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Risk Factors for Incident Venous Thromboembolism in Active Cancer Patients: A Population Based Case-Control Study

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Abstract

Background—Independent risk factors for cancer-associated incident venous thromboembolism (VTE) and their magnitude of risk are not fully characterized.

Aim—To identify non-cancer and cancer-specific risk factors for cancer-associated incident VTE.

Methods—In a population-based retrospective case-control study, we used Rochester Epidemiology Project and Mayo Clinic Cancer Registry resources to identify all Olmsted County, MN residents with active cancer-associated incident VTE, 1973-2000 (cases; n=570) and 1-3 residents with active cancer matched to each case on age, sex, date and duration of active cancer (controls; n=604). Using conditional logistic regression, we tested cancer and non-cancer characteristics for an association with VTE, including a cancer site VTE risk score.

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A.A.A. designed and performed the research, collected, analyzed, and interpreted the data and wrote the manuscript; R.E.G. collected data, performed the statistical analyses, and contributed to the manuscript; T.M.P. designed and performed the research, collected data, performed the statistical analyses, and contributed to the manuscript; R.S.M. collected and interpreted the data, and contributed to the manuscript; K.R.B. contributed to the study design, directed the statistical analyses, and contributed to the manuscript; and J.A.H. designed and performed the research, collected, analyzed and interpreted the data, and wrote the manuscript.

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The authors have no competing financial or conflict of interest to declare.

Results—In the multivariable model, higher cancer site VTE risk score (OR=1.4 per 2-fold increase), cancer stage 2 (OR=2.2), liver metastasis (OR=2.7), chemotherapy (OR=1.8) and progesterone use (OR=2.1) were independently associated with VTE, as were BMI<18.5 kg/m² (OR=1.9) or ≥35 kg/m² (OR=4.0), hospitalization (OR=7.9), nursing home confinement (OR=4.7), central venous (CV) catheter (OR=8.5) and any recent infection (OR=1.7). In a subgroup analysis, platelet count <350×10⁹/L at time of cancer diagnosis was marginally associated with VTE (OR=2.3, p=0.07).

Conclusion—Cancer site, cancer stage 2, liver metastasis, chemotherapy, progesterone, being underweight or obese, hospitalization/nursing home confinement, CV catheter, and infection are independent risk factors for incident VTE in active cancer patients.

Keywords

Venous thromboembolism; cancer; epidemiology; risk factors; deep vein thrombosis; pulmonary embolism

Introduction

Active cancer is an independent risk factor for VTE, with an overall 4- to 7-fold increased risk [1-7], and accounts for 20-30% of all new VTE events in the community.[8-11] VTE commonly complicates cancer and is associated with significant morbidity.[12-14] Acute VTE may delay or modify anti-cancer therapy, and usually leads to chronic anticoagulation. Compared to VTE patients without cancer, individuals with cancer and VTE have a higher risk for hemorrhage with anticoagulant therapy [15-21] such that primary or secondary pharmacologic VTE prophylaxis for all active cancer patients may be inappropriate. Furthermore, cancer patients with VTE have worse survival than cancer patients without VTE.[9, 14, 20, 22-28]

While the risk of VTE appears to vary by cancer site [6, 7, 15, 23, 29-34], cancer stage and grade [5, 6, 23, 35], chemotherapy use [2, 31, 36-39], and patient-related characteristics [5, 40-45], whether these cancer- and non-cancer characteristics are independent risk factors for VTE and the magnitude of the associated risk are uncertain and not fully characterized. To address this important gap in knowledge, we conducted a population-based case-control study of active cancer patients to test cancer and non-cancer characteristics as potential risk factors for incident VTE, as these data may allow identifying cancer patients at a high risk for developing incident VTE.

Methods

Study Setting and Design

Using the longitudinal and population-based resources of the Rochester Epidemiology Project (REP) [46], we identified all Olmsted County, MN residents with incident deep vein thrombosis (DVT) and/or pulmonary embolism (PE), over the 35-year period, 1966-2000, as previously described.[47, 48] For this study, we included all Olmsted County residents who consented to access of their medical records for research purposes and had a first lifetime symptomatic leg DVT or PE during the 28-year period, 1973-2000, and active

cancer in the three months prior to or after the VTE diagnosis as previously defined.[28, 49] Briefly, a cancer was considered as active if any evidence of cancer (i.e., diagnosis, treatment, progression, oncologist review) was found via medical record review within 92 days prior to the VTE event/index date. At a minimum, any newly diagnosed cancer was considered as active for 6 months from the diagnosis date if not treated by curative surgery. Patients undergoing curative surgery were considered cancer-free if the surgical margins were clear and no cancer recurred within three months after surgery. Questions regarding curative surgery were adjudicated by a committee of the investigators (AAA, JAH, RSM) who had access to all medical records. Multiple myeloma, myelodysplastic syndrome and myeloproliferative neoplasms (MPN) were considered as permanently active. Lymphoma, chronic lymphocytic leukemia (CLL) and prostate cancer were considered as active for as long as they were left untreated (assumed to reflect a planned observation of the cancer), and any stage 4 cancer was considered as permanently active (with the exception of stage 4 Hodgkin's lymphoma, intermediate/high grade non-Hodgkin's lymphoma, and testicular or germ cell cancer). With the exception of CLL, any cancer classified as stage 0 was not categorized as active until there was stage progression. Objectively diagnosed symptomatic VTE and those diagnosed by a physician where the level of suspicion was sufficiently high that the patient was treated by anticoagulants were included. We included the latter because physicians are hesitant to use anticoagulants in cancer patients due to the high bleeding risk such that any use of anticoagulant therapy would indicate a high suspicion of VTE. Patients with incidental VTE, jugular or isolated arm DVT, or sub-segmental PE were excluded.

Using the resources of the Mayo Clinic Cancer Registry and the REP, we identified all Olmsted County residents with first lifetime active cancer and no prior VTE whose cancer was diagnosed within ± 5 years of the case's cancer diagnosis date.[2] The Cancer Registry maintains patient demographics (including age, sex, race/ethnicity and residence at time of diagnosis), cancer information (i.e., primary site, histology and extent of disease), and cancer treatment information (i.e., surgery, radiation therapy, chemotherapy, hormone, immunotherapy, or other types of treatment). We further matched on sex, date of birth (± 5 years), date of first Olmsted County medical record (± 5 years), and duration of active cancer (i.e., the control's active cancer duration was the case's duration to ensure that the control would have equal exposure to the risk of VTE induced by cancer). From this, a random sample of potential controls was identified. The nurse abstractors confirmed no prior history of VTE and no VTE within 3 months post-index, and that control's active cancer duration was equal to or up to two years greater than the case's active cancer duration. The control index date was the first medical visit within this 2 year window.

For cases with more than one primary active cancer at the time of the incident VTE, a separate control was matched (matched on each primary active cancer) using the same criteria as above. For those individuals with multiple primary active cancers of the same type (breast cancer in both breasts, lung cancer in different lobes, etc.), we kept the case-control pair where the case had the higher stage. The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records in the community and collected data on date and type of incident VTE, baseline characteristics (age at incident VTE; sex; hospitalization with or without surgery [categorized as general, neurological, orthopedic, cardiac, or gynecologic surgery], anesthesia use, nursing home confinement, trauma/fracture, immobilization, infection and central venous catheter/ pacemaker, all within the 92 days prior to the VTE event/index date; any prior history of congestive heart failure, neurologic disease with leg paresis, chronic renal disease, liver disease, chronic lung disease, heart disease, diabetes, hyperlipidemia, autoimmune connective tissue disease, superficial vein thrombosis and thoracic outlet syndrome), and vital status at last clinical contact, as previously performed.[2, 28, 50-52] Body mass index was based on the nearest height and weight in the two years prior to the VTE event/index date, if available, or within three months after the event date. Additional data were collected from the Mayo Clinic Cancer Registry and medical records on the date of diagnosis of active cancer, cancer site and stage, tumor-node-metastasis (TNM) classification and cancer grade at the time of cancer diagnosis; cancer histopathology; presence of venous invasion by cancer, lymph node involvement, and metastasis to liver and/or bone; hormonal therapy, chemotherapy, and radiation therapy. We categorized chemotherapeutic agents into the following categories: a) Alkylators (e.g., cyclophosphamide, ifosfamide, busulfan, carmustine, melphalan, procarbazine, dacarbazine); b) Antimetabolites (e.g., cytarabine, 5-fluoro-uracil, methotrexate, hydroxyurea, gemcitabine); c) Anthracyclines (e.g., doxorubicin, daunorubicin, idarubicin, mitoxantrone); d) Alkaloids (e.g., etoposide, irinotecan, topotecan, vincristine, vinorelbine); e) Platinum (e.g., cisplatin, carboplatin, oxaliplatin); f) Hormonal modulators (e.g., goserelin, leuprolid); g) Immunomodulators (e.g., thalidomide, lenalidomide, interferon); and h) Other (e.g., imatinib, rituximab, L-asparaginase), and evaluated whether one subclass of chemotherapy was more strongly associated with VTE than others. In a subset of cases and controls diagnosed with active cancer between 1983 -2000, for whom laboratory data were available in the Mayo Clinic's electronic medical records, and who had a complete blood count performed within 14 days prior to or four days after the cancer diagnosis date, the hemoglobin, leukocyte count and platelet count closest to the date of cancer diagnosis were captured electronically. The study oncologists (AAA, RSM) also re-staged the cancer(s) at the time of the incident VTE or the control's index date. Cancer characteristics specific to the cancer (cancer site and stage) were recorded as present only if documented within the 92 days prior to the VTE event/index date, or, for cases only, within 92 days after the incident VTE event; chemotherapy, radiation therapy and hormone therapy characteristics were recorded as present if documented within the 92 days prior to the index event. All other cancer characteristics were recorded as present if documented any time prior to the index event. All cancer stage assignments were adjudicated by the study oncologists and based on the American Joint Committee on Cancer staging guidelines (6th edition).[53]

Analysis

All modeling was done using conditional logistic regression, which stratifies on the matched set. Because two controls could be matched on a single case but by differing criteria

(differing duration since the malignancy diagnosis for each malignancy) we used the robust sandwich estimator of Lin and Wei [54] for the covariance matrix to account for clustering within the strata. The individual sets of observations (1 case: 1-3 controls) were assumed to be independent.

Rather than arbitrarily choosing one cancer site as a comparison group in our modeling, we evaluated the association of cancer site and VTE using standardized morbidity ratios (SMR; “cancer site VTE risk score”) based on the ratio of observed cancers to expected cancers in each of 26 possible cancer sites among incident VTE cases, 1988-2000, as previously performed.[34] In brief, we identified all active cancers by cancer site among Olmsted County residents with incident VTE, 1988-2000. We used Iowa State Surveillance and Epidemiology and End Results (SEER) data to estimate the expected age- and sex-specific prevalence of cancer by cancer site among incident VTE cases, and calculated SMR for each cancer site by dividing the observed by the expected number of cancers.[34] Using the SMR as a “cancer site VTE risk score” had the advantage of using a continuous variable instead of 26 dichotomous variables and it jointly adjusted for cancer location and the magnitude of risk, giving greater weight to cancers with a higher risk for VTE. In turn this allowed us to focus more closely on cancer related variables other than cancer site. Because cancer site and stage are highly confounded, we adjusted for stage before the other cancer-related variables, choosing the combination of stages 2–4 that had the strongest association with incident VTE. Further, the cancer site VTE risk score was based on cancer prevalence, not incidence; we verified and adapted the score fit in the current context by first adjusting for cancer stage, then introducing into the model each cancer site in turn, one at a time. Cancer sites which showed a significant residual association with VTE were left in the model as these represented sites where the cancer site VTE risk score did not adequately fit the data. We then adjusted the multivariable conditional logistic model for the cancer site VTE risk score and the additional significant cancer site and stage variables. The remaining cancer-specific variables and the known non-cancer independent VTE risk factors were tested for an association with VTE using a forward stepwise selection with a p-value = 0.05 to stay in the model. We tested the variables in the final model for interactions with the matching variables (sex, age, time since cancer, calendar year) and for interactions among all main effect variables in the final model. The cancer site VTE risk score was highly skewed so we used the natural log in all modeling. Because the remaining cancers in the score comparison group had a score of 0, we added 1.0 to all scores before taking the natural log.

Because pre-chemotherapy platelet count $350 \times 10^9/L$, hemoglobin $<100g/L$, and leukocyte count $>11 \times 10^9/L$ have been shown to be risk factors for cancer-associated VTE [40, 43], we explored the association of these covariates with VTE univariately (after adjusting for the cancer site VTE risk score, additional cancer sites, and stage), and after adjusting for the final model determined above, in the subset of cases and controls where these data were available. Furthermore, as clinical practice in cancer diagnosis and therapy have evolved over time with introduction of new diagnostic procedures and therapeutic agents and/or combination chemotherapy regimens, we formally tested for interaction between VTE event year and the variables included in the final multivariable model. In addition, we estimated the risk of VTE over two time frames which represented milestones

in the introduction of new diagnostic procedures and therapeutic agents (1973-1985 [introduction of alkylators, nucleoside analogues, antimetabolites, and anthracycline] and 1986-2000 [introduction of computed tomography (CT) for staging; taxanes, platinum-based antineoplastic agents, hematopoietic growth factors, and targeted therapies such as rituximab; increase in outpatient cancer management]) to evaluate whether the association of VTE with cancer stage, chemotherapy and location of onset of VTE changed in these time frames.

Results

Over the 28-year period, 1973-2000, 2782 Olmsted County residents were diagnosed with incident VTE (DVT alone, n=1344; PE with or without $\pm$ DVT, n=1432; chronic thromboembolic pulmonary hypertension, n=6), of whom 570 (20.5%) had active cancer; 31 (5%) had more than one primary cancer site (28 residents had two primary cancers and 3 residents had three primary cancers for a total of 34 additional cancers). Nineteen (3.3%) had their underlying cancer diagnosed at autopsy, of whom 13 (68.4%) had their VTE diagnosed concomitantly at autopsy and the remaining six (31.6%) had their VTE event diagnosed within two weeks prior to autopsy date; 190 (33.3%) had their incident VTE event within 3 months after the cancer diagnosis date; and 61 (10.7% of 570 people) had their VTE event within three months prior to the cancer diagnosis. Eighty seven percent (n=495) of VTE were objectively diagnosed; 13% (n=75) were clinically diagnosed VTE where the level of suspicion was sufficiently high that these subjects were treated with anticoagulants. The distribution of VTE by event type was DVT alone (n=254) and PE $\pm$ DVT (n=316); 143 (45.2%) of all the PE's were discovered on autopsy (63 in 1973-1980; 49 in 1981-1990; 31 in 1991-2000). The mean (**SD**) and median (**IQR**) patient age at the incident VTE event date were 68.5 (14.7) and 70.9 (60.0 - 79.5) years, respectively; 49% were female. The mean (**SD**) control age and sex were 69.2 (14.0) years and 49% females, respectively. The mean (**SD**) and median (**IQR**) person-years of follow-up were 36.0 (20.3) and 37.0 (20 - 51) for cases; and 36.9 (20.0) and 38.0 (21 - 52) for controls respectively. Most VTE events occurred near the time of cancer diagnosis (median: 142.5 days; **IQR**: 19 - 592).

The cancer and non-cancer baseline characteristics and prevalence of VTE risk factors among VTE cases and controls are shown in Tables 1 and 2. Compared to controls, VTE cases had a higher cancer site VTE risk score; more stage 4 disease and liver and bone metastases; higher cancer grade; were more likely to have received chemotherapy, radiation therapy and progestins; more frequent cancer stage progression in the time interval between cancer diagnosis and VTE event/ index date; were more often underweight or markedly obese; underwent surgery or received anesthesia more frequently; were hospitalized or in a nursing home more frequently; and had a higher prevalence of neurological disease with leg paresis, renal disease, heart disease, autoimmune connective tissue disease, immobilization, trauma/fracture, central vein catheter, prior superficial vein thrombosis and infection (Tables 1 and 3b).

In an unadjusted conditional logistic model we evaluated the association of cancer site and VTE using the cancer site VTE risk score (Table 3a: Model 1).[34] The cancer site VTE risk

site score fit most cancers well, but needed some adjustment for lymphoma and MPN (Table 3a: Model 2). Low grade lymphoma (OR=0.34; 95% CI: 0.17, 0.68) was inversely associated with VTE, with lower risk of VTE than would be predicted by the cancer site VTE risk score for lymphoma (see Table 2). In contrast, MPN was positively associated with VTE (OR=18.26; 95% CI: 2.4, 139.1) and had a much higher risk of VTE than predicted by the cancer site VTE risk score (see Table 2; notably, of the 20 patients with MPN, 19 were cases and one was a control). These two cancers were left in the model to improve the fit to the data. After adjusting for these cancer site variables, we then assessed the association between cancer stage and VTE, and noted that the combined variable of stage 2, 3, and 4 versus stage 1 best fit the data (OR=2.38; 95% CI: 1.80, 3.16; Table 3a: Models 3 and 4). After adjusting for the cancer site VTE risk score and the significant cancer site and stage variables, the remaining cancer and non-cancer variables were tested for association with VTE, and the covariates with a p-value ≤ 0.1 are listed in Table 3b.

In the multivariable conditional logistic model, we found that a two-fold increase in the cancer site VTE risk score was independently associated with 1.4-fold increased odds of incident VTE (Table 4a). Cancer stage ≥ 2 independently increased the odds of VTE by 2.2-fold when compared to stage 1. Liver metastasis (OR=2.70), chemotherapy (OR=1.81), progestins (OR=2.13), being underweight (BMI<18.5 kg/m²; OR=1.93) or severely obese (BMI ≥ 35 kg/m²; OR=3.97), hospitalization (OR=7.91), nursing home confinement (OR=4.71), CV catheter use (OR=8.53) and any recent infection (OR=1.71) were independent risk factors for VTE (Table 4a). We did not note any difference in the risk of VTE between the various subclasses of chemotherapy.

We explored pre-chemotherapy platelet count $\geq 350 \times 10^9/L$, hemoglobin $<100g/L$, and leukocyte count $>11 \times 10^9/L$ [40, 43, 44] for an independent association with VTE in the subset of cases and controls where these data were available (Tables 3c and 4b). Of the 1208 cases and controls in this study, data were available on 344 (28.5%) subjects when their case-control pair status was preserved, and in 512 (42.4%) subjects overall. After adjusting for independent risk factors in the final multivariable model, only platelet count $\geq 350 \times 10^9/L$ at the time of cancer diagnosis was marginally associated with VTE (OR=2.3; p=0.07; Table 4b).

To test whether there were changes in VTE events over time due to evolution in clinical practice in cancer diagnosis and therapy during the study period, we tested for and noted no significant interaction between VTE event year and liver metastasis, chemotherapy use, progestin use, VTE location of onset, BMI, CV catheter use, or any infection within 92 days. To test the potential effect of new chemotherapies on VTE risk, we estimated the odds of VTE with chemotherapy use within 92 days over two time frames, 1973-1985 and 1986-2000, and found that the odds were similar in these time frames (OR=1.88 for 1973-1985, and OR=1.74 for 1986-2000), adjusting for all the other covariates in the final multivariable model. Similar odds of VTE were noted for cancer stage ≥ 2 in these two time frames (OR: 2.8 vs. 2.1, respectively). In the time frame 1973-1985, the odds of in-hospital VTE was higher than the odds of VTE within 92 days post-hospitalization (OR: 14.6 vs. 2.8 respectively); in contrast to the latter time frame 1986-2000, where the odds of in-hospital

VTE was similar to the odds of VTE within 92 days post-hospitalization (OR: 5.4 vs. 4.6, respectively).

Discussion

We found that cancer site and stage, both measures of biological aggressiveness and procoagulant potential of the underlying cancer, were associated with increased risk of VTE. Our previously-derived cancer site VTE risk score [34], applied as a continuous variable, functioned quite well in predicting the risk of VTE for most cancer sites; a two-fold increase in cancer site VTE risk score increased the risk of VTE nearly 1.4 fold after adjusting for all the other significant covariates listed in Table 4a. While the rank order of SMR for various cancer sites ("cancer site VTE risk score") among our incident VTE cases [34] was similar to that observed in other studies [6, 7, 15, 31, 32], we uniquely used our score as a continuous variable in this study. This strategy adjusted in a parsimonious way for the magnitude of VTE risk associated with each cancer site which allowed us to focus on other cancer and non-cancer characteristics. However, the cancer site VTE risk score for indolent cancer with long follow-up (e.g., low grade lymphoma and MPN) did not adequately represent the VTE risk, with low grade lymphoma (OR=0.34; Table 3a) being inversely associated with VTE, suggesting that the risk of VTE with low grade lymphoma is lower than would be predicted by the lymphoma cancer site VTE risk score (risk score: 28.8; Table 2). In contrast, MPN was positively associated with VTE (OR=18.26; Table 3a) and had a much higher risk of VTE than predicted by the MPN cancer site VTE risk score (risk score: 12.6; Table 2).

Higher cancer stage has been associated with increased VTE risk.[6, 23, 41] We noted that cancer stage 2 was independently associated with a 2.2-fold increased odds of VTE. Cancer grade was not associated with VTE risk, as was noted in the Vienna CATS study. [35] Cancer stage progression was not an independent risk factor for VTE after adjustment for cancer stage at cancer diagnosis. Liver metastasis was associated with 2.7-fold increased risk of VTE, independent of cancer stage 2 and other cancer and non-cancer risk factors. We speculate that this represents the biological aggressiveness and procoagulant potential of the underlying stage 4 cancer. Another possibility is vascular invasion by the underlying tumor, as patients with primary or metastatic liver cancer are at an increased risk of splanchnic vein thrombosis (n=22; 6.3%).

Recent hospitalization (with or without surgery) and nursing home confinement were associated with nearly 8- and 5-fold increased risks of VTE, respectively. Hospitalization and nursing home confinement likely are surrogate markers of relative immobility and the acuity and severity of their underlying illness. Hospitalization and nursing home confinement have also been identified as independent VTE risk factors in the general population.[2, 31, 37-39] Interestingly, in the time frame 1973-1985, the odds of in-hospital VTE was higher than the odds of VTE within 92 days post-hospitalization (OR: 14.6 vs. 2.8 respectively); in contrast to the latter time frame 1986-2000, where the odds of in-hospital VTE was similar to the odds of VTE within 92 days post-hospitalization (OR: 5.4 vs. 4.6, respectively). This probably reflects the decrease in hospital length of stay over time, and implies that although the VTE events may be occurring at about a similar rate following

admission to the hospital, in the recent era, more events are diagnosed following dismissal from the hospital due to shorter length of hospital stay. Although recent surgery was univariately associated with increased risk of VTE in cancer patients, on multivariate analysis, it was no longer an independent risk VTE factor, similar to the Dutch MEGA study [31] but in contrast to the Danish registry.[6] Surgical resection of cancer is typically a treatment modality for lower stage cancers. Furthermore, surgery is offered to individuals who have better performance status and less comorbidity. Interestingly, in a study of patients with colon cancer that utilized California patient discharge data, surgery was associated with a lower risk of VTE.[41]

Recent chemotherapy independently increased the odds of VTE 1.8-fold, as has been noted in other studies.[2, 6, 31, 36, 42] However, we did not detect any difference in VTE risk by type of chemotherapy, possibly due to inadequate power. While cancer therapy continuously evolves over time, the odds of VTE associated with chemotherapy were similar in the time frames, 1973-1985 and 1986-2000 (OR=1.88 and OR=1.75, respectively). As noted in a previous study, radiation therapy was not an independent risk factor for VTE.[31]

Progestin was associated with a two-fold increased risk of VTE, similar to previous studies where progestin was an independent risk factor for VTE in women. [2, 28, 50, 51] We initially postulated that this increased VTE risk would be confined to women where progesterone is typically used for suppression of menstrual bleeding in women undergoing chemotherapy or for treatment of breast or gynecologic cancers. However, the rates of progesterone use in female cases and controls were similar (9.7% and 8.1%, respectively; Table 1). In contrast, in men, 6% of the cases vs. 1% of the controls used progestins, predominantly for treatment of prostate cancer. Although it is biologically plausible that progestins independently increased the risk of VTE in cancer patients, progestin use may indirectly reflect the underlying prostate cancer and the cancer site VTE risk score may be under-adjusting for prostate cancer.

Underweight (BMI<18.5 mg/m²; OR=1.9) or severely obese (BMI ≥ 35 kg/m²; OR=3.97) cancer patients had an increased odds of VTE. Underweight cancer patients may have aggressive cancer, advanced stage disease, cancer cachexia or multiple comorbidities, thus increasing their VTE risk. Moreover, in the general population, being underweight has been associated with poorer survival following incident VTE.[55] On the other hand, severe obesity could predispose to VTE due to the physical effects of body fat impeding the venous return and/or a proinflammatory/ prothrombotic state seen in obesity.[56] Obesity is risk factor for incident VTE in the general population.[57-60]

We were surprised that CV catheter was independently associated with an 8.5-fold increased risk of VTE despite excluding isolated arm and jugular vein DVT. Thus, the risk imparted by CV catheter appears to be more systemic and could reflect chemotherapy and cancer site and/or stage despite adjusting for these characteristics. Recent infection also was independently associated with a 1.7-fold increased VTE risk, possibly due to a procoagulant state induced by infections.[61] Infection is a VTE risk factor for hospitalized cancer patients.[42]

Pre-chemotherapy platelet count $350 \times 10^9/L$, hemoglobin $<100g/L$, and leukocyte count $>11 \times 10^9/L$ are reported as risk factors for cancer-associated VTE within three months after starting chemotherapy.[40, 43, 44] In a subset of our cases and controls where complete blood count data at the time of cancer diagnosis were available, only platelet count $350 \times 10^9/L$ was marginally associated with VTE in the final multivariable model, likely due to differences in study design. In the Awareness of Neutropenia in Cancer Study Group Registry of 4066 cancer patients who were initiating a new chemotherapy regimen, there were a total of 88 VTE cases during a median follow-up of 2.4 months; the distribution of cancer types did not reflect the distribution of all the cancers occurring in the community (i.e., two-thirds had either breast, lung or colon cancer). [40]_The Vienna CATS cohort study included 819 either newly diagnosed cancer patients or those with progression of cancer who had not recently received therapy, of whom 61 developed VTE over a median follow-up of 656 days. [44]_Our study was a matched case-control study of subjects with active cancer, irrespective of whether they were receiving therapy, as one of the goals was to analyze whether chemotherapy use and type, radiation therapy and/ or surgical resection are independent VTE risk factors in cancer patients. As the complete blood count data were available on 172 VTE case-control pairs (i.e., 344 subjects) and 512 of 1208 subjects overall, we do not think that the differences are due to limited numbers in the subset analysis.

Our study has several important strengths. Due to the unique features of the REP, our study avoids referral bias. Our population-based study better reflects “real world” clinical practice in contrast to a highly selected population participating in clinical trials. All VTE cases met strict criteria for clinically or objectively-confirmed acute DVT and/or PE, and we confirmed that controls did not have VTE, based on direct review of their source documents (i.e., imaging, surgical and autopsy reports) rather than depending on administrative codes. We included only individuals who had active cancer, and the definition of active cancer was explicit. We included the entire spectrum of VTE disease occurring in the community, including persons with rapidly fatal and chronic care facility (e.g., nursing home) events who did not reach the hospital. We ensured a comparable control group by performing a population-based study where both cases and controls were residents from the same community with similar duration of active cancer, thus avoiding the issues of ‘immortal time bias’ [62], and lifetime access to medical care. By using the cancer site SMR as a continuous variable “cancer site VTE risk score” we were able to jointly adjust for cancer site and stage and quantify the magnitude of VTE risk associated with each of the risk factors identified after adjusting for the other risk factors. Although there has been evolution in clinical practice in cancer diagnosis and therapy during the study period, we did not note a significant interaction between VTE event year and the identified VTE risk factors including chemotherapy use, VTE location of onset, BMI, CV catheter use, or any infection.

Our study also has important limitations. The age-, sex- and racial-distribution of Olmsted County is similar to that for Minnesota, the upper mid-west, and the U.S. white population; however, residents of Olmsted County exhibit higher median income and education level compared to these geographic regions.[46, 63, 64] While no single geographic area is representative of all others, the under-representation of minorities may compromise the generalizability of our findings to different racial and ethnic groups. Due to matching,

patient age and sex could not be tested as a main effect for an association with cancer-associated incident VTE although we did test these for potential interactions and found none. Patients who had common cancers or who survived longer may have been more likely to be chosen as controls. Due to the generally lower autopsy rate in older individuals and the declining autopsy rate over the study period (the autopsy rates for men and women for 1973-1980, 1981-1990 and 1991-2000 were around 50%, 40%, 35% and 35%, 30% and 25%, respectively) [65], we may have missed fatal PE cases presenting as sudden death, as suggested by the declining number of PE's that were discovered on autopsy over time. Finally, due to our study timeframe we could not confirm the association of immune modulating drugs (e.g., thalidomide, lenalidomide) or angiogenesis inhibitors (e.g., bevacizumab) with VTE. Adjusting for cancer and non-cancer characteristics that we determined to be associated with VTE independent of chemotherapy will be important for future studies testing new chemotherapies for an association with VTE. However, despite the introduction of newer agents and potential changes in the standard chemotherapy regimens over time, the findings of this study are still currently relevant and applicable today as we have identified and quantified clinically important cancer and non-cancer related risk factors that are independently associated with VTE.

In conclusion, cancer site, as represented by the cancer site VTE risk score, cancer stage 2, liver metastasis, chemotherapy and progestin use, being underweight or obese, central venous catheter, hospitalization, nursing home confinement and infection are independent risk factors for incident VTE in individuals with active cancer. These characteristics can identify high VTE-risk active cancer patients for development of a risk score and for inclusion in future studies of VTE prophylaxis.

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Key Points

- We tested cancer and non-cancer characteristics as predictors of cancer-associated VTE
- Cancer site, stage, liver metastasis, chemotherapy, progestin increased VTE risk
- BMI, hospitalization, central venous catheter and infection increased VTE risk
- These characteristics can be used to identify high VTE-risk active cancer patients

Table 1
Baseline Characteristics of Patients with Active Cancer and Venous Thromboembolism - Cases and Controls

Baseline Characteristic	Cases (n=570)	Controls (n=604)
Age, mean $\pm$ SD	68.5 (14.7)	69.2 (14.0)
Female, n (%)	279 (49.0)	296 (49.0)
Body mass index (BMI, kg/m ²), mean $\pm$ SD	25.3 (6.5)	25.5 (5.1)
BMI <18.5 kg/m ² (Underweight), n (%)	66 (11.6)	37 (6.1)
BMI 18.5-25 kg/m ² (Normal), n (%)	225 (39.5)	253 (41.9)
BMI 25-30 kg/m ² (Overweight), n (%)	175 (30.7)	220 (36.4)
BMI 30-35 kg/m ² (Obese class I), n (%)	67 (11.8)	68 (11.3)
BMI >35 kg/m ² (Obese class II-III), n (%)	37 (6.5)	26 (4.3)
Cancer site VTE risk score ^{*†} , median (inter quartile range)	12.6 (7.9, 19.8)	8.6 (7.9, 13.9)
Stage [*] , n (%)		
0	7 (1.2)	26 (4.3)
1	137 (22.7)	214 (35.5)
2	117 (19.4)	120 (19.9)
3	122 (20.2)	102 (16.9)
4	221 (36.6)	140 (23.3)
Stage progression [*] , n (%)	148 (24.7)	100 (16.6)
Metastasis to liver [*] , n (%)	141 (23.5)	48 (8.0)
Metastasis to bone [*] , n (%)	97 (16.1)	66 (11.0)
Tumor grade 3 or 4 [*] , n (%)	394 (66.2)	321 (55.3)
Chemotherapy [‡] , n (%)	166 (29.2)	108 (17.9)
Alkylators [§]	67 (11.8)	59 (9.8)
Antimetabolites [§]	78 (13.7)	37 (6.2)
Anthracyclines [§]	44 (7.8)	21 (3.5)
Alkaloids [§]	33 (5.8)	20 (3.3)
Platinum [§]	35 (6.2)	20 (3.3)
Hormonal modulators [§]	0 (0.0)	3 (0.5)
Immunomodulators [§]	4 (0.7)	3 (0.5)
Other [§]	73 (12.8)	54 (9.0)
Radiation therapy [‡] , n (%)	54 (9.5)	32 (5.3)
Tamoxifen [‡] , n (%)	24 (4.2)	19 (3.2)

Baseline Characteristic	Cases (n=570)	Controls (n=604)
Estrogen/ Oral Contraceptives [‡] , n (%)	26 (4.6)	27 (4.5)
Women only, n (%)	18 (6.5)	24 (8.1)
Progestins [‡] , n (%)	44 (7.7)	28 (4.6)
Women only, n (%)	27 (9.7)	24 (8.1)
Diethyl stilbesterol [‡] , n (%)	17 (3.0)	18 (3.0)
Trauma/fracture [‡] , n (%)	32 (5.6)	16 (2.6)
Hospitalized , n (%)	392 (68.8)	206 (34.1)
ICU stay, n (%)	78 (14.2)	20 (3.4)
General surgery, n (%)	131 (23.0)	98 (16.2)
Neurological surgery, n (%)	12 (2.1)	2 (0.3)
Orthopedic surgery, n (%)	19 (3.3)	4 (0.7)
Gynecologic surgery [¶] , n (%)	21 (7.5)	12 (4.0)
Any anesthesia [‡] , n (%)	245 (43.0)	163 (27.0)
General anesthesia, n (%)	181 (31.8)	119 (19.7)
Epidural and spinal anesthesia, n (%)	64 (11.2)	44 (7.3)
Nursing home confinement [‡] , n (%)	22 (3.9)	20 (3.3)
Neurological disease with leg paresis, n (%)	40 (7.0)	7 (1.2)
Immobilization [‡] , n (%)	60 (10.5)	17 (2.8)
Central venous catheter [‡] , n (%)	66 (11.6)	11 (1.8)
Varicose veins, n (%)	159 (27.9)	145 (24.0)
Prior superficial vein thrombosis, n (%)	79 (13.9)	49 (8.1)
Diabetes, n (%)	62 (11.0)	71 (11.8)
Hyperlipidemia, n (%)	133 (23.5)	157 (26.0)
Lipid lowering drugs [‡] , n (%)	19 (3.4)	30 (5.0)
Statins, n (%)	10 (1.8)	24 (4.2)
Chronic renal disease, n (%)	17 (3.0)	5 (0.8)
Autoimmune connective tissue disease [#] , n (%)	16 (2.8)	7 (1.2)
Any heart disease, n (%)	192 (33.7)	173 (28.6)
Lung disease/ pulmonary hypertension, n (%)	130 (22.8)	131 (21.7)
Any infection [‡] , n (%)	227 (39.8)	100 (16.6)
Ever Smoker, n (%)	303 (53.2)	341 (56.5)
Anticoagulation use [‡] , n (%)	24 (4.2)	16 (2.6)

* Thirty-one of VTE cases had more than one cancer primary site (34 cancers), and each primary site was matched to a control, matching on age ($\pm$ 5 years), sex, cancer diagnosis date ($\pm$ 5 years), and duration of prior medical history ($\pm$ 5 years). The cancer specific characteristics are based on the 604 total malignancies as these elements were collected for each of malignancy diagnoses.

[†]The Cancer site VTE risk score is the cancer site standardized morbidity ratio for VTE (see Table 2. [34])

[‡]Within 92 days prior to the VTE event/ index date.

[§]The subclasses of chemotherapy do not add up to 100%, as subjects could be on combination chemotherapy.

// In hospital or within 92 days of previous hospitalization compared to no hospitalization in the past 92 days. Includes patients hospitalized with surgery or for acute medical illness.

[¶]Among women only (279 cases, 296 controls)

[#]includes rheumatoid arthritis, systemic lupus erythematosus, scleroderma

Table 2
Cancer Site and Standard Morbidity Ratio (SMR; “Cancer Site VTE Risk Score”)*
Distribution of Patients with Active Cancer and Venous Thromboembolism: by Case and Control Status

Cancer Site	Cases n (%)	Controls n (%)	Cancer site VTE risk score (SMR*)
Brain	18 (3.0)	14 (2.3)	47.2
Pancreatic	52 (8.6)	13 (2.2)	42.0
Other digestive	18 (3.0)	8 (1.3)	30.9
Lymphoma	41 (6.8)	38 (6.3)	28.8
Leukemia	20 (3.3)	34 (5.6)	19.8
Stomach	18 (3.0)	7 (1.2)	18.2
Multiple myeloma	8 (1.3)	15 (2.5)	14.0
Kidney	11 (1.8)	17 (2.8)	13.9
Lung	72 (11.9)	60 (9.9)	13.0
Ovary [†]	17 (5.7)	16 (5.4)	13.0
Myeloproliferative neoplasm	19 (3.2)	1 (0.2)	12.6
Bladder	27 (4.5)	19 (3.2)	11.0
Melanoma	10 (1.7)	11 (1.8)	9.7
Breast [‡]	61 (20.6)	100 (33.8)	8.6
Other gynecologic [‡]	24 (8.1)	22 (7.4)	8.4
Prostate [§]	71 (23.0)	104 (33.8)	7.9
Colon/rectal	75 (12.4)	74 (12.2)	7.3
Other cancers combined [‡]	36 (6.0)	51 (8.4)	-----

* Standard morbidity ratio (SMR; “Cancer site VTE risk score”) among Olmsted County, MN residents with incident venous thromboembolism, 1988-2000; adapted from Petterson, T.M., et al. [34]

[†] Women only (296 cases, 296 controls);

[§] Men only (308 cases, 308 controls).

[‡] Remaining cancers combined (head and neck, liver, other thorax, bone, soft tissue, myelodysplastic syndrome, other genitourinary, eye, misc. cancer [other] with scores of 4.1, 25.9, 0, 0, 5.0, 7.0, 10.6, 26.8, and 9.1, respectively).

Table 3a

Univariate Analysis for Association between Venous Thromboembolism in Cancer Patients and Cancer Site, and After Adjusting for Cancer Site VTE Risk Score, Individual Cancer Sites, and Cancer Stage

	Cancer Site and Stage	OR	95% CI*	p-value*
Model 1	Two-fold increase in cancer site VTE risk score	1.42	1.22 1.66	<.001
Model 2	Two-fold increase in cancer site score	1.52	1.28 1.82	<.001
	Low grade lymphoma	0.34	0.17 0.68	0.002
	Medium or high grade lymphoma	1.40	0.62 3.18	0.42
	Myeloproliferative neoplasm	18.26	2.40 139.08	0.005
Model 3	Two-fold increase in cancer site VTE risk score	1.44	1.20 1.73	<.001
	Low grade lymphoma	0.30	0.15 0.61	<.001
	Medium or high grade lymphoma	1.65	0.72 3.78	0.24
	Myeloproliferative neoplasm	23.96	3.05 188.00	0.002
	Stage 3, 4 vs stage 1, 2	2.00	1.55 2.59	<.001
Model 4	Two-fold increase in cancer site VTE risk score	1.50	1.25 1.81	<.001
	Low grade lymphoma	0.30	0.15 0.63	0.001
	Medium or high grade lymphoma	1.38	0.63 3.03	0.42
	Myeloproliferative neoplasm	28.64	3.53 232.17	0.002
	Stage 2, 3, 4 vs stage 1	2.38	1.80 3.16	<.001

* 95% Confidence intervals are calculated using the robust sandwich estimate of Lin and Wei [54] for the covariance and standard error. P-values are Wald p-values from the conditional logistic model using the robust sandwich estimate. Covariates that reached the statistical significance level p 0.1 are included in this table.

Table 3b
Univariate Analysis for Predictors of Venous Thromboembolism in Cancer Patients,
Adjusting for Cancer Site VTE Risk Score, Individual Cancer Sites and Cancer Stage
(Table 3a)

Characteristic	OR	95% CI*		p-value*
Stage change	1.99	1.39	2.85	<.001
Metastasis	1.70	1.27	2.29	<.001
Metastasis to liver	2.62	1.81	3.79	<.001
Metastasis to bone	1.56	1.05	2.32	0.027
Cancer grade 3 or 4	1.38	1.04	1.82	0.026
Chemotherapy	1.76	1.27	2.45	<.001
Radiation therapy	1.77	1.00	3.15	0.051
Progestins	1.76	1.03	2.99	0.038
Age, 10-year increase	0.67	0.43	1.06	0.084
BMI (continuous variable)	0.99	0.97	1.02	0.67
BMI (categorical; Reference: 18.5-25 kg/m ²)				
BMI <18.5 kg/m ² (Underweight)	1.93	1.18	3.17	0.009
BMI 25-30 kg/m ² (Overweight)	0.87	0.64	1.18	0.38
BMI 30-35 kg/m ² (Obese class I)	1.13	0.74	1.72	0.58
BMI >35 kg/m ² (Obese class II-III)	1.70	0.89	3.25	0.11
Location of onset of VTE (Reference: Community)				
Hospitalized	10.87	6.48	18.22	<.001
Hospitalization within 92 days	4.94	3.37	7.24	<.001
Nursing Home/no hospitalization	4.46	1.92	10.34	<.001
ICU stay	5.26	2.79	9.91	<.001
General surgery	2.28	1.57	3.31	<.001
Neurosurgery	8.48	0.93	77.52	0.058
Orthopedic surgery	3.75	1.34	10.46	0.012
Gynecologic surgery	2.32	1.09	4.95	0.028
General/cardiac/orthopedic/neuro/gynecologic surgery	3.27	2.25	4.74	<.001

Characteristic	OR	95% CI*		p-value*
Any anesthesia	2.91	2.09	4.06	<.001
Superficial vein thrombosis	1.91	1.28	2.87	0.002
Chronic renal disease	2.92	0.92	9.30	0.069
Neurologic disease	6.45	2.49	16.69	<.001
Any heart disease	1.41	1.04	1.90	0.026
Autoimmune connective tissue disease	3.50	1.18	10.37	0.024
Trauma/fracture	2.17	1.11	4.24	0.024
Immobilization	3.73	2.00	6.93	<.001
Central vein catheter	18.73	5.36	65.48	<.001
Any Infections	3.06	2.24	4.19	<.001

* 95% Confidence intervals are calculated using the robust sandwich estimate of Lin and Wei [54] for the covariance and standard error. P-values are Wald p-values from the conditional logistic model using the robust sandwich estimate. Covariates that reached the statistical significance level $p \leq 0.1$ are included in this table.

Table 3c
Univariate Analysis for Predictors of Venous Thromboembolism in Cancer Patients with Indicated Lab Values, Adjusting for Cancer Site VTE Risk Score, Individual Cancer Sites and Cancer Stage (Table 3a)

Characteristic	OR	95% CI*		p-value*
Leukocyte count $>11 \times 10^9/L$				
Preserving case-control pair matching [†]	1.38	0.81	2.35	0.23
Not preserving case control pair matching [‡]	1.57	0.01	172.80	0.85
Hemoglobin $<100g/L$				
Preserving case-control pair matching [†]	0.94	0.43	2.07	0.88
Not preserving case control pair matching [‡]	1.32	0.50	3.51	0.57
Platelet count $350 \times 10^9/L$				
Preserving case-control pair matching [†]	1.61	0.78	3.29	0.20
Not preserving case control pair matching [‡]	1.45	0.00	1239.26	0.91

* 95% Confidence intervals are calculated using the robust sandwich estimate of Lin and Wei [54] for the covariance and standard error. P-values are Wald p-values from the conditional logistic model using the robust sandwich estimate. Covariates that reached the statistical significance level $p < 0.1$ are included in this table.

[†] Subset of matched cases and controls where data were available in the electronic medical records, preserving the case-control pair status; N=344 sets.

[‡] Subset of cases and controls where data were available in the electronic medical records, not preserving the case-control pairing; N=512 individuals.

Table 4a
Multivariable Analysis for Predictors of Venous Thromboembolism in Cancer Patients

Characteristic	OR	95% CI*		P-Value*
Two-fold increase in Cancer site VTE risk score	1.37	1.09	1.71	0.007
Lymphoma: Low Grade	0.26	0.09	0.70	0.008
Lymphoma: Intermediate or High Grade	1.42	0.50	4.03	0.51
Myeloproliferative neoplasm	38.99	8.72	174.26	<.001
Stage 2 or 3 or 4	2.18	1.56	3.02	<.001
Metastasis to liver	2.70	1.69	4.31	<.001
Chemotherapy use within 92 days	1.81	1.17	2.81	0.008
Progestin use within 92 days	2.13	1.07	4.25	0.032
Body mass index (BMI) (Reference: 18.5-25 kg/m ²)				
BMI <18.5 kg/m ² (Underweight)	1.93	1.02	3.66	0.044
BMI 25-30 kg/m ² (Overweight)	1.10	0.76	1.61	0.61
BMI 30-35 kg/m ² (Obese class I)	1.67	0.98	2.86	0.062
BMI ≥35 kg/m ² (Obese class II-III)	3.97	1.48	10.66	0.006
Location of onset of VTE (Reference: Community)				
Nursing home	4.71	2.01	11.04	<.001
Hospitalized within 92 days	3.89	2.53	5.97	<.001
Hospitalized	7.91	4.44	14.10	<.001
CV catheter use within 92 days	8.53	2.76	26.40	<.001
Any infection within 92 days	1.71	1.19	2.45	0.004

* 95% Confidence intervals are calculated using the robust sandwich estimate of Lin and Wei [54] for the covariance and standard error. P-values are Wald p-values from the conditional logistic model using the robust sandwich estimate.

Table 4b
Multivariable Analysis for Predictors of Venous Thromboembolism in Cancer Patients
with Indicated Lab Values

Characteristic	OR	95% CI*		P-Value*
Leukocyte count $>11 \times 10^9/L$				
Preserving case-control pair matching [†]	1.09	0.58	2.06	0.79
Not preserving case control pair matching [‡]	1.32	0.00	517.71	0.93
Hemoglobin $<100g/L$				
Preserving case-control pair matching [†]	0.51	0.17	1.53	0.23
Not preserving case control pair matching [‡]	1.09	0.12	9.76	0.94
Platelet count $350 \times 10^9/L$				
Preserving case-control pair matching [†]	2.29	0.93	5.65	0.072
Not preserving case control pair matching [‡]	1.54	0.00	8518.00	0.92

* 95% Confidence intervals are calculated using the robust sandwich estimate of Lin and Wei [54] for the covariance and standard error. P-values are Wald p-values from the conditional logistic model using the robust sandwich estimate.

[†] Subset of matched cases and controls where data were available in the electronic medical records, preserving the case-control pair status; N=344 sets.

[‡] Subset of cases and controls where data were available in the electronic medical records, not preserving the case-control pairing; N=512 individuals.