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Prothrombotic genetic variants and cancer-associated venous thromboembolism: defining thrombotic risk across tumor types

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Data Sharing Statement

Data is available from researchers upon request.

Short Title: Prothrombotic genetic variants and cancer-associated venous thromboembolism

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Conflict of interest

H.S. declares no conflict of interest.

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Contributions

H.S. contributed to the design of the study, data analysis, data interpretation, drafting of the manuscript and final approval of the manuscript.

WH contributed to data analysis, data interpretation, drafting of the manuscript and final approval of the manuscript.

MS contributed to data analysis, data interpretation and final approval of the manuscript.

R.C. contributed to the data acquisition, data analysis, data interpretation and final approval of the manuscript.

H.T. contributed to the drafting and final approval of the manuscript.

F.T. contributed to the data analysis and interpretation, drafting and final approval of the manuscript.

K.P. contributed to design of the study, data interpretation, drafting and final approval of the manuscript.

J.D.M. contributed to the design of the study, data interpretation, drafting and final approval of the manuscript.

Abstract

Cancer-associated venous thromboembolism (CAT) is a major cause of mortality in cancer patients. Prothrombotic genetic variants increase venous thromboembolism risk in the general population, but contribution to CAT remains unclear, particularly within different tumor types. We sought to determine whether the presence of thrombophilic variants influence relative and absolute CAT risk, and may be utilised in thromboprophylaxis decision-making. We evaluated 398,053 UK Biobank participants, of whom 42,122 developed cancer. A panel of seven thrombophilic variants (ABO, FGG, FXI, FVL, PTM, SLC44A2 and TSPAN15) were evaluated using multistate models, and 2-year absolute risk was estimated using Aalen–Johansen methods. We report hazard ratios (HRs) adjusting for age, sex, and body mass index. CAT incidence was 7.82% versus 2.08% in non-cancer participants. In the non-cancer population, all seven variants were associated with a higher risk of VTE. In patients with cancer, FVL conferred the highest risk (HR 1.81 for one risk allele; HR 5.75 for two risk alleles), followed by SLC44A2 (HR 1.51 for one risk allele, 1.53 for two risk alleles). Genetic effects were greatest in high-risk cancers, including pancreatic and lung cancers. For FVL heterozygotes, 2-year absolute VTE risk approximately doubled in several malignancies, including 5.17% to 9.26% in colorectal cancer and from 4.16% to 10.59% in lymphoma. In conclusion, thrombophilic variants, particularly FVL and SLC44A2, significantly increase the relative risk of CAT, with the largest effects in high-risk cancers. FVL has a marked impact on absolute CAT risk. Integrating genetic variants with clinical predictors can improve personalized thromboprophylaxis strategies.

Introduction

Venous thromboembolism (VTE), including both deep vein thrombosis and pulmonary embolism, is a prevalent complication of cancer and is referred to as cancer-associated thrombosis (CAT). The incidence of CAT varies significantly by tumor type and individual risk factors, with the risk ranging from 1% to 10% at 12 months[1, 2], and several studies reporting that these rates continue to increase over time[2, 3]. Importantly, CAT is associated with a poorer prognosis and is one of the leading causes of death among cancer patients[2, 4, 5]. Preventing CAT is therefore critical, and thromboprophylaxis with low-dose anticoagulants is often considered. However, while randomized trials have demonstrated that thromboprophylaxis reduces CAT incidence, its use is associated with a higher risk of bleeding[6-8], so that routine thromboprophylaxis is not recommended in all patients with a cancer diagnosis[9-11].

To identify patients at high risk of CAT who may benefit from thromboprophylaxis, various clinical prediction models have been developed. The Khorana score is one of the original prediction models[12], with subsequent models such as the Vienna Cancer and Thrombosis Study (CATS) score, the PROphylaxis of ThromboEmbolism during CHemoTherapy (PROTECHT) and CONKO scores[13-15] incorporating biomarkers to enhance predictive accuracy. These models consider factors such as cancer type, performance status, body mass index, chemotherapy type and blood count parameters. Despite these advances, the accuracy of these models remains debated[16-19], necessitating ongoing research to optimize CAT risk prediction to ensure safe and appropriate thromboprophylaxis.

Whilst clinical and laboratory markers, as well as tumor type, are recognized determinants of CAT risk, the contribution of prothrombotic genetic variants, collectively termed inherited

thrombophilias, remains less well defined. Various studies have evaluated thrombophilias and CAT, with a focus on variants in Factor II (FII) such as prothrombin gene mutation (PTM)[20-25] , Factor V such as Factor V Leiden (FVL)[21-28], Factor XI (FXI)[22], ABO blood group[22, 25] and fibrinogen gamma gene (FGG)[22, 29], with development of risk scores based on some variants[30, 31]. Recently, novel genetic variants, such as in TSPAN15 and SLC44A2, have been associated with non-cancer VTE[32] but their potential impact on CAT has not been evaluated. Importantly, whether these common genetic variants influence CAT according to different tumor types is yet to be investigated.

To clarify the role of thrombophilic variants in CAT, we undertook a large, population-based study using the UK Biobank. Our primary aim was to determine whether these thrombophilic variants contributed to CAT risk in patients who develop cancer and, most importantly, identify potential indications for thromboprophylaxis.

To achieve this, we applied a multistate modeling framework that accounts for the competing risk of death and compared a panel of inherited thrombophilias among participants who developed cancer compared with those who remained cancer-free. We further examined these associations across tumor types associated with high, moderate, and low inherent thrombotic risk. Finally, to illustrate the potential clinical relevance of these findings, we quantified the absolute risk of CAT across all different tumor types. Through this approach, we define the contribution of inherited thrombophiilas in CAT and improve identification of patients at the highest risk of thrombosis.

Methods

Further information can be found in the **Supplementary Methods.**

Study design and population

Population-based cohort study using the UK Biobank, a prospective study of over 500,000 participants with linked health and genetic data[33]. The study design is shown in **Figure 1** and follows STROBE and STREGA guidelines.

Among 487,044 participants with linked data, analyses were restricted to individuals of European ancestry (n=408,709). Participants with missing body mass index (BMI) or smoking data (n=2,631) or prevalent warfarin use (n=4,081), to avoid attenuation of incident VTE risk due to baseline anticoagulation**,** were excluded. For multistate analyses, individuals with cancer diagnosed <14 days after enrolment were excluded (n=3,944), yielding 398,053 cancer-free participants (**Figure 1**)**.** Participants were followed from enrolment until first occurrence of non-cancer VTE, CAT, or death, or 9 February 2023, whichever occurred first.

Cancer definitions

Incident cancer was defined as first cancer diagnosis after study enrolment, identified through linkage to national cancer registries using ICD-10 codes (**Supplementary Table 1**). Time to cancer was calculated from enrolment to first cancer diagnosis. To examine differences in thrombotic risk across cancer types, tumor types were grouped according to observed cumulative lifetime incidence of CAT (**Figure 2**)**:** high-risk (≥10%), moderate-risk (5–<10%), and low-risk (<5%) (**Supplementary Table 2**).

Venous thromboembolism

VTE was identified using ICD-10 codes for pulmonary embolism (I26) and deep vein thrombosis (I80, I82). Time to first VTE was calculated from enrolment. CAT was defined as a VTE occurring within two years of cancer diagnosis.

Genetic variants

Seven genetic variants previously associated with inherited thrombophilia in non-cancer VTE were selected a priori: ABO rs8176719, FGG rs2066865, FVL rs6025, FXI rs2036914, PTM rs1799963, SLC44A2 rs2288904, and TSPAN15 rs78707713 (**Supplementary Table 3)**. Genotypes were coded additively according to the number of prothrombotic alleles (0, 1, or 2) and reference alleles were based on previous descriptions[34-40].

Outcomes

Primary outcomes were incident non-cancer VTE, CAT, and all-cause mortality. Outcomes were evaluated in the overall cancer population and tumor risk-stratified population.

Statistical analysis

Multistate models were used to describe disease progression and account for competing risk of death. Two multistate frameworks were specified:

1. Unselected cancer model **(Figure 3)** including five states:
   Healthy, non-cancer VTE, cancer, CAT, and death.
2. Tumor risk-stratified model **(Figure 4)** including seven states:
   Healthy, non-cancer VTE, low-risk cancer, moderate-risk cancer, high-risk cancer, CAT, and death.

States representing VTE, CAT, and death were treated as absorbing states. Transition diagrams and the number of participants in each state and transition are shown in **Figures 3 and 4.**

Cox proportional hazards regression was performed within the multistate framework to estimate hazard ratios (HR) and 95% confidence intervals (95% CI), adjusted for age, sex, smoking status, and BMI.

Cumulative incidence of CAT was estimated using the Aalen–Johansen estimator, which accounts for competing risks. Absolute two-year risks of CAT were calculated from the time of cancer diagnosis. Associations between genetic variants and CAT were assessed using Fine–Gray subdistribution hazard models. Multiple testing was addressed using the Benjamini–Hochberg false discovery rate, with $q<0.05$ considered statistically significant. All statistical analyses were conducted using R version 4.3.2.

Ethics

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (11/NW/0382). All participants provided written informed consent. This research was conducted under UK Biobank application 55469.

Results

Overall, 398,053 participants were included in the analysis. Of these, 42,122 developed cancer and 355,931 did not develop cancer. The clinical characteristics for the study cohort are shown in **Table 3**. The median age at baseline was 62 years (interquartile range [IQR] 9) in the cancer population and 58 years (IQR 13) for the non-cancer population. The median age at cancer diagnosis was 68 years (IQR 10). The median BMI was 27 (IQR 6) in both

study groups, and smoking was more common in the cancer population compared with the non-cancer population (12.37% vs 9.88%, respectively). The incidence of the risk alleles for the study populations is outlined in **Table 3.** The cumulative 2-year incidence of CAT was 7.82% in the cancer population and the overall cumulative incidence of VTE was 2.08% in the non-cancer population. Death during the total study follow-up period occurred in 14,210 (33.20%) participants within the cancer population and 19,975 (5.62%) individuals within the non-cancer population.

The first part of our study considered the effect of the prothrombotic genetic variants on developing CAT in the total cancer population and compared this to the risk of VTE in the non-cancer population. In both cancer and non-cancer states, using the subjects with 0 risk alleles as reference, we demonstrate that each of the genetic variants in both the heterozygous and homozygous forms are associated with a higher risk of CAT and non-cancer VTE **(Figure 5; Supplementary Table 4).** The exception was TSPAN15 (rs78707713), where only the homozygous state (T/T) was found to be significantly associated with non-cancer VTE, and we find no association with between TSPAN15 and CAT.

In the non-cancer population, the variants with the strongest association with VTE were PTM (rs1799963) and FVL (rs6025) both in the homozygous form (HR 5.37, 95% CI 2.23 – 12.91; HR 3.50, 95% CI 1.93 – 6.32, respectively) **(Figure 5; Supplementary Table 4)**. In the cancer population, the variant with the strongest association with CAT was FVL (rs6025) with both 1 or 2 risk alleles (HR for FVL 1 risk allele: 1.81; 95% CI 1.50 – 2.18; HR for 2 risk alleles: 5.75; 95% CI, 1.85 – 17.91), followed by the SLC44A2 (rs2288904) for either 1 risk allele (HR 1.51; 95% CI, 1.14 – 2.00) or 2 risk alleles (HR, 1.53; 95% CI 1.16 – 2.02).

These data demonstrate a novel association between SLC44A2 (rs2288904) and a higher risk of CAT **(Figure 5; Supplementary Table 4).**

It is well appreciated that different tumor types confer differing thrombotic risks. However, the contribution of inherited thrombophilias to these tumor-specific risks has not been investigated. To address this, we next evaluated the association between prothrombotic genetic variants and CAT across tumor types classified as high, moderate, or low risk for thrombosis as outlined in the methods. The 2-year cumulative incidence of CAT was 8.29% in the high-risk cancer population, 4.54% in the moderate-risk group, and 1.22% in the low-risk group **(Table 2).** The results are shown in **Supplementary Table 5**. Here, we show that the genetic associations with CAT differed significantly by cancer risk group. In the high-risk group, the strongest and most consistent associations were observed, including with FVL (rs6025) (HR for 2 risk alleles 9.24, 95% CI 2.28 – 37.39; HR for 1 risk allele 1.76, 95% CI 1.37 – 2.26) and SLC44A2 (rs2288904) (HR for 2 risk alleles 1.69, 95% CI 1.16 – 2.46; HR for 1 risk allele 1.64, 95% CI 1.12 – 2.39). We again demonstrate no association between TSPAN15 and CAT, and also found no association with PTM, likely due to small numbers. In the moderate-risk group, only 2 variants, FVL and PTM were found to have significant associations (HR 2.15 [1.54-3.02] and HR 1.76 [1.08–2.86], respectively), and in the low-risk group only FVL showed an association with CAT and only in the homozygous state (HR 12.18, 95% CI 1.69-87.62). Overall, we observed a graded pattern in which genetic effects were most pronounced and consistent in high-risk cancers, with diminishing and largely non-significant associations in the moderate- and low-risk categories.

Given the importance of absolute CAT risk in guiding thromboprophylaxis decisions, we assessed the effect of each genetic variant on the 2-year absolute risk of VTE within

individual tumor types **(Supplementary Part 6).** Among the inherited thrombophilias, FVL (rs6025) showed the most consistent trend toward higher absolute VTE risk across tumor groups. Comparing individuals with 0 versus 1 risk allele, absolute risk was approximately doubled in several tumor types, including pancreatic (12.23% vs 20.83%), CNS (8.94% vs 14.71%), colorectal (5.17% vs 9.26%), and lymphoma (4.16% vs 10.59%). Similar patterns were observed in tumor types with low baseline thrombotic risk (breast, prostate, testicular cancer, and melanoma), although absolute risks remained low (<1–2% over 2 years). However, adjusted p values (q-value) did not consistently reach statistical significance, reflecting limited sample sizes within tumor types despite directionally consistent trends.

Discussion

In this large population-based analysis of the UK Biobank we have shown that several established variants, and a novel prothrombotic genetic variant, SLC44A2, are associated with an increased risk of CAT. Associations were most consistent and of largest magnitude in cancers with high baseline VTE risk (e.g., pancreatic, lung and gastroesophageal cancers) and were attenuated or not present in moderate-risk and low-risk cancer groups. Notably, we report a novel association between SLC44A2 (rs2288904) and CAT and confirm strong associations for FVL (rs6025) in patients with cancer. Intriguingly, and in contrast to previous studies[32], we show that TSPAN15 (rs78707713) is associated with VTE in the homozygous form (T/T) and is not associated with CAT. Using multistate modelling and Aalen–Johansen cumulative incidence estimates to account for competing risk of death, we demonstrate how FVL significantly alters absolute VTE risk in specific tumor subtypes, and we establish a markedly higher 2-year cumulative incidence in several cancers, including colorectal cancer and lymphoma.

While the relationship between some genetic variants and CAT has been shown previously[20, 21, 27-29, 41], our study extends and clarifies the contribution of these prothrombotic variants in cancer by using a competing risk framework and leveraging the large sample size and long-term follow up of the UK Biobank. This approach allowed us to generate robust estimates within tumor subtypes with differing thrombotic risk and evaluate both relative and absolute VTE risk. We observed a pattern of stronger and more consistent genetic effects in the high-risk cancer group, with largely absent associations in the moderate- and low-risk groups, except for FVL. These differences could reflect synergy with genetically determined procoagulant mechanisms and tumor-related procoagulant processes, or increased exposure to treatments such as surgery or cytotoxic therapies. This apparent gradient in risk of CAT with inherited thrombophilias across tumor risk groups has not been demonstrated previously, and future studies could explore whether inherited thrombophilias exert an additive or synergistic effect, particularly within high-risk tumor types.

The association between SLC44A2 and CAT has not previously been described, and the exact mechanism by which it increases thrombotic risk is not fully understood. SLC44A2 has been linked to platelet activation, platelet-neutrophil interactions, and neutrophil extracellular trap formation[42-44], which are known to be central to the formation of venous thrombi[45-47]. Intriguingly, lower levels of SLC44A2 have been associated with improved survival in pancreatic adenocarcinoma[48], and elucidating the role of this gene and protein in hypercoagulability and the impact on the malignancy will provide valuable insights and may offer a novel therapeutic target. Intriguingly, while both SLC44A2 and TSPAN15 have been associated with modest increases in VTE risk in prior genome-wide association studies[49], only SLC44A2 demonstrated an association with CAT in this cohort. In contrast, TSPAN15 was associated with non-cancer VTE but not CAT suggesting potential context-specific

effects and highlighting differences in the mechanisms underlying cancer-related and non-cancer-related thrombosis.

In patients with cancer, the use of pharmacological thromboprophylaxis must balance the risk of thrombosis and bleeding. Primary thromboprophylaxis with low-dose anticoagulation reduces the risk of CAT but increases bleeding risk[6-8]. Therefore, accurately identifying patients at highest risk of CAT is crucial. The Khorana score, commonly used to predict risk of CAT has only a modest sensitivity of identifying patients at the highest risk of CAT[12, 17]. Recent studies have shown the addition of polygenic risk scores (PRS) to clinical predictors improves predictive accuracy, increasing VTE risk prediction by 1.9-fold independent of cancer type[31]. Despite these advancements, PRS are not yet widely used due to their complexity and cost, but support the role of genetic analysis in CAT. Our research demonstrates that several SNPs offer predictive value comparable to PRS. In particular, the evaluation of FVL in malignancies with high or moderate inherent risk of VTE can identify a cohort of patients with a 10 to 20% risk of CAT where thromboprophylaxis should be strongly considered. Importantly, testing for FVL is commonly performed and widely available and could be easily instituted within clinical practice. Our findings suggest that integrating a limited panel of thrombophilia testing into clinical practice could provide a more accessible and cost-effective approach for identifying patients at high risk of CAT.

The strengths of this study include the large and well-characterized study cohort with genotype data, long follow-up and rigorous competing-risk methods. Limitations of the study include the predominance of European ancestry in the UK Biobank which may limit the generalizability to other ethnic groups. In addition, detailed clinical data on key VTE risk modifiers, such as cancer stage, cancer therapies, thromboprophylaxis, and disease

recurrence, were not available. These factors are important determinants of CAT risk, and their absence may result in residual confounding and limit the precision of risk stratification in this study. Finally, family history of VTE is a recognised modifier of thrombotic risk in inherited thrombophilia and may further increase risk among carriers of variants such as factor V Leiden[50, 51]. However, family history data specific to VTE are not available in the UK Biobank, and thus this limitation may reduce the precision of individual risk estimates based on genotype alone. Further research is needed to explore these areas.

As the global population ages, the incidence of cancer and CAT is expected to rise, posing significant health challenges[2, 52]. Current methods to predict for CAT have moderate sensitivity, and up to 50% of all thrombotic events are diagnosed in patients deemed to be at low-risk of CAT[17]. Thus, a reliable gold standard risk assessment tool is highly sought-after. Our findings demonstrate that several prothrombotic genetic variants are significantly associated with CAT, particularly in tumor types considered to be at higher risk of thrombosis. Integrating prothrombotic genetic variants with clinical predictors, especially tumor types, holds promise to improve identification of cancer patients at high risk of VTE and inform personalized thromboprophylaxis strategies, with the ultimate goal of minimizing the significant morbidity and mortality of CAT.

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Table 1: Summary of Clinical Events by Cancer and Non-Cancer Populations

Cohort	Total entering	VTE	CAT	Death	No event
Non-cancer population, (%)	355931	8052 (2.26)	N/A	17911 (5.03)	329968 (92.71)
Cancer population	42122	N/A	1661 (3.94)	7155 (16.99)	33306 (79.07)

Abbreviations: CAT, cancer-associated venous thromboembolism; VTE, venous thromboembolism.

Table 2: Summary of Clinical Events When Comparing Cancer Risk Groups to the Non-Cancer Population

Cohort	Total entering	VTE	CAT	Death	No event
Non-Cancer, n (%)	355931	8052 (2.26)	N/A	17911 (5.03)	329968 (92.71)
Low-Risk Cancer, n (%)	20680	N/A	253 (1.22)	636 (3.08)	19791 (95.70)
Moderate-Risk Cancer, n (%)	9852	N/A	447 (4.54)	1707 (17.33)	7698 (78.14)
High-Risk Cancer, n (%)	11590	N/A	961 (8.29)	4812 (41.52)	5817 (50.19)

Abbreviations: CAT, cancer-associated venous thromboembolism; VTE, venous thromboembolism.

Table 3: Demographics and Clinical Characteristics of the Study Population

Characteristic	Non-cancer population	Cancer population
Individuals, n	355,931	42,122
Female, n (%)	196,087 (55.1%)	20,240 (48.1%)
Age at baseline, median (IQR)	58.0 (50.0–63.0)	62.0 (56.0–65.0)
Age at diagnosis/reference age, median (IQR)	–	67.6 (62.2–71.9)
BMI, median (IQR)	26.7 (24.1–29.8)	27.1 (24.5–30.2)
Current tobacco smoker, n (%)	35,231 (9.9%)	5,180 (12.3%)
VTE, n (%)	8,052 (2.3%)	1,661 (3.9%)
Deaths, n (%)	20,319 (5.7%)	8,279 (19.7%)
ABO (rs8176719)		
0	155,208 (43.6%)	18,330 (43.5%)
1	160,142 (45.0%)	18,909 (44.9%)
2	40,581 (11.4%)	4,883 (11.6%)
FGG (rs2066865)		
0	205,476 (57.7%)	24,263 (57.6%)
1	129,730 (36.4%)	15,370 (36.5%)
2	20,725 (5.8%)	2,489 (5.9%)
FVL (rs6025)		
0	339,755 (95.5%)	40,311 (95.7%)
1	16,010 (4.5%)	1,791 (4.3%)
2	166 (0.0%)	20 (0.0%)
FXI (rs2036914)		
0	81,833 (23.0%)	9,652 (22.9%)
1	177,565 (49.9%)	21,029 (49.9%)
2	96,533 (27.1%)	11,441 (27.2%)
PTM (rs1799963)		
0	347,585 (97.7%)	41,199 (97.8%)
1	8,301 (2.3%)	920 (2.2%)
2	45 (0.0%)	3 (0.0%)
SLC44A2 (rs2288904)		
0	17,628 (5.0%)	1,996 (4.7%)
1	123,557 (34.7%)	14,696 (34.9%)
2	214,746 (60.3%)	25,430 (60.4%)
TSPAN15 (rs78707713)		
0	5,977 (1.7%)	719 (1.7%)
1	80,370 (22.6%)	9,603 (22.8%)
2	269,584 (75.7%)	31,800 (75.5%)

Abbreviations: BMI, body mass index; FGG, Fibrinogen Gamma Gene; FVL, Factor V Leiden; IQR, interquartile range; N, number; PTM, prothrombin mutation; VTE, venous thromboembolism

Figure Legend

Figure 1: Overview of Study Design

Created in BioRender. Stevens, H. (2026) https://BioRender.com/kxhhzzk

Figure 2: Incidence of Cancer-associated Venous Thromboembolism by Tumor Type

Created in BioRender. Stevens, H. (2026) https:// BioRender.com/18wr3od

Figure 3: Overview of Multistate Model Comparing Risk of Venous Thromboembolism and Death in Cancer and Non-Cancer Cohorts

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Figure 4: Overview of Multistate Model Comparing Risk of Venous Thromboembolism and Death between Cancer Risk Groups and the Non-Cancer Population

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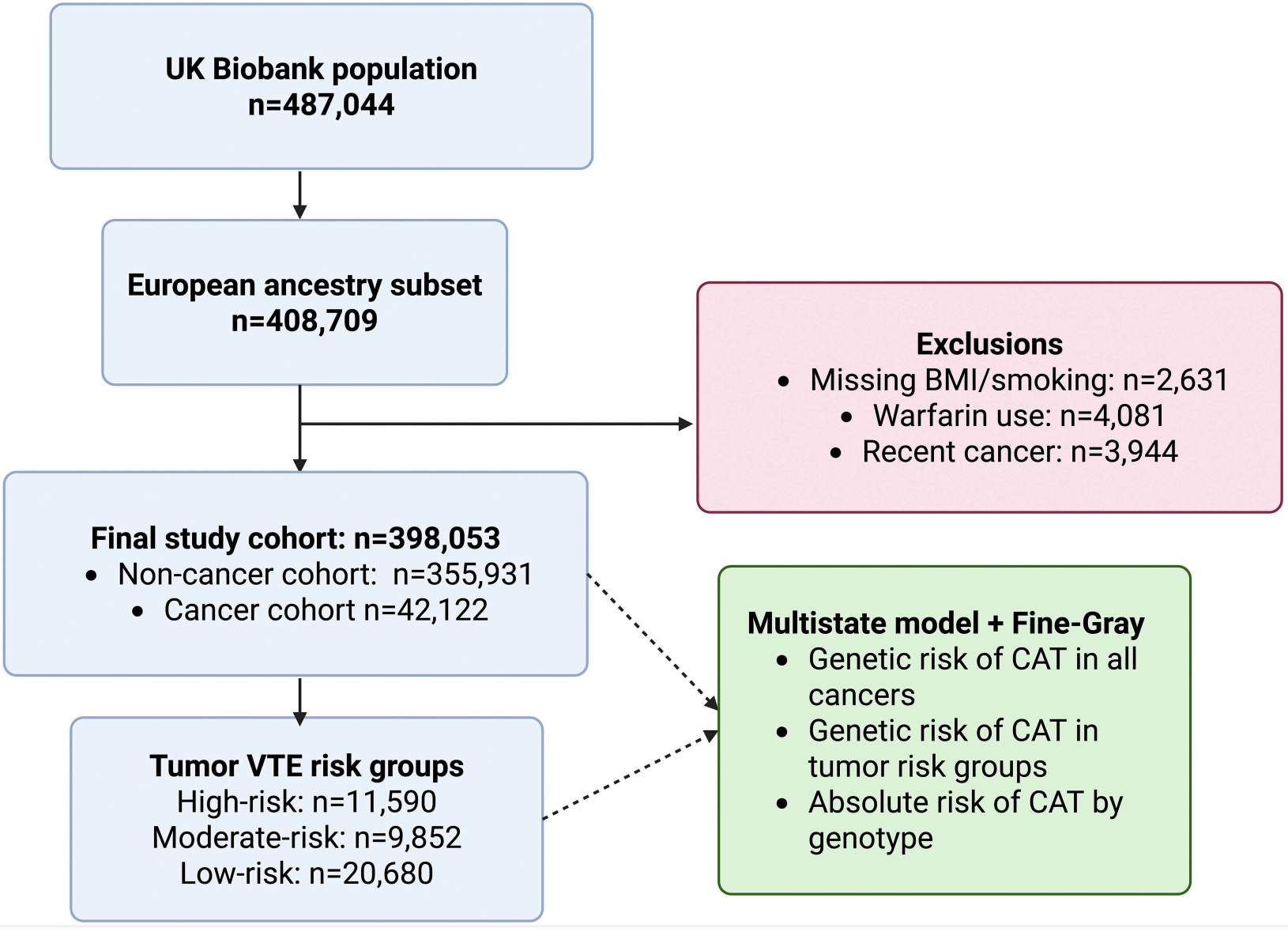
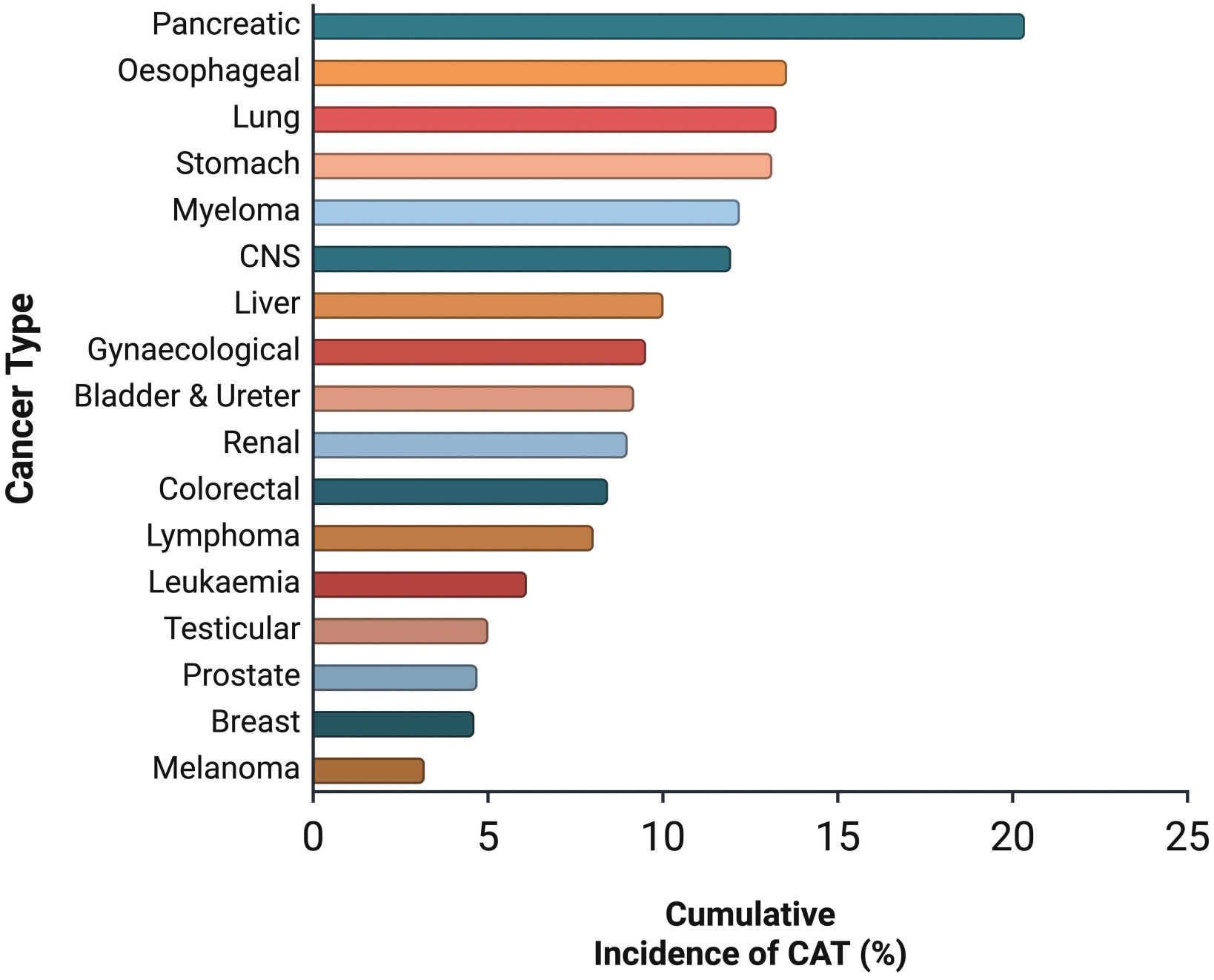
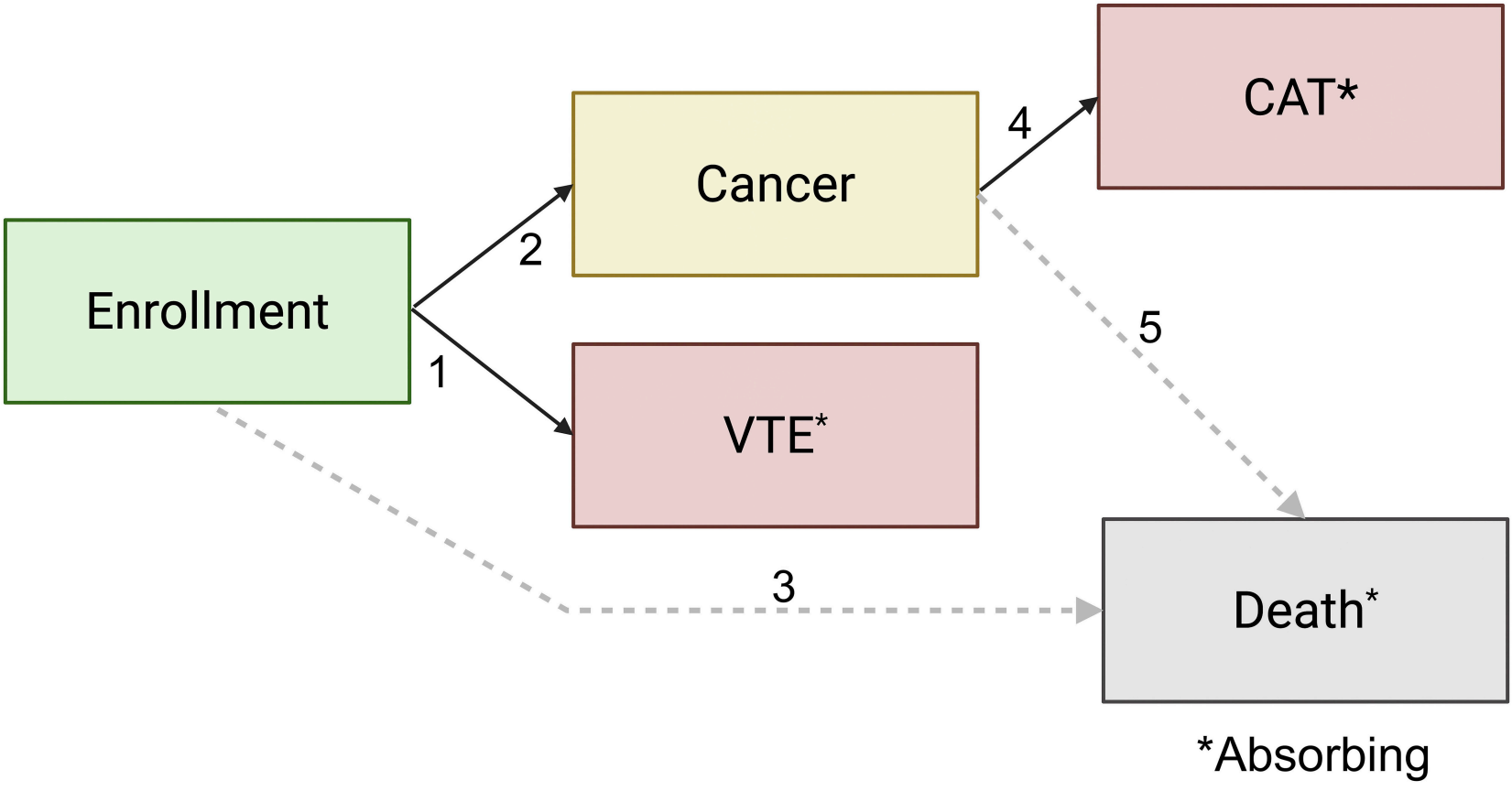
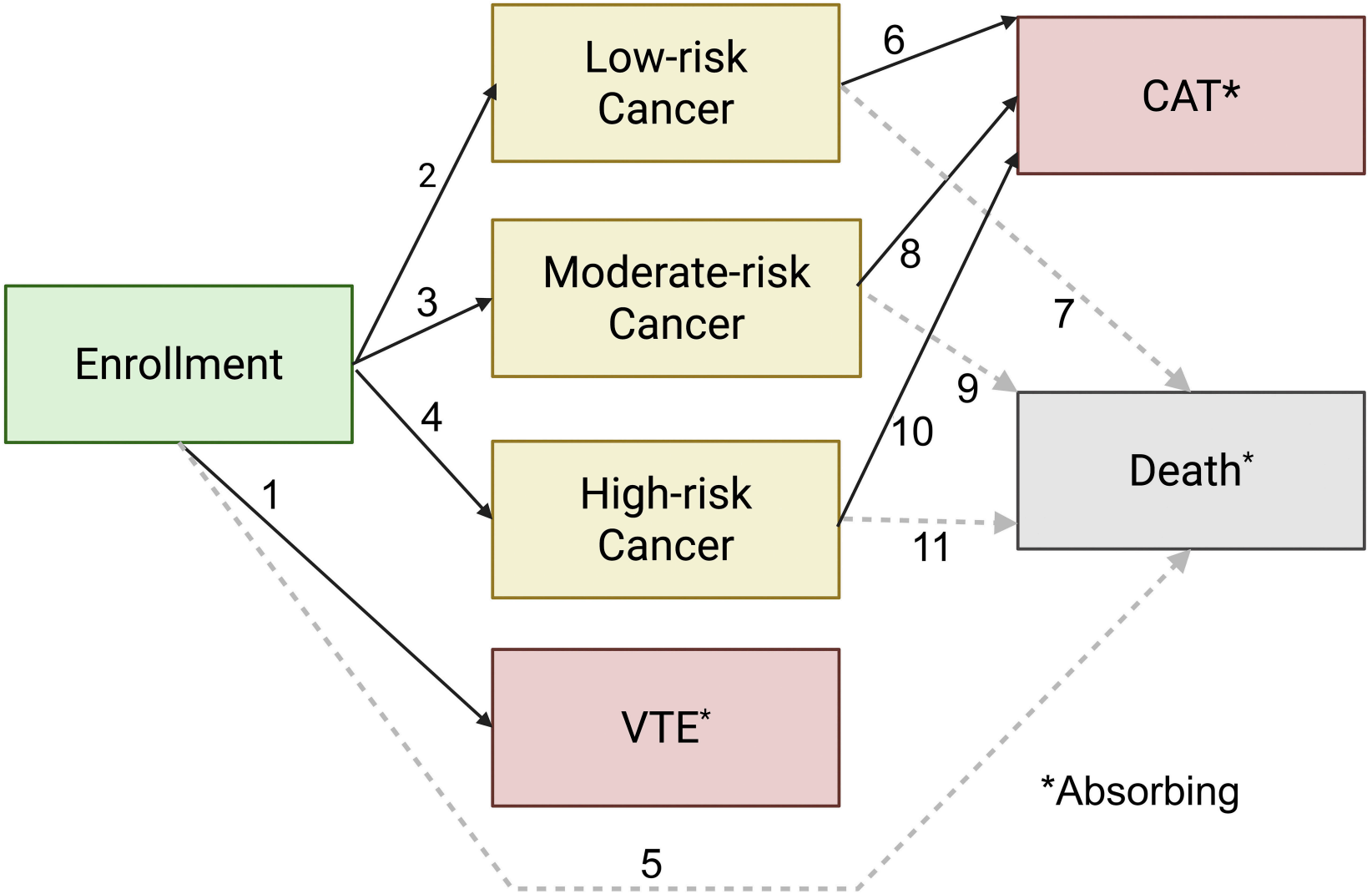
Figure 5: Hazard ratios for venous thromboembolism in the non-cancer and cancer populations for each of the thrombophilic variants

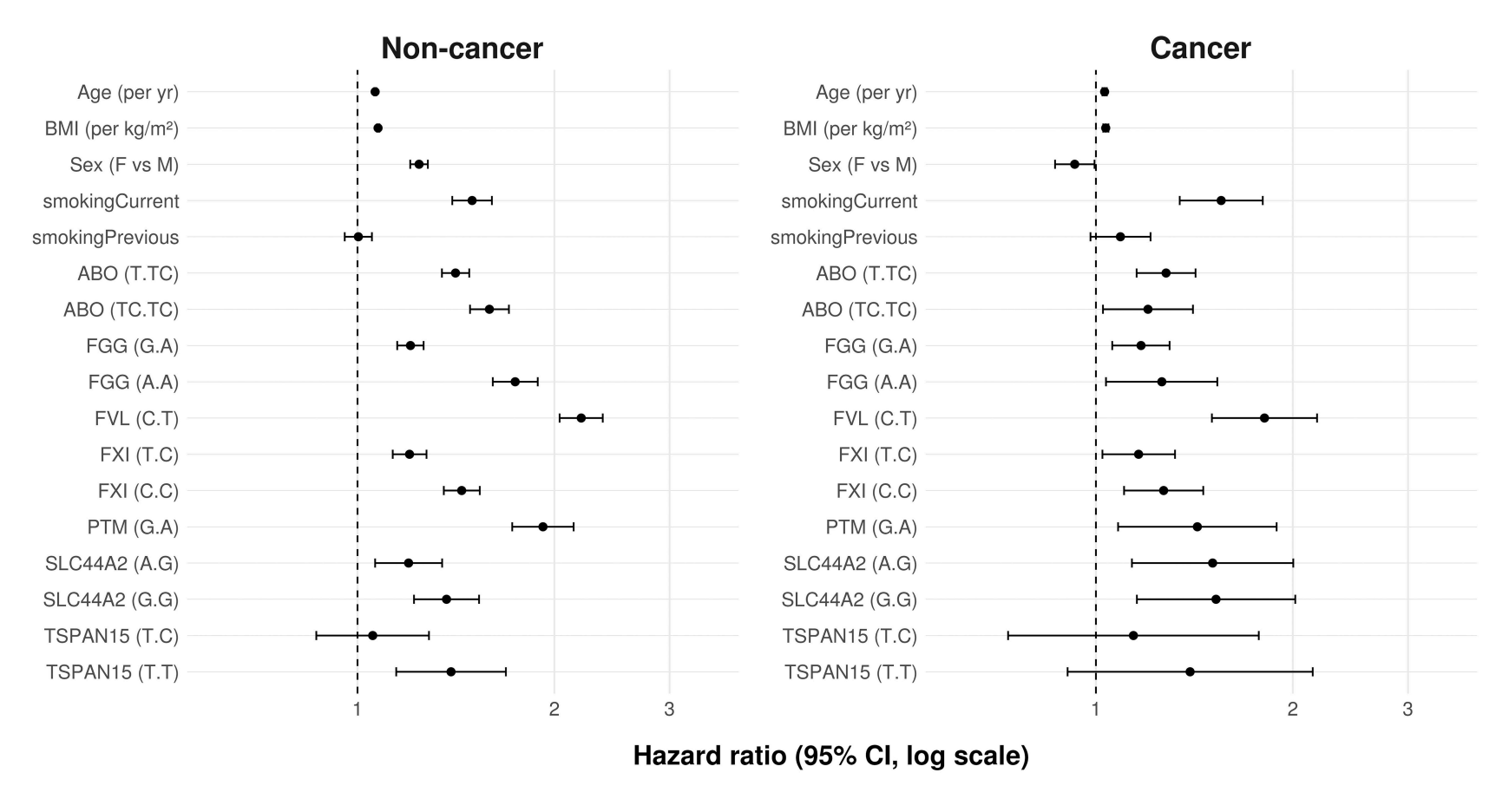
Homozygous variants for FVL and PTM in the cancer cohort were excluded from the plot due to low sample size (n=20 and n=3, respectively) and resulting wide confidence intervals/model instability; full data is available in Supplementary Table 4.


UK Biobank population
n=487,044
European ancestry subset
n=408,709
Exclusions
Missing BMI/smoking: n=2,631
Warfarin use: n=4,081
Recent cancer: n=3,944
Final study cohort: n=398,053
Non-cancer cohort: n=355,931
Cancer cohort n=42,122
Tumor VTE risk groups
High-risk: n=11,590
Moderate-risk: n=9,852
Low-risk: n=20,680
Multistate model + Fine-Gray
Genetic risk of CAT in all cancers
Genetic risk of CAT in tumor risk groups
Absolute risk of CAT by genotype


Pancreatic
Oesophageal
Lung
Stomach
Myeloma
CNS
Liver
Gynaecological
Bladder & Ureter
Renal
Colorectal
Lymphoma
Leukaemia
Testicular
Prostate
Breast
Melanoma
Cancer Type
0
5
10
15
20
25
Cumulative
Incidence of CAT (%)


Enrollment
Cancer
CAT*
VTE*
Death*
1
2
3
4
5
*Absorbing


Low-risk Cancer
Moderate-risk Cancer
High-risk Cancer
CAT*
Death*
VTE*
Enrollment
1
2
3
4
5
6
7
8
9
10
11
*Absorbing


Non-cancer
Cancer
Age (per yr)
BMI (per kg/m²)
Sex (F vs M)
smokingCurrent
smokingPrevious
ABO (T.TC)
ABO (TC.TC)
FGG (G.A)
FGG (A.A)
FVL (C.T)
FXI (T.C)
FXI (C.C)
PTM (G.A)
SLC44A2 (A.G)
SLC44A2 (G.G)
TSPAN15 (T.C)
TSPAN15 (T.T)
1
2
3
Hazard ratio (95% CI, log scale)

Supplementary online data

Supplementary Methods

UK Biobank cohort and data sources

UK Biobank is a large prospective cohort study that recruited over 500,000 participants aged 40–69 years at enrolment between 2006 and 2010. Participants provided detailed demographic, lifestyle, and health information at baseline, underwent physical measurements, and donated biological samples for genotyping. Longitudinal follow-up is achieved through linkage to national hospital admissions data, cancer registries, and death registries.

Ancestry determination

Genetic ancestry was determined using principal component analysis provided by UK Biobank. Analyses were restricted to participants of European ancestry to minimise population stratification.

Genotyping and quality control

UK Biobank participants were genotyped using the UK BiLEVE Axiom array or the UK Biobank Axiom array (Affymetrix). Standard quality control procedures were applied centrally by UK Biobank, including exclusion of poorly performing variants and samples. Genotype data were phased and imputed using the Haplotype Reference Consortium and UK10K reference panels. Imputed genotype dosages aligned to the GRCh37 reference genome were used for analysis.

Software

All analyses were performed using R version 4.3.2, with the survival, cmprsk, mstate, etm, and survminer packages.

Supplementary Table 1. ICD-10 Codes used for Cancer Classification

Cancer Type	ICD-10 code
Esophageal	C15*
Gastric	C16*
Colorectal	C18*, C19*, C20*, C21*
Liver	C22*
Pancreatic	C25*
Lung	C34*
Melanoma	C43*
Breast	C50*
Gynecological	C51*, C52*, C53*, C54*, C55*, C56*, C57*
Prostate	C61*
Testicular	C62*
Renal	C64*, C65*
Bladder and ureter	C66*, C67*, C68*
Central nervous system	C70*, C71*, C72*
Lymphoma	C81*, C82*, C83*, C84*, C85*, C86*, C88*
Myeloma	C90*
Leukemia	C91*, C92*, C93*, C94*, C95*, C96*

Abbreviations: ICD-10, International Classification of Diseases, 10th Modification

Supplementary Table 2. Incidence of Cancer-associated Venous Thromboembolism by Cancer Type

Type of Cancer	Number of cancer cases	Lifetime incidence of CAT, n (%)	Number of cancer cases (2-year incidence)	2-year cumulative incidence of CAT, n (%)
Pancreatic	1,253	255 (20.35)	1227	150 (12.23)
Oesophageal	1,100	149 (13.55)	1022	100 (9.80)
Lung	4,016	532 (13.25)	3866	303 (7.84)
Stomach	754	99 (13.13)	681	66 (9.69)
Myeloma	951	116 (12.2)	841	44 (5.23)
Central nervous system	837	100 (11.95)	750	67 (8.94)
Liver	619	62 (10.02)	599	32 (5.36)
Gynaecological	4,065	387 (9.52)	2691	160 (5.95)
Bladder and Ureter	1,612	148 (9.18)	1243	77 (6.20)
Renal	1,791	161 (8.99)	1521	55 (3.62)
Colorectal	7,085	597 (8.43)	5652	292 (5.17)
Lymphoma	3,018	242 (8.02)	2259	94 (4.16)
Leukaemia	1,604	98 (6.11)	1288	23 (1.79)
Testicular	479	24 (5.01)	86	2 (2.33)
Prostate	11,826	556 (4.70)	10065	115 (1.14)
Breast	13,864	639 (4.61)	8591	128 (1.49)
Melanoma	4,136	132 (3.19)	2923	18 (0.62)

Supplementary Table 3: Genetic Variants Included in the Thrombophilia Panel and Their Allele Frequencies in UK Biobank

Gene/locus	rsID	Reference allele	Risk/ alternative allele	Minor allele (UKB European ancestry)	Risk allele frequency (approx.)
FVL	rs6025	C (major)	T	T	2.2%
PTM	rs1799963	G (major)	A	A	1.2%
FGG	rs2066865	G (major)	A	A	24.2%
FXI	rs2036914	T	C (major)	T	52.3% (C allele)
ABO	rs8176719	T (deletion = O blood group)	TC insertion (non-O)	TC insertion	34.0% (non-O)
TSPAN15	rs78707713	C (minor)	T (major)	C	87.6% (T allele)
SLC44A2	rs2288904	A (minor)	G (major)	A	77.9% (G allele)

Supplementary Table 4: Associations of Selected Prothrombotic Genetic Variants with Venous Thromboembolism in Non-Cancer and Cancer Populations

Cohort	Variant	rsid	Level	HR (95% CI)	p-value	q-value^	Significance+
Non-cancer	ABO	rs8176719	T.TC	1.41 (1.35–1.48)	3.62E-45	5.07E-44	***
Non-cancer	ABO	rs8176719	TC.TC	1.59 (1.49–1.70)	2.67E-40	1.87E-39	***
Non-cancer	FGG	rs2066865	A.A	1.74 (1.61–1.89)	6.06E-43	5.66E-42	***
Non-cancer	FGG	rs2066865	G.A	1.20 (1.15–1.26)	2.77E-15	1.11E-14	***
Non-cancer	FVL	rs6025	C.T	2.20 (2.04–2.37)	7.97E-92	2.23E-90	***
Non-cancer	FVL	rs6025	T.T	3.50 (1.93–6.32)	3.37E-05	7.87E-05	***
Non-cancer	FXI	rs2036914	C.C	1.44 (1.35–1.54)	7.96E-30	3.72E-29	***
Non-cancer	FXI	rs2036914	T.C	1.20 (1.13–1.27)	1.21E-09	3.78E-09	***
Non-cancer	PTM	rs1799963	A.A	5.37 (2.23–12.91)	1.72E-04	3.71E-04	***
Non-cancer	PTM	rs1799963	G.A	1.92 (1.72–2.14)	2.38E-32	1.33E-31	***
Non-cancer	SLC44A2	rs2288904	A.G	1.20 (1.06–1.35)	2.72E-03	4.23E-03	**
Non-cancer	SLC44A2	rs2288904	G.G	1.37 (1.22–1.53)	8.55E-08	2.39E-07	***
Non-cancer	TSPAN15	rs78707713	T.C	1.05 (0.87–1.29)	5.97E-01	6.19E-01	
Non-cancer	TSPAN15	rs78707713	T.T	1.39 (1.15–1.69)	8.18E-04	1.53E-03	**
Cancer	ABO	rs8176719	T.TC	1.28 (1.15–1.42)	3.01E-06	7.66E-06	***
Cancer	ABO	rs8176719	TC.TC	1.20 (1.02–1.41)	2.37E-02	2.76E-02	*
Cancer	FGG	rs2066865	A.A	1.26 (1.04–1.53)	2.04E-02	2.57E-02	*
Cancer	FGG	rs2066865	G.A	1.17 (1.06–1.30)	2.06E-03	3.60E-03	**
Cancer	FVL	rs6025	C.T	1.81 (1.50–2.18)	3.47E-10	1.22E-09	***
Cancer	FVL	rs6025	T.T	5.76 (1.85–17.91)	2.49E-03	4.09E-03	**
Cancer	FXI	rs2036914	C.C	1.27 (1.10–1.46)	7.98E-04	1.53E-03	**
Cancer	FXI	rs2036914	T.C	1.16 (1.02–1.32)	2.11E-02	2.57E-02	*
Cancer	PTM	rs1799963	A.A	0.00 (0.00–6.32e+129)	9.59E-01	9.59E-01	

Cancer	**PTM**	**rs1799963**	**G.A**	**1.43 (1.08–1.89)**	**1.21E-02**	**1.61E-02**	*
Cancer	**SLC44A2**	**rs2288904**	**A.G**	**1.51 (1.14–2.00)**	**4.55E-03**	**6.36E-03**	**
Cancer	**SLC44A2**	**rs2288904**	**G.G**	**1.53 (1.16–2.02)**	**2.94E-03**	**4.33E-03**	**
Cancer	**TSPAN15**	**rs78707713**	**T.C**	**1.14 (0.73–1.77)**	**5.59E-01**	**6.02E-01**	
Cancer	**TSPAN15**	**rs78707713**	**T.T**	**1.39 (0.91–2.14)**	**1.32E-01**	**1.48E-01**	

Abbreviations: FVL, Factor V Leiden; FGG, fibrinogen gamma gene; FXI, factor XI; p -adj, Benjamini-Hochberg corrected p-value, PTM, prothrombin mutation; SLC44A2, solute carrier family 44 member 2; TSPAN15, tetraspanin 15;

[^]q-value shows Benjamini-Hochberg corrected p values, where q <0.05 is considered statistically significant.

[+] Significance codes:
<0.001: ***
<0.01: **
<0.05: *

Supplementary Table 5: Associations of Thrombophilias with Venous Thromboembolism within the Cancer Risk Groups and the Non-Cancer Population.

Cohort	Variant	rsid	Level	HR (95% CI)	p-value	q-value^	Significance+
No cancer	ABO	rs8176719	T.TC	1.41 (1.35–1.48)	3.62E-45	9.96E-44	***
No cancer	ABO	rs8176719	TC.TC	1.59 (1.49–1.70)	2.67E-40	3.67E-39	***
No cancer	FGG	rs2066865	A.A	1.74 (1.61–1.89)	6.06E-43	1.11E-41	***
No cancer	FGG	rs2066865	G.A	1.20 (1.15–1.26)	2.77E-15	2.18E-14	***
No cancer	FVL	rs6025	C.T	2.20 (2.04–2.37)	7.97E-92	4.39E-90	***
No cancer	FVL	rs6025	T.T	3.50 (1.93–6.32)	3.37E-05	1.43E-04	***
No cancer	FXI	rs2036914	C.C	1.44 (1.35–1.54)	7.96E-30	7.30E-29	***
No cancer	FXI	rs2036914	T.C	1.20 (1.13–1.27)	1.21E-09	8.35E-09	***
No cancer	PTM	rs1799963	A.A	5.37 (2.23–12.91)	1.72E-04	6.77E-04	***
No cancer	PTM	rs1799963	G.A	1.92 (1.72–2.14)	2.38E-32	2.62E-31	***
No cancer	SLC44A2	rs2288904	A.G	1.20 (1.06–1.35)	2.72E-03	7.88E-03	**
No cancer	SLC44A2	rs2288904	G.G	1.37 (1.22–1.53)	8.55E-08	5.23E-07	***
No cancer	TSPAN15	rs78707713	T.C	1.05 (0.87–1.29)	5.97E-01	6.84E-01	
No cancer	TSPAN15	rs78707713	T.T	1.39 (1.15–1.69)	8.18E-04	2.65E-03	**
CancerLow	ABO	rs8176719	T.TC	1.34 (1.02–1.76)	3.30E-02	6.51E-02	
CancerLow	ABO	rs8176719	TC.TC	1.47 (1.00–2.15)	4.92E-02	9.33E-02	
CancerLow	FGG	rs2066865	A.A	1.02 (0.59–1.77)	9.49E-01	9.93E-01	
CancerLow	FGG	rs2066865	G.A	1.18 (0.92–1.53)	1.98E-01	3.03E-01	
CancerLow	FVL	rs6025	C.T	1.59 (0.97–2.61)	6.40E-02	1.17E-01	
CancerLow	FVL	rs6025	T.T	12.18 (1.69–87.62)	1.30E-02	3.11E-02	*
CancerLow	FXI	rs2036914	C.C	1.12 (0.79–1.59)	5.13E-01	6.33E-01	

CancerLow	FXI	rs2036914	T.C	0.99 (0.72–1.36)	9.44E-01	9.93E-01	
CancerLow	PTM	rs1799963	G.A	1.42 (0.70–2.88)	3.27E-01	4.39E-01	
CancerLow	SLC44A2	rs2288904	A.G	1.39 (0.67–2.88)	3.73E-01	4.88E-01	
CancerLow	SLC44A2	rs2288904	G.G	1.56 (0.77–3.18)	2.18E-01	3.15E-01	
CancerLow	TSPAN15	rs78707713	T.C	3.34 (0.46–24.30)	2.33E-01	3.28E-01	
CancerLow	TSPAN15	rs78707713	T.T	4.93 (0.69–35.22)	1.11E-01	1.92E-01	
CancerMed	ABO	rs8176719	T.TC	1.25 (1.02–1.52)	2.88E-02	6.10E-02	
CancerMed	ABO	rs8176719	TC.TC	1.11 (0.81–1.52)	5.29E-01	6.33E-01	
CancerMed	FGG	rs2066865	A.A	1.50 (1.05–2.12)	2.43E-02	5.35E-02	
CancerMed	FGG	rs2066865	G.A	1.06 (0.87–1.29)	5.83E-01	6.82E-01	
CancerMod	FVL	rs6025	C.T	2.15 (1.54–3.02)	8.58E-06	4.37E-05	***
CancerMod	FVL	rs6025	T.T	NA (NA–NA)	9.91E-01	9.93E-01	
CancerMod	FXI	rs2036914	C.C	1.23 (0.94–1.61)	1.25E-01	2.08E-01	
CancerMod	FXI	rs2036914	T.C	1.17 (0.91–1.49)	2.13E-01	3.15E-01	
CancerMod	PTM	rs1799963	A.A	NA (NA–NA)	9.93E-01	9.93E-01	
CancerMod	PTM	rs1799963	G.A	1.76 (1.08–2.86)	2.22E-02	5.09E-02	*
CancerMod	SLC44A2	rs2288904	A.G	1.54 (0.91–2.61)	1.12E-01	1.92E-01	
CancerMod	SLC44A2	rs2288904	G.G	1.34 (0.80–2.26)	2.67E-01	3.67E-01	
CancerMod	TSPAN15	rs78707713	T.C	0.75 (0.36–1.55)	4.37E-01	5.59E-01	
CancerMod	TSPAN15	rs78707713	T.T	1.04 (0.52–2.11)	9.04E-01	9.93E-01	
CancerHigh	ABO	rs8176719	T.TC	1.34 (1.17–1.54)	2.39E-05	1.10E-04	***
CancerHigh	ABO	rs8176719	TC.TC	1.25 (1.02–1.55)	3.31E-02	6.51E-02	
CancerHigh	FGG	rs2066865	A.A	1.22 (0.94–1.58)	1.43E-01	2.24E-01	
CancerHigh	FGG	rs2066865	G.A	1.26 (1.10–1.44)	6.76E-04	2.32E-03	**

CancerHigh	FVL	rs6025	C.T	1.76 (1.37–2.26)	8.75E-06	4.37E-05	***
CancerHigh	FVL	rs6025	T.T	9.24 (2.28–37.39)	1.83E-03	5.59E-03	**
CancerHigh	FXI	rs2036914	C.C	1.38 (1.15–1.66)	6.30E-04	2.31E-03	**
CancerHigh	FXI	rs2036914	T.C	1.25 (1.05–1.48)	1.14E-02	2.86E-02	*
CancerHigh	PTM	rs1799963	A.A	NA (NA–NA)	9.85E-01	9.93E-01	
CancerHigh	PTM	rs1799963	G.A	1.35 (0.91–2.00)	1.31E-01	2.12E-01	
CancerHigh	SLC44A2	rs2288904	A.G	1.64 (1.12–2.39)	1.11E-02	2.86E-02	*
CancerHigh	SLC44A2	rs2288904	G.G	1.69 (1.16–2.46)	5.81E-03	1.60E-02	*
CancerHigh	TSPAN15	rs78707713	T.C	1.10 (0.61–1.97)	7.54E-01	8.47E-01	
CancerHigh	TSPAN15	rs78707713	T.T	1.20 (0.68–2.13)	5.25E-01	6.33E-01	

Abbreviations: CancerHigh, High-risk Cancer; CancerLow, Low-risk cancer; CancerMod, Moderate-risk cancer; FVL, Factor V Leiden; FGG, fibrinogen gamma gene; FXI, factor XI; p (BH), Benjamini-Hochberg corrected p value, PTM, prothrombin mutation; SLC44A2, solute carrier family 44 member 2; TSPAN15, tetraspanin 15;

[^]q-value shows Benjamini-Hochberg corrected p values, where q <0.05 is considered statistically significant.

[+] Significance codes for q-value:
<0.001: ***
<0.01: **
<0.05: *

Supplementary part 6: Absolute Cancer-associated VTE Risk by Tumor Subtype

Overview
These supplementary tables (**see Supplement part 6 excel tables**) present genotype-stratified estimates of 2-year VTE event risk across cancer types. Analyses are performed for candidate single nucleotide polymorphisms (SNPs), with results reported by genotype and corresponding allele dosage.

Methods summary
Participants were stratified by genotype for each SNP of interest, with allele dosage coded as 0, 1, or 2 according to the number of effect alleles. Event risk at 2 years was estimated using competing risk methods, accounting for death as a competing event. Subdistribution hazard models (Fine–Gray) were used to assess associations between genotype and outcome.
P values are derived from Fine–Gray models, and multiple testing was addressed using the Benjamini–Hochberg false discovery rate (FDR) correction.

Table structure
Each row represents a genotype stratum within a given SNP and cancer type. Columns are defined as follows:

Gene: Gene corresponding to the SNP
rsID: Reference SNP identifier
Genotype: Observed genotype (e.g. homozygous reference, heterozygous, homozygous alternate)
Allele dosage: Number of effect alleles (0, 1, or 2)
Total (n): Number of individuals in the genotype group
Events (n): Number of observed events within the group
2-year risk (%): Estimated cumulative incidence of cancer-associated venous thromboembolism at 2 years
95% CI: 95% confidence interval for the risk estimate
p value (Fine–Gray): P value from subdistribution hazard model
q value: Benjamini–Hochberg adjusted p value

Notes
Estimates based on small sample sizes should be interpreted with caution.
Confidence intervals are derived from competing risk models.
Missing or non-estimable values are denoted by "—".