



Jacky Tiplady. *Terry's Creek*. Photograph.

*Patients with cancer are at high risk for venous thromboembolism so surveillance and monitoring for this complication are keys to good oncologic practice.*

# Cancer and Venous Thromboembolism: Scope of the Problem

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## Introduction

Venous thromboembolism (VTE), especially pulmonary embolism (PE), is a complication of concern for cancer patients and hematology/oncology practitioners.<sup>1,2</sup> Thrombosis is now recognized as one of the most common complications faced by cancer patients and hematologists/oncologists, related to the cancer itself as well as the various therapies and interventions for treating cancer. Of all new VTE events, approximately 20% are associated with active malignancy.<sup>3</sup> It is notable that patients with cancer have a 4- to 6-fold higher risk for VTE compared with noncancer patients.<sup>4</sup> Hospitalization for a VTE occurs more commonly in cancer patients than in noncancer patients.<sup>5</sup> Even more significant is the fact that cancer patients who have a thrombotic event — com-

pared with cancer patients who do not have a thrombotic event — experience reduced survival.<sup>5,6</sup>

The seriousness of VTE as a complication in cancer patients is becoming recognized as an important medical issue. That recognition is evidenced in the 2004 publication of *The American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines*.<sup>7,8</sup> The guidelines reflect the growing body of literature with respect to the increased risk of VTE in cancer patients. With greater attention being given to VTE in the cancer setting, there arises a need for broader understanding of VTE pathophysiology, epidemiology, and diagnosis among cancer patients, topics that are the subjects of this review.

## Pathophysiology

There are numerous hypotheses concerning the causal relationship between active cancer and the development of VTE. The hypercoagulable state associated with active cancer involves many complex, interdependent mechanisms (Fig 1).<sup>9-11</sup> Activation of the coagulation system is manifest in some patients by an increased plasma fibrin D-dimer and a positive soluble fibrin monomer complex, indicative of intravascular coagulation and fibrinolysis/disseminated intravascular coagulation. However, evaluations

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*Abbreviations used in this paper:* VTE = venous thromboembolism, PE = pulmonary embolism, TF = tissue factor, CP = cancer procoagulant, DVT = deep vein thrombosis.

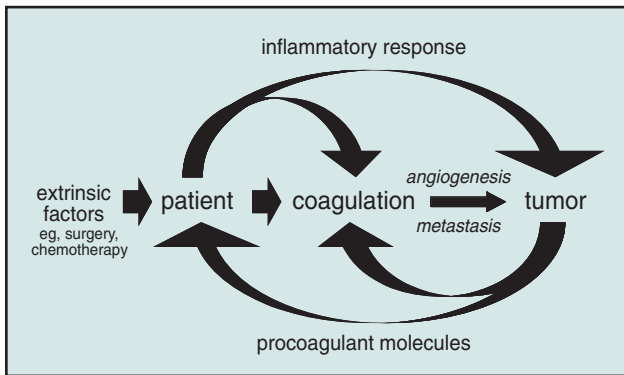


Fig 1. — Mechanisms of thrombogenesis in patients with cancer. Multiple and interdependent processes between the tumor and the patient act to promote a hypercoagulable state.

of cancer patients with VTE show that these laboratory findings are relatively uncommon.<sup>12</sup>

There is increasing evidence that dysregulated cancer cells can produce tissue factor (TF) and a cancer procoagulant (CP), which activate the coagulation system (Fig 2).<sup>15</sup> TF is expressed by many solid tumor cells, leukemia blast cells, tumor-associated macrophages, and endothelial cells.

TF expression is upregulated in response to cytokines.<sup>11</sup> In addition to hemostasis, TF plays a role in cellular signaling, resulting in angiogenesis, tumor growth, and the metastatic potential of some cancers.<sup>14-16</sup> CP is found only on malignant cells. Although the protein sequence and cDNA encoding CP is not clear, CP is likely a cysteine protease that directly activates factor X in the absence of factor VIIa.<sup>17</sup> According to recent evidence, in a mechanism similar to thrombin, CP can induce dose-dependent platelet activation. The expression of CP by acute promyelocytic leukemia blasts parallels their degree of malignant transformation and response to all-*trans*-retinoic acid.<sup>18</sup> Procoagulant activity is enhanced in multiple ways. First, it is enhanced as tumor cells release inflammatory cytokines and chemokines such as tissue necrosis factor- $\alpha$ , interleukin-1, and vascular endothelial growth factor. In turn, these act on leukocytes and endothelial cells to synthesize and express TF as well as a number of other cell adhesion molecules that might predispose or promote venous thrombosis.<sup>11</sup>

In addition, VTE may occur in active cancer patients due to intraluminal or external obstruction of veins.

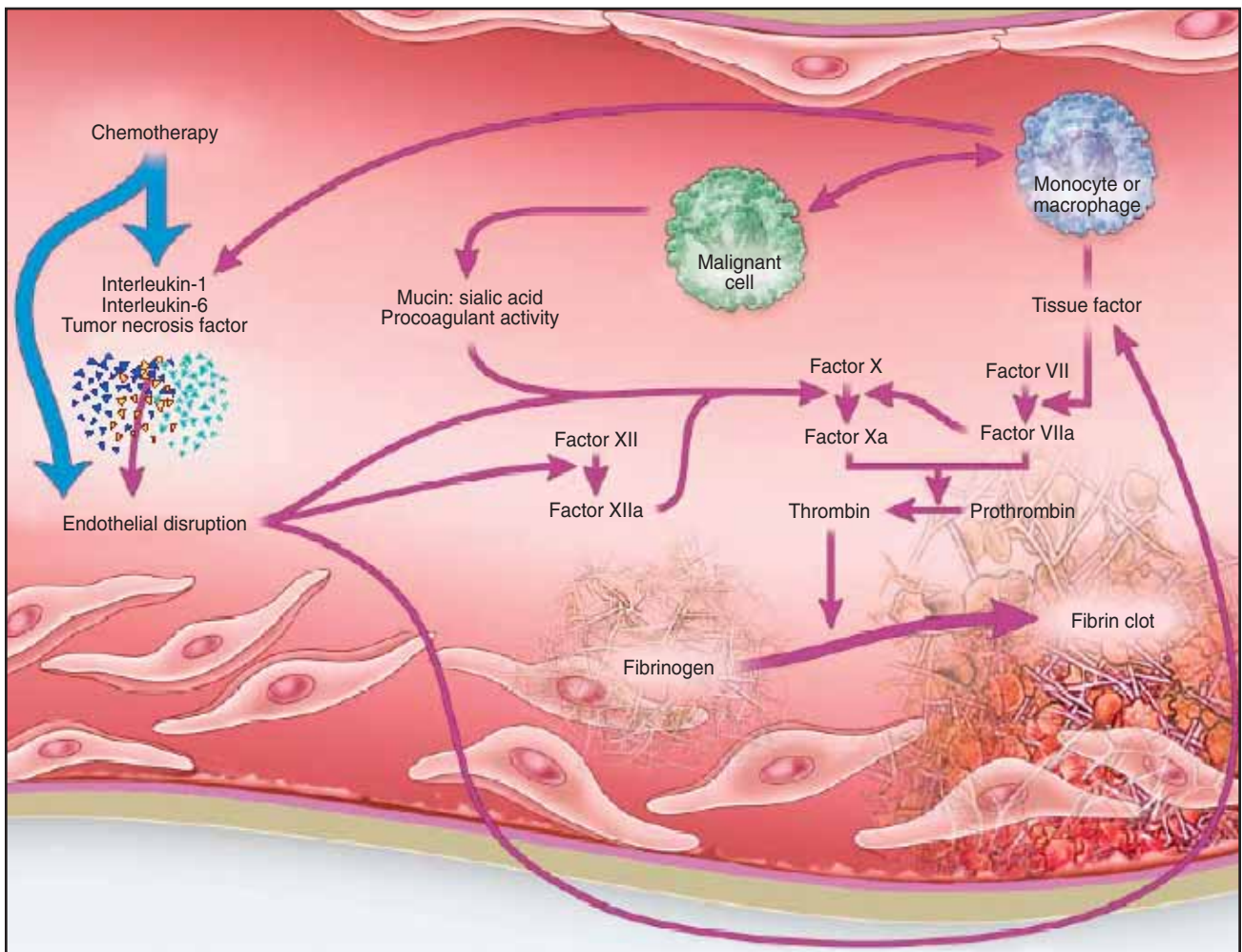


Fig 2. — Mechanisms of thrombosis in cancer. From Bick RL. Cancer-associated thrombosis. *N Engl J Med.* 2003;349:109-110. Copyright © 2003 Massachusetts Medical Society. All rights reserved.

Internally, this may be due to cancer metastasis or growth within a vein. Tumors may also cause venous stasis or venous outflow obstruction by external compression of the vein.<sup>19</sup>

## Epidemiology

The overall incidence of VTE in the general population is 117 per 100,000 person-years. The incidence of deep vein thrombosis (DVT) and PE are 48 and 69 per 100,000 person-years, respectively. Incidence rates for both DVT and PE increase dramatically with advancing age among both men and women. Incidence rates are higher in women during their childbearing years and in men older than 45 years of age. Overall, men are at a greater risk of developing a VTE, with an age-adjusted male-to-female ratio of 1.2:1. The incidence of VTE is not much different since the 1980s, despite extensive efforts to better identify patients at risk, increase the utilization of prophylaxis, and develop more effective prophylactic drugs and drug regimens.<sup>20</sup>

Survival after VTE is lower than expected in cancer patients. For about one quarter of all PE patients, the initial clinical manifestation is sudden death.<sup>21</sup> Consequently, there is often insufficient time to recognize, diagnose, and treat patients presenting with PE. Survival among active cancer patients with VTE differs by gender. Women with active cancer who are not receiving chemotherapy have a 7-fold increased risk of death within 7 days after a VTE (odds ratio [OR] 7.04, 95% confidence interval [CI] 4.26-11.63). In contrast, men with active cancer who are not receiving chemotherapy have only a little more than a 2-fold increased risk (OR 2.38, 95% CI 1.47-3.86). The risk of death within 7 days post-VTE for men and women who have active cancer and are receiving chemotherapy changes radically: for women the risk increases 4-fold, and for men the risk increases to more than 8-fold. In general, the risk of death post-VTE is increased about 2- to 8-fold depending on gender and presence or absence of chemotherapy.<sup>22</sup>

Active cancer has also been observed as an independent predictor of recurrent VTE.<sup>21</sup> Rehospitalization with a recurrent VTE was significantly higher among Medicare patients with active cancer compared to noncancer patients with a VTE or cancer patients without a VTE (cumulative probabilities: cancer patients with VTE, 0.22; cancer patients without VTE, 0.14; noncancer patients with VTE, 0.06;  $P < .0001$ ).<sup>5</sup> Other independent predictors of VTE recurrence included increasing patient age and body mass index, as well as and chronic neurologic disease with extremity paresis.<sup>21</sup>

In addition to reduced survival and VTE recurrence, long-term complications of VTE include venous stasis syndrome and venous ulcer, which occur in almost 30% of DVT patients.<sup>23</sup> These complications are essentially incurable and can be extremely difficult to treat.

## Risk Factors

To improve survival and prevent recurrence and complications, the incidence of VTE must be decreased. The best way to decrease the incidence of VTE is to identify patients who are at greatest risk and either modify risk or provide prophylaxis. Table 1 summarizes the attributable contribution of independent risk factors for the development of VTE.<sup>3</sup> Active cancer is a major risk factor for the development of VTE, accounting for almost one fifth of all VTE occurring in the community.

The risk of VTE among cancer patients is compounded by exposure to other independent VTE risk factors. For example, cancer patients undergoing surgery have twice the risk of postoperative VTE and three times the likelihood of experiencing a fatal PE compared to noncancer patients.<sup>7,24</sup> An analysis of a large administrative database evaluating 1,653,275 surgical cases finds that VTE occurred in 13,533 cases (0.8%), with PE occurring in 5,049 (37% of all VTE). The presence of a malignancy is a predictor of VTE (OR 1.7, 95% CI 1.6-1.8). This unique study allows categorization of different surgeries as low, intermediate, high, and very high risk for VTE.<sup>24</sup> The risk of VTE formation is based on the type of surgery, patient age, type of anesthesia, and general perioperative care, including mobility, fluid status, and transfusions.<sup>7</sup> The surgical cancer patient has two of the primary mediating factors that compose the triad of pathogenic conditions for VTE: hypercoagulable states and vascular endothelium injury, with the third factor being venous stasis.<sup>25</sup>

A 6-fold increase in upper-extremity VTE occurs in patients with a central venous catheter (CVC) or transvenous pacemaker (OR 6.5, 95% CI 1.6-19.6).<sup>4</sup> Cancer patients often require placement of a CVC for administration of chemotherapy and/or blood sample collection. Although a CVC is the most common cause of an upper-extremity DVT, the incidence of CVC-associated upper-extremity DVT is relatively low at 1.14 per 1,000 catheter days.<sup>26</sup>

In an early study, Bern et al<sup>27</sup> found that warfarin

**Table 1. — Independent Risk Factors for Developing a VTE**

Baseline Characteristic	Attributable Risk (%)*
Hospitalization or nursing home confinement	61.2
Hospitalization with surgery	24.2
Hospitalization without surgery	22.5
Nursing home confinement	14.4
Active malignant neoplasm	19.8
Malignancy without chemotherapy	6.8
Malignancy with chemotherapy	13.0
Trauma	12.5
Congestive heart failure	11.8
Prior central venous catheter or pacemaker	10.5
Neurologic disease with extremity paresis	8.2
Varicose vein/vein stripping	6.0
Prior superficial vein thrombosis	4.3

\* Adjusted for age, sex, and year.

(Coumadin®, Bristol-Myers Squibb Co, New York, NY) 1 mg daily was effective for the prevention of CVC-associated VTE in cancer patients. However, subsequent studies have clearly demonstrated that low-dose warfarin is ineffective in preventing VTE and some patients develop significant prolongation of their prothrombin time.<sup>28,29</sup> A number of well-designed studies also have found that low-molecular-weight-heparin prophylaxis also is ineffective.<sup>30,31</sup> Therefore, the most recent ACCP guidelines have not recommended prophylaxis for patients with CVCs, including cancer patients.<sup>7</sup>

Although the risk of VTE is increased among cancer patients, the actual incidence (“absolute risk”) is relatively low — 0.6% according to one study.<sup>5</sup> Cancer patients, due to the very nature of their disease processes, may be at increased risk for bleeding complications associated with anticoagulant-based prophylaxis. Therefore, universal prophylaxis is not feasible in this patient population. Additional research is focusing upon correlating tumor type or therapeutic intervention and risk of VTE.

## Tumor Type

The risk of VTE among cancer patients has been observed to vary by tumor type. Patients with cancer of the brain, ovary, pancreas, colon, stomach, lung, and kidney have been considered as at highest risk for VTE.<sup>5,32,33</sup> In a study of hospitalized Medicare patients, the highest incidence of VTE occurred among women with ovarian cancer, followed by patients with cancer of the brain and pancreas, lymphoma, cancer of the stomach and kidney, leukemia, and cancers of the colon, liver, rectum, lung and prostate.<sup>5</sup> However, in a population-based study of Olmsted County, Minnesota,

active cancer patients with an incident VTE over a 7-year period (1991 to 1997), the relative risk of VTE by tumor type was substantially different.<sup>34</sup> In this study, the observed tumor type frequency among VTE patients was compared to the expected frequency based on patient age and gender and derived from the Surveillance, Epidemiology and End Result (SEER) national cancer database. The relative risk of VTE for pancreatic cancer, lymphoma, and brain cancer was greater than 25, while the VTE risk associated with cancer of the ovary, stomach, kidney, colon, rectum, and lung was much lower, albeit still increased compared with persons without cancer. Table 2 compares the incidence or relative risk of VTE stratified by tumor type from three reports.<sup>5,33,34</sup>

Thodiyil et al<sup>33</sup> utilized the same data set as Levitan et al<sup>5</sup> used but with further analysis to calculate relative risk by tumor site. The differences noted likely reflect differences in study design and study populations. Patients with high-grade glioma who have extremity paresis are at especially high risk.<sup>35</sup> The effect of tumor histology, stage, and site of invasion or metastases on individual VTE risk currently is unknown.

## Intervention

Cancer patients receiving cytotoxic or immunosuppressive chemotherapy have a 6.5-fold increased risk for VTE. The mechanism for the increased risk of VTE with chemotherapy is not well defined; however, many chemotherapeutic agents induce vascular damage.<sup>13</sup> L-asparaginase (Elspar®, Merck & Co, West Point, PA) is also associated with an increase of VTE, presumably because of reduced hepatic synthesis of the natural anticoagulant proteins (eg, antithrombin).<sup>36,37</sup>

Table 2. — Incidence or Relative Risk of Venous Thromboembolism by Tumor Type

Levitan et al <sup>5</sup> Administrative Data Set, Medicare, Hospitalized Patients		Thodiyil et al <sup>33</sup> Administrative Data Set, Medicare, Hospitalized Patients		Heit et al <sup>34</sup> Population-Based	
Cancer Type	Incidence*	Cancer Type	Relative Risk	Cancer Type	Relative Risk
Ovary	120	Uterus	3.40	Pancreatic, lymphoma, brain	>25
Brain	117	Brain	2.37		
Pancreas	110	Leukemia	2.18	Liver, leukemia, other gastrointestinal	>17
Lymphoma	98	Ovary	2.16	(esophagus, gallbladder, small intestine, other biliary), other gynecological (cervical)	
Stomach	85	Pancreas	2.05		
Renal	84	Lymphoma	1.80	Breast, colorectal, lung, prostate	9<RR<12
Leukemia	81	Stomach	1.49		
Colon	76	Renal	1.41		
Liver	69	Colon	1.36		
Rectal	62	Lung	1.13		
Lung	61	Rectum	1.11		
Prostate	55	Prostate	0.98		
Cervix	49	Liver	0.92		
Uterus	44	Cervix	0.90		
Esophagus	43	Esophagus	0.76		
Breast	22	Breast	0.44		
Bladder	22	Bladder	0.42		
Head/neck	16	Head/neck	0.29		

\* Incidence per 10,000 person-years.

Women who are treated with tamoxifen for breast cancer have a 2- to 5-fold increased risk of VTE.<sup>38</sup> The risk of VTE becomes even greater after menopause and when chemotherapy is combined with tamoxifen (generic, multiple manufacturers).<sup>38,39</sup>

An additional concern has been raised with regard to VTE and cancer patients who are receiving erythropoietin — either epoetin alfa (Procrit®, Ortho Biotech LP, Raritan, NJ; Epogen®, Amgen Inc, Thousand Oaks, CA) or darbepoetin (Aranesp®, Amgen Inc, Thousand Oaks, CA). In one trial, patients with cervical cancer receiving chemoradiotherapy and epoetin alfa had a 10-fold increased risk (OR 10.3, 95% CI 2.3–46.2) of developing a VTE compared with patients with cervical cancer who were receiving chemoradiotherapy and no epoetin alfa.<sup>40</sup> Similarly, the incidence of VTE in patients receiving chemotherapy and darbepoetin was 6.2% compared with 4.1% in patients receiving chemotherapy and placebo.

It is believed that there is a synergistic relationship in the formation of VTE with the concurrent use of chemotherapeutic and radiation modalities associated with specific types of cancers and the use of erythropoietin. Erythropoietin results in increased reticulocytosis, increased platelet reactivity, and endothelial activation. More studies are needed to evaluate the VTE risk of erythropoietin therapy in specific types of cancer patients receiving a variety of other treatment modalities. Erythropoietin may be an independent risk factor for VTE in cancer patients.<sup>40</sup>

## Diagnostic Features

Cancer patients presenting with signs and/or symptoms suggestive of acute DVT or acute PE should undergo objective diagnostic testing. For most patients, the current standard of care warrants a venous compression duplex ultrasound as the initial diagnostic test for a suspected acute DVT. There are exceptions, such as with isolated pelvic vein thrombosis associated with pelvic cancer. Because the iliac veins dive deep in the pelvis, iliac vein thrombosis (especially internal iliac vein thrombosis) often cannot be imaged with venous duplex ultrasound. Moreover, contrast venography may also be inadequate for imaging pelvic vein thrombosis. In these cases, computed tomography (CT) scan with contrast or magnetic resonance venography (MRV) may be required.<sup>41</sup>

With regard to PE, ventilation/perfusion (V/Q) lung scanning has been largely replaced by high-resolution CT angiography for several reasons. First, CT angiography is sufficiently sensitive to diagnose most PEs that are at the segmental pulmonary artery level or larger in size. CT angiography may not be quite as sensitive for smaller PEs. In that circumstance, pulmonary angiography may be a better choice. Second, CT angiography can more often make an alternative diagnosis, which is particularly com-

mon among cancer patients. This approach is important, considering how often cancer may metastasize to the lung or be associated with mediastinal lymphadenopathy or malignant pleural effusions, all of which can make a diagnosis of PE by lung scanning difficult.<sup>41,42</sup>

Although tumor embolism is uncommon, hematologists/oncologists should always be alert to the possibility of tumor embolism as opposed to thromboembolism. Tumor embolism may be difficult to distinguish from thromboembolism by standard diagnostic imaging. Moreover, tumor and thromboembolism often occur concomitantly. Tumor embolism most often occurs in patients with renal cell carcinoma or pelvic or leg sarcoma.<sup>43</sup>

The plasma fibrin D-dimer level may be useful in excluding VTE. The operating characteristics (eg, sensitivity and specificity) of the D-dimer depend on the assay method, the duration of symptoms, and possibly the presence of heparin therapy. In general, a quantitative assay that uses either an enzyme-linked immunosorbent assay (ELISA) or a latex immunoassay (LIA) is more sensitive and preferable, for example, to a semiquantitative assay, such as a latex agglutination. If the patient has had symptoms for quite some time or has received heparin therapy, the sensitivity of the D-dimer may be reduced.<sup>44</sup> The D-dimer is best used in patients with acute symptoms, particularly outpatients.<sup>45</sup> Frequently, the D-dimer will be positive among inpatients because they have had other procedures, such as surgery or biopsies, that will cause the D-dimer to be increased independent of VTE.<sup>46</sup> The negative predictive value of the D-dimer is dependent on the pretest probability (prevalence) of VTE. Because the prevalence of VTE among cancer patients is increased, the D-dimer negative predictive value is lower for cancer patients and may be insufficient to exclude a diagnosis of VTE with sufficient diagnostic certainty. Plasma D-dimer is still potentially useful for cancer patients if one observes the caveats discussed.<sup>12,45,47,48</sup>

Numerous reports and studies have evaluated the utility of performing extensive diagnostic testing — particularly imaging studies — of patients with idiopathic or recurrent VTE that have looked for evidence of occult cancer.<sup>49-52</sup> In general, these studies have found that the prevalence of occult cancer among those patients was somewhat increased, but finding the occult cancer appears to have no effect on survival, probably because therapy for those cancers was such that survival was not improved.

The current recommendations are that these patients should undergo a standard history, physical examination, and standard health maintenance studies that would be indicated for the patient's age. For example, smokers would receive chest radiography. Among adult women, mammography would be appropriate. Otherwise, extensive screening studies are not useful. It should also be noted that for both men and women of appropriate age, colon screening and evaluation — whether colonoscopy or some other screening evaluation — are appropriate.

## Conclusions

Among active cancer patients, VTE is a common and potentially lethal disease. Where possible, cancer patients exposed to other VTE risk factors (eg, surgery, trauma, hospitalization for acute medical illness) should receive appropriate VTE prophylaxis. However, despite a great deal of effort, the incidence of VTE remains unchanged. Additional studies are needed to identify independent risk factors for VTE among active cancer patients and estimate the magnitude of risk for each. With such information, physicians can stratify cancer patients into higher or lower risk for VTE, and target VTE prophylaxis to those high-risk patients who would benefit most.

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