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Cancer-associated thrombosis

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Introduction

Venous thromboembolism (VTE) is one of the three most common cardiovascular diseases in the United States. It is also a leading cause of death among patients with cancer. Cancer-associated thrombosis is a topic of increased interest and importance. The goal of this review is to explore the increased risk of thrombosis among patients with cancer and to identify and discuss the various options for prophylaxis and treatment.

Epidemiology

VTE is a largely preventable disease and represents a leading cause of morbidity and mortality among patients with cancer.[1] The percentage of all cases of a disease in a population attributed to malignancy (population-attributable risk), has been studied with consistent results. In a population-based, nested case–control study in Olmsted County, Minnesota, 625 residents with new deep vein thrombosis (DVT) or pulmonary embolism (PE) were matched by age and gender to 625 unaffected residents. The population-attributable risk was 18% (95% CI: 13.4–22.6) for active malignancy.[2] In a cohort of 21,002 hospitalized patients with venous thrombosis from the California discharge data, cancer-associated thrombosis was reported in 20% (4368) of patients.[3] These results were comparable to the Worcester, Massachusetts metropolitan area where out of 1399 individuals with a confirmed episode of venous thrombosis, 29% had a recent or active neoplasm.[4] These results indicate that in the United States, approximately one of every five cases of VTE is cancer-associated. Globally, the estimates are the same. In the RIETE (Registro Informatizado de Enfermedad Thromboembolica) registry, an international registry of patients with VTE, active cancer was reported in 17% of 35,000 patients with symptomatic venous thrombosis from 2001 to 2011.[5] In Norway, the Tromsø study, a population-based prospective follow-up study of 26,000 patients from 1994 to 2007, 23% of patients had an active cancer among 467 patients with a first-ever venous thrombosis event.[6] In conclusion, there is robust evidence that 20–30% of all first VTE events are associated with malignancy.[2–8]

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Abundant data indicate that cancer is an independent risk factor for thrombosis. Patients with cancer have a four to sevenfold increased risk of VTE[9–12] which may be even higher depending on the cancer type.[9] In the Olmsted County population study, cancer showed a fourfold increased risk of venous thrombosis (odds ratio [OR] = 4.1, 95% CI: 1.9–8.5).[11] In the MEGA (multiple environmental and genetic assessment of risk factors for venous thrombosis) study, a Dutch population-based case–control study, the probability of venous thrombosis was seven times higher in patients with cancer (OR = 6.7, 95% CI: 5.2–8.6).[9] In the United Kingdom, a cohort study was done using data from the Clinical Practice Research Datalink, linked to Hospital Episode Statistics, Cancer Registry data and the Office for National Statistics. They found a relative risk (RR) of venous thrombosis in cancer patients of 4.7 [hazard ratio (HR) = 4.7, 95% CI: 4.5–4.9].[12] A Danish population-based cohort of 57,591 cancer cases revealed an adjusted relative risk of venous thrombosis that was 4.7 times higher in cancer patients (RR = 4.7, 95% CI: 4.3–5.1).[10] This study was adjusted for comorbid conditions including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, peptic ulcer disease, liver disease, renal disease, diabetes, obesity, acute pancreatitis, alcoholism, and hypertension.

Despite the robust association of cancer and thrombosis, better understanding of how to apply this association into planning prevention strategies hinges on description of the rate of VTE by cancer and cancer type.[13] The reported absolute risk (cumulative incidence) of venous thrombosis in cancer patients varies widely (1–8%).[2–6,9–12,14–25] By linkage of the California Cancer Registry to the California Patient Discharge Date Set of 235,149 patients from time of cancer diagnosis, only 1.6% (5032) of the patients developed VTE within 2 years.[18] Sallah et al.,[23] reported a cumulative incidence of venous thrombosis of 7.8% in 26 months in cancer patients referred to hematology/oncology services. In the Vienna CATS (cancer and thrombosis study) study, a prospective follow-up of 840 selected cancer patients showed that 8% of the cancer patients developed a VTE within 1 year after diagnosis or progression of disease.[25] In contrast, in the large PROTECHT (prophylaxis of thromboembolism during chemotherapy) study which included 1150 patients with cancer, and the SAVE-ONCO (semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer) which included 1608 cancer patients, the cumulative incidences of VTE were 3.9% and 3.4% despite being selected populations.[26,27] A recent meta-analysis described the incidence rates of venous thrombosis in cancer patients, stratified by background risk of venous thrombosis. Among cohorts with average-risk patients, defined as cancer patients representative of all patients with cancer, the incidence rate of venous thrombosis was estimated to be 13 per 1000 person-years (95% CI: 7–23) compared to 68 per 1000 (95% CI: 48–96) person-years among high-risk patients, defined as cancer patients with high-grade or metastatic disease or treated with therapeutic strategies that increase thromboembolic risk. Overall, the highest risk was observed among brain cancer and pancreatic cancer. In the abovementioned study with linkage of four United Kingdom databases, the incidence rate of venous thrombosis in all cancer was 13.9 per 1000 person-years (95% CI: 13.4–14.4).[12] The baseline stratification of additional risk factors among patients with cancer has a major impact on the probability of VTE. These patients must be stratified in order to accurately predict the risk of cancer-associated thrombosis.

An increasing frequency of VTE in cancer patients has been reported over the years.[12,13,20,28,29] Data from the US National Hospital Discharge Survey showed that the cumulative incidence of venous thrombosis increased from late 1980s onward (1.5% in 1989), and this trend continued to late 1990s (3.5% in 1999).[29] An increase of 28% was also observed in a study of hospital discharge data, where the cumulative incidence of venous thrombosis was 3.6% in 1995–1996 and 4.6% in 2002–2003.[20] Similar rates were observed in the linkage of four United Kingdom databases.[12] Several factors could explain this finding, including a greater awareness of the association between cancer and venous thrombosis, improvements in diagnostic testing, and more aged patients undergoing more cancer treatments. These facts indicate that the incidence of VTE is expected to rise further in the future.