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Genetic thrombophilia in cancer-associated thrombosis: the fly plowing with the ox or an old player's new role ?

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Contributions

VDS developed the conceptual framework for the editorial, drafted the manuscript, and designed the figure. KAB contributed significant intellectual input, conducted critical revisions, and granted final approval of the manuscript for publication. Both authors reviewed and approved the final version.

In this issue of Haematologica, Stevens et al.[1] present the findings of a comprehensive, population-based study involving 398,053 participants from the UK Biobank, among whom 42,122 developed cancer during the observation period. The study investigated a panel of seven genotypes associated with an elevated risk of venous thromboembolism (VTE) using a multistate model: ABO rs8176719, FGG rs2066865, FVL rs6025, FXI rs2036914, PTM rs1799963, SLC44A2 rs2288904, and TSPAN15 rs78707713. The cumulative risk of VTE two years post-diagnosis was 7.82% in cancer patients, compared with 2.08% in control subjects.

In a large Danish population-based cohort study [2], the risk of cancer-associated VTE within the first six months after diagnosis was approximately 11 times higher than in the control population. The magnitude of this risk varied depending on cancer type, with patients diagnosed with pancreatic cancer experiencing a risk increase of up to 50-fold. Cancer patients not receiving treatment demonstrate a six-fold increase in VTE risk compared to controls without cancer. The administration of antineoplastic therapies further elevated thrombotic risk, increasing it by 22 to 71 times relative to controls, depending on the specific therapeutic agent used (e.g., chemotherapy, protein kinase inhibitors, antiangiogenic therapy, immunotherapy, and other targeted treatments).[2] Within the cancer cohort, a prior history of VTE is associated with an 8.1-fold increased risk of subsequent VTE, while the use of various antineoplastic agents confers a 3.3- to 5.9-fold increase in risk compared to untreated cancer patients.[2] (Figure)

It is well established that VTE is linked to the presence of genetic risk factors. The most common are the Factor V Leiden and prothrombin G20210A mutations, which are present in approximately 7% of the general population.[3] Heterozygous individuals exhibit a 2- to 4-fold increased risk, while homozygosity for factor V Leiden carries an up to an 11-fold increased risk.[4]

The association between thrombophilia and an increased risk of cancer-associated VTE has been explored in several cancer cohorts yielding negative or only marginally positive results.[5] A meta-analysis found that cancer patients with non-O blood type had a higher risk of VTE (Odds Ratio [OR] 1.56 compared to O blood type) as did carriers of factor V Leiden (OR 2.28) and prothrombin G20210A (OR 2.14).[6] These findings were corroborated by a subsequent meta-analysis, which reported odds ratios for VTE among cancer patients heterozygous for factor V Leiden and prothrombin G20210A of 2.75 and 2.17, respectively, compared to cancer patients without thrombophilic mutations.[7] (Figure)

In contrast to previous studies of the role of thrombophilia in cancer-associated thrombosis, the study by Stevens et al.[1] provided robust statistical power through the analysis of over 40,000 cancer patients. All genetic factors assessed were linked to an increased risk of VTE. Factor V Leiden was associated with the highest risk, conferring a 1.8-fold increase in VTE risk among heterozygotes

and a 5.7-fold increase among homozygotes. However, for all other genotypes analyzed, the increased risk did not exceed an odds ratio of 1.5; in nearly all instances, these values were lower than those observed in non-cancer populations. The impact of genetic factors was most pronounced for Factor V Leiden in high-risk tumor types (1.76-fold in heterozygotes and 9.24-fold in homozygotes). However, the increase in risk was modest for other genotypes at less than 1.5-fold with the exceptions of SLC44A2 (1.6-fold in both heterozygotes and homozygotes). The lack of an additive effect between cancer and genetic risk factors for VTE is likely attributable to the overwhelming impact of cancer and antineoplastic therapies, which overshadow the contribution of genetic risk factors. To borrow from a classic metaphor, genetic thrombophilia in this context is akin to a fly sitting on the ox's horn and claiming “let's plow the field together.” The only genotype with notable clinical significance is homozygosity for factor V Leiden; however, this condition is extremely rare, occurring in just 20 out of 42,122 cancer patients (approximately 1 in 2,000), thus limiting its practical relevance.[1]

A fundamental limitation of this analysis, shared by most prior studies, is the focus on associations between thrombotic events and single genetic factors, without accounting for potential interactions between multiple genetic variants. In an analysis of 3,241 lung cancer patients from the UK Biobank, a high Polygenic Risk Score was associated with an increased risk of VTE. Though even with an elevated Polygenic Risk Score, the increase did not exceed 1.4-fold, irrespective of the presence of the Factor V Leiden or prothrombin G20210A mutations. Notably, clinical factors such as a history of prior VTE or the presence of metastases were linked to substantially higher risks (5.5-fold and 2.5-fold, respectively).[8]

However as emphasized by Stevens et al.[1], the combined analysis of genetic data and clinical features - such as tumor type - may provide more clinically meaningful insights for predicting thrombotic risk and personalizing antithrombotic prophylaxis. Indeed, evidence suggests that integrating genetic scores or multiple genetic risk factors with the Khorana classification or clinical data, such as BMI, cancer type, and disease stage, enhances prognostic stratification as compared to the Khorana Score alone.[9,10] Therefore, to optimize personalized risk profiling and obtain clinically useful data, future analyses of genetic risk factors for VTE must comprehensively account for all pertinent variables, including tumor type, disease stage, antineoplastic treatment modalities, and patient-specific risk factors such as age and history of thrombosis. Additionally, potential gene-gene interactions should be thoroughly evaluated and scored.

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Figure Legend

Risk factors for cancer-associated thrombosis. The size of the squares representing each risk factor is approximately proportional to its impact on the likelihood of thrombosis.

Risk factors for cancer-associated thrombosis

Multiple patient-, cancer-, and treatment-related factors contribute to thrombotic risk in cancer

Cancer-related factors

- Metastatic disease
- High tumor burden
- Pancreatic, gastric, brain, lung, ovarian, renal, and hematologic cancers
- Mucin-producing adenocarcinomas
- Release of procoagulant factors (e.g., tissue factor, cancer procoagulant)
- Inflammation and cytokine activation

Treatment-related factors

- Chemotherapy (especially platinum agents, L-asparaginase)
- Hormone therapy (e.g., tamoxifen)
- Anti-angiogenic agents (e.g., bevacizumab)
- Immunomodulatory agents (e.g., thalidomide, lenalidomide)
- Immunotherapy (e.g., checkpoint inhibitors)
- Radiotherapy
- Surgery (especially major or pelvic surgery)
- Central venous catheters

Cancer-associated thrombosis

Result of interactions between patient, cancer, and treatment factors leading to a prothrombotic state

Patient-related factors

- Prior history of venous thromboembolism
- Increasing age
- Reduced performance status (ECOG ≥2)
- Obesity (BMI ≥30 kg/m^2)
- Immobility or reduced mobility
- Comorbidities: cardiovascular disease, diabetes, chronic inflammatory diseases, infection

Genetic factors

- Factor V Leiden (F5 G1691A)
- Prothrombin G20210A mutation
- ABO group (non-O vs. O)
- Other SNPs
- Polygenic risk score

The contribution of genetic factors is of limited importance in comparison with cancer- and treatment-related factors or other patient-related factors such as prior history of venous thromboembolism or age.

CAT is multifactorial: risk assessment should be individualized to guide thromboprophylaxis and management.