Neoplasia • Vol. 4, No. 6, 2002, pp. 465–473

www.nature.com/neo

The Hypercoagulable State of Malignancy: Pathogenesis and Current Debate[1]

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Abstract

A hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate the coagulation system. It has been estimated that hypercoagulation accounts for a significant percentage of mortality and morbidity in cancer patients. Prothrombotic factors in cancer include the ability of tumor cells to produce and secrete procoagulant/fibrinolytic substances and inflammatory cytokines, and the physical interaction between tumor cell and blood (monocytes, platelets, neutrophils) or vascular cells. Other mechanisms of thrombus promotion in malignancy include nonspecific factors such as the generation of acute phase reactants and necrosis (i.e., inflammation), abnormal protein metabolism (i.e., paraproteinemia), and hemodynamic compromise (i.e., stasis). In addition, anticancer therapy (i.e., surgery/chemotherapy/hormone therapy) may significantly increase the risk of thromboembolic events by similar mechanisms, e.g., procoagulant release, endothelial damage, or stimulation of tissue factor production by host cells. However, not all of the mechanisms for the production of a hypercoagulable state of cancer are entirely understood. In this review, we attempt to describe what is currently accepted about the pathophysiology of the hypercoagulable state of cancer. We also discuss whether or not to screen patients with idiopathic deep venous thrombosis for an underlying malignancy, and whether this would be beneficial to patients. It is hoped that a better understanding of these mechanisms will ultimately lead to the development of more targeted treatment to prevent thromboembolic complications in cancer patients. It is also hoped that antithrombotic strategies may also have a positive effect on the process of tumor growth and dissemination.

Neoplasia (2002) **4,** 465–473 doi:10.1038/sj.neo.7900263

Keywords: cancer, cancer therapy, hypercoagulation, procoagulants, thrombosis.

Introduction

There is considerable evidence that thrombosis is a common complication of malignancy, and represents the second most frequent cause of death in cancer patients [1,2]. Postmortem studies have identified an increased incidence of thromboembolic deaths in cancer, in particular in patients who died of mucinous carcinoma of the pancreas, lung, and gastrointestinal tract [3]. Alternatively, cancer patients represent 20% of all patients in whom deep venous thrombosis (DVT) and pulmonary embolism (PE) are diagnosed.

The close relationship between the coagulation cascade and thrombosis has been suggested by numerous studies [4–12] (Table 1). Clinically detectable venous thromboembolism (VTE) is present in 15% of all cancer patients, and the number is likely to be even higher when subclinical thromboembolism (TE) is taken into account [13,14]. There is evidence that certain cancers are more likely to be prothrombotic, and this is likely to be influenced by disease staging, bedrest, as well as therapeutic intervention. One study found evidence of TE in 5% to 10% of patients with breast cancer undergoing adjuvant chemotherapy and up to 15% of those with metastatic disease [14]. Recurrent TE is also twice as likely in patients with cancer, even when established on oral anticoagulant therapy [15,16]. These patients also tend to require longer hospitalization, respond less well to oral anticoagulant therapy, and have a poorer prognosis after their first episode of VTE.

However, even in the absence of obvious thrombosis, cancer patients with solid tumors and leukemias commonly present with abnormal laboratory coagulation tests, characterized by varying degrees of clotting activation, indicating a subclinical hypercoagulable condition [17–19].

The purpose of this review is to outline our knowledge about the interactions between the hemostatic system and malignancy, and to review the pathogenetic mechanisms of the increased thrombotic tendency associated with cancer.

Clinical Manifestations and Epidemiology

Thromboembolic disease is often one of the earliest clinical signs of an underlying malignancy. In 1865, Trousseau [20] first noted that "in cancer a special condition of the blood

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[1]This work is dedicated to the late Lilian Agnes Caine.

Received 18 April 2002; Accepted 14 May 2002.

Table 1. Examples of Studies Demonstrating a Relationship between Cancer and Thrombosis.

• Fibrin deposited in and around tumor cells of patients with small cell carcinoma of the lung, and breast and renal cell cancer [4]
• Prolonged survival rate of patients with small cell lung cancer who received warfarin [5,6]
• Lower mortality rates in cancer patients who receive unfractionated or low-molecular-weight heparin [7–10]
• Reduced angiogenesis and tumor invasion in patients treated with heparin [11,12].

predisposed to spontaneous coagulation even in the absence of inflammatory reactions.'' Clinical manifestations can range from abnormal coagulation tests in the absence of symptoms to overt, clinically defined VTE, normally associated with primary solid tumor growth, and disseminated intravascular coagulation (DIC), more common in patients with hematological cancers and metastatic disease [21,22]. Severe DIC with life-threatening hemorrhagic complications is usually caused by the large consumption of clotting factors and platelets, and is thought to be responsible for 10% to 20% of early fatal events in acute leukemia [23].

DVT and PE are the two most common thromboembolic complications in cancer. The risk of lower extremity DVT is about twice that of noncancer patients after abdominal surgery, and the risk of fatal PE postoperatively is even increased four-fold in cancer patients [24–26].

DVT of the upper extremities is associated with specific risk factors: axillary lymphomas, mediastinal tumor masses, central venous catheters, and intravenous chemotherapy. Upper extremity DVT is frequently complicated by PE (8–36%) and chronic venous insufficiency (20–50%). DVT of the upper extremity, if untreated, may lead to central venous thrombosis and clinical superior vena cava syndrome [27].

Trousseau's syndrome is a rare variant of VTE that is characterized by recurrent, migratory thrombosis in superficial veins and in uncommon sites, such as the chest wall and arms. This syndrome is particularly associated with pancreatic and lung cancer [28].

Hepatic vein thrombosis (Budd–Chiari syndrome) with rapid development of ascites and hepatomegaly is specifically seen in patients with myeloproliferative syndromes, or in patients with a hepatocellular carcinoma [29].

Marantic endocarditis is characterized by the presence of sterile, thrombotic vegetations on cardiac valves. This rare syndrome is complicated by arterial emboli, leading to stroke and myocardial infarction [28]. Marantic endocarditis is associated with lung cancer and mucin-producing adenocarcinoma [28,29].

Up to 15% of cancer patients presents with VTE throughout the progression of the disease [28,29]. Interestingly, VTE is not equally common in all types of cancer. The highest incidence is found in mucin-producing adenocarcinomas, pancreas and gastrointestinal tract, lung cancer, and ovarian cancer. TE occurs less often in breast and renal cell carcinoma and rarely in patients with prostate cancer, melanoma, and cancer of unknown primary origin [3,28,29] (Table 2).

Table 2. Estimated Prevalence of VTE during the Course of Common Types of Cancer.

Cancer Site	Prevalence (%)
All malignancies	10–15
Pancreas	28
Lung	27
Stomach	13
Colon	3
Breast premenopausal	1–2
Breast postmenopausal	3–8
Prostate	2
Unknown primary tumor	1

Prothrombotic Mechanisms

Several factors involved in the immune response to neoplasia, such as the development of acute phase reactants, abnormal protein metabolism, necrosis, and hemodynamic rearrangements, can all contribute to the overall activation of blood coagulation in cancer patients. However, a prominent role is attributed to tumor-specific prothrombotic mechanisms, which include a number of tumor cell properties. Malignant cells can interact with the hemostatic system in multiple ways, but the two principal categories of interaction are: 1) the capacity to produce and release procoagulant and fibrinolytic activities, as well as inflammatory cytokines; and 2) direct interaction with other blood cells, i.e., endothelial cells, platelets, and monocytes. The principle modes of interaction are summarized in Table 3. We will now consider each of these mechanisms in more detail.

Procoagulant Activity (PCA)

Procoagulant properties of tumor cells enable them to promote the formation of fibrin deposits at sites of extravasation and in the tumor microenvironment at an extracellular level [30,31]. The best-characterized procoagulants are tissue factor (TF) and cancer procoagulant (CP).

Table 3. Prothrombotic Properties of Tumor Cells.

Property	
Procoagulant activity	Production of • TF • CP • FV receptor
Fibrinolytic activity	Expression of • u-PAR • u-PA • t-PA • PAI-1 • PAI-2
Cytokine release	Release of • IL-1β • TNF-α • VEGF
Cell–cell interactions	Interaction with • Endothelial cells • Monocytes–macrophages • Platelets

Tissue Factor TF is a 47-kDa transmembrane glycoprotein that forms a complex with factor VII (FVII)/FVIIa. This TF/FVII complex initiates blood coagulation by proteolytically activating FIX and FX [32,33]. TF is the cellular procoagulant expressed in normal resting cells, including endothelial cells and monocytes–macrophages. However, these cells do not express TF under normal resting conditions, TF is produced in response to proinflammatory stimuli, i.e., the cytokines IL-1β, TNF-α, and bacterial endotoxins [33,34]. However, in contrast to normal cells, malignant cells express TF constitutively and thus have constant PCA.

Cancer Procoagulant CP is a cysteine protease of 68 kDa with an isoelectric point (p*I*) of 4.8, containing 674 amino acids and no detectable carbohydrate. The only known physiological substrate for CP is coagulation FX [35,36]. CP can activate FX independently of FVII and cleaves the FX heavy chain at a different site compared with other known FX activators [35,36]. CP has been detected in extracts of tumor cells and in amnion–chorion tissues, but not in extracts of normal cells [37–41]. CP antigen, measured by enzyme-linked immunosorbent assay (ELISA), has been shown to be elevated in 85% of cancer patient subjects [42]. These findings also correlate with the PCA of CP in cancer patients [43]. The presence of TF and CP has been shown in several human and animal tumor tissues [44].

Fibrinolytic molecules Tumor cells can express everything required for regulation of the fibrinolytic pathway on their cell surface. They possess both the urokinase-type (u-PA) and the tissue-type plasminogen activator (t-PA) and can also produce plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2) [45]. Among activators, u-PA is the most widely expressed within cancerous lesions [46]. Indeed, tumor cells are known to carry the specific PA receptors (u-PAR) on their membranes, which can facilitate the activation of the fibrinolytic system [47]. These receptor-mediated events are presumed to play an important role in the pathogenesis of the bleeding symptoms in some patients with leukemia [23]. In addition to their role in hemostasis, recent data strongly suggest that the delicate balance between plasminogen activators and their inhibitors plays a role in tumor invasion, tumor cell progression, and metastasis. Levels of one or more of these markers have been recognized as predictors of disease-free interval and long-term survival in some patients with malignant disease [45].

Cytokines Tumor cells produce and secrete a number of different proinflammatory cytokines [48,49], some of which can adversely affect the normal anticoagulant system in the vascular endothelium. For example, TNF-α and IL-1β (as well as bacterial endotoxins) can induce the expression of TF by vascular endothelial cells (VECs) [50,51] and downregulate the expression of thrombomodulin (TM), the surface receptor for thrombin [52]. A drop in TM thrombin levels leads to reduced activation of the protein C system, which is one of the main anticoagulant defense systems. In addition to the upregulation of TF, this can cause a conversion of a normal endothelium to a prothrombotic endothelium [53].

The release of vascular endothelial growth factor (VEGF) by tumor cells may account for the increased microvascular permeability found in a wide variety of tumors [54,55], and is considered to play a role in tumor angiogenesis [55]. VEGF induces separation of VEC in the postcapillary venules, is a selective mitogen, and is a chemotactic factor for cultured VECs [56]. In addition to VECs, VEGF is chemotactic for macrophages and induces a number of genes in these cells, including TF [56]. IL-8 is also a potent proangiogenic cytokine elaborated by a number of cells, including VECs. Recent data shows that cross-linked fibrin (XLF), formed on the surface of VECs in tissue culture, can upregulate the IL-8 gene and induce the synthesis and release of increasing concentrations of functional IL-8 in endothelial cells in a dose-dependant manner [57]. This would suggest that blood coagulation reactions can contribute to induction of new vessel formation by more than one pathway. Thus, the regulation of VEGF synthesis by TF in tumor cells and the regulation of IL-8 synthesis by XLF binding to receptors on the surface of VECs could provide a potentially important link in cancer patients among activation of coagulation, the inflammatory cytokine cascade, clinical VTE, angiogenesis, and the growth and metastasis of malignant tumors [58–64].

Angiogenesis Several recent findings suggest a link between tumor angiogenesis and the hypercoagulable state in malignancy [65–68]. For example, the presence of TF expression in the vascular endothelium of breast cancer tissue was shown to strongly correlate with the initiation of angiogenesis [65]. TF expression has also been shown to correlate positively with microvessel density and expression of the angiogenic modulator, VEGF [67]. Animal models suggest that the way in which TF and angiogenesis interact may include the regulation of growth regulatory molecules of the endothelium, a mechanism distinct from TF-mediated activation of coagulation mechanisms [68]. Interestingly, VEGF induces hyperpermeability by a direct action on the endothelium [69] and (unlike basic fibroblast growth factor) promotes platelet activation and adhesion [70] *in vitro*.

Tumor Cell–Host Cell Interactions

Endothelium Tumor cells can interact with the vascular endothelium by both direct and indirect mechanisms. Indirect mechanisms include those that are induced by inflammatory cytokines synthesized and released by tumor cells (as previously described), which suppress the antithrombotic state and enhance the prothrombotic state of endothelial cells. Direct mechanisms include those that are affected by

the direct interaction of tumor cells adhering to the endothelium and/or the extracellular matrix through membrane adhesion molecules [71,72]. Malignant cells attached to the vessel wall may play a major role in promoting localized clotting activation and thrombus formation by the release of cytokines, and the subsequent adhesion of other cells, including leukocytes and platelets. The adhesion of tumor cells to each other or to vascular cells may also facilitate cell migration and extravasation [73]. In addition, the overexpression of EC TF may have major implications in tumor angiogenesis [65].

Platelets Patients with advanced cancer have been shown to exhibit increased platelet activation, also indicated by increased platelet turnover and decreased platelet survival time [74–80]. Laboratory studies have shown that mitogenic cell extracts, cell membrane fragments, and secreted chemicals from various animal and human cancers can directly aggregate platelets, as well as increase platelet turnover and decrease platelet survival time [74,75]. A link has also been proposed among the degree of cell surface sialylation of tumor cells, their ability to aggregate platelets, and the incidence of thrombosis in cancer patients [76]. Indeed, the ability of tumor cells to produce platelet-aggregating ability and plasminogen activator mirrors their metastatic potential in human and experimental models [31]. Intravenous injection of tumor cells into experimental animals leads to platelet aggregation *in vivo*, whereas many human and animal tumor cells provoke platelet aggregation *in vitro* [81–83]. Several distinct mechanisms appear to be involved. Tumor cells and tumor vesicles shed from many tumor cells bind to platelets, raising the possibility of platelet aggregation by physical bridging [81,84,85].

Other causes of the increased platelet activation in cancer include cancer-induced thrombin generation, adenosine 5′-diphosphate (ADP), and a cathepsin B–like cysteine proteinase production by tumor cells and raised levels of von Willebrand factor [86–89]. Platelet aggregation is a recognized important mechanism for thrombus formation in many diseases, including cancer. Such platelet microthrombi may afford tumor cells some protection against the host's immune response, thus contributing further to disease progression.

Monocytes–macrophages Tumor cells also have the ability to interact with the monocyte–macrophage system and induce TF expression by these cells [90]. Monocytes–macrophages circulate in the bloodstream or congregate on the vascular surfaces in response to inflammatory stimuli. Mononuclear phagocytes do not express TF under resting conditions, like endothelial cells, but can generate this procoagulant on their surface in response to various stimuli, including bacterial endotoxins, inflammatory molecules, complement, immune complexes, and lymphokines. *In vitro* data show that tumor cells (and tumor cell products) can induce the expression of monocyte TF [34]. Mononuclear cell activation may also occur *in vivo* as well. In fact, tumor-associated macrophages from experimental and human tumors have been shown to express significantly increased TF than control cells [34,91]. This mechanism may contribute to the activation of the hemostatic system and the deposition of fibrin within tumor tissue. In addition, circulating monocytes from cancer patients have been shown to express increased TF activity [92]. The generation of procoagulant substances by monocytes–macrophages *in vivo* could be a mechanism of clotting activation in cancer [34]. Furthermore, there is evidence that tumor-associated macrophages respond to tumor-derived mediators not only by exposing TF, but also by increasing their fibrinolytic enzyme production [93].

Cancer Therapy and Risk of Thrombosis

Treatments for cancer, including surgery, hormonal therapy, cytotoxic chemotherapy, and also the placement of central venous catheters, contribute to the hypercoagulable state and, hence, are independent risk factors for VTE in cancer patients [94–98].

Surgery, usually the first choice for benign solid tumors, can increase the risk of TE due to activation of the hemostatic system [99]. The risk of postoperative thrombosis is raised approximately two-fold in cancer patients compared to noncancer patients, and the risk of fatal PE postoperatively is even increased four-fold in cancer patients [100,101]. One study suggests that a preoperative laboratory evaluation of thrombosis markers, i.e., thrombin–antithrombin levels, may be useful in identifying at-risk patients for postoperative DVT [102].

Chemotherapy can increase the risk of thrombosis in cancer patients. This has been best studied in breast cancer, where tamoxifen and cytotoxic chemotherapy both appear independently to increase the risk of venous thrombosis [103–108]. This increase in risk appears to be greatest in postmenopausal patients. An increased risk for arterial thrombosis has also been observed [105,109]. However, it should be noted that many of the chemotherapy regimens in these studies contained more drugs (up to seven) than are present normally in modern day regimens (up to three).

Thrombotic complications have been shown in association with specific chemotherapeutic agents, including L-asparaginase, mitomycin C, cisplatin, as well as high-dose chemotherapeutic regimens for bone marrow transplantation [110]. Controlled studies have shown that conventional chemotherapy routinely used for treating breast cancer can also increase the risk of TE [108] and that prophylactic treatment with warfarin can reduce this risk [111]. Moreover, hormone therapy with tamoxifen is an additional risk factor for thrombosis in breast cancer. In premenopausal women, the combination of cytotoxic chemotherapy and tamoxifen has shown to have a greater degree of thrombotic complications than chemotherapy alone [105]. Additionally, the use of hematopoietic growth factors [i.e., granulocyte colony-stimulating factor (G-CSF) or granulocyte–macrophage colony-stimulating factor (GM-CSF)]

may be implicated in hypercoagulation and clot formation in breast cancer [112,113].

Cancer patients with indwelling long-term central venous catheters are also prone to thrombotic complications [97,114]. Two kinds of catheter-related thrombi may develop: sleeve thrombi developing on the outside of intravenous catheters, and occlusive DVT [114,115].

Screening for Cancer in Idiopathic Thromboembolic Disease

Although venous thrombosis is a well-known complication of cancer, it could also be considered to be a marker of an otherwise occult cancer. If this is the case, it raises the issue of whether otherwise healthy patients presenting with a venous thromboembolic episode should be investigated for an underlying cancer on the grounds that a cancer diagnosed early may be more responsive to medical intervention.

Whether screening for an occult cancer is a good use of resources will depend on the incidence of the particular cancer; the cost, accuracy, and acceptability of the screening tests; and, most importantly, whether early detection of such cancers would improve patient outcome.

Large prospective studies of patients presenting with VTE find an incidence of previously undiagnosed cancer of 4% to 6.5%, giving standardized incidence ratios of 1.3 to 3.2 [116–118]. Smaller retrospective and prospective studies looking particularly at patients with no obvious risk factors for their thrombosis find higher incidences of cancer, of 7.3% to 12%, compared with 1.9% to 2.9% for patients with risk factors [119–121]. In these studies, patients were not specifically investigated for an underlying cancer, the diagnosis being made after routine investigation on admission or after 6 to 12 months follow-up. Two studies in which patients underwent intensive investigations for cancer at the time of presentation found an incidence as high as 19% in patients with no risk factors [122,123].

In patients presenting with VTE, the prevalence of concomitant cancer, defined as cancer not known before VTE, discovered by routine examination [history taking, physical examination, simple laboratory tests like erythrocyte sedimentation rate (ESR), whole blood count, liver and kidney function tests, urinalysis, and chest X-ray] varies considerably between studies (Table 4). This variation might relate to the depth of the routine examinations and to the characteristics of the excluded patients. Another part of the explanation is the variability of definition used for secondary thrombosis and differences in threshold of suspicion. It seems that some of the differences can also be explained by the age of the patients. The studies of Ahmed and Mohyuddin [124] and Subira et al. [125], which both found a zero prevalence, contained almost exclusively patients younger than 40 years. They did not find any concomitant cancer in this age category.

Early detection of cancer would possibly improve patient outcome if the patient has a carcinoma of the breast, ovary, colon, or cervix, but there is no evidence for improved outcomes in carcinomas of the lung, brain, prostate, or pancreas, all of which have been associated with venous thrombosis. Moreover, we cannot assume that these occult cancers are at an early stage of their development because they have already had a major clinical impact. One study recently reported on the survival of patients who were diagnosed with cancer at or around the time of presentation with a thromboembolic event [132]. When these patients were compared with age-matched controls with similar cancers but without an associated thrombosis, 44% was found to have metastases at the time of diagnosis compared with 35% of controls. One-year survival was only 12% compared with 36% in the controls. If the cancer was diagnosed within 12 months of a thromboembolic event, 1-year survival was 38% compared with 47% in the controls. The study concludes that patients with cancer diagnosed at or around the time of a thromboembolic event have a significantly worse prognosis than those patients without such an association.

This raises the question of whether screening for cancer in patients who present with a venous thromboembolic event be an effective use of resources. In the absence of an obvious risk factor for thrombosis, there is a clear increase in the incidence of an underlying carcinoma in these patients.

Table 4. Prevalence of Patients with Concomitant Diagnosis of VTE and Cancer.

Reference	Study Type	Type of Screening	Prevalence of Occult Cancer in Patients with VTE		
			All (%)	Secondary VTE (%)	Idiopathic VTE (%)
[124]	RET	Unknown	0/196 (0)	0/83 (0)	0/113 (0)
[125]	RET	Routine	0/40 (0)	0/30 (0)	0/10 (0)
[126]	PRO	Extensive*	18/232 (8)	5/154 (3)	13/78 (17)
[123]	PRO	Routine	13/293 (4.4)	4/207 (1.9)	7/86 (8.1)
[127]	RET	Routine	6/104 (5.8)	1/83 (1.2)	5/21 (23.8)
[122]	PRO	Routine	8/113 (7.1)	4/82 (4.9)	4/31 (12.9)
[128]	PRO	Routine	11/685 (1.6)	4/573 (0.7)	7/112 (6.3)
[119]	PRO	Routine	5/260 (1.9)	0/107 (0)	5/153 (3.3)
[129]	RET	Routine	26/809 (3.2)	8/530 (1.5)	18/279 (6.5)
[120]	RET	Routine	–	–	16/142 (11.3)
[130]	PRO	Routine		–	15/343 (4.4)
[131]	RET	Routine	–	–	3/21 (14.3)

RET, retrospective; PRO, prospective.
*Extensive = routine + tumor markers, abdominal and pelvic CT scans, mammography >40 years; prostate ultrasonography >60 years; and, in some, thoracic CT scan.

Estimates range from 7.3% to 19% at the time of presentation. Assuming an incidence of perhaps around 10%, screening for cancer becomes a reasonable option. However, on the basis of current evidence, intensive investigation cannot be recommended.

Firstly, cancers associated with venous thrombosis seem to have a relatively poor prognosis, and early diagnosis of many of these cancers has not been shown to improve survival. Secondly, we should not underestimate the potential harm to patients, both psychological and physical, which can be associated with any kind of screening program, as increasingly invasive investigations may be used to follow up abnormal screening tests for what may turn out to be benign or untreatable disease.

Conclusion

Cancer can confer a prothrombotic or hypercoagulable state through an altered balance between the coagulation and fibrinolytic systems, which can be related to long-term prognosis and treatment. The hypercoagulable state reflects the interaction of different mechanisms involving the activation of various hemostatic components, such as the coagulation and fibrinolytic pathways, the vascular endothelium, monocytes, and platelets. Tumor cells interact with all parts of the hemostatic system. They can directly activate the coagulation cascade by producing their own procoagulant factors, or they can stimulate the prothrombotic properties of other blood cell components. Additional mechanisms of clotting activation are initiated by cytotoxic chemotherapy or other cancer therapies. In the last decade, research has greatly improved our understanding of tumor-associated hypercoagulability. At the present time, intensive investigation for cancer in patients presenting with thromboembolic disease is not justified, firstly because there is no evidence of improved survival, and secondly because of the psychological and physical damage a screening program may cause to the patient.

A sound knowledge of the molecular basis of the underlying mechanisms of tumor-associated hypercoagulability may help to identify more targeted strategies to prevent thromboembolic complications in cancer patients, in particular when surgical or chemical therapy is involved.

Acknowledgements

We thank the City Hospital NHS Trust Research and Development Program for support of the Hemostasis, Thrombosis and Vascular Biology Unit.

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