unwanted side-effects (minor or major bleeding) of the anticoagulant treatment. Cohort studies are best suited for this purpose because they provide absolute risks.

The reported absolute risk (cumulative incidence) of venous thrombosis in cancer patients varies widely (1% - 8%) depending on patient population, duration of follow-up, calendar period and the method of detecting and reporting venous thrombotic events (Table 1). The heterogeneity of the studies makes it difficult to compare rates of venous thrombosis between these studies. Some follow-up studies include cancer patients with a diagnosis long before start of follow-up, in others follow-up is started at the beginning of cancer treatment. When comparing studies and generalizing results to other populations, follow-up should start at the same time, preferably at time of cancer diagnosis. When follow-up starts at a later time, some patients may have died and are therefore missing in the analyses. By linkage of the California Cancer Registry to the California Patient Discharge Data Set, Chew and colleagues followed 235 149 cancer patients from time of cancer diagnosis. Within 2 years 5032 patients developed a venous thrombotic event (1.6%).[14] The cumulative incidence reported in populations of such cancer registries or hospital discharge data is generally lower compared with rates reported in, for example, patients admitted to an inpatient oncology service. This is indeed observed in data from Sallah et al. who reported a cumulative incidence of venous thrombosis of 7.8% in 26 months in cancer patients referred to hematology/oncology services.[15] In the CATS study, a prospective follow-up of 840 cancer patients admitted to the Medical University in Vienna, 8% of the cancer patients developed a venous thrombotic event within one year after diagnosis or progression of disease.[16]
A recent meta-analysis by Horsted et al described incidence rates of venous thrombosis in cancer patients, stratified by ‘background risk’ of venous thrombosis.[17] Among cohorts with average-risk patients, defined as cancer patients representative of all patients with cancer, the incidence rate of venous thrombosis was estimated to be 13 per 1000 person-years (95%CI; 7-23). Among cohorts with high-risk patients, defined as cancer patients with high-grade or metastatic disease or treated with therapeutic strategies that increase thromboembolic risk, the overall incidence rate was 68 per 1000 person-years (95%CI; 48-96). In the abovementioned study with linkage of four United Kingdom databases, over 82 000 cancer patients and over 577 000 age-matched control participants were followed in time for venous thrombotic events. The incidence rate of VT in all cancers was 13.9 per 1000 person-years (95%CI; 13.4-14.4).[13]

Over the years the incidence of venous thrombosis in cancer patients has increased (Table 1).[18,19] Among patients hospitalized with cancer between 1979 and 1999 the cumulative incidence of venous thrombosis was reported by Stein and coworkers. Data was obtained from the US National Hospital Discharge Survey. The cumulative incidence of venous thrombosis increased from the late 1980s onward (1.5% in 1989) and this trend continued to the late 1990s (3.5% in 1999).[19] A similar trend was seen in another study of hospital discharge data. In this study the cumulative incidence of venous thrombosis was 3.6% in 1995-1996 and 4.6% in 2002-2003 (28% increase).[18] A similar rise in VT incidence over time in cancer patients, but not in non-cancer controls, is seen in the study with linkage of four United Kingdom databases by Walker (Figure 1).[13] In this study the rise in VT incidence is reported for different cancer types. Several factors could explain this finding, including a greater awareness of the association between cancer and venous thrombosis and improvements in diagnostic tests. Also, due to improved treatment strategies patients with cancer currently survive longer, leading to more aged patients undergoing more cancer treatments, which in themselves also increase thrombosis risk. For these reasons, the incidence is expected to rise further in the future.

Risk factors for venous thrombosis in cancer patients
Cancer is a heterogeneous disease and its different types and stages should be taken into account when determining the risk of venous thrombosis. Also several patient-associated and treatment-associated factors are known to increase the risk of thrombosis.

Extensive work has been published on type of malignancy and subsequent risk of venous thrombosis (Table 1). Overall, pancreas, brain, lung and ovarian cancer are reported to induce highest risks.[11,13,17,20] In the literature high risks are additionally reported for lymphomas, myeloma and kidney, stomach and bone cancer.[11,14,18,21] Relatively low risks are generally seen in patients with breast or prostate cancer. Horsted and colleagues summarized in their meta-analysis incidence rates of venous thrombosis for eight different types of malignancy (Figure 2).[17] For the absolute risks presented in this figure only cohort studies with start of follow-up at
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It appears that especially the cancer types that are biologically aggressive, as evidenced by short survival time and early metastatic spread, are correlated with a high incidence of venous thrombosis. Figure 3 shows VT incidence rates for different types of cancer (according to results of Horsted[17], Walker[13] and Cronin-Fenton[11]) plotted against the one-year relative mortality for each cancer type. One-year relative mortality rates were derived from Eurocare.it[23]. Although VT incidence per type of cancer varies for the different studies, a clear positive association can be observed with one-year relative mortality of the cancer type, as a measure of biological aggressiveness of the cancer, and an associated thrombogenic potential.

Such an association between aggressiveness of cancer and thrombogenic potential can also be observed when taking stage of cancer into account, which is highly correlated with risk of venous thrombosis (Table 1).[10,11,14,17] In the Danish follow-up study, mentioned above, where 55 000 cancer patients and over 285 000 matched non-cancer controls from the general population were followed in time, the risk of venous thrombosis in cancer patients appeared to be strongly dependent on stage of the cancer, with adjusted relative risks of 2.9, 2.9, 7.5 and 17.1 among patients with stage I, II, III, and IV disease.[11] Also in the California Cancer Registry study, increased relative risks of venous thromboembolic events in metastatic cancer patients compared with patients with localized disease were reported for 12 different types of cancer (range of hazard ratios 1.1-21.5).[14] In this study metastatic disease at time of cancer diagnosis was found to be the strongest predictor of subsequent venous thrombosis. Figure 4 shows two-year cumulative incidence rates of venous thrombosis per type and stage of cancer, according to data from this California Cancer Registry.[14] For every type of cancer presented, VT incidence increases from localized, to regional to remote cancer. Lastly, in the Vienna Cancer and Thrombosis study (CATS), which included 740 patients with newly diagnosed (or progressed after remission) patients with solid tumors, tumor grade (G3+G4 vs G1+G2) was also significantly associated with risk of venous thrombosis (HR 2.0; 95%CI; 1.1-3.5).[24] This was after correction for age, sex, tumor histology, types and stage.

The incidence of venous thrombosis is clearly highest in the first few months after cancer diagnosis and decreases thereafter (Table 1). In the MEGA-study, the risk of venous thrombosis was highest in the first three months after cancer diagnosis (OR 54 (95%CI; 8.6-334.3)), was decreased but still high in the period between three and twelve months (OR 14.3 (95%CI; 5.8-35.2)) and decreased to almost no elevated risk ten years after cancer diagnosis.[10] In a retrospective analysis of over 68 000 colorectal cancer patients from the California Cancer Registry, incidence rates of symptomatic venous thrombosis were calculated.[25] The incidence was reported to decrease over time from 5.0/100 person years in the first 6 months after cancer diagnosis, 1.4/100 person years 6-12 months after cancer diagnosis to 0.6/100 person years 12-24 months after cancer diagnosis. This phenomenon has been shown for all types of cancer in the large
follow-up study by linkage of four United Kingdom databases.[13] This change in risk over time again illustrates why follow-up studies into incidence of venous thrombosis in cancer patients need to start at time of cancer diagnosis. If follow-up is started at a later point in time, the incidence will be lower and studies can not be compared directly.

There are several possible explanations for a higher risk of venous thrombosis in the first few months after diagnosis compared with the period thereafter. First, several cancer treatment modalities increase the risk of venous thrombosis (see below), inducing a high risk directly after diagnosis and start of treatment. Second, a proportion of treated cancer patients will go into remission, leading to a reduced thrombotic risk thereafter. A third explanation is that over time a considerable proportion of the cancer patients will succumb to the disease. The occurrence of such a competing event (death) will prevent thrombotic events from being observed.

In addition to type and staging of cancer, cancer treatment modalities also substantially increase the thrombotic potential (Table 1). Surgery, chemotherapy, hormonal therapy, anti-angiogenic drugs, immunomodulatory agents, erythropoiesis stimulating agents, blood transfusions and central venous catheters are all reported to be associated with an increased risk.[26,27] Surgery is a well-known risk factor for venous thrombosis, also in non-cancer patients. In cancer patients, risk of 90-day post-operative venous thrombosis is reported to be twice as high as in non-cancer patients.[28] Incidence rates in patients treated with chemotherapy are high, with an annual incidence of 11%-20%.[29] Also, other new systemic cancer treatments and supportive therapies are reported to predispose to venous thrombosis.[29] An important caveat, however, in interpreting these risks is that most studies on this topic are observational studies. In observational studies the decision on (type of) treatment is made by the treating physician, depending on several patient’s characteristics, such as stage of disease and prognosis. Therefore treated and untreated patients are not directly comparable and it cannot be discerned whether increased risk of venous thromboembolism is due to the treatment, the cancer or the patients’ prognosis. This phenomenon is called confounding by indication and plays a role in all observational studies. In randomized clinical trials exposure (treatment) is assigned in a random fashion, for which reason patients are directly comparable with respect to their thrombotic risk. A direct comparison of different treatment modalities is even more difficult when thrombosis prophylaxis is indicated for specific types of treatment. For example, the risk in patients who underwent surgery cannot be directly compared with the risk in patients treated with chemotherapy as thromboprophylaxis is common practice after surgery, but not during chemotherapy. A disadvantage of clinical trials is the highly selected patient population, limiting the generalizability of the results.

Out of the large literature on this topic, we will present some examples of randomized clinical trials as an illustration of increased risk induced by several types of treatment. Several randomized clinical trials in women with breast cancer have shown a clear link between chemotherapy and/or hormone therapy and venous thrombosis risk. [30-33] In a randomized trial in postmenopausal women with node-positive primary operable breast cancer (with positive estrogen and progesterone receptor status), the cumulative incidence of thromboembolic events was assessed for women randomized to 2 years of tamoxifen or to tamoxifen (2 years) plus chemotherapy for 6 months. [33] The cumulative incidence in the tamoxifen only group was 2.6% versus 13.6% in the combined treatment group. Similarly, results from a clinical trial in advanced gastro-esophageal cancer patients showed varying rates of venous thrombosis for either one of four epirubicin/platinum/fluoropyrimidine combination regimens during treatment until 30 days after the last treatment cycle. A higher cumulative incidence of venous thrombosis was observed in patients receiving a cisplatin-containing combination regimen (12.2%) as compared with oxaliplatin (6.5%).[34] A systematic review of randomized controlled trials demonstrated that cancer patients treated with erythropoiesis-stimulating agents (ESAs) in addition to red blood cell transfusions had an increased risk of thromboembolic events over patients not additionally treated with ESAs (relative risk 1.7).[35] These results are supported by a systematic review from Bennett et al.[36] In another large meta-analysis of clinical trials, patients with cancer receiving the angiogenesis inhibitor bevacizumab, had a somewhat increased risk of venous thrombosis (relative risk 1.3 95%CI; 1.1-1.6).[37]

Apart from cancer-related factors, patient-related factors play a role in the development of thrombosis in cancer patients (Table 1). Several traditional risk factors for thrombosis are additionally present in many cancer patients like older age, prolonged immobility, prior history of venous thrombosis and comorbidities. In the California Cancer Registry study in colorectal cancer patients, a significant predictor of venous thrombosis during the first year after diagnosis was the presence of three or more comorbid conditions (HR 2.0 (95%CI; 1.7-2.3)).[25] In a retrospective cohort study using discharge databases of all cancer patients admitted to US academic medical centers, over 1 000 000 cancer patients were followed for venous thrombosis. [18] Variables associated with VT in a clinically significant way were ethnicity and the presence of comorbidities. Such comorbidities included arterial thromboembolism, pulmonary disease, renal disease, infection and anemia which all increased the risk of venous thrombosis (ORs 1.5, 1.4, 1.5, 1.8 and 1.4 respectively). Patients with black ethnicity seemed to be at increased risk (OR 1.2 (95%CI; 1.1-1.2)), while patients with Asian ethnicity had a decreased risk of venous thrombosis when compared with Caucasians (OR 0.7 (95%CI; 0.7-0.8)). Similarly, in colorectal cancer patients from the abovementioned California Cancer Registry, the risk of venous thrombosis was significantly reduced among Asians/Pacific Islanders (HR 0.4 (95%CI; 0.3-0.4)) compared with Caucasian patients.[25] This is probably explained by an overall lower risk of venous thrombosis in Asians/ Pacific Islanders.[9] Prothrombotic mutations are additionally reported to influence risk of thrombosis in cancer patients.[10,38] For example, the Factor V Leiden mutation seems to interact with cancer with respect to VT risk. Cancer patients with Factor V Leiden were reported to have a 2-fold increased risk of venous thrombosis compared with non-carriers with cancer (adjusted OR 2.2 (95%CI; 0.3-17.8).[10]
Clinical presentation
A limited number of studies have looked at differences in the clinical presentation of venous thrombosis between patients with and without cancer. Bilateral DVT seems to be more common among cancer patients than in non-cancer patients.[39,41] A recent study by Limbert showed that rates of symptomatic bilateral lower limb DVT, symptomatic iliofemoral thrombosis and upper limb DVT were higher in cancer patients compared with patients free from cancer (8.5% vs 4.6%), (22.6% vs 14.0%) and (9.9% vs 4.8%); respectively.[6] In this study rates of PE and symptomatic proximal DVT were similar. The relatively high incidence of upper limb DVT in cancer patients is at least partly explained by the frequent use of a central venous catheter.[42] Furthermore, cancer is reported to be common in rare forms of thrombosis such as Budd-Chiari syndrome, extrahepatic portal vein obstruction and mesenteric vein thrombosis.[43]

Prognosis
In general, cancer patients with venous thrombosis do not fare well. Thrombotic events are reported to be the second leading cause of death in cancer patients.[44] Patients with cancer-associated venous thrombosis have higher risks of bleeding complications during anticoagulant treatment and of recurrent venous thrombosis than patients with venous thrombosis but without cancer.[4,45,46] In a Norwegian study of 740 patients with a first venous thrombotic event, the one-year case fatality rates (the proportion of deaths within one year after the venous thrombotic event) were 5-fold higher in patients with cancer-associated venous thrombosis (63.4% (95%CI; 54.5-71.8)) than in venous thrombosis patients without cancer (12.6% (95%CI; 10.1-15.5)).[7] In the RIETE registry, a large prospective cohort of over 35 000 VT patients, three month mortality was much higher in the patients with cancer-related VT as compared with VT patients without cancer (26% vs 4% respectively).[4]

Furthermore, cancer patients who develop a venous thrombotic event have a lower survival rate than cancer patients without venous thrombosis.[14,47-50] In a large, Danish, population-based study, patients diagnosed with cancer at the time of venous thrombosis were matched to control cancer patients without venous thrombosis, based on age, sex, type of cancer and year of diagnosis.[50] The one-year survival rate for the group with cancer and venous thrombosis was 12%, as compared with 36% in the control group. Chew and colleagues investigated the survival of over 235 000 cancer patients and compared these survival rates between cancer patients with and without a subsequent diagnosis of venous thrombosis.[14] In a multivariate analysis with adjustment for age, race and stage of cancer, a diagnosis of venous thrombosis was a significant predictor of decreased survival within one year for all cancer types (hazard ratios ranging from 1.6 to 4.2). We studied mortality rates in participants of the Tromsø study, a large Norwegian follow-up study in participants free of cancer and venous thrombosis at baseline in 1994-1995.[3] In total, 25,983 subjects were followed until September 1, 2007, of whom 1751 subjects developed cancer and 417 developed venous thrombosis (109 of which cancer-related). By means of a time-dependent analysis mortality rates and hazard ratios for death were estimated for disease free subjects, subjects with cancer only, subjects with venous thrombosis only and subjects with cancer-related venous thrombosis (Table 2). Subjects with cancer-related venous thrombosis had a 30-fold increased risk of death during follow-up as compared with disease-free subjects (HR 31.2 (95%CI; 24.6-39.6)), while subjects with cancer only or venous thrombosis only had a 7-fold and 3-fold increased risk respectively. An explanation for the difference in mortality rates could be the more aggressive course of the malignancies associated with high thrombosis risk (Figure 3). It is unknown to what extent the high mortality rates in patients with cancer and venous thrombosis can be attributed to the thrombotic events themselves. In a study in 4466 cancer patients in the US starting with chemotherapy and followed for a median of 75 days, thrombosis (including both venous and arterial events) was the second leading cause of death (n=13; 9%) after cancer progression (n=100; 71%).[44] In this study causes of death were assigned by the treating physicians, mainly based on clinical data, rather than autopsies. Among patients from a large database comprised of Multiple-Cause Mortality Files from 1979 to 1998 in whom pulmonary embolism was reported on the death certificates, 23% were reported to have cancer.[51] Causes of death according to the treating physician or death certificate may not be that reliable and autopsy studies should be used to answer this question. In two autopsy studies from Sweden and the US, the incidence of pulmonary embolism in cancer patients was 26% and 17%, respectively, of which 8% and 14% were fatal pulmonary emboli.[52]

Table 2. Crude mortality rates and age- and sex-adjusted hazard ratios of death in participants without cancer and with cancer-related venous thrombosis, with venous thrombosis only, with cancer only and with cancer-related venous thrombosis, The Tromsø study 1994-2007

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Person years</th>
<th>Deaths (n)</th>
<th>MR per 100 pyrs (95%CI)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>277713</td>
<td>1750</td>
<td>0.63 (0.60-0.66)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>VT only</td>
<td>1317</td>
<td>67</td>
<td>5.1 (4.0-6.4)</td>
<td>2.6 (2.0-3.3)</td>
</tr>
<tr>
<td>Cancer only</td>
<td>5650</td>
<td>721</td>
<td>12.7 (11.9-13.7)</td>
<td>7.4 (6.8-8.2)</td>
</tr>
<tr>
<td>Cancer-related VT</td>
<td>131</td>
<td>72</td>
<td>55.0 (43.6-69.3)</td>
<td>31.2 (24.6-39.6)</td>
</tr>
</tbody>
</table>

MR denotes mortality rate; pyrs, person-years; CI, confidence interval; HR: hazard ratio; VT, venous thrombosis.
Hazard ratios were calculated by means of a time-dependent Cox regression analysis.

Thromboprophylaxis
It is hypothesized that anticoagulant treatment for the prevention of venous thrombotic events in cancer patients might improve prognosis and quality of life. However, such treatment comes with a disadvantage of an increased risk of bleeding, which is especially pronounced in cancer patients.[46,53,54] In a prospective follow-up of 842 DVT patients, Prandoni et al. investigated bleeding rates during anticoagulant treatment. The 12-month cumulative incidence of major bleeding was about two-
Chapter 3

Epidemiology of cancer-associated venous thrombosis

Table 3. Predictive model for chemotherapy-associated venous thrombosis

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<th>Patient characteristic</th>
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<tr>
<td>Site of cancer</td>
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</tr>
<tr>
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</table>

From Khorana Blood 2008.[59]

Recurrent venous thrombosis and cancer

The overall risk of recurrent venous thrombosis in patients who suffered once from VT is high, with a five to ten year cumulative incidence ranging from 25% to 30%.[66-68] Cancer patients are at an approximately two to three-fold increased risk of recurrent venous thrombosis compared with non-cancer patients.[46,67-69] Prandoni and coworkers followed 355 consecutive patients with a first episode of DVT for eight years and found a two-fold risk of recurrent venous thrombosis in cancer patients compared with non-cancer patients (hazard ratio 1.7 95%CI; 1.3-2.3).[68] The same group of investigators found a 12-month cumulative incidence of recurrent venous thrombosis of 20.7% in cancer patients on conventional anticoagulant treatment versus 6.8% in patients without cancer on anticoagulant treatment in a prospective cohort study including 842 DVT patients.[46] Recurrence appeared to be related to extent of disease, classified according to the tumor-node-metastasis (TNM) classification, with highest recurrence rates in patients with extensive vs moderately or less extensive cancer. This again reflects the apparent relation between aggressiveness of cancer and thrombogenic potential. In the RITE study patients with symptomatic, acute venous thrombosis were enrolled and three-month outcomes of the participants were studied.

fold higher in patients with active cancer (12.4% (95%CI; 6.5-18.2%)) than in patients without cancer (4.9% (95% CI; 2.5-7.4%).[46] Several randomized clinical trials have investigated the effects of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy. A recent Cochrane review summarized results of 9 of those trials.[55] Thromboprophylaxis was reported to significantly reduce the incidence of symptomatic VT (RR 0.62 (95%CI; 0.41-0.93). However, this treatment was also associated with an increase in bleeding events. The number needed to treat to prevent one venous thrombotic event, was 60. Thromboprophylaxis should therefore be targeted only at cancer patients with a high risk of venous thrombosis, which outweighs the risk of bleeding events. Several biomarkers have been associated with risk of venous thrombosis in cancer patients, like P-selectin, D-dimer, tissue factor-bearing microparticles, pre-chemotherapy hemoglobin, platelet and leukocyte counts, factor VIII and C-reactive protein.[16,56-63] A recent clinical trial randomized advanced cancer patients with higher levels (> 3.5 x 10^9 microparticles/µL) of circulating tissue factor-bearing microparticles (TFMP) to either enoxaparin for two months (n=23) or observation without any treatment (n=11).[64] Advanced cancer patients with lower levels of TFMP were followed without treatment (n=32). Patients with higher TFMP levels, not randomized to enoxaparin, had a significantly higher two-month cumulative incidence of venous thrombosis (27%) as compared with patients with lower TFMP levels (7%). Patients with high TFMP levels randomized to enoxaparin had the lowest cumulative incidence of venous thrombosis (6%). Median survival was 17.8 months in patients treated with enoxaparin as compared with 11.8 months in untreated patients with higher levels of TFMP.

Although this clinical trial using risk stratification based on one biomarker shows promising results, prediction models incorporating several risk factors, instead of one, are probably more useful for guiding decisions on prophylaxis in individual patients. Such a risk assessment model has been developed by Khorana et al.[59] In a randomly selected development cohort of 2701 cancer patients initiating a new chemotherapy regimen, baseline clinical and laboratory risk factors for venous thrombosis were included in a risk model, which was validated in an independent cohort of 1365 cancer patients from the same population. Patients were followed for symptomatic venous thromboembolic events for a median of 73 days. Five predictive variables present before initiation of chemotherapy were identified in the final multivariate analysis and used for a risk score model: primary site of cancer, platelet count ≥350 000/µL, hemoglobin less than 10 g/dL and/or use of red cell growth factors, leukocyte count more than 11 000/ µL and body mass index ≥35 kg/m^2 (Table 3). Rates of venous thrombosis in the development and validation cohort were 0.8% and 0.3% in low-risk (score=0), 1.8% and 2% in intermediate-risk (score=1-2) and 7.1% and 6.7% in high-risk patients (score≥3), respectively. Ay and colleagues applied this risk model to their prospective observational cohort study of patients with newly diagnosed cancer or with progression of disease after complete or partial remission who had not recently received chemotherapy, surgery and/or radiotherapy (CATS study).[65] Additionally, they expanded the model by adding two predictive biomarkers, i.e. soluble P-selectin (≥53.1 ng/mL) and D-dimer levels (≥1.44µg/mL) and they added additional types of cancer to the high and very high risk groups. In the expanded risk model the cumulative probabilities of VT after six months of follow-up were 35% in patients with a score ≥5, 10.3% in patients with score 3 and 1.0% in patients with score 0. The disadvantage of this expanded risk model is that additional laboratory tests have to be performed since D-dimer and P-selectin levels are not routinely measured in the clinic. Intervention trials based on risk assessment models are necessary to demonstrate the effectiveness and safety of prophylactic anticoagulant treatment in high-risk patients. In an ongoing study, the use of thromboprophylaxis in patients deemed high-risk, based on the original prediction model by Khorana, is currently being tested (www.clinicaltrials.gov No. NCT00876915).

Table 3. Predictive model for chemotherapy-associated venous thrombosis

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From Khorana Blood 2008.[59]
Of 18 883 participants, 3805 had been diagnosed with active cancer. A relative risk for recurrent PE of 2.0 and for recurrent DVT of 2.4 was found for patients with a cancer diagnosis less than three months before their first venous thrombosis.[69] Not much is known about the risk of recurrent venous thrombosis for different types of cancer and results from previous studies are contradictory.[46,69] A clinical prediction rule (Ottawa prognostic score) has been developed for recurrent venous thrombosis during the first six months of anticoagulant treatment in a retrospective cohort study of 543 patients with a cancer-associated venous thrombotic event.[70] The final model included four predictors (sex, primary tumor site, stage and number of prior venous thrombotic events) leading to a score sum that ranged between -3 and 3 points. Patients with a score ≤0 had a low risk of recurrence (4%) while patients with a score ≥1 had a relatively high recurrence risk (16%). The prediction rule was validated by the investigators in an independent set of patients from two randomized clinical trials and results appeared to be consistent. Another group of investigators from the Netherlands assessed the reproducibility of the Ottawa score in an independent sample of 419 patients with cancer-associated venous thrombosis.[71] Their results were similar to those reported by Louzada and coworkers in their validation sample. Recently the Ottawa score was additionally validated in an independent patient population in a tertiary hospital in Korea.[72] In 546 patients with cancer-associated VT the model was less discriminatory compared with the derivation study. Of patients in the low-risk group (score ≤0) 13.2% were identified with recurrent venous thrombosis, while 22.4% of patients in the high-risk group (score ≥1) were identified with a recurrence. Thrombosis risk as well as cancer predominance is known to be different in the Asian population, which may be an explanation for the different findings. Furthermore differences in study design, like different durations of follow-up or definition of recurrences may explain these findings.

**Screening**

Acute venous thrombosis can be the first manifestation of an occult cancer. Rates of occult cancer detection at the time or shortly after diagnosis of venous thrombosis vary in the literature, depending on patient population, duration of follow-up and detection methods. While some articles published in the eighties contradict each other as to whether there is an association between venous thrombosis and an increased risk of subsequent cancer diagnosis,[73-75], recent articles show a clear association between the two. In a nationwide, retrospective cohort study in Scotland almost 60 000 patients with DVT or PE diagnosed between 1982 and 2000 were followed for the occurrence of cancer until the end of 2000.[76] The ratio of the observed cases of cancer and the number of cases expected based on national cancer incidence rates was calculated, which gives a standardized incidence ratio (SIR). For all malignancies combined there was an excess risk of being diagnosed with cancer in VT patients which remained up to 2 years after diagnosis of VTE. Especially in the first one to six months after diagnosis of venous thrombosis the risk was high (SIR 4.2 (CI 3.9-4.5)). Two other follow-up studies, quite alike in design, showed similar results with respect to risks and types of cancer (liver, pancreas, ovary, brain and lymphoma) for which the association was most pronounced.[77,78] In a recent systematic review by Carrier and colleagues, data from 34 studies that reported prevalence of undiagnosed cancer at the time of an acute, first thromboembolic event were combined.[79] In 4.1% (95%CI; 3.6-4.6%) of the included patients, a previously undiagnosed cancer was detected within a month after the venous thrombotic event. Within a year after the event 6.3% (95%CI; 5.6-6.9%) of the patients were diagnosed with cancer.

Patients with an idiopathic venous thrombosis have a higher risk of detection of an occult cancer than patients with a venous thrombotic event secondary to a provoking risk factor.[79,80] In the abovementioned study by Carrier the period prevalence of previously undiagnosed cancer between baseline (venous thrombotic event) and 12 months was 10.0% (95%CI; 8.6-11.3%) for patients with unprovoked venous thrombosis versus 2.6% (95%CI; 1.6-3.6%) for patients with a secondary event. This raises the question whether only patients with an idiopathic venous thrombosis should be screened for occult cancer. Van Doormaal and colleagues prospectively followed 630 idiopathic venous thrombosis patients who underwent either baseline cancer screening (consisting of history, physical examination, basic laboratory tests and chest X-ray) or extensive cancer screening (consisting of additional abdominal and chest CT scan and mammography), based on the center in which patients were treated.[81] After baseline screening 7 out of 288 patients (2.4%) were diagnosed with cancer versus 12 out of 342 patients (3.5%) after extensive screening methods. Survival did not differ between the groups, which led the authors to conclude to not support extensive routine screening for cancer in patients with a first episode of idiopathic venous thrombosis.

In one randomized clinical trial by Piccioli and colleagues,[82] acute idiopathic venous thrombosis patients were randomized to either an extensive screening for occult cancer or to no further testing. Unfortunately the trial was terminated prematurely due to a lower than anticipated number of participating centers and an increasing tendency among physicians to perform screenings tests for occult cancer in control patients. Extensive screening was found to be able to detect hidden malignancies and to lead to identification of malignancies at an earlier stage. However, due to the limited sample size, effects on prognosis of patients remained again unclear. Cancer related mortality during the 2-year follow-up period did not significantly differ between both groups (absolute difference 1.9% (95%CI; -5.5-10.9%)). The effect of extensive screening in idiopathic venous thrombosis patients on prognosis remains elusive.[83,84] Further studies are needed to investigate whether screening procedures are cost-effective and affect cancer-related mortality.

**Superficial venous thrombosis and cancer**

Superficial vein thrombosis (SVT), or superficial thrombophlebitis, is a common condition of which the incidence in general has so far not been properly assessed, possibly because in the past SVT was considered a benign, self-limiting, disease. However, it is thought to occur at least as often as deep vein thrombosis. Interest in
the disease was renewed when more and more studies in the past decade described an association between SVT and deep venous thrombosis.[12,85,86] Many conditions have been reported to predispose to SVT, mostly also well-known risk factors for deep venous thrombosis. For this reason it would be reasonable to suspect an association between cancer and SVT.[87-90] The incidence of SVT in cancer patients has not been studied. Whether SVT should be seen as a marker of occult cancer is also controversial. In a sub-study of the Calisto trial, a trial in which ~3000 SVT patients with isolated SVT were randomized to either fondaparinux or placebo, Prandoni and coworkers compared 737 SVT patients with 1438 control patients with regard to cancer diagnoses during an average of 26 months of follow-up.[91] They concluded that occurrence of SVT in the legs does not represent a risk factor for subsequent malignancies. The same conclusion was drawn in a small study performed in the Netherlands.[92] However, Sørensen et al. did find a relation between a diagnosis of SVT and a subsequent cancer diagnosis in the Danish population.[93] The occurrence of cancer in 7663 SVT patients was compared with the expected number of cancer diagnoses based on national incidence rates and a SIR of 2.6 (95% CI: 2.1-2.9) for the first year of follow-up was reported. A possible explanation for the difference in findings is that in the study by Sørensen unrecognized concomitant deep vein thrombosis was possibly present, which increased the risk of a cancer diagnosis. Prandoni and colleagues excluded cases with a concomitant venous thrombotic event confirmed by ultrasonography. Future epidemiologic studies are needed to study the strength of the relationship between SVT and cancer and the incidence of SVT in cancer patients.

Concluding remarks

Despite the fact that the strong association between cancer and venous thrombosis has been known for more than 150 years, cancer-associated thrombosis is still a topic of extensive (epidemiologic) research from which there is much to gain for patients. Future studies need to be targeted at development and validation of prediction models to categorize cancer patients into high or low risk of venous thrombosis. Randomized trials should study the benefit of thromboprophylaxis in patients deemed at high risk based on these models. Furthermore, studies are needed to investigate whether cancer screening procedures in idiopathic venous thrombosis patients are cost-effective and affect cancer-related mortality.

Reference List

Chapter 3

Epidemiology of cancer-associated venous thrombosis


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Chapter 3


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

Jasmijn F. Timp, Linda E. Flinterman, Astrid van Hylckama Vlieg, Frits R. Rosendaal, Suzanne C. Cannegieter

Submitted for publication