Frequency, demographics and risk (according to tumour type or site) of cancer-associated thrombosis among patients seen at outpatient DVT clinics

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Summary
Venous thromboembolism (VTE) is a clinically important complication for both hospitalised and ambulatory cancer patients. In the current study, the frequency, demographics and risk (according to tumour site) of VTE were examined among patients seen at outpatient DVT (deep- vein thrombosis) clinics. Of 10,015 VTE cases, 1,361 were diagnosed with cancer, for an overall rate of cancer-associated VTE of 13.6% in this outpatient population. Patients with cancer-associated VTE were significantly older than cancer-free VTE cases (66.4 ± 12.7 vs. 58.8 ± 18.5 years; p<0.0001). The frequency of cancer-associated VTE peaked earlier among females than males, occurring in the sixth (137/639, 21.4% vs. 98/851, 11.3%; p<0.001) and seventh decades (213/980, 21.7% vs. 197/1096, 18%; p=0.036). VTE was described most frequently in common cancers – breast, prostate, colorectal and lung (56.1% of cases). The risk of VTE varied widely across 17 cancer types. Calculating odds ratios (OR) to assess the effect size of cancer type on VTE risk, the highest odds were observed for patients with pancreatic cancer (OR 9.65, 95% confidence interval [CI] 5.51–16.91). Tumours of the head and neck had higher odds than previously reported (OR 8.24, 95% CI 5.06–13.42). Reduced risk estimates were observed for skin cancers (melanoma and non-melanoma: OR 0.89, 95% CI 0.42–1.87; OR 0.74, 95% CI, 0.32–1.69, respectively). We conclude that outpatients have a similar rate of cancer-associated VTE as VTE patient populations previously reported, that cancer-associated VTE occurs in an older age group and earlier in females and that outpatients exhibit distinct tumour site-specific risk from that described among hospitalised cancer patients.

Keywords
Clinical studies, cancer, venous thrombosis

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Introduction
Venous thromboembolism (VTE) is a clinically relevant disease in cancer patients (1), with recent studies suggesting it is becoming more frequent (2). Large studies have shown that clinically apparent VTE is associated with worse mortality in cancer patients than non-cancer patients. In hospitalised cancer patients undergoing potentially curative surgery, fatal pulmonary embolism (PE) detected at autopsy was three-fold higher than in patients without cancer undergoing surgery at the same sites (3). A Dutch cancer registry that matched cancer patients with and without VTE showed a 2.2-fold mortality increase in those with cancer-associated VTE (4). More recently, a study of ambulatory cancer patients beginning chemotherapy showed that thromboembolism (including arterial events) was a leading cause of death, accounting for up to 9% of mortality (5).

The distinction between hospitalised cancer patients and those patients receiving outpatient care is important when considering thrombosis risk and prevention. The benefit of heparin-based thromboprophylaxis has been proven in selected cancer surgery inpatients (6), but this is not the case for cancer outpatients with metastatic breast or lung cancer (7), or for those patients with intravenous catheters (8), for whom clinical trials of low-molecular-weight heparin (LMWH) showed no benefit. These findings are reflected in current guidelines that do not recommend thromboprophylaxis in cancer outpatients (9, 10). This suggests that high-risk populations have not been accurately identified and that a greater understanding is required of cancer-associated thrombosis in outpatients to ident-
ify appropriately high-risk subgroups of cancer patients. In the current study, we conducted an analysis to define the frequency, demographics and risk (according to tumour site) of cancer-associated VTE among patients seen at outpatient DVT clinics.

Materials and methods

Patients

UK hospitals participating in the VEnous thromboembolism RegIsty (VERITY) prospectively enroll patients attending DVT outpatient clinics. Details of the VERITY registry have been published previously (11, 12). Data (demographic characteristics, medical history, presenting symptoms, diagnosis, treatment practices including location of treatment and follow-up data) are collected by trained hospital staff in a standardised electronic case report form and submitted to the electronic database. Patient data are anonymised. Centers enroll patients presenting with suspected VTE and are requested to complete the case report form irrespective of whether the final diagnosis of VTE is positive. A variety of algorithms, mainly based on D-dimer measurement and pre-test probability, are used to exclude VTE. Confirmatory, objective testing is undertaken according to local protocols, usually including ultrasonography or venography for suspected DVT and pulmonary angiography, lung scintigraphy or helical computed tomography scan for suspected PE (12).

This analysis included patients who presented with suspected VTE for whom the VTE diagnosis was recorded, together with the presence or absence of a cancer diagnosis. Data were validated to eliminate, as far as possible, data entry problems. Cancer is defined in the database as current or having received treatment for cancer in the last six months. On the cancer screen, 17 specific cancer types are listed [bone/sarcoma, breast, central nervous system (CNS), colorectal, endocrine, gynecologic, head/neck, leukemia, lung, lymphoma, melanoma, myeloma, non-melanoma, pancreas, prostate, urological, upper gastrointestinal (GI)] with other. No record is made of metastatic disease, but patients with multiple cancer sites are recorded; no histological description, tumour grade or stage are recorded. We included patients who had a diagnosis of cancer after the initial presentation for VTE in the analyses.

Statistical analysis

The Chi^2 test was used to analyse the difference in categorical variables. The mean age at consultation was compared between groups using the independent samples t-test and one-way analysis of variance (ANOVA); the Games-Howell post-hoc test was used for pairwise comparisons. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for individual cancer types. Age- and sex-matched comparisons were made using a matched dataset derived from the main dataset. A p-value <0.05 was considered statistically significant. All analyses were conducted using a commercial software package (SPSS version 16; SPSS Inc., Chicago, IL, USA).

Results

Patients

Between February 2005 and March 2008, 49,044 patient entries were made online in the VERITY registry by 43 hospitals in the UK. VTE status (confirmed or excluded) and cancer status (malignancy or no malignancy) was known for 41,367 patient entries. Data validation excluded 166 entries, for reasons of no hospital name specified (n=86), female prostate cancer (n=11) and others (n=69). In total, 41,201 patient entries from 39,618 individual patients were included in this analysis (Fig. 1).

VTE and cancer

VTE was diagnosed in 10,015 (25.3%) of the 39,618 patients in the registry and cancer was diagnosed in 2,804 patients. Cancer type was specified in 2,308 (82.3%) cancer cases; in 207 cases, cancer type was recorded as "other" (i.e. not one of the 17 cancer types listed) and in 298 cases, no record of cancer type was made. In 165 cases, more than one cancer site was reported. Among VTE cases, 13.6% (1,361/10,015) carried a diagnosis of cancer (Table 1). There were 1,164 DVT, 22 cases of DVT and PE, 116 cases of PE and 59 cases designated as VTE.

The diagnosis of cancer was more frequent in VTE cases than in VTE-negative patients: 13.6% vs. 4.9% (1,443/29,603), OR 3.07
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(95% CI 2.84–3.31; p<0.001). VTE was more frequent in patients with cancer (48.5%, 1,361/2,804) than those without cancer (23.5%, 8654/36,814; p<0.001).

Age and cancer-associated thrombosis

Age data are presented in Table 2. Comparing non-cancer VTE cases with cancer-associated VTE cases, patients with cancer were significantly older (66.43 ± 12.7 vs. 58.85 ± 18.5 years; p<0.0001).

There were marked differences in age distribution; cancer-associated VTE was less prevalent in the first five decades of life, but markedly more prevalent in the seventh and eighth decades (Fig. 2). Among VTE patients, the proportion of those with cancer increased with increasing age, with gender-specific differences (Fig. 3). The peak incidence of cancer-associated VTE occurred earlier among females than males, in the sixth (137/639, 21.4% vs. 98/851, 11.3%; p<0.001) and seventh decades (213/980, 21.7% vs. 197/1096, 18%; p=0.036), and was more frequent in males than females in the eighth (198/934, 21.2% vs. 183/1054, 17.4%; p=0.035) and ninth decades (65/350, 18.6% vs. 82/708, 11.6%; p=0.001). Cancer was uncommon in VTE patients younger than 31 years (19/745; 2.6%).

Cancer sites in VTE patients

Four common cancers (breast, prostate, colorectal and lung) accounted for 56.1% (724/1290) of the VTE cases (for whom cancer site was specified). Certain tumour sites were more common in VTE cases than non-VTE cases, including CNS, pancreas, upper GI and head/neck (Fig. 4).

Effect size of cancer type on VTE risk

The ORs and adjusted ORs for the association of specific cancers with VTE are presented in Table 3. The ORs of the four most common cancers ranged from 1.94 (95% CI 1.57 – 2.39) for prostate cancer to 4.01 (95% CI 3.26–5.32) for lung cancer. The highest

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**Table 1: Cancer and VTE status for patients included in the study.**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VTE</td>
<td>28,160</td>
</tr>
<tr>
<td>VTE</td>
<td>8654</td>
</tr>
<tr>
<td>No</td>
<td>1443</td>
</tr>
<tr>
<td>Yes</td>
<td>1361</td>
</tr>
<tr>
<td>Total</td>
<td>36,814</td>
</tr>
</tbody>
</table>

(95% CI 2.84–3.31; p<0.001). VTE was more frequent in patients with cancer (48.5%, 1,361/2,804) than those without cancer (23.5%, 8654/36,814; p<0.001).

**Table 2: Age, cancer and VTE.**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>VTE</th>
<th>Non-cancer</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>39,609</td>
<td>10,008</td>
<td>8647</td>
<td>1361</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Mean, years</td>
<td>60.38</td>
<td>59.88</td>
<td>58.85</td>
<td>66.43</td>
</tr>
<tr>
<td>Median, years</td>
<td>63.00</td>
<td>62.00</td>
<td>61.00</td>
<td>68.00</td>
</tr>
<tr>
<td>Standard deviation, years</td>
<td>18.23</td>
<td>18.05</td>
<td>18.54</td>
<td>12.70</td>
</tr>
<tr>
<td>Range, years</td>
<td>4–102</td>
<td>4–102</td>
<td>4–102</td>
<td>22–96</td>
</tr>
</tbody>
</table>

**Figure 2: Age distribution in all VTE cases and cases with cancer-associated VTE.**

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ORs for VTE [both adjusted (9.65, 95% CI 5.51–16.91) and unadjusted (16.75, 95% CI 5.22–53.71)] were found in patients with pancreatic cancer. Tumours of the head and neck had high odds (OR 8.24, 95% CI 5.06–13.42). Reduced risk estimates were observed for skin cancers (melanoma and non-melanoma: OR 0.89, 95% CI 0.42–1.87; OR 0.74, 95% CI 0.32–1.69, respectively). The OR for VTE in patients with more than one cancer site was 3.46 (95% CI 2.67–4.48).

Discussion

This analysis of more than 10,000 patients with VTE in an outpatient treatment setting found that one in seven had a diagnosis of cancer. This is similar to the overall prevalence of cancer-associated thrombosis reported in the literature, which is described as approximately 15% (1). This is despite the selected population of cancer patients treated in an outpatient setting. Indeed, a recent prospective clinical trial confirmed that cancer was the most common reason cited for in-hospital treatment of VTE (13). In our study, cancer was three times more common in VTE cases than in non-VTE cases, which is low in comparison with previous findings (14, 15) but reflects the selected nature of the registry population, in which patients with suspected VTE who subsequently had that diagnosis excluded would be expected to have an over-representation of thrombosis-related risk factors such as cancer.

We found that cancer-associated VTE was most prevalent in the seventh and eighth decades of life, with peaks occurring significantly earlier in females than males reflecting, we suspect, the ear-
Table 3: Odds ratios and adjusted odds ratios for VTE for specific cancer types or tumour sites.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>9.65</td>
<td>5.51–16.91</td>
<td>5.22–53.71</td>
<td></td>
</tr>
<tr>
<td>Head/neck</td>
<td>8.24</td>
<td>5.06–13.42</td>
<td>3.60–15.78</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>7.19</td>
<td>2.98–17.34</td>
<td>1.56–18.33</td>
<td></td>
</tr>
<tr>
<td>Upper GI</td>
<td>6.41</td>
<td>3.99–10.31</td>
<td>2.19–7.38</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>4.93</td>
<td>1.79–13.57</td>
<td>1.28–78.20</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>4.17</td>
<td>3.26–5.32</td>
<td>2.73–5.49</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>4.01</td>
<td>3.23–4.97</td>
<td>2.94–5.55</td>
<td></td>
</tr>
<tr>
<td>Multiple sites</td>
<td>3.46</td>
<td>2.67–4.48</td>
<td>2.14–4.35</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>3.33</td>
<td>2.07–5.37</td>
<td>1.52–5.95</td>
<td></td>
</tr>
<tr>
<td>Bone/sarcoma</td>
<td>3.30</td>
<td>2.09–5.22</td>
<td>1.11–3.27</td>
<td></td>
</tr>
<tr>
<td>Gynaecologic</td>
<td>3.05</td>
<td>2.38–3.91</td>
<td>2.56–5.47</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>2.78</td>
<td>2.06–3.73</td>
<td>1.80–4.12</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>2.52</td>
<td>2.11–3.01</td>
<td>2.27–3.82</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>1.94</td>
<td>1.57–2.39</td>
<td>1.14–1.92</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.92</td>
<td>1.32–2.78</td>
<td>1.19–3.39</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.84</td>
<td>1.09–3.10</td>
<td>0.90–3.50</td>
<td></td>
</tr>
<tr>
<td>Non-melanoma</td>
<td>0.89</td>
<td>0.42–1.87</td>
<td>0.40–2.52</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.74</td>
<td>0.32–1.69</td>
<td>0.29–2.09</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3.44</td>
<td>2.62–4.53</td>
<td>2.51–5.71</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>1.55</td>
<td>1.21–1.97</td>
<td>1.44–2.86</td>
<td></td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval; CNS, central nervous system; GI, gastrointestinal.

The most common cancer types found in VTE outpatients were breast, prostate, lung and colorectal, mirroring previous findings and reflecting the high prevalence of these cancers in the general population (17). Among patients with cancer, our analysis showed that those with pancreatic, head and neck, CNS and upper GI cancers had the highest incidence of VTE. Our outpatient findings are largely consistent with previous reports, which describe high risk associated with pancreatic cancer, brain and gastric cancer (18), but differ for head and neck cancers. Head and neck cancers have been shown to be at the lowest risk of thrombosis, both in hospitalised patients with a discharge diagnosis of VTE in the Medicare Provider Analysis and Review Record database (19) and in outpatients enrolled in the Awareness of Neutropenia in Chemotherapy Study Group Registry (20). In the former, head and neck patients had a relative risk of 0.29, and in the latter, a stage-adjusted OR of 1.0 was reported. In our analysis, head and neck cancers had the second highest OR of 8.24, which is very similar to the risk experienced by patients with pancreatic cancer. This extreme difference in risk of VTE we found for head/neck cancer outpatients is hard to explain, but it is conceivable that inpatients have a markedly different risk profile for VTE. However, for the comparison with the Chemotherapy Study Group Registry that enrolled outpatients, we feel that our finding is more likely to be accurate given the large number of cases with cancer-associated VTE (n=1,361) and head/neck associated VTE (n=61) reported here and the small numbers of VTE cases reported overall in the Chemotherapy Study Group Registry (n=60). Again, we suggest that these findings should contribute to study design for the development of risk assessment models for cancer outpatient VTE prevention.

Ovarian cancer was previously identified as conferring high risk for VTE (21), but our specified cancer list used a more generalised term (gynaecologic cancer), which does not allow us to distinguish between different cancer types in this grouping and may explain the relatively low OR found in our analysis. We found reduced risk estimates for skin cancers (melanoma and non-melanoma: OR 0.89, 95% CI 0.42–1.87; OR 0.74, 95% CI, 0.32–1.69, respectively). These findings are in keeping with the annual incidence rates of first time VTE in California residents in Olmsted County, with the lowest cumulative VTE incidence reported for melanoma (21).

Our data are not sufficiently detailed to provide further insight into the role of metastatic disease or cancer stage and grade in VTE risk. Nonetheless, an OR of 3.46 for patients with more than one cancer site recorded is in keeping with the elevated risk of VTE known to be associated with metastatic disease (2). Furthermore, our data were not sufficiently detailed to allow us to determine the impact of tumour- or stage-specific chemotherapy regimens, central venous catheter placement or the timing of surgery on VTE risk and we did not review the prophylaxis history. To address these limitations of the registry, we have initiated further data collection with a revised CRF for cancer patients to include metastatic disease fields and treatment history with the hope of offering more precise, tumour-specific VTE risk profiles.

The ORs in this study were calculated by comparing the incidence of cancer in the VTE sample with the incidence in the non-VTE sample. A more appropriate denominator is the population-based incidence of each cancer type, but such data on ambulant, non-VTE cases are not available. Thus, our denominator is a selected group of cancer patients with VTE (21), but our specified cancer list used a more generalised term (gynaecologic cancer), which does not allow us to distinguish between different cancer types in this grouping and may explain the relatively low OR found in our analysis. We found reduced risk estimates for skin cancers (melanoma and non-melanoma: OR 0.89, 95% CI 0.42–1.87; OR 0.74, 95% CI, 0.32–1.69, respectively). These findings are in keeping with the annual incidence rates of first time VTE in California residents in Olmsted County, with the lowest cumulative VTE incidence reported for melanoma (21).
What is known about this topic?
- Venous thromboembolism (VTE) is a clinically relevant disease in cancer patients.
- In patients with cancer-associated thrombosis, there are few data describing the relationships among age, sex and cancer type.
- There is interest in defining outpatient-specific VTE risk.

What does this paper add?
- Patients attending outpatient DVT clinics have a similar rate of cancer-associated VTE as VTE patient populations previously reported.
- Cancer-associated VTE has distinct age- and sex-specific differences from the overall outpatient VTE group.
- We confirm previous reports of marked differences in tumour-specific VTE risk, and our data show that outpatients exhibit distinct tumour site-specific risk from that described among hospitalised cancer patients, in particular for patients with head/neck cancers who are at higher risk than previously reported.

References