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Review

A review of the interaction between the coagulation system and cancer

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Abstract

Background: Interaction between cancer cells and the coagulation system could have reciprocal effects on both groups. Coagulation-fibrinolytic cascade is a process that regulates the homeostasis of the body, and this process can be disrupted by several factors; one of the most important factor is cancer. In contrast, the coagulation-fibrinolytic system can also act as a factor in cancer growth and metastasis. Our aim in this study is to investigate this relationship.

Methods: The present study is based on Pubmed database information (2010-2023) using the words "Cancer", "Coagulation", "Platelet ", "Tissue factor" and " VTE ".

Results: Cancer cells disrupt the coagulation process by activating pro-oncogenic factors or inhibiting tumor suppressors, thereby inducing changes in platelets and coagulation factors, and increasing proteins involved in coagulation. These aberrations in the coagulation system result in coagulation abnormalities such as venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC). In various cancers, the activity of the coagulation and fibrinolytic systems increases, leading to an increase in coagulation and fibrinolysis factors. These factors are closely related to tumor size, tumor stage, cancer progression and metastasis.

Conclusions: The coagulation-fibrinolytic system is closely related to cancers.Cancer cells can disrupt the coagulation-fibrinolysis process. Also, coagulation-fibrinolytic agents can both lead to cancer progression and can be used as a marker for the prognosis of some cancers.

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1. Introduction

In cancer patients, the balance of the coagulation and fibrinolytic systems is disturbed. This event can be due to the high ability of cancer cells to express the tissue factor and microparticles derived from it, increase in anticoagulant proteins, change in platelet function, production of cancerous procoagulants and increased release of microparticles expressing these substances (1, 2). Cancer cells are naturally prothrombotic and cancer is one of the most important causes of venous thromboembolism (VTE). One of the risk factors for VTE is The type and stage of cancer and the type of treatment received by the patient (surgery, chemotherapy, radiation therapy, and treatment

Supportive)(3). Some cancer cells, by increasing tissue factor expression, activate some Pre-oncogenic factors such as K-ras, PML-RARA, and EGFR and inhibit some tumor suppressor genes, including P53, and increase coagulation activity (3). Expression of tissue factors by cancer cells can lead to Disseminated Intravascular Coagulation (DIC) in people with malignant tumors. Moreover,microparticles derived from this factor can play an important role in tumor-associated VTE (3-5). Also Circulating Tumor Cells (CTCs) can play an important role in tumor growth and metastasis and increase VTE. As a result, Increased CTCs are associated with low survival and poor prognosis (6).

Reciprocally, the role of the coagulation system in the growth and metastasis of cancer cells is important. In cancer patients, the fibrinolytic system increases the expression of annexin 2, which is a receptor of Tissue plasminogen activator (tPA), plasminogen, and urokinase plasminogen activator (uPA) in various tumor cells (1). uPA and uPA receptor (uPAR) can react with matrix metalloprotease enzymes and cause cancer cell metastasis (4, 5). Plasma fibrinogen is associated with tumor size and depth, lymph node metastasis, liver metastasis, and tumor stage (7). Platelets can promote cancer by secreting growth and chemotactic factors and increasing angiogenesis. The release of growth factors, such as transforming growth factor-beta (TGFβ), by platelets could activate signaling pathways like TGFβ/SMAD and expand cancer cells' metastasis (8). Also, after chemotherapy, the increased platelet counts, leads to incrasing in coagulation and thrombosis by changing in the coagulation activity (9-11). Toatally, platelet count is associated with tumor size and invasion, lymph node metastasis, and distant metastasis (7).

D-Dimer is a determinant factor in homeostatic balance that can predict the stage of cancer, malignancy or benignity of cancer and thrombosis. (12). DIC can be caused by the secretion of tissue factor by malignant cancer cells, causing the cancer cells to metastasize to the bone marrow and reduce survival (4, 5). Previous studies have reported that significant oncogenic events can lead to coagulation cascade activation, thromboembolic events, and coagulation disorders. Also, effective factors in coagulation can affect the progression, invasion and metastasis of various cancers in different ways (12-14). Our aim in this study is to investigate the relationship between coagulation system-fibrinolysis and cancer.

2. Breast Cancer

The incidence of coagulation abnormalities and thromboembolic is significantly higher in women with breast cancer than the normal population (15). In these patients, protease-activated receptor 2 (PAR2) is activated by trypsin and triggers angiogenesis, differentiation, and metastasis. PAR2 can also upregulate the expression of active-matrix metalloproteinases (MMP2) in breast cancer cells through nuclear factor kappa B (NF-kB)/PI3K/AKT signaling pathway. Consequently, PAR2 by destroying the extracellular matrix, boosting invasion, and inducing autocrine actines recombination signal could expand the immigration of cancer cells (16). Signal peptide-cub-epidermal growth factor domain-containing protein-1 (SCUBE1) is a protein released in inflammation and hypoxia conditions from platelet alpha granule and could be utilized for the diagnosis of thrombotic diseases, including acute coronary syndrome, acute brain ischemia, and cancer. The level of this marker is high in breast cancer patients, marking an increased coagulation activity and risk of thrombosis in these patient (17). Abnormal expression of microparticle tissue factor (MPTF) can activate the coagulation system via the NF-kB pathway in the breast cancer patient. Higher levels of MPTF have been reported in patients with breast cancer than normal individuals; also, its level increases along with cancer development. While results of PT and APTT are lower in these patients, levels of fibrinogen and D-Dimer are higher than normal counterparts (15). Also, there is a relation between D-Dimer level and the incidence of thrombosis and invasion in these patients (18). Furthermore, uPA can contribute to fibrinogen destruction, and increase metastasis owing to the destruction of the base membrane and extracellular matrix. High levels of uPA could be associated with poor prognosis in patients with breast cancer (6). Also, plasminogen could be activated by thrombin activatable fibrinolysis inhibitor (TAFI), thereby causing proteolysis of extracellular matrix and eventually metastasis in patients with breast cancer (4, 5). After evaluating 370 frequent Single Nucleotide Polymorphisms (SNPs) in 70 TF-related genes, it was shown that there is a relation between six SNPs related to three separate genes (including four introns in F5 gene, an upstream region in F10 gene, and an intron in EPCR gene), and increased coagulation activity in breast cancer (19).

The thrombotic complication is the second cause of death in patients with breast cancer. These patients are prone to thrombosis which is mainly due to the rise in the number of cancer cells and cytokines and growth factors released from these cells, particularly during metastasis. Breast cancer cells can alter platelet morphology and function, increase the release of coagulation factors and increase coagulation and thrombosis (20). Coagulopathy in cancer patients could be derived from the secretion of procoagulant cancer cell-derived microparticles. The interaction between tumor and normal cells could be a cause of coagulation expansion, as this reciprocal connection enhances the release of coagulation factors (21). Endothelial protein C receptor (EPCR) is a biomarker in hematopoietic, endothelial and nerve cells that is involved in the growth of breast cancer in the orthotopic environment of the mammary glands. Tumor-associated macrophages are also a source of coagulation proteases that are involved in activating cell responses related to EPCR and TF (22). Elevation of CTCs is associated with poor prognosis and decreased survival rate and, can increase the risk of VTE in patients with metastatic breast cancer (6). Plasma levels of D-Dimer, thrombin-antithrombin complex and fibrin degradation product (FDP) increase in patients with breast cancer after mastectomy and increases lower extremity DVTFDP is the best marker for predicting lower extremity DVT after radical mastectomy (**Figure 1-A**) (**Table 1**) (23).

3. Lung Cancer

In lung cancer, Tissue Factor (TF) expression in epithelial-mesenchymal transition is increased and causes the increase in the coagulation activity of cancer cells. . This provides the first step in the metastatic colonization of these cells (2). Furthermore, tumor-derived TFs could induce coagulation in the microenvironment, activate the complement system, accelerate tumor progression, and expand the growth of tumor cells via signaling pathways, including PAR2 and integrin (2, 24, 25). Platelets through the secretion of growth factors and chemokines, stimulate angiogenesis could have a role in non-small cell lung cancer (NSCLC) occurrence. After chemotherapy, platelets could decrease clotting time and increase the formation of the thrombin-antithrombin complex. Platelet phosphatidylserine is exposed after chemotherapy or cisplatin therapy. Phosphatidylserine increases the binding site of the prothrombinase complex and factor Xa and, increases the formation of thrombin and fibrin (26).

Platelet-derived microparticles (PMPs) increase one day after chemotherapy, and the body is unable to clear this amount of microparticles. Microparticles express abundant phosphatidylserine on the membrane surface, so platelet activation and accumulation of PMPs after chemotherapy lead to increased coagulation activity and is associated with thrombotic complications in these patients. The combination of antiplatelet and anticoagulants after chemotherapy reduces the risk of thrombosis in these patients (27-31). In patients with lung cancer with thromboembolic disease, the rates of APTT and PT after surgery decrease and increase, respectively, indicating hypercoagulability in these patients. The levels of D-Dimer and fibrinogen also increase in these patients after treatment, which is associated with increased mortality (32).

Lung cancer is the most associated type of cancer with VTE occurrence, which mainly occurs due to the increased tendency to coagulation and decreased fibrinolytic activity (33). Coagulation activated by TF in the tumor microenvironment can activate the complement system and subsequently, myeloid-derived suppressor cells (MDSC) to promote tumor growth (2). There is an increase in coagulation and fibrinolysis in patients with deep vein catheterization after surgery, and early detection of coagulation and fibrinolytic biomarkers can reduce the risk of thrombosis and its complications after surgery. Before starting treatment for lung cancer, increased fibrinogen predicts thromboembolic disease in these patients and can be a marker to identify patients at risk for thromboembolism at the time of diagnosis of lung cancer. In NSCLC, the incidence of venous and arterial thrombosis is high and has a poor prognosis. In this disease, the activity of tissue factor pathway inhibitor (TFPI) and TAFI is increased. The progression of cancer and surgery affects the level of D-Dimer in patients with NSCLC and increases it (34). Decreased thrombin and antithrombin complexes as well as plasmin and plasmin inhibitors are seen in the advanced stage of this cancer (**Figure 1-B**) (**Table 1**) (27-29).

4. Brain Cancer

Patients with a brain tumor could experience the increased activity of the coagulation system after surgery that can raise the risk of VTE. The probability of VTE occurrence is higher in patients

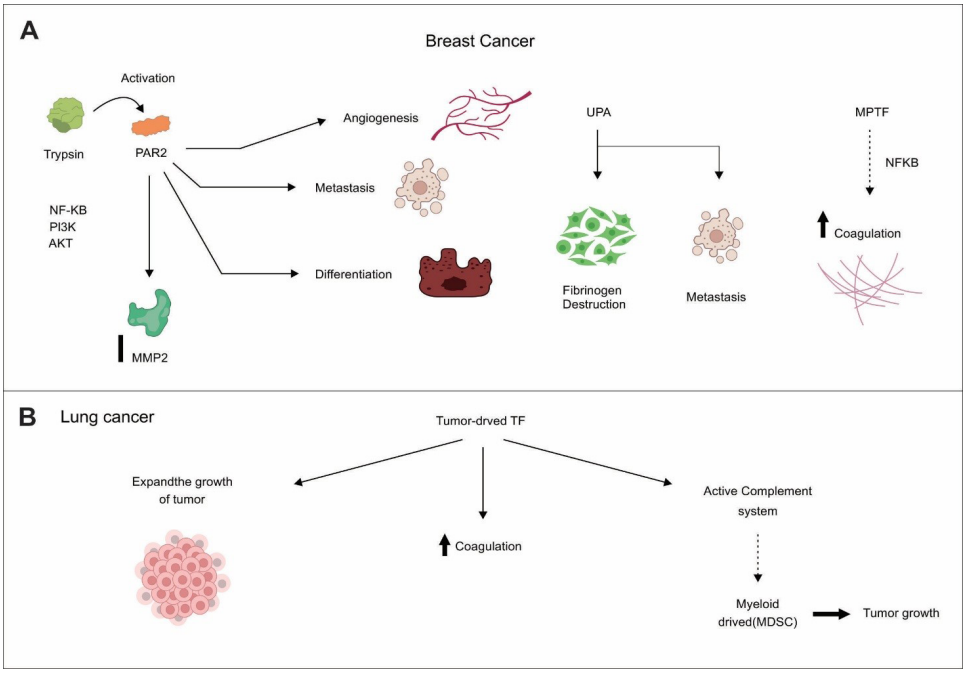

Figure 1. Association of cancers with coagulation-fibrinolytic system.

Table 1. The role of effective factors involved in coagulation disorder and, progression and invasion of cancer.

Cancer	Factors	Function	Ref
Gastric, Lung, Breast, Pancratic, Colorectal, Brain	TF, MPFT	Activate the complement system-Growth & differentiation & metastasis of tumor cells, Increasing activity of the coagulation system	(2, 9, 10, 27-31, 36, 54, 62)
Gastric, Lung, Breast, Pancratic, Colorectal, Brain, Ovary	Platelet	Prevent the destruction of cancer cells- Increased secretion of growth factor & chemotactic factor-angiogenesis-Increased risk of thrombosis	(9, 10, 27-31, 35, 39, 48, 63)
Breast-gastric	Scube	Increasing activity of the coagulation system	(17)
Breast-prostate	tPA-uPA	Increased metastasis- Demolition of base membrane-destruction of fibrinogen	(5, 6, 64)
Brain- PDAC	HO-1	Increased production of CO- Increasing activity of the coagulation system	(18, 36)
Lung- Breast	PAR2	Increased growth of tumor cells. Expression of MMP2-angiogenesis-Increased cell migration-differentiation & metastasis of tumor cells.	(16)
lung	Complement system	Growth & differentiation of tumor cells-angiogenesis	(2)
	MDSC	Inhibition of the immune system in the tumor environment	
Breast	MMP2	Extirpation of the extracellular matrix metastasis	(16)
	TAFI	Proteolysis of the extracellular matrix-Increased metastasis	(4, 5)
	SNP	Increasing activity of the coagulation system	(19)
	CTC	Growth & differentiation & metastasis of tumor cells-Increased of uPA-Increased risk of VTE	(6)
	EPCR	Growth of cancer cells in orthotopic mammary glands	(22)
PDAC	asTF	Increased angiogenesis-Increased thrombosis	(55)
Gastric	Neutrophil	Release of NETs & Increase coagulation	(39)

Abbreviations: TF: Tissue factor; MPFT: microparticle tissue factor; MMP2: active matrix metalloproteinases; PAR2: protease activated receptor 2; SCUBE; Peptide-Cub-Epidermal growth factor domain-containing protein-1; HIF1: hypoxia-inducible factor1; TAFI: Thrombin activatable fibrinolysis inhibitor; SNP: single nocleotid polymorphism; CTC: Circulating Tumor Cells; tPA:Tissue plasminogen activator; uPA: urokinase plasminogen activator; EPCR: Epethelial Protein C Reseptor; HO-1: Hemeoxygenase1; asTF: alternatively spliced TF; PDAC: Pancreatic-ductal adenocarcinoma; VTE: Venous thromboembolism; NET: neutrophil extracellular trap.

with a brain tumor (3-60%) than those with other tumors, along with a poor prognosis and high mortality in these patients (35). Deep vein thrombosis (DVT) is the most important clinical form in brain tumor patients with an incidence rate of 10.5% in patients who undergo a surgical operation. Various studies show that a significant decrease of platelets after surgery in these patients could indicate a rapid DVT development and, an increase of fibrinogen concentration could be accompanied by thrombophilia. D-Dimer could be applied as a regulatory marker in patients undergoing brain tumor surgery (36). In patients with a brain tumor, the risk of intracranial hemorrhage (ICH) depends on early diagnosis or whether or not the disease is metastatic. ICH could be frequently seen in the early phase and/or metastatic phase of brain tumor patients without an anticoagulant. Although anticoagulant drugs could not increase ICH occurrence, they could raise the risk of ICH in Glioblastoma patients (37).

In patients with a brain tumor, APTT and bleeding time is reduced, and due to the release of thromboplastin from brain tissue the amount of fibrinogen, thrombin, anti-thrombin, prothrombin fragments, and D-Dimer increases (35). MPTFs with a high concentration in patients with a brain tumor is found and increase coagulation. Furthermore, high levels of endogenous CO production and carboxyhemefibrinogen (COHF) formation could be seen in brain tumor. Rise of CO and hemeoxygenase-1 (HO-1) related to the brain tumor can induce coagulation (36).

In patients with Glioblastoma, an increase in plasma D-Dimer levels and an increase in von Willebrand factor occur, and the rate of PT and APTT in these patients is short, which generally indicates excessive coagulation profile, tumor increase, and poor overall survival (OS) (38) (**Table 1**).

5. Gastric Cancer

The rise of vein thrombosis in patients with gastric cancer could be a result of the elevated levels of TF, MPFT and platelet and leukocyte activation. Gastric cancer stimulates neutrophils to release neutrophil extracellular traps (NETs), which play an important role in cancer-associated thrombosis. An increase of phosphatidylserine positive platelets and their derivative microparticles is reported in patients with gastric cancer that can result in platelets' activation and rise in blood coagulation in advanced stages of this disease (39, 40). D-Dimer levels in people with gastric cancer who undergo gastrectomy surgery can predict tumor recurrence and non-recurrent survival (41). Measurement of fibrinogen-to-platelet ratio (FPR) level as a coagulation index in gastric cancer is useful for predicting the prognosis of the disease and can be easily calculated. This index shows the binding of fibrinogen to platelets and provides a better prognosis for the disease than fibrinogen level or platelet count. This index is also related to the level of D-Dimer and can be helpful in the diagnosis of venous thromboembolism. Increased FPR, especially in patients under 65 years of age, patients with stage I, II disease, and patients with undifferentiated tumors, indicates that the patient needs more severe chemotherapy (7). The fibrinogen to albumin ratio can also be a useful marker for predicting progression-free survival and OS in patients receiving first-line chemotherapy for gastric cancer (42) (**Figure 2-A**) (**Table 1**).

6. Colorectal cancer

Colorectal cancer cells activate platelets by expressing TF, thrombin and activating PAR4 on the surface of platelets. Following platelet activation, platelet-derived vesicles are released and enhance prothrombic events. (43). Patients with colorectal cancer show high levels of vascular endothelial growth factor (VEGF) and the thrombin and antithrombin complex during chemotherapy. Endothelium-derived microparticles are also higher in these patients than in healthy individuals, which in total can lead to tumor angiogenesis and increased coagulation in these patients. Elevation of these biomarkers along with D-Dimer can lead to poor treatment response, reduced survival and increased mortality in patients with metastatic colorectal cancer (44, 45). In patients with colorectal cancer, high levels of PT and APTT before surgery indicates a poor prognosis. The combination of PT and APTT may be used as a prognostic marker to predict OS and disease-free survival in patients with colorectal cancer (46).

Patients with end-stage and metastatic colorectal cancer show higher platelet counts and platelet-to-lymphocyte ratios than stages I and II. Platelet markers can be a marker for the diagnosis of this cancer, although other diagnostic markers should be considered due to the influence of various

factors such as inflammation on platelets (47). High levels of D-Dimer in patients with progressive and recurrent colorectal cancer is associated with their reduced life span. In this cancer, there is a relation between D-Dimer plasma level before surgery and diagnostic marker carcinoembryonic antigen (CEA) (18). Also, there is a relation between increases of international normalized ratio (INR) value and diagnostic marker CA19-9. However, D-Dimer is a better predictor of lymph nodes involvement compared to CEA and CA19-9 (21) (**Table 1**).

7. Ovarian Cancer

Ovarian tumor cells can stimulate platelet production. Besides, it has been reported that the prescription of thrombopoietin in the chemotherapy of this disease could increase platelet count (48). Serum fibrinogen levels show a significant increase in patients with ovarian cancer. This rate increases with the progression of the disease stage so that the level of fibrinogen in stages III-IV shows a significantly higher level than stages I-II of cancer. D-Dimer level in these patients also increased similarly to fibrinogen and is a marker for predicting cancer progression. A combination of D-dimer and INR can also improve prognostic accuracy for epithelial ovarian cancer (EOC) patients (49, 50). Preoperative fibrinogen and neutrophil lymphocyte ratio (F-NLR) is a useful prognostic marker for EOC patients, especially those with advanced stages or lymph node metastasis. This marker is based on inflammation (51). In the final stages of ovarian cancer, clot production increases and extracellular vesicles (EVs) play a key role in this process. Circulating EVs can be used to diagnose ovarian cancer as a non-invasive marker (52, 53) (**Figure 2-B**) (**Table 1**).

8. Other Cancers

Alternative spliced TF (asTF) is an isoform of full-length tissue factor that could expand angiogenesis via adherence to α6β1.αvβ3 integrins. It was seen that asTF along with flTF has a synergistic role in increasing thrombosis in pancreatic ductal adenocarcinoma (PDAC) (54, 55).

Colon and pancreatic cancers increase HO-1 and consequently increase CO production, which leads to increased plasma coagulation. The risk of thromboembolism in people with pancreatic and colon cancers is 36-20% and 10%, respectively. These tumor cells are the source of the production and release of thrombin and TF -derived microparticles (55).

The most prevalent coagulation abnormality in prostate cancer is DIC. The increase of uPA and tPA by prostate cancer cells is accompanied by a rise in the activity of the fibrinolysis system (56, 57) (**Figure 2-C**). Albumin-to fibrinogen ratio can be an independent predictor marker for OS and disease-free survival for patients with preoperative bladder cancer. In patients with bladder cancer whose disease is limited to the mucosa or submucosa (nonemuscle-invasive bladder cancer), high levels of plasma fibrinogen and D-Dimer before surgery indicate a poor and bad prognosis (58, 59).

In cervical cancer reduced clotting time in PT could contribute to DIC, thereby shortening patients' life span (60). In esophageal cancer, increased levels of D-Dimer could be related to worsening disease invasion (18). Levels of fibrinogen and D-Dimer increase in patients with AFP-negative hepatocellular carcinoma, and this increase leads to the progression of cancer. D-Dimer may be used as a diagnostic indicator in this disease (61) (**Table 1**).

9. Conclusion

In general, it can be concluded that cancer and coagulation-fibrinolysis system is closely related to each other. Cancer cells are capable of disrupting coagulation. Various mechanisms are related to this disruption, including the expression of TF, MPTF by tumor cells, elevated levels of pro-coagulation proteins, altered platelet function, an increase of proteases activating coagulation factors, increase of mucin glycoproteins derived from P-selectin adherent tumor cells, and the activity of oncogenes such as K-ras, PML-RARA, and MET. Cancer cells lack sufficient power to increase coagulation activity, and with the release of procoagulant factors, especially microparticles that induce the expression of TF and procoagulant phospholipid, expand coagulation activity in the tumor environment (8, 65). Coagulation proteins, especially extrinsic and common pathway proteins, have hemostatic and non-hemostatic roles in tumor growth; therefore, targeting initial proteins of the coagulation system, which inhibit the formation of subsequent coagulation factors, could be a promising tool against tumor progress (66). As one of the most important factors involved in coagulation and initial factor of extrinsic pathway, TF along with MPTF has a crucial role in complement system activation, growth, differentiation, and metastasis of tumor cells, and cancer development. So, it appears that cancer development could be harnessed by applying

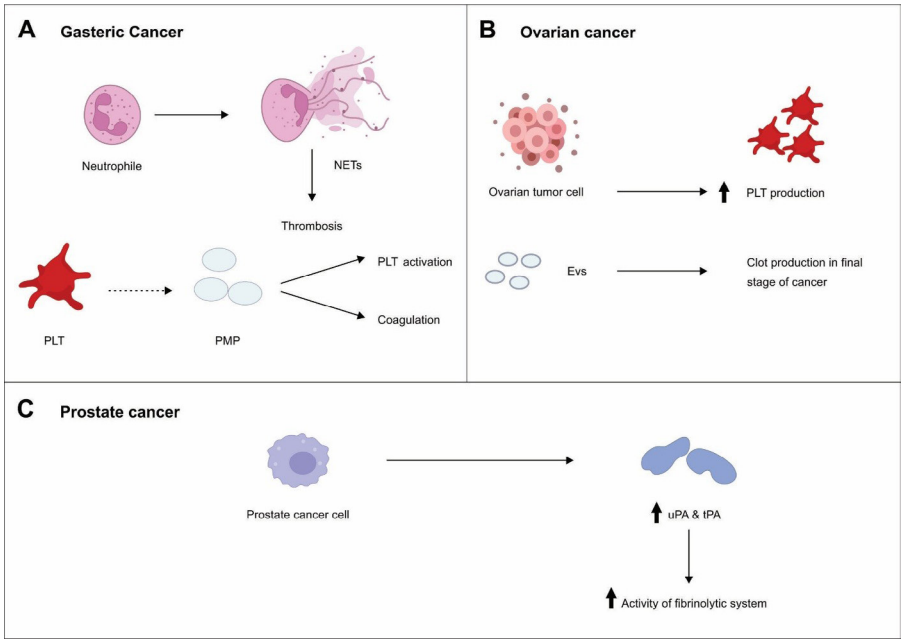

Figure 2. Association of cancers with coagulation-fibrinolytic system

preventative strategies in the expression of TF, or decrease and clearance of microparticles containing TF (66, 67). Therefore, in general, it can be said that the crosstalk between coagulation system and cancer, can cause a disturbance in the balance of the human body.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

The authors declare no conflict of interest.

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