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Summary

Background: Studies have reported that the combination of some prothrombotic genotypes and overt cancer yields a synergistic effect on VTE risk. Whether individual prothrombotic genotypes or number of risk alleles in a genetic risk score (GRS) affect VTE risk in occult cancer have not been addressed. The aim of this study was to investigate the joint effect of five prothrombotic genotypes and occult cancer on VTE risk.

Methods: Cases with incident VTE (n=1566) and a subcohort (n=14537) were sampled from the Scandinavian Thrombosis and Cancer Cohort (1993-2012). Five single nucleotide polymorphisms previously reported in a GRS were genotyped: ABO (rs8176719), F5 (rs6025), F2 (rs1799963), FGG (rs2066865) and F11 (rs2036914). Hazard ratios (HRs) for VTE by individual SNPs and GRS were estimated according to non-cancer and occult cancer (one year preceding a cancer diagnosis) exposure.

Results: Occult cancer occurred in 1817 subjects, and of these, 93 experienced a VTE. The VTE risk was 4-fold higher (HR 4.05, 95% CI 3.28-5.00) in subjects with occult cancer compared with those without cancer. Among subjects with occult cancer, those with VTE had a higher proportion of prothrombotic and advanced cancers than those without VTE. The VTE risk increased according to individual prothrombotic genotypes and GRS in cancer-free subjects, while no such effect was observed in subjects with occult cancer (HR for ≥4 versus ≤1 risk alleles in GRS: 1.14, 95% CI 0.61-2.11).

Conclusions: Five well-established prothrombotic genotypes, individually or combined, were not associated with increased risk of VTE in individuals with occult cancer.

Keywords: Epidemiology, genetics, neoplasms, polymorphisms single nucleotide, venous thromboembolism

1. Introduction

Venous thromboembolism (VTE) is a frequent, severe and often fatal complication of cancer [1, 2]. The incidence of cancer-related VTE is increasing [2], and about 15% of cancer patients develop a symptomatic VTE during the course of their disease [3]. Unprovoked VTE may occur as the first sign of an undetected (i.e. occult) cancer [4-6], and approximately 5% of patients with unprovoked VTE are diagnosed with cancer within the first year following a VTE event [7-12]. VTE patients with occult cancer are more often diagnosed with prothrombotic cancers such as pancreatic, lung, gastrointestinal and hematological cancers [2, 5, 7, 13-15], and more advanced stages (higher degree of regional and distant metastasis) at the time of cancer diagnosis [5, 14, 16].

VTE has a strong hereditary component, and single nucleotide polymorphisms (SNPs) in genes encoding for factor V Leiden (FVL) [17, 18], fibrinogen gamma (FGG) [19], factor 11 (F11) [20], prothrombin (F2) [21-24] and ABO blood group [25, 26] are found to increase the VTE risk in cancer patients. Moreover, the combination of cancer and variations in the F5 (rs6025 and rs4524) and FGG (rs2066865) genes has been shown to increase the VTE risk on a supra-additive scale, indicating a biological interaction between the individual prothrombotic SNPs and active cancer [18, 19]. Similarly, a genetic risk score (GRS) based on five prothrombotic SNPs was associated with VTE risk in overt cancer, and the combination of cancer and a high GRS (≥4 risk alleles) yielded a synergistic effect on VTE risk [27].

The risk of VTE is found to be increased already one year prior to a cancer diagnosis [5, 28]. This could be due to the occult cancer alone, or occult cancer in combination with other patient-related predisposing factors for VTE. It is unknown to what extent individual prothrombotic genotypes and the 5-SNP GRS affect the VTE risk in occult cancer. Therefore, we aimed to investigate the effect of individual prothrombotic genotypes and number of risk alleles in the GRS on the risk of VTE in occult cancer, using a large case-cohort recruited from the general population.

2. Methods

2.1 Study population

We used individual data from The Scandinavian Thrombosis and Cancer (STAC) cohort, which is a large population-based study established to provide comprehensive data to investigate the impact of cancer on VTE risk in the general population [29]. The STAC cohort consists of merged data from three large Scandinavian cohorts with enrollment in 1993-1997: the fourth survey of the Tromsø Study (Tromsø 4, Norway), the second survey of the Nord-Trøndelag health study (HUNT2, Norway) and the Diet, Cancer and Health Study (DCH, Denmark). All three individual cohorts [30-32] and the complete STAC cohort [29] have been previously described in detail. The STAC cohort has a wide age-distribution (19-101 years), long-term follow-up and thorough validation of VTE events and cancer [29]. All subjects with cancer or VTE prior to enrollment were excluded, yielding a study population of 144952 participants. The participants were followed from date of inclusion to date of migration, death, incident VTE or end of follow-up (2007-2012). All first lifetime, symptomatic VTE events in both in- and outpatients included in the STAC cohort were validated by review of medical records, and objectively confirmed by diagnostic tests. The identification and adjudication process of VTE events has previously been published in detail [30, 31, 33]. During follow-up, 2444 VTE events occurred. In 400 VTE cases, blood samples were missing or of insufficient quality for DNA analysis, and they could therefore not be included in the present study.

We created a case-cohort by including all incident VTE cases in which blood samples were available for genotyping (n=2044) and an age-weighted subcohort (n=14432) randomly sampled from the STAC cohort (Figure 1). We excluded participants with missing values for one of the SNPs studied (n=380) or body mass index (n=83). A total of 372 VTE cases were censored from the analysis as they occurred after the cancer diagnosis date. However, these subjects contributed with person-years prior to censoring. Finally, our case-cohort consisted of 16013 participants of whom 1566 were VTE cases. In case-cohort

designs, every person in the cohort, including the cases, has the same chance of being selected to the subcohort, and thus, 231 of the subjects randomly selected to our sub-cohort were also cases. All participants provided informed written consent, and the respective regional committees for research ethics in Norway and Denmark approved the individual cohort studies and the collaboration study.

2.2 Baseline measurements and genotyping

Baseline information was obtained by physical examination, self-administered questionnaires and non-fasting blood samples for each study. Body height and weight were measured at the physical examination with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by body height in meters (m) squared (kg/m^2). Information regarding history of diabetes mellitus, cardiovascular disease (myocardial infarction, angina or stroke), smoking status, alcohol consumption, physical activity and level of education was obtained by the self-administered questionnaires. Detailed information regarding assessment of baseline variables in each cohort is provided elsewhere [32, 34, 35].

We genotyped the following SNPs: ABO rs8176719 (non-O blood type), F5 rs6025 (Factor V Leiden), F2 rs1799963 (prothrombin G20210A), FGG rs2066865 and F11 rs2036914. These SNPs were chosen because they were previously included in a parsimonious GRS model presented by de Haan *et al.* [36], which performed just as good as a comprehensive model including 31 SNPs. In Tromsø 4, rs1799963 (F2), rs6025 (F5), rs2036914 (F11) and rs8176719 (ABO) were genotyped with the Sequenom platform, and rs2066865 (FGG) with the TaqMan platform, as previously described in detail [37]. In HUNT2, genotyping was performed with the Illumina HumanCore Exome array. In the DCH study, the genotypes were determined using predesigned TaqMan SNP genotyping assays, as described in detail elsewhere [38].

Subjects were defined as carriers of the prothrombotic SNPs when one or two risk alleles were present, with no differentiation between heterozygous (one risk allele) and homozygous (two risk alleles) carriers. Normally, the minor allele is used as risk allele. However, due an inverse association with VTE risk, the minor allele of the F11 SNP (rs2036914) was used as the common allele [39]. No risk allele at ABO rs8176719 was defined as O blood type. Hence, one or two risk alleles at ABO rs8176719 were classified as non-O blood type. Further, we used the GRS by de Haan *et al.,* which was created by summarizing the number of risk alleles from the five sequenced SNPs [36].

2.3 Cancer assessment

Information on cancer diagnosis, such as location (ICD10 codes C00-96), histological grade (ICO-3) and cancer stage (localized, regional, distant or unknown) was obtained by linkage to the cancer registries of Norway and Denmark where cancer registration is mandatory by law. Reports have found both cancer registries complete and valid, reporting a completeness of 98.8% in Norway and 95-98% in Denmark [40, 41]. The percentage of microscopically confirmed diagnoses in the registries were 94% in Norway and 93% in Denmark, respectively [40, 41]. Subjects with non-melanoma skin cancers (ICD10 C44) and no other cancer diagnosis were regarded as cancer-free, due to the non-metastatic potential of this disease.

Temporal proximity to cancer is shown to be a strong predictor for VTE risk [2, 5, 18]. Studies have found an increased VTE risk the year before a cancer diagnosis, with a seven-fold increased risk six months prior to the cancer diagnosis date [5, 6, 28]. Further, previously undiagnosed cancer is frequent in patients with unprovoked VTE, with a period prevalence of undiagnosed cancer increasing from 6.1% at baseline to 10.0% from the time of VTE diagnosis to 12 months after [6]. Hence, we defined the occult cancer period as one year prior to a cancer diagnosis. Cancer patients who were not diagnosed with VTE and still alive at the end of the defined occult cancer period were censored at the cancer diagnosis date. To test the

robustness of our occult cancer variable, we additionally performed two sensitivity analyses where we defined the occult cancer period as 2 years and 6 months prior to cancer diagnosis, respectively.

2.4 Statistical analysis

Statistical analyses were performed with STATA version 16.0 (Stata Corporation, College Station, TX, USA). Occult cancer was entered as a time-varying co-variate. In those who developed cancer during follow-up, the data was split on the date one year before the cancer diagnosis date to differentiate between cancer free and occult cancer. Thus, subjects who developed cancer during follow-up were considered to be *cancer-free* until one year prior to a cancer diagnosis date, and subsequently they were classified as *occult cancer*. When cancer was diagnosed, the cancer patients changed exposure status to *overt cancer* and were censored from the analysis. Accordingly, subjects who developed cancer contributed to both non-exposed and occult cancer-exposed person-years (PY) at risk in our analysis.

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE according to the different prothrombotic genotypes or categories of risk alleles by the GRS (i.e. 0-1, 2-3, and ≥ 4 risk alleles) in subjects with and without occult cancer. Subjects with 0-1 risk alleles and no cancer were used as reference group. We adjusted all analyses for age, sex and BMI. The proportional hazards assumption was tested by the use of Schoenfeld residuals and was found not to be violated.

To investigate the combined effect of occult cancer and risk alleles on VTE risk, we used the relative excess risk attributable to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (SI) with corresponding 95% CIs [42, 43]. RERI can be understood as part of the total effect on an outcome (e.g. VTE) that is attributable to interaction (e.g. the different exposures occult cancer and SNPs), and the AP as the proportion of the combined effect that is attributable to interaction between the

two exposures. A RERI > 0, an AP > 0 and a synergy index > 1.0 suggest a positive interaction greater than an additive effect, i.e., the combined effect of occult cancer and SNPs bigger than the sum of the separate effects [42].

3. Results

During a median follow-up of 12.2 years, 1817 subjects developed occult cancer, of whom 93 (5.1%) experienced a VTE event. Overall, the risk of VTE in occult cancer was 4-fold higher (HR 4.05, 95% CI 3.28-5.00) than in cancer-free subjects in analysis adjusted for age, sex and BMI. The baseline characteristics of study participants with and without occult cancer and/or VTE are summarized in Table 1. In cancer-free subjects, those who developed VTE were older, had a higher BMI and a higher proportion were men. In subjects with occult cancer, those suffering a VTE were more often women. In both cancer-free subjects and subjects with occult cancer, the prevalence of prothrombotic genotypes were higher in VTE patients than in those without VTE (Table 1). The distribution of risk alleles of the GRS in cancer-free subjects and subjects with occult cancer was essentially similar (data not shown).

The distribution of cancer sites and stages in subjects with and without VTE in the occult cancer period are presented in Table 2. Among subjects with occult cancer, those who developed VTE were more frequently diagnosed with prothrombotic cancers such as pancreatic-, lung- and hematological cancers compared with those who did not develop VTE. Further, the cancers diagnosed within one year after a VTE were more advanced with a higher proportion of metastasis at the time of cancer diagnosis (Table 2).

HRs for VTE by categories of prothrombotic SNPs and cancer status (cancer-free/occult cancer) are presented in Table 3. In cancer-free subjects, the VTE risk increased with the presence of risk alleles for all prothrombotic genotypes, with the highest risk estimates for F5 (rs6025) (HR 2.68, 95% CI 2.34-3.06), F2 (rs1799963) (HR 1.94, 95% CI 1.41-2.65), and ABO (rs8176719) (HR 1.50, 95% CI 1.34-1-67). In subjects with occult cancer, the VTE risk was not affected by any of the prothrombotic SNPs (Table 3). The

risk estimates were essentially unchanged when the definition of the occult cancer period were changed to six months (Supplementary Table 1) and two years (Supplementary Table 2).

The VTE risk in cancer-free subjects increased by the number of risk alleles, displaying a 2.4-fold increased VTE risk (HR 2.39, 95% CI 1.26-1.69) in subjects with more ≥4 risk alleles compared with subjects with 0-1 risk alleles (Table 3 and Figure 2). In subjects with occult cancer, the VTE risk did not increase by the number of risk alleles in the GRS (Table 3 and Figure 2). Similar results were found in sensitivity analyses when the occult cancer period was changed to six months or two years (Supplementary Tables 1 and 2, respectively). Measures of biological interaction (RERI, AP, SI) showed that the combination of occult cancer and presence of prothrombotic genotypes did not yield a more than additive effect on VTE risk (Supplementary Table 3).

4. Discussion

In this large population-based case-cohort study, we investigated the risk of VTE by the presence of prothrombotic genotypes, both as individual SNPs and number of risk alleles in a GRS, in subjects with and without occult cancer. In agreement with previous studies, we confirmed that the VTE risk increased by the individual prothrombotic genotypes and the number risk alleles in the GRS in cancer-free subjects [36]. In contrast, the prothrombotic genotypes were not associated with VTE risk in subjects with occult cancer, and accordingly, the combination of occult cancer and individual risk alleles or number of risk alleles in the GRS, did not yield any supra-additive effect on the VTE risk. Similar findings were observed in sensitivity analyses where the occult cancer period was altered to six months and two years, respectively. Subjects with VTE in the occult cancer period had a higher frequency of prothrombotic cancer types and more advanced cancers at the time of cancer diagnosis. Our findings suggest that the mechanisms related to VTE risk in occult cancer supersede the effect of prothrombotic genotypes.

The mechanisms for VTE in cancer are multifactorial and involve overlapping pathways related to the cancer itself and patient-related factors [44]. Several studies have explored the impact of prothrombotic genotypes on the risk of VTE in patients with overt cancer, and reported an increased risk for SNPs encoding for factor V Leiden, prothrombin mutation and non-O blood type [17-26]. Moreover, we previously showed that in combination with overt cancer, SNPs in F5 (rs6025, rs4524) and FGG (rs2066865), as well as a high number of risk alleles in the GRS (≥ 4 risk alleles), increased the VTE risk on a supra-additive level [18, 19, 27]. Therefore, we hypothesized that prothrombotic genotypes could influence the risk of VTE also in occult cancer. In contrast, we found no effect of the established prothrombotic genotypes on the VTE risk in subjects with occult cancer. This suggests that prothrombotic mechanisms related to the cancer itself are more important than inherent patient-related factors for risk of VTE in the occult cancer period.

Several studies have confirmed the significance of cancer stage, grade and site on VTE risk in overt malignancy, and patients with metastatic cancers, with regional or distant spread, have a higher VTE risk than patients with localized cancers [45]. Moreover, pancreas, brain, lung, ovarian, kidney and stomach cancers, as well as lymphomas, are considered high-risk sites for VTE [45]. In agreement with these findings, we showed that subjects who developed VTE during the occult cancer period had a higher proportion of regional and distant metastasis, as well as a higher proportion of cancers at high-risk sites, when compared with those who did not develop VTE during the occult cancer period. Tissue factor (TF), the main initiator of the coagulation system, is shown to be involved in cancer-progression processes such as tumor growth, angiogenesis and metastasis [46]. Upregulation of TF has been reported in advanced cancer stages [46], as well as in high-risk sites for VTE, including brain, pancreatic, lung, ovarian and colorectal cancers [47, 48]. In addition to TF expression, inflammatory responses with increased levels of circulating proinflammatory cytokines [49-51], inhibition of fibrinolytic activity through expression of plasminogen activator inhibitor-1 (PAI-1) [52-54], and formation of neutrophil extracellular traps (NETs) from neutrophils [55], may substantially contribute to a prothrombotic state in rapidly developing, aggressive, occult cancers. Thus, a massive orchestra of prothrombotic pathways induced by an advancing occult cancer, is likely sufficient to push an individual's thrombotic potential above the threshold for thrombus development, regardless of the presence of inherent prothrombotic risk factors.

The main strengths of our study include the prospective design with participants recruited from the general population, large number of genotyped subjects, long-term follow-up and thorough assessment of both VTE and cancer. In agreement with previous studies, we confirmed that 5% of the VTE events were related to occult cancer [7-12], and similar anatomical sites for cancers [2, 5, 7, 13-15], and degrees of metastatic diseases were found in VTE-patients with occult cancer [5, 14, 16], which supports a high external validity. Some study limitations must be addressed. In some rare genetic variants, the number of cases was low, resulting in limited statistical power. Unfortunately, we did not have sufficient

power to stratify our data by different cancer sites or stages of cancer, as it would be interesting to explore whether the impact of prothrombotic SNPs and combination of SNPs on VTE risk would differ within different sites and stages of occult cancer. In order to be registered with occult cancer, patients had to survive until their cancer diagnosis. Thus, participants with occult cancer who died from a VTE or other causes before a cancer was diagnosed would be misclassified as cancer-free. Such misclassification would likely lead to underestimation of the VTE risk in occult cancer. However, the five prothrombotic SNPs are not expected to increase the death-rate in the general population [56, 57], and thus, we believe that such misclassification, if present, would have negligible impact on our results.

In conclusion, five common prothrombotic genotypes, alone or in combination, were not associated with risk of VTE in occult cancer. Our findings suggest that prothrombotic mechanisms related to rapidly advancing cancers at high-risk sites are prominent for VTE risk in occult cancer and supersede the effect of prothrombotic genotypes.

Author contributions

Conception and design: JB. Hansen and S.K. Brækkan; data collection: JB. Hansen, S.K Brækkan, K. Hindberg, M.E. Gabrielsen, IA. Næss, A. Tjønneland, S.R. Kristensen, M.T. Severinsen; data analysis and statistical support: H. Skille, K. Hindberg, S.K. Brækkan; draft of manuscript: H. Skille, JB. Hansen, and S.K. Brækkan; revision of manuscript for intellectual content: all authors. All authors read and approved the final version of the manuscript.

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Conflicts of interest

The authors report no conflict of interest.

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Tables

Table 1. Baseline characteristics of the study population with and without occult cancer and VTE.

	No cancer		Occult cancer	
	Sub-cohort	**VTE**	**Sub-cohort**	**VTE**
Participants, n*	12723	1473	1724	93
Age, years	49.6±15.4	59.5±12.9	61.1±11.5	61.1±12.1
Male sex	47.5 (6043)	51.5 (759)	52.8 (910)	44.1 (41)
BMI, kg/m^2	26.1±4.1	27.6±4.6	26.7±4.3	27.0±4.4
rs8176719 (ABO)†	61.0 (7760)	70.0 (1031)	62.4 (1075)	64.5 (60)
rs6025 (F5)†	6.8 (868)	17.8 (262)	8.2 (142)	10.8 (10)
rs1799963 (F2)†	1.4 (172)	2.7 (40)	1.5 (25)	1.1 (1)
rs2066865 (FGG)†	42.5 (5413)	47.0 (692)	43.0 (741)	46.2 (43)
rs2036914 (F11)†	77.7 (9891)	82.6 (1216)	78.8 (1359)	78.5 (73)

Values are in % (n) or mean ± standard deviation. BMI, body mass index.

* Subjects with cancer contributed to observation periods in both the no cancer and occult cancer group.

† Percentage of participants with ≥1 risk allele

Table 2. Distribution of cancer sites and stages in subjects with occult cancer, defined as one year prior to cancer diagnosis, with and without venous thromboembolism (VTE).

	No VTE (n=1724)	**VTE (n=93)**
Cancer site	Number (%)	Number (%)
Colorectal	272 (15.8)	8 (8.6)
Pancreatic	54 (3.1)	6 (6.4)
Lung	205 (11.9)	18 (19.4)
Breast	198 (11.5)	2 (2.2)
Gynecological	101 (5.9)	4 (4.3)
Prostate	224 (13.0)	10 (10.8)
Urological	150 (8.7)	8 (8.6)
Central nervous system	69 (4.0)	1 (1.1)
Hematological/Lymphoma	138 (8.0)	11 (11.8)
Upper GI	90 (5.2)	7 (7.5)
Malignant melanoma	66 (3.8)	0 (0)
Other*	157 (9.1)	18 (19.4)
Cancer stage	Number (%)	Number (%)
Localized	473 (27.4)	10 (10.8)
Regional lymph nodes	431 (25.0)	14 (15.1)
Distant metastasis	292 (16.9)	34 (36.7)
Metastasis diagnosed, unknown where	408 (23.7)	25 (26.9)
Not staged	120	10

*Cancers of ear, nose and throat, eye, endocrine, heart, sarcomas, connective tissue and unknown site

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by categories of single nucleotide polymorphisms (SNPs) and occult cancer defined as the occurrence of a cancer diagnosis within one year after VTE diagnosis.

		Events	HR (95% CI)*	HR (95% CI)*
Cancer	**rs8176719 (ABO)†**			
-	**-**	442	Ref.	Ref.
-	**+**	1031	1.50 (1.34-1.67)	1.50 (1.34-1.67)
+	**-**	33	Ref.	5.01 (3.51-7.14)
+	**+**	60	1.10 (0.72-1.69)	5.43 (4.14-7.12)
Cancer	**rs6025 (F5)†**			
-	**-**	1211	Ref.	Ref.
-	**+**	262	2.68 (2.34-3.06)	2.68 (2.34-3.06)
+	**-**	83	Ref.	4.45 (3.56-5.57)
+	**+**	10	1.26 (0.64-2.45)	5.60 (3.00-10.44)
Cancer	**rs1799963 (F2)†**			
-	**-**	1433	Ref.	Ref.
-	**+**	40	1.94 (1.41-2.65)	1.94 (1.42-2.66)
+	**-**	92	Ref.	4.11 (3.33-5.09)
+	**+**	1	0.82 (0.11-6.03)	3.10 (0.44-22.05)
Cancer	**rs2066865 (FGG)†**			
-	**-**	781	Ref.	Ref.
-	**+**	692	1.18 (1.06-1.30)	1.17 (1.06-1.30)
+	**-**	50	Ref.	4.08 (3.06-5.44)
+	**+**	43	1.10 (0.73-1.67)	4.72 (3-47-6.42)
Cancer	**rs2036914 (F11)†**			
-	**-**	257	Ref.	Ref.
-	**+**	1216	1.31 (1.14-1.50)	1.31 (1.14-1.49)
+	**-**	20	Ref.	5.33 (3.38-8.40)
+	**+**	73	0.95 (0.58-1.57)	4.94 (3.81-6.42)
Cancer	**Genetic risk score‡**			
-	**0-1**	224	Ref.	Ref.
-	**2-3**	836	1.46 (1.26-1.69)	1.46 (1.26-1.69)
-	**≥4**	413	2.39 (2.03-2.82)	2.39 (2.03-2.81)
+	**0-1**	21	Ref.	6.75 (4.31-10.56)
+	**2-3**	52	0.84 (0.50-1.39)	5.44 (4.02-7.37)
+	**≥4**	20	1.14 (0.61-2.11)	8.04 (5.09-12.72)

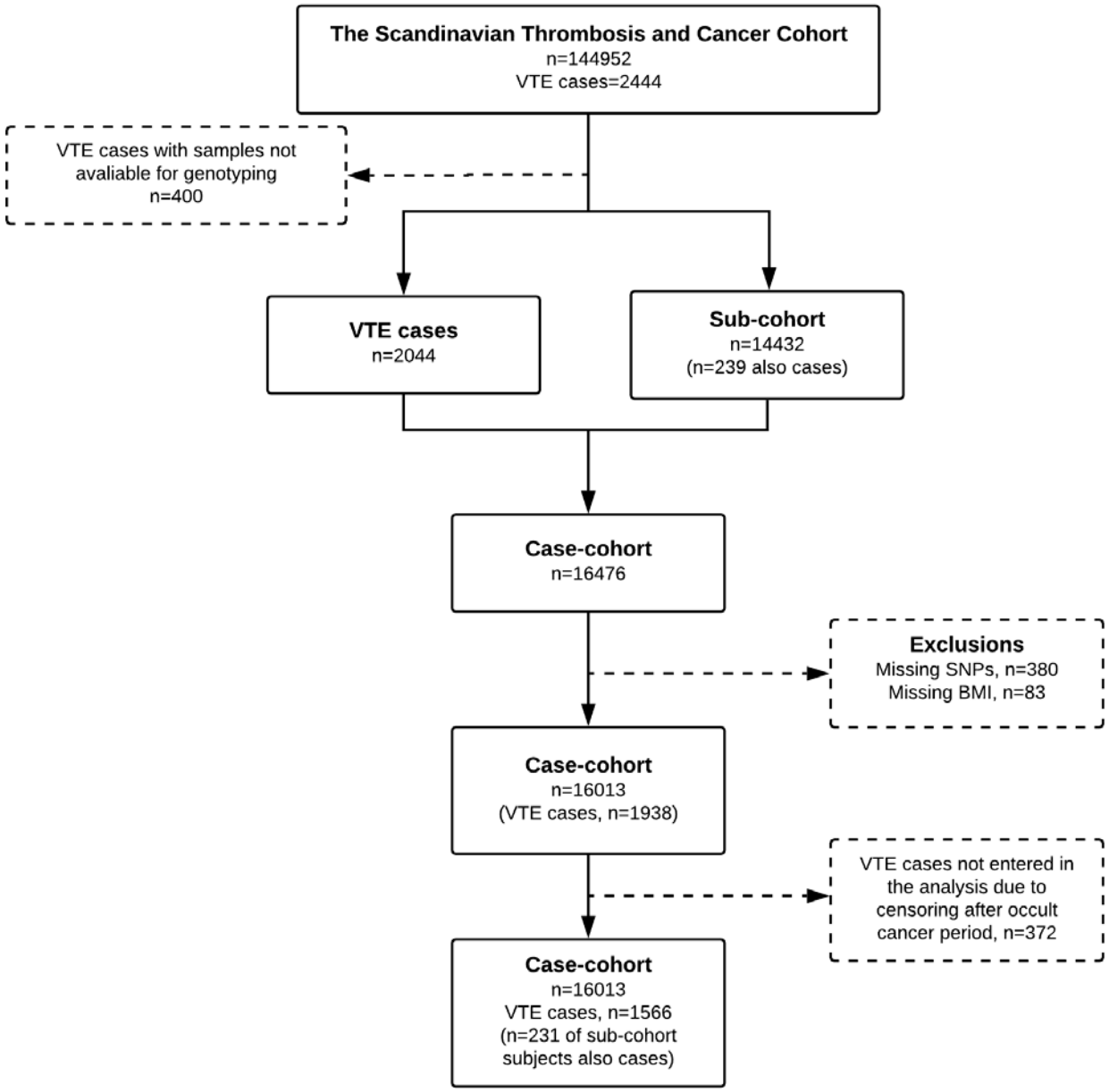
* Adjusted for age, sex and body mass index (BMI)

† Positive indicating subjects with one or two risk alleles

‡ Number of risk alleles

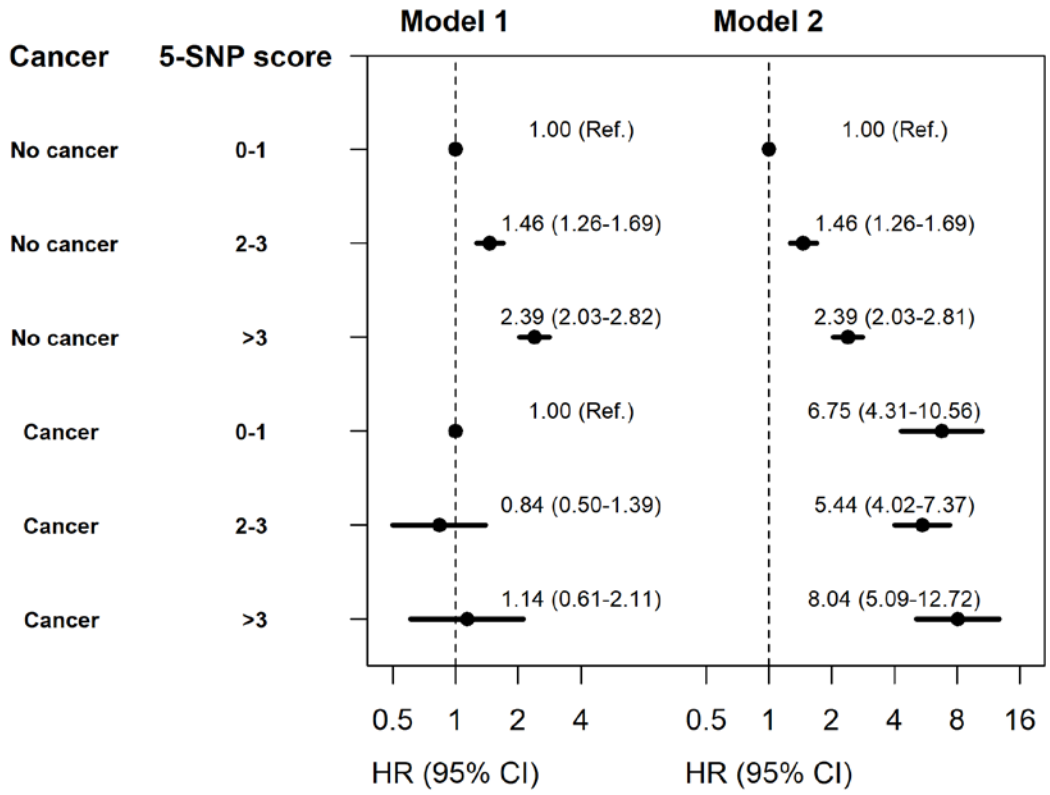
Figures

Figure 1. Study population. Participants were recruited from The Scandinavian Thrombosis and Cancer Cohort (1993-1997).



VTE indicates venous thromboembolism; SNPs, single nucleotide polymorphisms.

Figure 2. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by categories of single nucleotide polymorphisms (SNPs) and occult cancer defined as the occurrence of a cancer diagnosis within one year after VTE diagnosis.



Supplementary

Supplementary Table 1. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by categories of single nucleotide polymorphisms (SNPs) and occult cancer defined as six months prior to cancer diagnosis.

		Events	HR (95% CI)*	HR (95% CI)*
Cancer	**rs8176719 (ABO)†**			
-	**-**	447	Ref.	Ref.
-	**+**	1044	1.50 (1.34-1.67)	1.50 (1.34-1.67)
+	**-**	28	Ref.	8.22 (5.60-12.05)
+	**+**	47	1.05 (0.65-1.68)	8.41 (6.22-11.37)
Cancer	**rs6025 (F5)†**			
-	**-**	1228	Ref.	Ref.
-	**+**	263	2.65 (2.31-3.03)	2.65 (2.31-3.03)
+	**-**	66	Ref.	6.94 (5.41-8.90)
+	**+**	9	1.45 (0.71-2.97)	9.74 (5.05-18.76)
Cancer	**rs1799963 (F2)†**			
-	**-**	1451	Ref.	Ref.
-	**+**	40	1.91 (1.40-2.62)	1.92 (1.40-2.62)
+	**-**	74	Ref.	6.49 (5.13-8.21)
+	**+**	1	1.13 (0.15-8.38)	5.85 (0.82-41.67)
Cancer	**rs2066865 (FGG)†**			
-	**-**	789	Ref.	Ref.
-	**+**	702	1.18 (1.07-1.31)	1.18 (1.07-1.31)
+	**-**	42	Ref.	6.71 (4.91-9.17)
+	**+**	33	1.04 (0.65-1.66)	7.15 (5.03-10.13)
Cancer	**rs2036914 (F11)†**			
-	**-**	264	Ref.	Ref.
-	**+**	1227	1.28 (1.12-1.47)	1.28 (1.12-1.46)
+	**-**	13	Ref.	6.60 (3.78-11.54)
+	**+**	62	1.27 (0.69-2.32)	8.13 (6.16-10.74)
Cancer	**Genetic risk score‡**			
-	**0-1**	231	Ref.	Ref.
-	**2-3**	841	1.42 (1.23-1.64)	1.42 (1.23-1.64)
-	**≥4**	419	2.35 (2.00-2.76)	2.35 (2.00-2.76)
+	**0-1**	14	Ref.	8.59 (5.00-14.74)
+	**2-3**	47	1.15 (0.63-2.12)	9.44 (6.89-12.94)
+	**≥4**	14	1.25 (0.59-2.65)	11.01 (6.41-18.90)

* Adjusted for age, sex and body mass index (BMI)

† Positive indicating subjects with one or two risk alleles

‡ Number of risk alleles

Supplementary Table 2. Hazard ratios (HR) with 95% confidence intervals (CI) for venous thromboembolism (VTE) by categories of single nucleotide polymorphisms (SNPs) and occult cancer defined as two years prior to cancer diagnosis.

		Events	HR (95% CI)*	HR (95% CI)*
Cancer	**rs8176719 (ABO)†**			
-	**-**	431	Ref.	Ref.
-	**+**	1020	1.52 (1.36-1.70)	1.52 (1.36-1.70)
+	**-**	44	Ref.	3.49 (2.56-4.77)
+	**+**	71	0.97 (0.67-1.42)	3.35 (2.60-4.31)
Cancer	**rs6025 (F5)†**			
-	**-**	1195	Ref.	Ref.
-	**+**	256	2.66 (2.32-3.04)	2.66 (2.33-3.05)
+	**-**	99	Ref.	2.75 (2.24-3.38)
+	**+**	16	1.57 (0.92-2.69)	4.52 (2.75-7.40)
Cancer	**rs1799963 (F2)†**			
-	**-**	1412	Ref.	Ref.
-	**+**	39	1.91 (1.39-2.63)	1.92 (1.40-2.64)
+	**-**	113	Ref.	2.61 (2.15-3.17)
+	**+**	2	1.37 (0.34-5.64)	3.28 (0.82-13.13)
Cancer	**rs2066865 (FGG)†**			
-	**-**	770	Ref.	Ref.
-	**+**	681	1.17 (1.06-1.30)	1.17 (1.06-1.30)
+	**-**	61	Ref.	2.59 (1.99-3.36)
+	**+**	54	1.12 (0.78-1.63)	3.03 (2.30-4.00)
Cancer	**rs2036914 (F11)†**			
-	**-**	256	Ref.	Ref.
-	**+**	1195	1.29 (1.13-1.48)	1.29 (1.13-1.48)
+	**-**	21	Ref.	2.86 (1.83-4.46)
+	**+**	94	1.18 (0.73-1.90)	3.26 (2.57-4.13)
Cancer	**Genetic risk score‡**			
-	**0-1**	219	Ref.	Ref.
-	**2-3**	826	1.48 (1.27-1.71)	1.48 (1.27-1.72)
-	**≥4**	406	2.41 (2.04-2.84)	2.40 (2.04-2.83)
+	**0-1**	26	Ref.	4.36 (2.90-6.55)
+	**2-3**	62	0.80 (0.51-1.27)	3.40 (2.56-4.52)
+	**≥4**	27	1.23 (0.72-2.12)	5.56 (3.72-8.30)

* Adjusted for age, sex and body mass index (BMI)

† Positive indicating subjects with one or two risk alleles

‡ Number of risk alleles

Supplementary Table 3. Measures of interaction on an additive scale between occult cancer and the individual single-nucleotide polymorphisms (SNPs) or ≥4 risk alleles in the genetic risk score.

	RERI (95% CI)	AP (95% CI)	Synergy index (95% CI)
Individual SNPs (genes)			
rs8176719 (ABO)	-0.07 (-2.27-2.12)	-0.01 (-0.42-0.39)	0.98 (0.60-1.61)
rs6025 (F5)	-0.53 (-4.15-3.09)	-0.10 (-0.80-0.61)	0.90 (0.41-1.95)
rs1799963 (F2)	-1.96 (-8.12-4.21)	-0.63 (-3.85-2.59)	0.52 (0.03-9.47)
rs2066865 (FGG)	0.47 (-1.35-2.28)	0.10 (-0.26-0.46)	1.14 (0.68-1.92)
rs2036914 (F11)	-0.69 (-3.29-1.92)	-0.14 (-0.68-0.40)	0.85 (0.48-1.52)
Genetic risk score (≥4 vs ≤1)	-0.06 (-4.67-4.54)	-0.01 (-0.58-0.56)	0.99 (0.52-1.89)

AP, proportion attributable to interaction; CI, confidence interval; RERI, relative excess risk attributable to interaction.