

# D-dimer as an alarming biomarker in various cancers: A review of literature

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## Abstract

Today cancer is the major health threat; and lot of efforts are being taken by many researchers; to fight against it. Even after these advancements in technologies, still death rate is gradually increasing, and the reason is late detection, delayed treatments and vascular complications, such as venous thromboembolic events (VTE). To overcome this; there is need of accurate and prompt investigation; which will guide during intervention with its effectiveness and feasibility, recently one of such investigations is to assess levels of D-dimer.

The review is compiled through the search of electronic media; mainly Google search, Ebscohost and Pub-med etc. During search relevant key words inserted such as, D-dimer, oral cancer, Fibrinogen, Fibrinogen-degradation product (FDP), Head-neck cancer and VTE etc.

Blood plays crucial role in many investigations; and very important in cancers. This is proved that, a degradation component of blood called D-dimer, may play important role during interventions of oral & other cancers.

## Introduction

Even after many innovations; oral cancer related death toll is rising [1,2], and to overcome this problem, nowadays researchers are focussing on molecular biomarkers. Presently researchers are working on D-dimer; which shows close association with cancers with comparatively better specificity and sensitivity [3].

D-dimer is the breakdown product; derived from action of plasmin; a clot degrading enzyme, and this works as primary diagnostic tool in various diseases such as; deep venous thrombosis (DVT), systemic illness and cancers. Here D stands for domain and is written as D-dimer or d-dimer [4,5]. The viscosity of blood is maintained by equilibrium between coagulation phenomena and fibrinolysis, and this coagulation cascade needs transformation of soluble plasma fibrinogen into insoluble fibrin. This mechanism is also very useful in removal of accumulated fibrin and fibrinogen, which again depends on proteolytic action of plasmin [6-8].

Fibrinogen is a basic and important component of blood, which is structurally; a heterohexameric glycoprotein. The fibrinogen is formed by two sets of tri-non-identical polypeptide chains A $\alpha$ , B $\beta$  and Y; which are linked to each other by disulfide bonds [9]. The A $\alpha$  chain once split into fragments of D; they point in the direction of E fragment and after that there is formation of  $\alpha$ C domain [10]. Apart from isoform II, isoform I also is present (A $\alpha$ E); and it may be seen in a pool of fibrinogen of 420 kDa and it constitute around 4% of total human fibrinogen [11]. There are enough studies; showing association between blood clotting proteins and their contribution in tumour metastasis. These proteins such as, fibrinogen, fibrin and their degradation products affect pathophysiology of many tumours; by participating in blood clotting, inflammation, angiogenesis and metastasis.

There is close association between cancers and inflammations, where inflammatory response is always associated with progression

of tumours, which depend on host response against transformed neoplastic cells and role of secretory cytokines. These factors interfere with coagulation cascade, resulting in endothelial dysfunction, platelet activation, coagulation stimulation and formation of fibrin [12]. The transformed and moving cells release numerous cytokines such as IL-1, IL-6, IL-8, IL-13, TNF- $\alpha$  and transforming growth factor  $\beta$  (TGF- $\beta$ ) [13]. Factors such as IL-1 $\beta$  and TNF- $\alpha$  also stimulate endothelium to produce tissue factor (TF). Along with routine physiology; the tissue factors also contribute in activation of coagulation process and further induces mitogenic and thrombin formation which are helpful for growth and metastasis of cancers in future [14,15]. The generated thrombin improves synthesis of different components such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), IL-6, TGF- $\beta$ , MMP-2 and TF [16,17]. This change from coarse to fine clot is due to specific binding property of Cl; which acts during polymerization [18]. The basic fibrinogen is inert in blood but once it is converted to fibrin it plays important role in physiologic circulating system; mainly in fibrinolysis.

This article was prepared through electronic searches in various sites, such as; Google, Ebscohost and Pub-med, where D-dimer and cancer related articles were searched for around 1 year. The key words used for search were; D-dimer, oral cancer, Fibrinogen, Fibrinogen-degradation product (FDP), Head-neck cancer and VTE etc (Table 1).

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**Key words:** cancer, fibrinogen, d-dimer, intervention

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**Table 1.** Prothrombotic action on inflammation (Wang *et al.* 2005)

Mechanisms/Proinflammatory factors	Impact on haemostatic system and blood coagulation process
Leukocytes	Platelet activation Release of neutrophil elastase secretion of thrombomodulin by endothelial cells. Inactivation of antithrombin.
Proteins of complement system	Increase of coagulation factors Increase of tissue factor expression
Proinflammatory cytokines	Stimulation of tissue factor production Decrease of protein S level Increase of adhesive protein expression platelet activation Increase of PAI-1 synthesis
Chemokines	Activation of aggregation and adhesion of platelets Stimulation of leucocyte influx

## Discussion

There is long history of D-dimer and its association with other diseases of body; such as deep vein thrombosis and venous thromboembolism etc. Nowadays researchers are focussing towards biological markers such as D-dimer and their role in interventions of oral and other cancers of body. So today this is essential to know in and out about D-dimer and its association with oral cancer. During transformation from fibrinogen to fibrin, there is activation at high affinity binding site of alpha C-domains, which is very important for regulating fibrinogen. Sometimes this is helpful to reduce degradation of circulating fibrinogen and confine fibrinolysis at places of fibrin deposition [19]. However, lysates of plasma clots, plasma of fibrinogen and both; are main components of fibrinogen and fibrin; capable of being discriminated by SDS-PA gel electrophoresis and presence of D-dimer in plasma explains efficacy of heparin in management of haemorrhagic situations [20]. There are many regulatory components in fibrin degradation, such as gamma-dimer and alpha-polymers, thrombin and activated factor XIII. which act upon fibrinogen to form complexes; those are subsequently lysed by plasmin to produce soluble cross-linked derivatives of fibrin [21,22].

Earlier studies explained that, plasma D-dimer a circulating soluble fibrin polymer; i.e. thrombus precursor protein (TpP), shows remarkable levels during fibrinolytic process; which alarm for thromboembolic events [23-25] Weisman Z *et al.* (1978). According to recent studies; its role in various cancers; including oral potentially malignant and malignant disorders has been discovered as a useful marker during interventions. Leena Gharat *et al.* [3]. These raised levels are in proportion to advancements in grades of tumor. Koopman J *et al.* [26]. Cancer and cancer related disseminated intravascular coagulopathies (DIC), are useful tools for angiogenesis and metastasis. Trousseau in (1865), Billorth (1878) [27]. Number of cancers; such as colorectal and breast cancers have association between D-dimer and various parameters of colorectal cancers such as; tumour stage, metastasis and thromboembolic events and growth and progress of cancers [26-30].

To improvise quality assurance, some researchers developed a solid phase enzyme immunoassay (EIA), using monoclonal antibody (No FDP-14) in plasma. Moreover, the EIA for FDP in plasma is challenging diagnostic marker for various pathological conditions, including cancers [31]. Majority of chemotherapeutic regimes affect platelet synthesis which arise as principal dose-limiting side effect [32]. According to studies, D-dimer levels are useful factors; to predict the clinical outcome and survival of lung cancer patients. The preoperative plasma D-dimer level is an important prognostic marker in patients

with operable NSCLC [33,34]. Some other studies also highlight importance of raised D-dimer levels in operable hormone receptor-negative breast cancer; and survival of these patients [35,36]. There is detailed analysis, which revealed patients with cancer who had elevated D-dimer and elevated F 1 + 2 had the highest risk of developing VTE [37]. The D- dimer levels are not only useful in cancers, but this can also be utilized during pregnancy, where; diagnostic accuracy can be assessed for adnexal torsion (AT) in pregnant women [38]. Sometimes it needs to differentiate between other lesions such as fungal, bacterial and viral infections may also result DIC [39]. The D-dimer levels guide the dose of anticoagulant therapy in patients of previous history of venous thromboembolism (VTE) [3,40,41]. D-dimer and fibrinogen/fibrin degradation products (FDP) levels are elevated in thromboembolic disorders, and the assays for detection of D-dimer and FDP are used in many laboratories for the investigation of these disorders and its more commonly noticed with malignancies and immune systems [42-44].

This is also explained that fibrin (ogen) is a critical determinant of the metastatic potential of circulating tumour cells. The recent generation of viable mouse lines with selected deficits in key haemostatic factors has provided an opportunity to directly test this long-standing hypothesis [45].

The level of D-dimer was positively correlated with tumour load, number of metastatic sites, progression kinetics and the cytokines related to angiogenesis: serum vascular endothelial growth factor, calculated vascular endothelial growth factor load in platelets and serum interleukin-6 [46]. The role of primary VTE prophylaxis in high-risk patients, during secondary prevention of recurrent VTE, remains a continuing challenge during interventions [47,48].

Concentrations of cross-linked fibrin degradation products (XL-FDPs) in plasma, measured by enzyme-linked immunosorbent assays (ELISAs) based on monoclonal antibodies (MAbs) raised against fragment D-dimer of cross-linked fibrin, increase when patients are given fibrinolytic agents [3,49]. In 1865 Trousseau reported the association between phlegmasia alba dolens and advanced malignancy, whereas in 1935 James and Matheson reported the association of VTE with occult malignancy [41] and these understanding of potential pathways helped to determine the activated haemostatic and fibrinolytic activities during novel therapeutic targets [50]. Plasma levels of D-dimer are elevated in cancer patients and the activation of the extrinsic coagulation system and the fibrinolytic cascade within a tumour is thought to be related with growth, invasion and metastasis [46].

According to Masatoshi Oya, *et al.* [51], there was synergistic association; between elevated levels of plasma D-dimers with TNM staging and prognosis after surgery. The study concludes that high level of D-dimer is associated with advanced TNM stage and is associated with short survival after surgery.

## Summary and conclusion

Even after advances in medical technologies, cancer is a major health threat. The reason behind this is; complicated etio-pathogenesis and deviation in age factor, which resulted in younger age involvement, earlier it was common in older age group. Today many studies are targeting at molecular levels; for early detection and management. One of such recent investigation is to assess the D-dimer levels in blood plasma. Basically D-dimer is a fragment of fibrinogen formed by action of plasmin and its active presence helps to assist growth and progress of cancer towards metastasis and ultimately determine the prognosis of patient. Further studies on D-dimer levels; with authentic data and accuracy, can act as marker and help to fight against cancers.

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