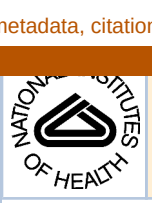

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Increased Microparticle Tissue Factor Activity in Cancer Patients with Venous Thromboembolism

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Venous thromboembolism (VTE) is the second leading cause of cancer-associated mortality (1). However, cancer patients, particularly in the ambulatory setting, do not routinely receive thromboprophylaxis. This is because there are no validated biomarkers to identify patients at high risk of VTE. A number of candidate biomarkers of thrombotic risk have been proposed, including D-dimer, soluble P-selectin, C-reactive protein, and tissue factor (TF) (2–5). TF is the transmembrane receptor for factor VII/VIIa and functions as the primary initiator of blood coagulation (6). Patients with various diseases have elevated levels of TF in their plasma in the form of membrane-associated microparticles (MPs) as well as a soluble form (7,8). MPs are submicron membrane vesicles generated from activated or apoptotic cells. Their procoagulant activity is increased by the presence of TF and the anionic phospholipid phosphatidylserine.

TF-positive MPs are highly procoagulant and they have been linked to thrombosis in a variety of diseases, such as cancer, sickle cell disease, and endotoxemia (9,10). Several studies have measured the levels of MP TF antigen and activity in cancer patients (11–13). There have been two retrospective studies investigating MP TF activity in cancer patients. Tesselaar and colleagues found increased levels of MP TF activity compared with controls in pancreatic and breast adenocarcinoma patients. In addition, Hron and colleagues reported a two-fold higher level of TF-positive MPs in patients with advanced colorectal cancer compared to controls (11,12). A prospective study by Khorana and colleagues reported that MP TF activity may be predictive of VTE in patients with pancreatic cancer (13).

In this study, we analyzed MP TF activity in patients with a variety of different cancers with or without acute VTE. We hypothesized that increased MP TF activity would be present in patients with VTE, irrespective of the type of cancer. Cancer patients (n=66) were recruited for this study at the University of Southern California in Los Angeles. Patients were enrolled in an ongoing IRB approved treatment trial for the management of malignancy-related VTE. Blood was drawn from cancer patients without VTE (n = 13) and from cancer patients with VTE within 24 hours of diagnosis (n = 53). All patients had to have either deep vein thrombosis

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confirmed by compression ultrasound and/or pulmonary embolism confirmed by computed tomography (CT) angiography utilizing a 16 slice-multi-detector CT. The distribution of cancer types in the 66 patients recruited for this study were as follows: 14 colon (10 VTE), 10 lung (7 VTE), 6 bladder (6 VTE), 5 pancreatic (3 VTE), 3 prostate (3 VTE), 3 rectal (2 VTE), 2 bile duct (2 VTE), 2 brain (2 VTE), 2 cholangio (2 VTE), 2 liver (2 VTE), 2 lymphoma (2 VTE), 2 renal cell (1 VTE), 2 testis (2 VTE), and 11 other types of cancer (9 VTE). All 66 subjects who participated in this study gave informed consent.

We have recently developed an assay to measure levels of TF activity on MPs isolated from plasma (13). Importantly, healthy individuals have very low levels of MP TF activity (0.21 ± 0.11 pg/mL) (13). In this study, we found a statistically significant increase in MP TF activity in cancer patients with VTE compared to cancer patients without VTE (1.7 ± 3.8 pg/mL vs. 0.5 ± 0.5 pg/mL, $p < 0.05$, Figure). Data is represented as mean ± standard deviation and statistical analysis was performed using a heteroscedastic Student's T-test. After the completion of our study, Tesselaar and colleagues (14) reported an increase in MP TF activity in cancer patients with VTE (n=51) compared with cancer patients without VTE (n=49). The two groups were matched for age, sex, type of cancer, stage of disease and type of cancer treatment.

Next, we compared levels of MP TF activity in pancreatic, lung, and colon cancer patients. One limitation of the study is that we had relatively small numbers in the three groups. Pancreatic cancer patients had the highest MP TF activity (6.6 ± 10.8 pg/mL), followed by lung (2.4 ± 2.5 pg/mL) and colon cancer (0.7 ± 0.8 pg/mL). This finding is consistent with the respective thrombosis rates in these types of cancer; it has been reported that 28.3% of pancreatic cancer patients develop VTE within a year of metastatic malignancy, compared to 7.4% for lung, and 5.7% for colon (15).

Plasma D-dimer and interleukin-6 (IL-6) levels were measured using commercial enzyme-linked immunoassays (IMUCLONE D-Dimer ELISA, American Diagnostica, Stamford, CT.; Human IL-6 Quantikine HS ELISA, R & D Systems Inc, Minneapolis, MN.). Cancer patients with VTE had a significant increase in D-dimer levels compared to cancer patients without VTE (4500 ± 6200 ng/mL vs. 670 ± 1800 ng/mL, $p < 0.05$). A recent study showed that elevated levels of D-dimer predict VTE in patients with cancer (16). IL-6 levels were also significantly elevated in cancer patients with VTE compared to those without VTE (9.1 ± 4.9 pg/mL vs. 6.6 ± 5.3 pg/mL, $p < 0.05$). Recent studies indicate a link between inflammation and cancer development (17). Inflammation may also induce TF expression within the vasculature and this would increase the risk of thrombosis in cancer patients. Interestingly, there was only a weak correlation between D-dimer and IL-6 compared to MP TF activity ($r = 0.145$ and $r = 0.283$, respectively). Tesselaar and colleagues (14) also found a weak correlation between MP TF activity and levels of thrombin-antithrombin complex in cancer patients.

The results of this study add to the growing body of evidence that MP TF activity may play an important role in the development of VTE in cancer patients. Our data show that MP TF activity is significantly increased in a broad population of cancer patients with acute VTE compared to cancer patients without VTE. However, as this was a cross sectional study, we are unable to conclude that MP TF activity can be used a biomarker of risk in these patients. Prospective studies are underway to test the predictive power of MP TF activity as a novel candidate biomarker for assessing the risk of VTE in cancer patients.

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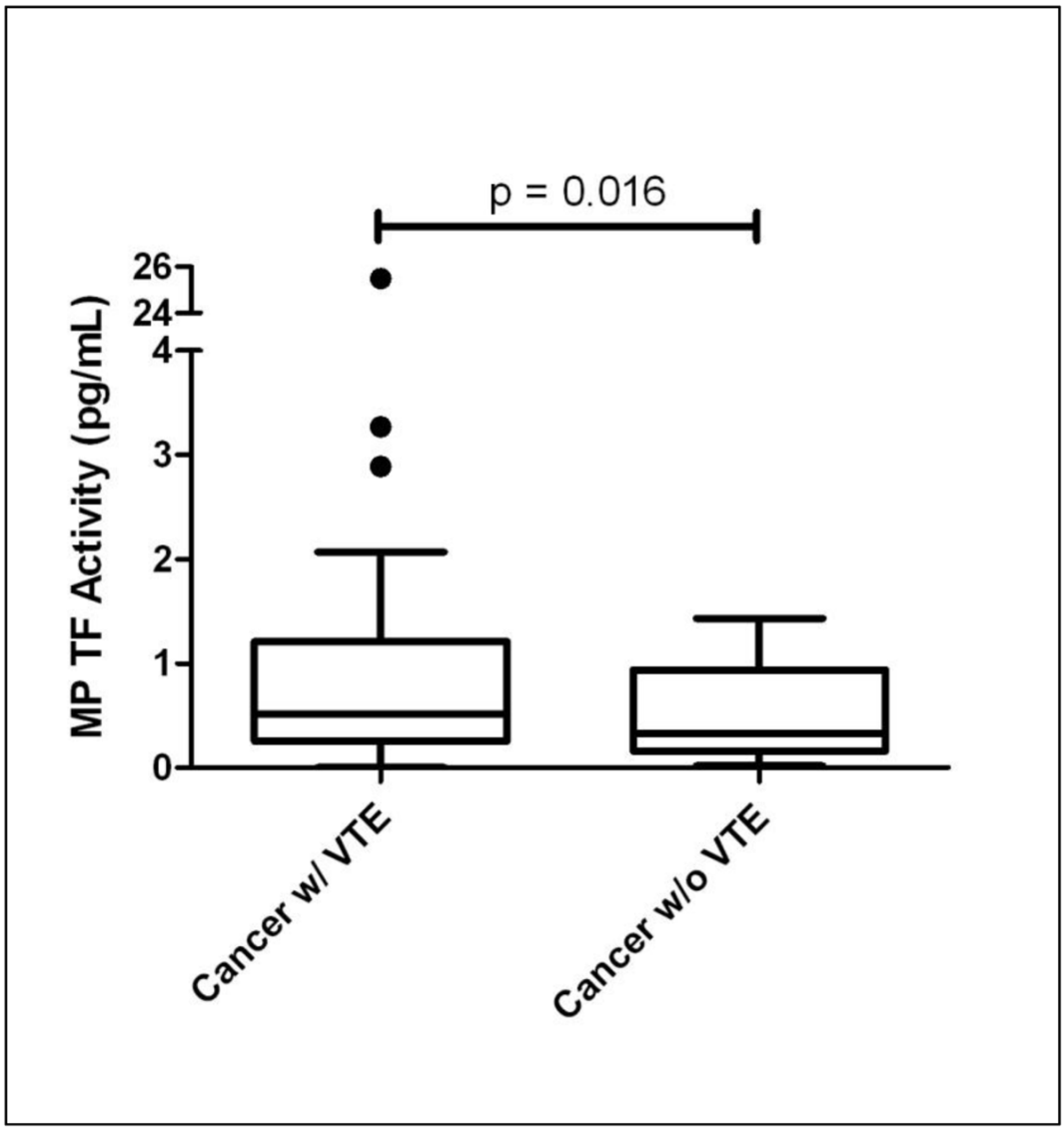

Figure.
Comparison of MP TF activity between cancer patients with VTE (n=53) and cancer patients without VTE (n=13) (Median, Inter-quartile Range, 2 Standard Deviations). Dots represent MP TF activity levels beyond 2 standard deviations.