The link between cancer and thrombosis is well established, with malignancy recognised as the most important individual risk factor for venous thromboembolism (VTE), especially in the first few months after diagnosis. In fact, the overall risk of venous thrombosis is increased seven-fold in cancer patients compared to persons without malignancy.

As cancer-associated thrombosis (CAT) is a complex and multifactorial event, some cancer patients are more at risk for developing deep vein thrombosis (DVT) or pulmonary embolism (PE) than other patients with cancer. A recent meta-analysis quotes the incidence of venous thrombosis in cancer patients ranging from 0.5% to 20%. The absolute risk may depend on several factors including the type of cancer, stage of disease, certain active therapies, hospitalisation, recent surgery, an indwelling central venous catheter, age, plus previous history of VTE.

Cancer type

Some cancers, particularly mucin-secreting adenocarcinoma of the ovary, pancreas, stomach, brain tumours and haematological malignancies, are associated with a higher risk of VTE. A recent UK study investigated the incidence rates of VTE separately for 24 cancer sites. While there was an absolute VTE rate in all cancers of 13.9 per 1,000 person–years, this varied greatly by cancer site; from 98 per 1,000 in pancreatic cancer to 3.1 per 1,000 in thyroid cancer.

The MEGA study – a population-based case-control study involving more than 3,200 patients – found that the greatest VTE risk was among patients with haematological malignancies (28-fold increased risk), lung cancer (22-fold), and gastrointestinal cancer (20-fold). Other research also found a widely varied VTE-risk rate among cancer types, ranging from 16 per 10,000 patients with head/neck cancer to 120 per 10,000 patients with ovarian cancer.

Cancer stage
Cancer-associated thrombosis also appears to be adversely influenced by the extent of the malignancy, with data indicating that advanced metastatic cancer places the patient at a higher risk for VTE. Risk-adjusted models have shown that metastatic disease at the time of diagnosis is the strongest predictor of VTE within the first year of diagnosis.

The MEGA study found that cancer patients with distant metastases had a 19.8-fold increased risk of CAT versus patients without distant metastases. Similarly, the risk for VTE recurrence may be higher in patients with more extensive disease: a nearly fivefold higher recurrence rate has been reported in patients with advanced disease compared with a two- to threefold higher risk in those with more localised tumours.

Active therapy

Cancer therapy itself has been shown to increase the risk for VTE, including chemotherapy, anti-angiogenic therapy, hormonal therapy, and erythropoietin-stimulating agents. The underlying mechanisms are poorly understood, but it has been suggested that many of these therapeutic agents induce vascular damage.

Chemotherapy can increase the risk of thrombosis by at least four mechanisms:

- Acute damage to vessel walls
- Non-acute damage to the endothelium
- A decrease in natural coagulation inhibitors (reduced level of C and S proteins or antithrombin III)
- Platelet activation

The annual incidence of venous thrombosis in patients receiving chemotherapy is estimated at 11% – climbing to 20% or higher depending on the type of drug or drugs being administered. In a population-based study identifying risk factors for VTE in the general population, the use of chemotherapy was associated with a 6.5-fold greater risk of VTE compared with a 4.1-fold risk in cancer patients not on chemotherapy.

Khorana et al found that the overall incidence of VTE was 1.93% in an ambulatory population starting a new chemotherapy (over a median follow-up period of 2.4 months). The rate observed in this study – about 0.8% per month – was significantly higher than the estimated 0.04% per month for the entire cancer population.

Hormonal therapy

Hormonal therapies, particularly tamoxifen and anastrozole, have been linked to an elevated risk of VTE among cancer patients. In a large study of over more than 9,000 patients with early-stage breast cancer, the incidence of VTE was 2.1% in the anastrozole group, 3.5% in
Studies in women with late-stage breast cancer found VTE rates up to 8% in those treated with tamoxifen and up to 6.7% among those treated with anastrozole.\textsuperscript{15}

**Antiangiogenic therapy**

Antiangiogenic agents such as thalidomide, lenalidomide and bevacizumab have been found to contribute to higher rates of thrombosis in cancer patients – an effect that is amplified by the co-administration of chemotherapy and steroids.\textsuperscript{16} A recent Italian study found that the combined use of an antiangiogenic plus a cytotoxic agent increased the risk of developing VTE in patients (8.9%) as compared to 3.5% of patients treated with other regimens.\textsuperscript{16}

**Erythropoietin-stimulating agents**

Erythropoiesis-stimulating agents such as erythropoietin and darbepoetin stimulate red blood cell production and are approved to reduce the number of blood transfusions required during chemotherapy;\textsuperscript{17} however, concerns have been raised about the risks of VTE.\textsuperscript{18} Hershman and colleagues recently confirmed that the use of erythropoiesis-stimulating agents was associated with an increased risk of VTE but not of mortality.\textsuperscript{19} VTE developed in 14.3% (1,796) of the 12,522 patients in the study who received erythropoiesis-stimulating agent, and in 9.8% (3,400) of the 34,820 patients who did not.\textsuperscript{19}

**Hospitalisation**

Hospitalisation – often associated with prolonged immobility – is a strong risk factor for cancer-associated thrombosis. In the hospitalised setting, the rate of VTE in cancer patients is twice that of non-cancer patients.\textsuperscript{20} Of note, among hospitalised cancer patients, those who develop VTE have a greater than 2-fold increased risk of death during their hospitalisation when compared with patients without VTE.\textsuperscript{21}

**Surgery and thrombosis**

Thrombosis is also a common complication of cancer-related surgery. The frequency of VTE in patients undergoing cancer surgery is roughly twice that seen in patients without malignancies who have similar operations.\textsuperscript{22} Higher rates of postoperative VTE are seen in patients undergoing abdominal surgery in comparison with urologic or gynaecologic surgeries. Postoperative VTE is the most common cause of death at 30 days following surgery, and is often a late complication of surgery, with 40% of events occurring more than 21 days after surgery.\textsuperscript{23}

In a study analysing the effect of surgery in patients with glioma who underwent invasive neurosurgery or brain biopsy, patients were 70% more likely to develop VTE within three months compared with cases that did not undergo surgery.\textsuperscript{24} In contrast, some studies did not show an increased risk of VTE associated with surgery in patients with cancer. For example, Blom et al did not find an elevated VTE risk associated with surgery in a large cohort of 66,329
cancer patients, however, as this data did not include any information about thromboprophylaxis, and it is not clear if this finding reflects aggressive peri-operative prophylaxis.

**Other Risk Factors**

**Central venous catheters**

Central venous catheters (CVC), commonly inserted for chemotherapy and hyperalimentation, are also associated with a risk of VTE. The incidence of CVC-related deep vein thrombosis (DVT) assessed by venography has been reported to vary from 30% to 60% but catheter-related DVT in adult patients is symptomatic in only 5% of cases.

The wide variability in the incidence of catheter-related thrombosis may be due to differences in catheter type, position, duration of insertion, type of malignancy, and use of different chemotherapeutic agents.

**Obesity as a risk factor**

Obesity is also an important risk factor for DVT/PE in both men and women. Studies have shown that obese individuals have nearly twice the risk of both PE and DVT, and obese patients less than 40 years of age have nearly a fivefold risk than those who are not obese.

The risk of development of PE is nearly six times higher among women with a BMI of 35 kg/m² or more.

The thrombotic risk in cancer patients is likely to be further increased because of concomitant non cancer-specific VTE risk factors such as advanced age and the presence of co-morbid conditions such as respiratory failure or congestive heart failure. For example, a UK study found that age significantly increased the risk of thrombosis VTE rate in cancer patients, from 4.9 per 1000 (person-years) for those under 30 years to 16.9 per 1,000 for patients over 80 years.

**Assessing risk of CAT**

The risk of CAT is not equal for all cancer patients or even in the same patient over time. As a result, risk factor assessment is an ongoing process throughout the course of care for the cancer patient. A simple model for predicting chemotherapy-associated VTE in ambulatory cancer patients, based on clinical and laboratory variables, was developed by Khorana et al. They identified five variables based on the site of cancer, pre-chemotherapy platelet and leukocyte count, haemoglobin level and body mass index. This model allows the physician to discriminate between ambulatory patients with low (score 0), intermediate (score 1 or 2) and high risk (score ≥3) of chemotherapy-associated thrombosis.

**CAT predictive model. Five variables:**

- Site of cancer - very high risk (stomach, pancreas: risk score (2), high risk (lung, lymphoma,
gynaecological, genitourinary: risk score (1) and low risk (breast, colorectal, head and neck: risk score (1)

- Pre-chemotherapy platelet count of $\geq 350 \times 10^9/l$ (risk score (1)
- Haemoglobin level <10 g/dl or use of erythropoiesis-stimulating agents, or both (risk score 1)
- Leukocyte count $>11 \times 10^9/l$ (risk score 1)
- Body mass index of $\geq 35$ kg/m² (risk score 1).

The Vienna Cancer and Thrombosis Study subsequently validated this model in another cohort of cancer patients and expanded it with two additional laboratory markers - soluble P-selectin ($\geq 53.1$ ng/ml = VTE risk score 1), and D-dimer ($\geq 1.44$ µg/ml = VTE risk score 1) - increasing the predictive value of estimating a patient's risk of CAT.³⁰

**Recurrent CAT risk**

Research has shown that patients who develop CAT are at higher risk for recurrent thromboembolic disease and death in comparison with non-cancer patients with VTE.³¹, ³⁶ In fact, the risk for recurrent thrombotic events is twice as high in cancer patients compared to those without cancer, and four times higher if patients are concurrently receiving chemotherapy.³¹ Another study found that the probability of readmission for recurrent VTE within 183 days was 22% for cancer patients compared with 6.5% for those without malignancy.⁶

**Post-thrombotic syndrome**

Approximately 30% of patients who develop DVT develop post-thrombotic syndrome (PTS), a chronic, potentially disabling condition with symptoms including debilitating leg pain, painful swelling and fibrosis.²² Post-thrombotic syndrome occurs between 2 and 10 years after the precipitating event. In severe cases, post-thrombotic syndrome may lead to painful leg ulcers that require long-term nursing care.

**Risk of death**

Since the mid-1990s, thrombosis has been a significant cause of death in cancer patients.³³, ³⁴ Patients with both malignancy and cancer have been shown to have a 94% probability of death at six months – more than twice the rate of death for patients with malignant disease alone and nearly three times the rate for patients with VTE and non-malignant disease.⁶

Pulmonary embolism (PE) is the cause of death in one in every seven hospitalised cancer patients. Of patients who die from a PE, 60% have localised cancer or limited metastatic disease, which would otherwise have allowed for reasonably long survival in the absence of a fatal PE.³⁵ Venous thromboembolism is also responsible for nearly half (46.3%) of all deaths following cancer surgery.²³
References


