BRIEF REPORT

Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism

SHORT TITLE: Risk factors for occult cancer

Ryma Ihaddadene1,2, Daniel J. Corsi2, Alejandro Lazo-Langner3,4, Sudeep Shivakumar5,6, Ryan Zarychanski7,8, Vicky Tagalakis9,10, Susan Solymoss11,12, Nathalie Routhier13,14, James Douketis15,16, Gregoire Le Gal1,2,17 and Marc Carrier1,2,17.

1 Department of Medicine, University of Ottawa, Ottawa, ON, Canada;
2 Ottawa Hospital Research Institute, Ottawa, ON, Canada;
3 Department of Medicine, University of Western Ontario, London, ON, Canada;
4 Department of Epidemiology and Biostatistics, University of Western Ontario, London, ON, Canada;
5 Department of Hematology, Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada;
6 Department of Medicine, Dalhousie University, Halifax, NS, Canada;
7 Department of Medicine, University of Manitoba, Winnipeg, MB, Canada;
8 Department of Hematology and Medical Oncology, Cancercare Manitoba, Winnipeg, MB, Canada;
9 Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada;
10 Center for Clinical Epidemiology, Lady Davis Institute, Montreal, QC, Canada;
11 Department of Medicine, McGill University, Montreal, ON, Canada;
12 Division of Hematology, Montreal General Hospital and St. Mary’s Hospital, Montreal, QC, Canada;
13 Department of Medicine, Université de Montréal, Montreal, QC, Canada;
14 Sacre Coeur Hospital, Montreal, QC, Canada;
15 St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada;
16 Department of Medicine, McMaster University, Hamilton, ON, Canada;
17 The Ottawa Hospital, Ottawa, ON, Canada

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Address of correspondence and requests for reprints:

Dr. Marc Carrier MD FRCPC MSc (Epidemiology)
Senior Scientist, Ottawa Hospital Research Institute
Associate Professor, University of Ottawa
Director, Thrombosis Fellowship Program
501 Smyth Road, Box 201A
Ottawa, ON, Canada
Tel-613-737-8899 ext. 73034
Fax-613-739-6837
Email-mcarrier@toh.on.ca
KEY POINTS

• It remains unclear if a subgroup of high risk patients could potentially benefit from a more extensive screening strategy.
• Age, prior provoked VTE and smoking status may be important predictors of occult cancer detection in patients with first unprovoked VTE.

ABSTRACT

Unprovoked venous thromboembolism (VTE) may be the earliest indication of cancer. Risk factors predictive of occult cancer detection in patients with a first unprovoked symptomatic VTE are unknown. Cox proportional hazard models and multivariate analyses were performed to assess the effect of specific risk factors on occult cancer detection within one year of a diagnosis of unprovoked VTE in patients randomized in the SOME trial. The SOME trial is a multicenter open-label randomized controlled trial assessing the efficacy for occult cancer screening strategies in patients with a first unprovoked VTE. A total of 33 (3.9%; 95% C.I. 2.8-5.4) out of the 854 included patients received a new diagnosis of cancer at 1-year follow-up. Age ≥ 60 years (hazard ratio [HR] of 3.11 (95% C.I. 1.41-6.89, p=0.005), previous provoked VTE (HR=3.20, 95% C.I. 1.19-8.62, p=0.022) and current smoker status (HR=2.80, 95% C.I. 1.24-6.33, p=0.014) were associated with occult cancer detection. Compared with patients without any of these characteristics, the hazard of cancer in patients with one of these risk factors was increased four-fold (HR=4.59, 95% CI: 1.89-11.11). Age, prior provoked VTE and smoking status may be important predictors of occult cancer detection in patients with first unprovoked VTE. The SOME trial is registered to www.clinicaltrials.gov as NCT00773448.
INTRODUCTION

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal condition.\textsuperscript{1-3} Unprovoked events, which occur in the absence of a major thrombogenic risk factor, represent approximately 40\% of all VTE.\textsuperscript{4} Unprovoked VTE may be the earliest indication of cancer.\textsuperscript{5,6} It was previously demonstrated that between 3.2 and 10.0\% of patients presenting with unprovoked VTE will be subsequently diagnosed with cancer, with the highest risk in the first year after the diagnosis of VTE.\textsuperscript{7-9} This has led to a debate as to whether an extensive screening for occult cancer in these patients is warranted. Two recently published studies have reported that using an extensive screening strategy is unlikely to provide benefit to all patients with unprovoked episodes of VTE.\textsuperscript{9,10} However it remains unclear if a subgroup of high risk patients could potentially benefit from a more extensive occult cancer screening strategy. Identification of risk factors associated with early detection of occult cancers in order to stratify patients with higher risk of cancer detection following an unprovoked VTE might be of potential clinical importance, and provide a basis for effective screening and preventive strategies. We sought to assess the risk factors predictive of occult cancer detection in patients with a first objectively proven unprovoked symptomatic VTE.

METHODS

Post-hoc, pre-defined analyses of the SOME trial\textsuperscript{10} were performed. The SOME trial is a multicenter open-label randomized controlled trial of patients with a first unprovoked VTE that compared a limited evaluation for occult cancer screening (basic laboratory
testing, chest radiography, and breast, cervical, and prostate cancer screening) with a more comprehensive strategy (limited evaluation plus CT of the abdomen and pelvis). Unprovoked VTE was defined as occurring in the absence of known malignant disease in the past 5 years, trauma of the leg or lower-extremity plaster cast, surgery using general anesthesia 3 months previous to the event, immobilization for 3 or more days, previous unprovoked VTE, thrombophilia (hereditary or acquired), and current pregnancy. Methods have been previously described in detail.

All patients enrolled (n=854) in the SOME trial were included in the analyses. The influence of the following potential risk factors was analyzed: (i) demographic characteristics (age and gender); (ii) medical history (hypertension, myocardial infarction [MI], stroke, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease [COPD], previous cancer, previous provoked VTE and smoking history); (iii) qualifying episode of VTE (DVT only, PE only, DVT and PE); and (iv) baseline medications (oral contraceptive pill, exogenous estrogen, antiplatelet agent). Cox proportional hazard models were used to analyze the effect of these specific risk factors on the outcome of occult cancer detection within 1-year of a diagnosis of unprovoked VTE. Multivariate analyses were performed using Cox proportional hazard models that included all variables that achieved a p value of ≤ 0.20 in univariate analyses.

RESULTS AND DISCUSSION

A total of 33 (3.9%; 95% C.I. 2.8-5.4) patients received a new diagnosis of cancer at 1-year follow-up. In total, 471 (55.2%) had a DVT only, 278 (32.6%) had a PE only and
105 (12.3%) had both a DVT and PE. Among the participants included in the analysis, 187 (21.9%) had hypertension, 50 (5.9%) had a previous cancer, 47 (5.5%) had a previous provoked VTE and 132 (15.5%) were current smokers (Table 1). In terms of baseline medications, 48 (5.8%) were taking an oral contraceptive pill, 19 (2.2%) an exogenous estrogen, and 40 (4.7%) an antiplatelet agent. (Table 1)

Age ≥ 60 years was associated with cancer with a corresponding hazard ratio (HR) of 3.11 (95% C.I. 1.41-6.89, p=0.005). When exploring age as a continuous variable, an increase in 1-year of age was also associated with an increase hazard of occult cancer detection (HR=1.06, 95% C.I. 1.03-1.08, p<0.0001). Patients with a previous provoked VTE (HR=3.20, 95% C.I. 1.19-8.62, p=0.022) or currently smoking (HR=2.80, 95% C.I 1.24-6.33, p=0.014) were associated with higher hazard of being detected with cancer during the one-year follow-up period. (Table 1) The combined effect of these three characteristics in the adjusted model was associated with a hazard ratio for occult cancer of 3.33 (95% CI: 1.73-4.92, p<0.001). Sex and baseline medications were not associated with occult malignancy. Predicted risks at 2 and 5 years based on adjusting the baseline risk from the Cox proportional hazards regression model using different combinations of risk factors are reported in Table 2.

Our most salient finding is that simple characteristics of age at unprovoked VTE diagnosis, prior provoked VTE and being a current smoker are important predictors of occult cancer diagnosis among patients with VTE. Some of our results are consistent with previously published literature. The increased risk in elderly patients has been
reported in a subgroup analysis of a randomized controlled trial comparing extensive screening for occult cancer with no further testing in patients with acute unprovoked VTE.\textsuperscript{11} Although a prior history of provoked VTE has never been described as an important risk factor for occult cancer detection, it is plausible that patients with prior provoked events (e.g. post-surgery) might be more susceptible to VTE complications in the presence of an underlying occult cancer. Finally, smoking has been associated with oral, lung, colorectal and urothelial cancers. Up to 25\% of cancers diagnosed with the trial (colorectal (n=5) and urothelial (n=3)) might have been related to smoking. Our findings may help identify patients with first unprovoked VTE who are at particularly high-risk and who may benefit from closer surveillance and additional testing. Our results need to be validated in other cohort of patients and further prospective studies are needed to assess if occult cancer screening is beneficial in this high risk group of patients.

Our study has a number of strengths including prospective data collection within a multi-centre trial, good measurement of a priori identified and potentially important predictors of cancer. Our study has limitations. First, it has a relatively small number of events limiting the ability to adjust for important confounders and to provide actual accurate absolute estimates for each possible risk factor combinations, although it is largest trial population studied on this topic. Nevertheless, we were able to identify clinically relevant predictors for occult cancer. Second, potentially relevant risk factors, such as laboratory measurements, were not collected at study baseline. Finally, the definition of unprovoked VTE is heterogeneous and other clinical settings might have different
patient’s demographics (e.g. older patient population) and therefore, our results might not be generalizable all clinical practices.

In conclusion, age, prior provoked VTE and smoking may be predictors of occult cancer in patients presenting with a first unprovoked VTE. Our results might help to identify patients with acute unprovoked VTE at high risk of underlying cancer.
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AUTHORS CONTRIBUTIONS:

RI: designed, performed research; analyzed, and interpreted data; statistical analysis; wrote manuscript.

DC: analyzed, and interpreted data; statistical analysis; wrote manuscript.

MC: designed research; interpreted data; wrote manuscript.

AL, SS, RZ, VT, SS, NR, JD, GL: collected, and interpreted; provided vital reviews to the manuscript.

CONFLICTS OF INTEREST

All authors have fulfilled the conditions required for authorship. AL reports receiving honoraria from Pfizer, LEO Pharma, and Bayer and grant support from Alexion and participating in research studies funded by Pfizer, LEO Pharma, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Novartis, and Celgene. JD reports receiving fees for serving on advisory boards from Biotie Therapies, Portola Pharmaceuticals, and The Medicines Company; honoraria from Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis; consulting fees from Boehringer Ingelheim, Bayer, Janssen, Bristol-Myers Squibb, Daiichi Sankyo, and Actelion Pharmaceuticals; and grant support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.
Reference List


Table 1. Risk factors of occult malignancy among patients with a first unprovoked VTE.

<table>
<thead>
<tr>
<th></th>
<th>Patients without cancer (%)</th>
<th>Patients with cancer (%)</th>
<th>Absolute risk (%)</th>
<th>Univariate analysis</th>
<th>P value</th>
<th>Multivariable analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 821)</td>
<td>(n = 33)</td>
<td></td>
<td>Hazard Ratio (95% C.I.)</td>
<td></td>
<td>Hazard Ratio (95% C.I.)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis ≥ 60 years</td>
<td>288 (35.1)</td>
<td>20 (60.6)</td>
<td>6.5</td>
<td>2.90 (1.44-5.83)</td>
<td>0.003</td>
<td>3.11 (1.41-6.89)</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex</td>
<td>555 (67.6)</td>
<td>21 (63.6)</td>
<td>3.6</td>
<td>0.72 (0.35-1.46)</td>
<td>0.358</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>176 (21.4)</td>
<td>11 (33.3)</td>
<td>5.9</td>
<td>2.06 (1.00-4.26)</td>
<td>0.050</td>
<td>1.33 (0.60-2.96)</td>
<td>0.485</td>
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<tr>
<td>Myocardial infarction</td>
<td>21 (2.6)</td>
<td>1 (3.0)</td>
<td>4.5</td>
<td>1.52 (0.21-11.17)</td>
<td>0.679</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Stroke</td>
<td>10 (1.2)</td>
<td>1 (3.0)</td>
<td>9.1</td>
<td>2.34 (0.32-17.18)</td>
<td>0.402</td>
<td>-</td>
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<tr>
<td>Congestive heart failure</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (4.4)</td>
<td>3 (9.1)</td>
<td>7.7</td>
<td>2.89 (0.87-9.55)</td>
<td>0.082</td>
<td>2.09 (0.60-7.22)</td>
<td>0.258</td>
</tr>
<tr>
<td>COPD</td>
<td>18 (2.2)</td>
<td>1 (3.0)</td>
<td>5.3</td>
<td>0.93 (0.13-6.84)</td>
<td>0.945</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Previous cancer</td>
<td>46 (5.6)</td>
<td>4 (12.1)</td>
<td>8.0</td>
<td><strong>2.92 (1.03-8.33)</strong></td>
<td><strong>0.045</strong></td>
<td>1.87 (0.61-5.72)</td>
<td><strong>0.274</strong></td>
</tr>
<tr>
<td>Prior provoked VTE</td>
<td>42 (5.1)</td>
<td>5 (15.2)</td>
<td>10.6</td>
<td><strong>3.57 (1.38-9.25)</strong></td>
<td><strong>0.009</strong></td>
<td><strong>3.20 (1.19-8.62)</strong></td>
<td><strong>0.022</strong></td>
</tr>
<tr>
<td>Current smoker</td>
<td>123 (15.0)</td>
<td>9 (27.3)</td>
<td>6.8</td>
<td>2.15 (1.00-4.63)</td>
<td>0.050</td>
<td><strong>2.80 (1.24-6.33)</strong></td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td>Past smoker</td>
<td>271 (33.0)</td>
<td>13 (39.4)</td>
<td>4.6</td>
<td>1.32 (0.66-2.66)</td>
<td>0.435</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type of current VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT only</td>
<td>447 (54.4)</td>
<td>24 (72.7)</td>
<td>5.1</td>
<td>1.89 (0.88-4.07)</td>
<td>0.104</td>
<td>1.89 (0.87-4.10)</td>
<td>0.108</td>
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<tr>
<td>PE only</td>
<td>271 (33.1)</td>
<td>7 (21.2)</td>
<td>2.5</td>
<td>0.60 (0.26-1.38)</td>
<td>0.229</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DVT + PE</td>
<td>103 (12.6)</td>
<td>2 (6.1)</td>
<td>1.9</td>
<td>0.54 (0.13-2.24)</td>
<td>0.392</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive pill</td>
<td>48 (5.8)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exogenous estrogen</td>
<td>18 (2.2)</td>
<td>1 (3.0)</td>
<td>5.3</td>
<td>1.51 (0.21-11.07)</td>
<td>0.685</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>39 (4.8)</td>
<td>1 (3.0)</td>
<td>2.5</td>
<td>0.62 (0.09-4.56)</td>
<td>0.641</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin
Table 2 Predicted 2-year and 5-year risk (%) of occult cancer among patients with a first unprovoked VTE based on age, prior provoked VTE, and smoking.

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 60 years</th>
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<th>Age ≥ 60 years</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Non VTE</td>
<td>Prior provoked VTE</td>
<td>Non VTE</td>
<td>Prior provoked VTE</td>
</tr>
<tr>
<td></td>
<td>Non-smoker</td>
<td>Smoker</td>
<td>Non-smoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>2y risk</td>
<td>0.2</td>
<td>0.6</td>
<td>0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>5y risk</td>
<td>1.8</td>
<td>5.0</td>
<td>5.7</td>
<td>15.2</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism.
Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism

Ryma Ihaddadene, Daniel J. Corsi, Alejandro Lazo-Langner, Sudeep Shivakumar, Ryan Zarychanski, Vicky Tagalakis, Susan Solymoss, Nathalie Routhier, James Douketis, Gregoire Le Gal and Marc Carrier