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CHAPTER 11

The long-term risk of cancer in patients with a first episode of venous thromboembolism.

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Summary

Background: In patients with venous thromboembolism (VTE), 15–20% will have prevalent cancer when VTE is diagnosed but little is known about such patients long-term risk, time course and predictors of new cancer. Patients and methods: We studied an inception cohort of patients with a first VTE who were not diagnosed with cancer within 3 months after VTE and who had follow-up for up to 120 months. We determined the annual risk for a new cancer (number of events and 95% confidence interval (CI)) per 100 person-years in all patients and in those with unprovoked VTE and identified predictors for new cancer. Results: We studied 1852 patients with VTE who received anticoagulant therapy for 12 months (mean) and were followed for 4.2 years (mean). During follow-up, there were 105 (5.7%) patients diagnosed with new cancer during the period after the initial 3 months from diagnosis, for an annual risk of 1.32 (CI, 1.09–1.60) per 100 person-years. The risk for new cancer appeared uniform over time. The annual risk for new cancer was more than 2-fold higher in patients presenting with unprovoked compared with those with provoked VTE (1.76 (CI, 1.39–2.20) vs. 0.83 (CI, 0.58–1.16) per 100 person-years; P < 0.001). Clinical predictors for new cancer were increasing age (hazard ratio (HR), 1.23; CI, 1.05–1.44) and unprovoked VTE (HR, 1.86; CI, 1.21–2.87). Conclusion: In patients with a first VTE and without prevalent cancer, the risk for new cancer is about 1–2% per year, appears to be uniform over time, and is higher in patients with unprovoked VTE and those with advanced age.

Introduction

In patients diagnosed with venous thromboembolism (VTE), 15–20% will have prevalent cancer, defined as pre-existing cancer or a new cancer that is diagnosed, typically, within 3 months after the diagnosis of VTE (1). New cancers may be detected when radiological imaging is done in patients with suggestive symptoms or if they have risk factors for malignancy such as a history of smoking. Other prevalent cancers may be detected soon after anticoagulant therapy is initiated, for example with colorectal cancers that present with new onset lower gastrointestinal bleeding (2). Less is known about the long-term risk that patients with VTE will develop a new (or incident) cancer (3). Thus, the question we posed is: what is patients’ long-term risk for developing cancer if cancer is not diagnosed within 3 months after VTE is diagnosed? We also asked what this long-term risks in patients with unprovoked VTE in whom an occult cancer may be a contributing pathogenic factor. In such patients, occult cancer may induce a hypercoagulable state but may remain clinically silent and undetectable by radiological imaging (4). These questions have not been adequately addressed by previous studies. Most studies assessed the short-term risk of having cancer diagnosed after VTE, with patient follow-up of 6–24 months (5–15). Studies with a longer duration of follow-up were retrospective cohorts (16–20) or relied on linked administrative databases (21–25) and, consequently, ascertainment of new cancer diagnoses may have been inaccurate. Furthermore, such studies might have misclassified the etiology of VTE (provoked or unprovoked) because of unreliable documentation of antecedent risk factors. One long-term prospective study showed a clustering of new cancers after unprovoked VTE (26), although this study was limited by a small patient sample and contrasting findings were reported by another prospective study that was also limited by a small sample (27). Against this background, our primary aim was to provide reliable and precise estimates of the long-term risk for a new (or incident) cancer in patients with VTE (in all patients and in those with unprovoked VTE) and to determine the time course when such cancers will present. To do this, we studied an inception cohort of patients with a first VTE who were without known cancer at the time of and 3 months after the diagnosis of VTE. Our secondary aim was to determine the effect of VTE etiology and other potential clinical predictors of a new cancer.
Patients and methods

Inception cohort characteristics and follow-up the inception cohort was derived from the patient population of a prospective cohort study of patients with a first VTE (28). This source study was approved by local Institutional Review Boards of participating hospitals and all patients provided informed consent to participate in this study. The inception cohort had the following clinical characteristics: (i) consecutive patients presenting to a primary care facility (emergency department or family practice clinic) in Italy with a first episode of symptomatic VTE that was confirmed by objective diagnostic imaging; (ii) patients received at least 3 months of anticoagulation, consisting of 5–10 days of a heparin followed by a vitamin K antagonist, the latter administered to achieve an international normalized ratio of 2.0–3.0; and (iii) patients were free of known cancer at 3 months after the diagnosis of VTE. Patients were excluded from the inception cohort if they had one or more of the following conditions concurrent with the diagnosis of VTE that would warrant life-long anticoagulation: active cancer; long-term immobility; high-risk thrombophilia (i.e. deficiency of protein C, protein S or antithrombin, or antiphospholipid antibody syndrome); or another permanent VTE risk factor. The period of observation for the inception cohort began 3 months after the start of anticoagulation and ended when patients were diagnosed with cancer, they died or the study ended (after a maximum of 120 months follow-up). We identified new (or incident) cancers that presented 3 months or more after VTE was diagnosed, thereby excluding prevalent cancers that would have been present at the time of VTE diagnosis.

Inception cohort sub-groups

Patients from the inception cohort were placed into sub-groups according to the etiology of VTE (unprovoked or provoked) and mode of presentation (deep vein thrombosis, pulmonary embolism or both). Provoked or secondary VTE was defined as occurring in the presence of one or more of the following transient risk factors: surgery, leg trauma, leg fracture or childbirth within 3 months; bedridden for >1 week due to medical or rheumatologic illness; pregnancy; or hormone therapy use. Unprovoked (or idiopathic) VTE was defined as VTE occurring in the absence of any of the above risk factors. Detection and diagnosis of incident cancer there was no standardized screening for occult cancer in the inception cohort, although some patients may have had cancer screening in accordance with recommended practice guidelines, such as biennial mammography for women aged ≥50 years. Thus, all cancer outcomes that presented 3 months or more after the diagnosis of VTE were detected based on clinical features that would prompt diagnostic imaging or cancers that were detected by screening that was independent of the diagnosis of VTE. The diagnosis of new cancer was based on histologic criteria. All new cancer diagnoses were confirmed by an independent adjudication committee that was blinded to patients' initial presentation and other clinical characteristics. Non-melanomatous (basal cell or squamous cell) skin cancers were not considered as new cancer events.

Statistical analysis

Annual risk and time course of new cancer we used mean and range to describe the clinical characteristics of patients at the time VTE was diagnosed. The annual risk for a new cancer was expressed as the number of events (and 95% confidence interval (CI)) per 100 person-years of follow-up so as to standardize for different lengths of patient follow-up across the inception cohort. We used the Kaplan–Meier method to determine the time course of new cancers after the diagnosis of VTE. Risk for cancer after unprovoked and provoked VTE we determined the annual risk of cancer separately in patients with unprovoked and provoked VTE. We compared the risk for cancer in patients with unprovoked and provoked VTE in two ways. First, we used Fishers exact test to compare the incidence of cancer in the two sub-groups; and secondly, we used multivariable regression analysis whereby unprovoked VTE, as compared with provoked VTE, was a variable in the regression model aimed at identifying independent predictors.
of cancer. To interpret the absolute incidence of new cancer in patients with unprovoked and provoked VTE would, ideally, require determining the incidence of cancer in an age-matched control group without VTE. As such data were not available for our analysis, we used the standardized incidence ratio (SIR) to provide a surrogate comparison of the incidence of cancer in patients with unprovoked and provoked VTE with that in the general population. The SIR can be defined as the ratio of the observed (in our study) to expected new cases of cancer, where the expected number is the age-specific rates of cancer in the general population (29). Clinical predictors of new cancer to identify clinical predictors for new cancer, the following variables, if present at the time of initial presentation, were considered a priori as putative risk factors: age (10-year increments); sex; mode of presentation; duration of anticoagulant therapy (1-month increments); and VTE etiology. We used Cox multivariable regression analysis to assess an association between the predictor variables and the risk for a new cancer. Using backward modelling, only variables with P < 0.10 were retained in the final model. We estimated the hazard ratio (HR) for a new cancer (and associated 95% CIs) for each risk factor in the regression model. All P-values were 2-sided. SASV8.2 software (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Characteristics of inception cohort

There were 1852 patients with a first episode of symptomatic VTE who received anticoagulant therapy for, on average, 12 months and had follow-up for, on average, 4.2 years. There were 1018 (55%) patients who were classified as having unprovoked VTE. Annual risk and time course of new cancer There were 105 (5.7%) patients diagnosed with a new cancer during follow-up, for an annual risk of 1.32 (CI, 1.09–1.60) per 100 person-years of follow-up. For patients with recurrent non-fatal VTE, the annual risk for a new cancer after the occurrence of recurrent VTE was 1.26 (CI, 0.72–2.06) per 100 person-years of follow-up. The time course for new cancer is shown in Fig. 1 for all patients and separately for patients with unprovoked and provoked VTE. In all patient groups, the incidence of new cancers appeared uniform overtime, with no clustering of new cancers during the initial 3–12 months after VTE was diagnosed. Risk of cancer in patients with unprovoked VTE, the annual risk for a new cancer after the occurrence of recurrent VTE was 1.76 (CI, 1.39–2.20) per 100 person-years, whereas in the control group with provoked VTE it was 0.83 (CI, 0.58–1.16) per 100 person-years. The greater than 2-fold higher incidence of cancer in patients with unprovoked than those with provoked VTE was statistically significant (P = 0.00084). The SIR for all cancers combined was significantly higher in both the patient groups with unprovoked and provoked VTE compared with the general population. In addition, consistent with our other findings, it appeared that the SIRs were higher in patients with unprovoked than provoked VTE.

Clinical predictors of new cancer

Presentation with both deep vein thrombosis and pulmonary embolism compared with pulmonary embolism alone conferred non-significant increased risk for new cancer (HR, 1.73; CI, 0.89–3.37). Patient sex, the presence of thrombophilia, recurrent VTE and the duration of anticoagulant therapy did not appear to affect the risk for a new cancer.

Discussion

We aimed to provide reliable and precise estimates of the long-term risk for new cancer in patients with a first VTE based on an inception cohort of over 1800 patients (approximately 1000 with unprovoked VTE) who were followed, on average, for approximately 4 years after the diagnosis of VTE. We found that in patients in whom cancer was not diagnosed within the initial 3 months after VTE, the cumulative risk for developing cancer during the subsequent time period was 5.7%, with an annual incidence of 1.32 per 100 person-years. The
The incidence was more than 2-fold greater in patients with unprovoked VTE than those with provoked VTE (1.76 vs. 0.83 per 100 person years). The incidence of cancer appeared uniform over time, with no clustering of cancers between 3 and 12 months after the diagnosis of VTE. Finally, apart from having unprovoked VTE, increasing age was the only other identifiable clinical risk factor for new cancer. We believe our findings are valid because the study population was a large, well-defined inception cohort that was followed prospectively. All patients had a first symptomatic VTE, did not have pre-existing cancer when VTE was diagnosed, received standardized anticoagulant therapy, and had careful follow-up, thereby making it likely that all new cancers were identified. Furthermore, the diagnosis of a new cancer was reliable, based on histologic testing, and was confirmed by an independent adjudication committee. Finally, patient selection bias was minimized and generalizability of findings was enhanced as consecutive patients were identified from a primary care setting. Our findings add to the literature relating to the risk for cancer after VTE in two ways. First, this is the first prospective study, to our knowledge, that assesses the long-term risk for new cancer in a large population of patients with a first VTE with almost 8400 person years of follow-up. Our findings complement those of a large patient registry that assessed the short-term risk for cancer within the initial 3 months after a diagnosis of VTE (7). In this study, 16% of patients had prevalent cancer diagnosed before or during hospitalization for VTE, whereas cancer was diagnosed in only 1.2% of the remaining patients during the 3-month follow-up. Combined with our findings, it appears that if cancer is not pre-existing or detected around the time VTE is diagnosed, the subsequent risk of developing cancer is relatively low. Second, our finding that the increased risk for cancer, though low in absolute terms, persists for several years in patients with unprovoked VTE on the one hand supports the hypothesis that cancer may induce an hypercoagulable state that can aid the pathogenesis of VTE and can exist for several years before the cancer is clinically overt, (1,30) and on the other hand raises the hypothesis that cancer and thrombosis may share common risk factors. Our findings also support data from retrospective studies in which the risk for cancer persisted for up to 10 years after the development of VTE (11,12). We found that presentation with unprovoked VTE (HR,1.87) and increased age (HR, 1.22) conferred an increased risk for new cancer, which is consistent with findings reported in previous but smaller studies (3,30). Whereas the association between increased age and cancer is self-evident, an association with unprovoked VTE and cancer is less clear and may relate to sub-clinical cancer manifesting through the release of procoagulant constituents such as tissue factor to create a prothrombotic milieu (4). Presentation with deep vein thrombosis and pulmonary embolism conferred an increased risk for cancer (HR, 1.73 and, although not statistically significant, this association is consistent with the premise that a greater overall thrombus burden may be predictive of the development of new cancer (31). The main limitation of our study is the lack of a control group without VTE in which the annual risk for cancer could be determined without the influence of prior VTE as a potential cancer-related factor. As a surrogate for a control group, we used data from the general population to generate SIRs of cancer in patients we studied. Our finding that the SIRs were highest in patients with unprovoked VTE is consistent with our other findings that this group appears to be at increased risk for developing cancer relative to patients with provoked VTE and those in the general population. Our finding that the SIRs in patients with provoked VTE were also higher than those of the general population may be due to differences in the two populations relating to risk factors for cancer that we could not assess. We also acknowledge that our assessment of risks for cancer did not include all potential risk factors that may predispose to the development of cancer. Finally, some cancers might have been detected by routine screening for cancers such as breast and prostate. Consequently, our estimates of new cancers may include those that were symptomatic and those that were occult and detected only due to screening. The clinical implication of our findings is that based on the low incidence of cancers that will become clinically overt after VTE is diagnosed (1–2% per year), widespread screening for occult cancer in patients with VTE is unlikely to confer a high diagnostic yield. If cancer screening is considered, our findings suggest it should be limited to patients of advanced age who present with unprovoked VTE. The key unresolved question with regard to cancer screening in patients with VTE is whether early detection of cancer improves survival or whether survivalist spuriously
prolonged due to lead time bias. Given that we observed no clustering of cancers after VTE was diagnosed, this suggests that one-time screening after diagnosis may not detect many cancers. Additional studies are needed to assess the diagnostic yield of targeted screening vs. no screening for cancer and to determine the effect of these approaches on patient survival. To summarize, in patients with a first episode of VTE in whom there is no prevalent cancer, the risk for new cancer is about 1–2% per year and appears to be uniform over time. The risk for new cancer is higher in patients with unprovoked VTE and in those with advanced age.
References


