Supplementary appendix for the manuscript:

Fibrinogen gamma gene rs2066865 and risk of cancer-related venous thromboembolism

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Methods

VTE identification and validation

All first lifetime events of VTE occurring among the participants in this period were identified using the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry from University Hospital of North Norway (UNN), which is the sole provider of diagnostic radiology and treatment of VTE in the Tromsø area. Trained personnel adjudicated and recorded each VTE by extensive medical records review. The adjudication criteria for VTE were presence of signs and symptoms of PE or DVT combined with objective confirmation by radiological procedures, which resulted in treatment initiation (unless contraindications were specified). A VTE-event was classified as either a DVT or a PE. When a PE and DVT occurred concurrently, the event was classified as a PE. The identification and adjudication process of VTEs has been previously described in detail [1].

Baseline measurements

Baseline information regarding lifestyle and vital parameters was obtained through physical examination, blood samples and self-administered questionnaires. Body height and weight were measured with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2). Information on medical history (e.g. cardiovascular diseases and diabetes mellitus), life style factors (e.g. smoking status, amount of physical activity) and level of education was derived from the questionnaires.

Cancer exposure

Registration of cancer is mandatory by law in Norway; and The Cancer Registry of Norway (CRN) performs surveillance of cancer diagnoses on a national basis. Information on date of diagnosis, malignancy location (International Classification of Disease, Revision 7 (ICD-7) codes 140-205), morphology and histology, and initial treatment was obtained by linking The Tromsø Study to the CRN using the unique national civil registration numbers. Diagnoses of non-melanoma skin cancer (ICD 190.0-191.9) was regarded as non-cancer. The cancer registry of Norway is of high quality when it comes to completeness and validation. An evaluation of the CRN performed by Larsen et al, estimated 98.8% completeness of the cancer diagnoses, with a histological verification of 94% [2].

Genotyping and quality control

We genotyped one SNP at the fibrinogen gamma gene (rs2066865), which has previously been implicated as a candidate marker of VTE [3], using the Taqman platform and an initial input of 100 ng DNA. Samples were genotyped with the Applied Biosystems 7900HT (Foster City, CA, USA) according to the recommended protocol and processed using SDS 2.4 (Thermo Fisher, Foster City, CA, USA). Genotypes passing a quality value threshold of 95 were used.

Statistics

Synergism refers to the phenomenon where the presence of two or more elements produces a stronger effect than the sum of the individual components. Rothmans synergy index (RSI) [4], relative excess risk caused by interaction (RERI) and attributable portion due to interaction (AP) were calculated to adjudicate whether the combined effect of risk alleles and active cancer on VTE risk exceeded the sum of the risks that each factor yielded alone. RSI measures departure from additive risks, and a value of 1 suggests that there is no interaction between the exposures or perfect additivity, whereas RSI>1 suggests positive interaction or more than additivity. RERI and AP measures of 0 indicates no biological interaction, while measures >0 suggest positive interaction (i.e. more than additivity).

Supplementary Table 1:

	Subcohort-members	
FGG risk alleles	**Observed**	**Expected**
0	2133 (54.3%)	2157.6 (55.0%)
1	1552 (39.6%)	1502.7 (38.3%)
2	237 (6.0%)	261.7 (6.7%)

Distribution of observed and expected allele-combination of FGG rs2066865 among individuals in the sub-cohort.

References

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