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Mutational Profiling and Cancer-Associated Thrombosis

Six mutations are associated with an increased risk for cancer-associated thrombosis, independent of cancer type.

The etiology of cancer-associated thrombosis (CAT) is multifactorial, with influence from cancer stage, chemotherapy, postoperative state/immobility, prior thrombosis history, and presence of vascular access. The Khorana score incorporates cancer type, prechemotherapy blood cell counts (including use of erythropoietin stimulating agents), and body-mass index to create a risk score; however, greater precision in identifying at-risk patients would be welcomed. These investigators reviewed a large database, including more than 14,000 tumor samples (11,695 patients), to look for associations between tumor molecular profile and CAT.

Key findings include:

- There were 693 episodes of CAT, with the highest event rate in patients with pancreatic cancer.
- Clinical risk factors for CAT included cytotoxic chemotherapy (hazard ratio, 1.63), prior venous thromboembolism (HR, 2.2), and metastatic disease (HR, 2.6).
- Independent of tumor type, mutations in *KRAS* (HR, 1.34), *STK11* (HR, 2.12); *KEAP1* (HR, 1.84), *CTNNB1* (HR, 1.73); *CDKN2B* (HR, 1.45) and *MET* (HR, 1.83) were associated with CAT.
- Thirty percent of patients were found to have clonal hematopoiesis mutations, but surprisingly, these mutations, including *JAK2* V617F, were not associated with CAT.

COMMENT

This novel study adds to our understanding of risk factors for CAT. Six mutations were independently associated with an increased risk for thrombosis in patients with solid tumors, most of whom had metastatic disease. More work is needed to identify the mechanism by which these mutations contribute to CAT pathophysiology; the investigators suggested that *STK11* mutations may associate with increased tumor granulocyte colony-stimulating factor (G-CSF) production and neutrophil extracellular trap formation. *JAK2* V617F clearly increases thrombosis risk in patients with myeloproliferative neoplasms and in other studies of patients with *JAK2* V617F clonal hematopoiesis; the finding that this mutation did not add to thrombosis risk was unexpected. The authors acknowledge limitations from a retrospective study and need for further validation. However, in the future, CAT prognostication could certainly include information from tumor mutational sequencing. ***— Brady L. Stein, MD, MHS***

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Dunbar A et al. Genomic profiling identifies somatic mutations predicting thromboembolic risk in patients with solid tumors. **Blood** *2021 Apr 15; 137:2103. (https://doi.org/10.1182/blood.2020007488)*