Heparins, cancer and thrombosis: clinical and experimental studies
Smorenburg, S.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
SUBSEQUENT DIAGNOSIS OF MALIGNANCY IN PATIENTS PRESENTING WITH VENOUS THROMBOEMBOLISM

A REVIEW AND AN ANALYSIS OF NUMBER NEEDED TO SCREEN

Rohan J.K. Hettiarachchi, Susanne M. Smorenburg, Martin H. Prins, Harry R. Büller
ABSTRACT

Context
The benefits and efficiency of screening patients presenting with venous thromboembolism (VTE) for underlying malignancy is controversial. The number needed to screen to detect one extra case of cancer in excess of the population based expected numbers is not known. This is one of the factors, which will determine the efficiency of a screening program.

Objective
To determine the number needed to screen to detect one extra cancer and to evaluate whether screening could be efficient and beneficial in these patients.

Data Sources
A computerized and manual literature search was performed to find population-based studies, where occurrence of cancer was investigated after an episode of symptomatic VTE.

Study Selection
Population-based cohort studies with at least one-year follow-up period and the availability of population-based expected data or standard incidence ratios of specific cancers subsequent to VTE.

Data Extraction
Observed and expected (population-based) incidence of diagnosis of different types of cancers within the first year of diagnosing of VTE.

Data Synthesis
Of a total of 88651 patients with VTE, the pooled Standard Incidence Ratio (SIR) for first-year diagnoses of cancer was 3.7 (95% confidence interval (CI) 3.6-3.8). Cancers with statistically significant and high SIR were ovarian (10), pancreatic (7.2), brain (6.5), liver (6.3), and renal cancer (4.3). In contrast, of the total 3069 cancers diagnosed in the first year, prostate (13.5%) was the most frequent followed by lung (10.5%), colon (8.6%), pancreatic (7.3) and gastric cancer (5.9%). The number needed to screen to detect one extra cancer of the prostate was 143. Other cancers where low numbers of patients with VTE were needed to screen were ovarian (288), lung (365), colon (459), pancreatic (460), gastric (676) and liver cancer (684).

Conclusions
Screening patients presenting with (unexplained) VTE for underlying cancers may be effective especially for specific malignancies like prostate, lung, ovarian and colon cancers.
INTRODUCTION

Whether screening of patients presenting with idiopathic venous thromboembolism (VTE) for an underlying occult malignancy is beneficial has been a long-standing debate (1;2). The main reason for this is the inconsistency of results from studies that investigated the association between VTE and the subsequent diagnosis of malignancy. These studies were hospital-based and relatively small. In some studies, up to 18% of the patients presenting with idiopathic VTE were diagnosed to have an underlying cancer, albeit following extensive screening procedures (3). Some investigators therefore suggest screening for occult malignancy in all patients presenting with unexplained VTE, while others express uncertainty about the benefits of such a program (4;5). For a screening program to be successful it is essential to know which cancers can be expected and how often they occur. Further, it is important to assess the potential efficiency of a screening procedure. This can partially be achieved by determining the number of patients needed to screen to detect one extra case of cancer.

Recently, two large studies from Scandinavia reported data on subsequent diagnosis of malignancy in patients with VTE (6;7). Both studies were based on national registrations of hospital discharges and cancer diagnoses which enable the evaluation of an association between malignancy and VTE on a population basis. In total, 88651 thrombosis patients were retrospectively investigated for the subsequent diagnosis of cancer. Cancer was diagnosed in 3069 of these patients (3.5%) within the first year of a thrombotic event. The incidence of newly diagnosed cancer was 2 to 4 fold more than the expected incidence in a comparable population of same age and sex without VTE. Consequently, the increased risk of malignancy after a diagnosis of (idiopathic) VTE seems established. The large number of cancers identified in these studies allows an analysis to evaluate the potential usefulness of screening per type of cancer in patients presenting with VTE.

Therefore, in the present study we pooled and re-interpreted the data presented in these two studies. First we calculated the first-year incidence and the standard incidence ratio for different types of cancers. Then we examined the frequency and the percentage of specific cancers diagnosed in the first year of thrombosis. Finally we determined the excess number of diagnoses (observed – expected) and the number needed to screen to detect one extra case of cancer.

METHODS

A literature search was performed to identify publications on population-based studies, where occurrence of cancer was investigated after an episode of symptomatic venous thromboembolism. A computerized search was performed in MEDLINE, Current Contents and EMBASE databases using the following key and text words: deep-vein thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, cancer and malignancy. A manual search was also
performed by checking the reference lists of the identified publications. Criteria for eligibility were: population-based cohort studies with at least one-year follow-up period and the availability of population-based expected data or standard incidence ratios in the publication.

Only two large recent population-based studies that reported on Scandinavian registries fulfilled these criteria (6;7). Two other similar publications were found but were not population-based and did not present population-based expected rates of diagnoses for different cancers (8;9). Nevertheless, the findings in these studies are compared with our results in the discussion.

From the two selected population-based studies, the inclusion and exclusion criteria and the expected and observed incidences of cancer during the first year after the diagnosis of VTE were extracted from each report. The standardized incidence ratio for the first-year incidence of newly diagnosed cancers was calculated, using the observed and expected incidence in each report. The expected incidence was presented according to standard national population data. Then data were pooled and a weighted common standard incidence ratio was calculated for each type of cancer.

In the second analysis, the number of specific types of cancers observed was expressed as a proportion of total cancers diagnosed in the first year after thrombosis. This analysis was performed both separately and pooled for the two reports.

In the third analysis, the pooled observed first-year incidence of diagnoses of specific cancers in the two cohorts with VTE and the expected incidence of the same cancers in the standard population were calculated. Then the excess number of diagnoses for each type of cancer in the VTE population was determined (observed-expected). The number of patients needed to screen to detect one extra case of the specific cancer was calculated by dividing the total number of patients (N) in both cohorts by excess diagnoses of each type of cancer. If applicable, (e.g. for prostate cancers) it was assumed that the male/female ratio in this population was 1/1.

RESULTS

DESIGN OF THE STUDIES

The Swedish study reported data of 61,998 patients with VTE diagnosed between 1965 and 1983, and the subsequent incidence of diagnoses of malignancy (7). These data were obtained from Swedish inpatient and national cancer registries. The investigators observed a statistically significant higher first-year incidence of newly diagnosed cancers in these patients (standard incidence ratio (SIR): 4.4, 95% confidence interval (CI): 4.2-4.6).

In a similar study from Denmark, data were analyzed from 26,653 patients with VTE listed in the national registry between 1977 and 1992 (6). The investigators analyzed data separately for patients with deep-vein thrombosis and for those with pulmonary embolism. The first-year incidence of a subsequent malignancy was significantly higher in both groups, with a common SIR of 2.2 (95% CI: 2.0-2.4).
**Pooled incidence and standard incidence ratio**

In total, 88651 patients diagnosed with VTE were followed-up. In the first year following the thrombotic event 3069 patients were diagnosed with cancer, whereas 826 cases would have been expected according to national population standards. The pooled standard incidence ratio was 3.7 (95% CI 3.6-3.8). When analyzed separately for types of cancers, ovarian cancer appeared to have the highest SIR of 10 (95% CI 8.6-11.6). The other cancers with high SIR were pancreatic (SIR 7.2), brain (SIR 6.5), liver (SIR 6.3) and renal cancer (SIR 4.3). The observed and expected numbers and common SIR for the different types of cancer are presented in Table 1.

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Danish study (n=26,653)</th>
<th>Swedish study (n=61,998)</th>
<th>Common SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed / expected</td>
<td>SIR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observed / expected</td>
<td>SIR (95% CI)</td>
</tr>
<tr>
<td>Ovary</td>
<td>27 / 4.5</td>
<td>6.0 (4.0-8.7)</td>
<td>144 / 12.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44 / 8.2</td>
<td>5.4 (3.9-7.2)</td>
<td>180 / 23.1</td>
</tr>
<tr>
<td>Brain</td>
<td>17 / 4.7</td>
<td>3.6 (2.1-5.8)</td>
<td>96 / 12.6</td>
</tr>
<tr>
<td>Liver</td>
<td>11 / 2.7</td>
<td>4.1 (2.0-7.3)</td>
<td>143 / 21.7</td>
</tr>
<tr>
<td>Kidney</td>
<td>17 / 7.1</td>
<td>2.4 (1.4-3.8)</td>
<td>99 / 19.8</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>14 / 6.2</td>
<td>2.3 (1.2-3.8)</td>
<td>61 / 12.2</td>
</tr>
<tr>
<td>Lung</td>
<td>84 / 34.7</td>
<td>2.4 (1.9-3.0)</td>
<td>237 / 43.1</td>
</tr>
<tr>
<td>Prostate</td>
<td>64 / 19.2</td>
<td>3.3 (2.6-4.3)</td>
<td>349 / 83.1</td>
</tr>
<tr>
<td>Uterus</td>
<td>11 / 4.9</td>
<td>2.2 (1.1-4.0)</td>
<td>51 / 11.6</td>
</tr>
<tr>
<td>NH Lymphoma</td>
<td>14 / 4.9</td>
<td>2.9 (1.6-4.8)</td>
<td>55 / 13.1</td>
</tr>
<tr>
<td>Colon</td>
<td>39 / 22.8</td>
<td>1.7 (1.2-2.3)</td>
<td>225 / 47.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>20 / 9.8</td>
<td>2.0 (1.3-3.2)</td>
<td>160 / 39.0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7 / 2.5</td>
<td>2.8 (1.1-5.8)</td>
<td>12 / 6</td>
</tr>
<tr>
<td>Bladder</td>
<td>19 / 16.7</td>
<td>1.1 (0.7-1.8)</td>
<td>67 / 26.8</td>
</tr>
<tr>
<td>Breast</td>
<td>24 / 20.4</td>
<td>1.2 (0.8-1.8)</td>
<td>99 / 55</td>
</tr>
<tr>
<td>Rectum</td>
<td>12 / 12.8</td>
<td>0.9 (0.5-1.6)</td>
<td>69 / 38.3</td>
</tr>
</tbody>
</table>

Table 1. The observed first-year incidences of newly diagnosed malignancies in two cohorts of patients with VTE, population-based expected incidence and the standard incidence ratios (SIR).

**Frequency of different types of cancers**

Of the total 3069 cancers diagnosed in the first year, prostate cancer was the most frequently occurring (13.5%), followed by cancers of the lung (10.5%), colon (8.6%), pancreas (7.3%) and stomach (5.9%). The different types of cancers as a percentage of all diagnosed cancers are presented in Table 2.
<table>
<thead>
<tr>
<th>Primary site</th>
<th>Danish study (n=560 cancers in first-year)</th>
<th>Swedish study (n=2509 cancers in first-year)</th>
<th>Percentage of all diagnosed cancers in both studies (n=3069)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Percentage of all cancers (n=560)</td>
<td>Observed</td>
</tr>
<tr>
<td>Prostate</td>
<td>64</td>
<td>11.4</td>
<td>349</td>
</tr>
<tr>
<td>Lung</td>
<td>84</td>
<td>15.0</td>
<td>237</td>
</tr>
<tr>
<td>Colon</td>
<td>39</td>
<td>7.0</td>
<td>225</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44</td>
<td>7.8</td>
<td>180</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>3.6</td>
<td>160</td>
</tr>
<tr>
<td>Ovary</td>
<td>27</td>
<td>4.8</td>
<td>144</td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>2.0</td>
<td>143</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>14</td>
<td>2.5</td>
<td>61</td>
</tr>
<tr>
<td>Breast</td>
<td>24</td>
<td>4.3</td>
<td>99</td>
</tr>
<tr>
<td>Kidney</td>
<td>17</td>
<td>3.0</td>
<td>99</td>
</tr>
<tr>
<td>Brain</td>
<td>17</td>
<td>3.0</td>
<td>96</td>
</tr>
<tr>
<td>Bladder</td>
<td>19</td>
<td>3.4</td>
<td>67</td>
</tr>
<tr>
<td>Rectum</td>
<td>12</td>
<td>2.1</td>
<td>69</td>
</tr>
<tr>
<td>NH Lymphoma</td>
<td>14</td>
<td>2.5</td>
<td>55</td>
</tr>
<tr>
<td>Uterus</td>
<td>11</td>
<td>2.0</td>
<td>51</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7</td>
<td>1.3</td>
<td>12</td>
</tr>
</tbody>
</table>

*Table 2. Frequency of first-year diagnoses of different types of cancer in two cohorts of patients with VTE.*

**Number needed to screen to detect one extra case of cancer**

To detect one extra case of prostate cancer than the expected number, 143 male patients with VTE are needed to be screened (Table 3). One extra ovarian cancer may be detected by screening 288 female patients presenting with VTE. Other types of cancers where low numbers of patients are needed to screen to detect one extra case include lung cancer (365 patients), colon cancer (459 patients) and pancreatic cancer (460 patients).

**Discussion**

The two large cohort studies demonstrated a 2-4 fold increase in risk of diagnosing cancer in the first year following a thromboembolic event, an association that was suggested previously by smaller, hospital-based studies (6;7). Nevertheless, a search for malignancy in patients with VTE who have no other complaints is still a matter of debate, because it is unknown whether such a search is effective and whether an early detection of an underlying cancer indeed improves prognosis.

In the present analysis, the first-year incidence of specific types of malignancies in patients presenting with VTE was determined by pooling data from the two cohort studies. Subsequently, we calculated the number of patients with VTE needed to screen to detect one extra case of cancer.
Primary site | Observed incidence in VTE population | Expected incidence in standard population | Number needed to screen to detect one extra cancer: \( N /(observed - expected) \)
--- | --- | --- | ---
Prostate | 413 | 102.3 | 143* 
Ovary | 171 | 17.1 | 288* 
Lung | 321 | 77.8 | 365 
Colon | 264 | 70.7 | 459 
Pancreas | 224 | 31.3 | 460 
Stomach | 180 | 48.8 | 676 
Liver | 154 | 24.4 | 684 
Breast | 123 | 75.4 | 931* 
Uterus | 62 | 16.5 | 974* 
Brain | 113 | 17.3 | 926 
Kidney | 116 | 26.9 | 995 
Leukaemia | 75 | 18.4 | 1566 
NH Lymphoma | 69 | 18 | 1738 
Bladder | 86 | 43.5 | 2086 
Rectum | 81 | 51.1 | 2965 
Esophagus | 19 | 8.5 | 8443 

* If male/female ratio was 1/1 in the study population 88651 patients (N)

Table 3. The observed first-year incidence of diagnoses cancer in patients with VTE in both studies \( (N = 88651) \) as compared to standard population rates, and the number (of patients) needed to screen to detect one extra case of cancer in patients with VTE.

The incidence of cancer in the first year after VTE was higher in the Swedish study than in the Danish study (SIR of 4.4 and 2.2, respectively). This difference may be related to differences in observation years (1965-1983 versus 1977-1992, respectively), differences in inclusion criteria used between the respective studies and also to the differences in the diagnosis criteria of VTE.

Our analysis revealed that the incidence of diagnoses of ovarian malignancies is 10 times higher in patients with VTE as compared to the standard population rates. Other malignancies with high relative incidences were cancers of the pancreas (7.2), brain (6.5), liver (6.3), kidney (4.3), lung (4.1), prostate (4.0) and leukemia (4.1). When we examined the absolute frequency of the diagnoses of specific types of cancer, this sequence changed. Of all 3069 diagnoses made in the first year of thrombosis, 13.5% were prostate cancers (n=413). The other frequently diagnosed cancers were lung (10.5%; n=321), colon (8.6%; n=264), pancreatic (7.3%; n=224) and gastric cancer (5.9%; n=180). Further calculations revealed that only 143 male patients presenting with VTE need to be screened to detect one extra case of prostate cancer. The other malignancies where one extra case can be detected with screening less than 500 patients with VTE are cancers of the ovary (n=288), lung (n=365), colon (n=459) and pancreas (n=460).

How should these findings be interpreted? For some internationally accepted screening programs, the number of patients needed to screen to prevent one death has been calculated (10). For example, in the widely applied breast cancer screening programs, approximately 1000 to 1500 healthy women between 50 and 70 years of age need to be screened for 5 years to prevent one death due to...
breast cancer (10). The number needed to screen to prevent one death is larger than the number needed to screen to detect one extra case of cancer. If we assume that the prognosis of at least one out of the three diagnosed patients can be significantly improved and if the figure of screening 1000 to 1500 subjects are considered as an yardstick, our findings indicate that screening for prostate, ovary, lung, colon and pancreatic cancer in patients with VTE may potentially be effective. In contrast, our results indicate that screening for malignancies such as bladder or esophageal cancer would be inefficient in this study population, since far more than 2000 patients are needed to be screened to detect one extra case of malignancy.

It should be realized that the effectiveness of a screening program does not solely rely on the high incidence of the disease in a given population or, subsequently, on the small number needed to screen to detect one extra case. The malignancies should be detected in an early stage, with simple, sensitive, and specific screening tests. Further, a standard treatment should be available which can enable a favorable outcome with an acceptable cost-effectiveness.

There is suggestive evidence that screening of the normal population for prostate, lung, ovarian, and colorectal cancer results in a favorable shift of cancer stage, whereas in contrast, evidence for the effectiveness of screening for pancreatic cancer is lacking (11-15). For the former type of cancers, the serum prostate-specific antigen (PSA) assay, rectal examination, ultrasound of the abdomen, CA125 measurement, chest radiograph, fecal occult blood test, followed by colonoscopy can be used as effective screening tools. Whether screening leads indeed to a better prognosis and consequently an improved quality of life, is at present less clear, although recent evidence suggests that survival of colon cancer can indeed be improved by screening (13;16-17).

In a hospital-based study by Monreal and colleagues, 15 occult malignancies (9-prostate, 2-colon, 1-gastric and 2-pancreatic cancers) were diagnosed after screening 678 patients with VTE (8). Of these 15, seven patients with prostate cancer and two patients with colon cancer have been cured. For four other patients no curative treatment was available. Although based on small numbers, this report also indicates that screening for specific types of cancers may be beneficial in patients with VTE.

In conclusion, the findings of the present study indicate that screening for specific types of cancer, including prostate, lung, ovarian and colon may be beneficial in patients presenting with idiopathic VTE. The small number of patients needed to be screened to detect one extra case of cancer and the presence of preliminary evidence that early detection of these cancers indeed results in a shift of cancer stage further supports this conclusion. The true effect on survival of cancer screening in this population can only be evaluated by a randomized trial. However, the conduct of such a trial would be a formidable task, since thousands of patients with VTE should be included to detect a significant cancer-related mortality difference between the screened and unscreened group. In the absence of such a trial, based on our analysis, it seems justifiable to screen patients presenting with idiopathic
VTE for prostate, ovarian, lung and colon cancer, by means of PSA assay, rectal examination, ultrasound of the abdomen and CA125 measurement, a chest radiograph, and a fecal occult blood test followed by colonoscopy if indicated.

REFERENCES
