Mortality risk after cancer-related venous thromboembolism has decreased over the last three decades: the HUNT and Tromsø studies

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SUPPLEMENTARY DATA

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Supplementary Methods

Study population and design

This study was conducted using a cohort design and included data from The Trøndelag Health Study (HUNT) and The Tromsø Study.[1-3] The HUNT and Tromsø Study are two Norwegian cohort studies with repeated health surveys of inhabitants of the (former) Nord-Trøndelag county and the municipality of Tromsø, respectively. The HUNT surveys were conducted in 1995-97 (HUNT2) and 2006-08 (HUNT3), with 78,959 unique participants. The Tromsø Study surveys were conducted in 1994-95 (Tromsø4), 2001-02 (Tromsø5), 2007-08 (Tromsø6), and 2015-16 (Tromsø7), with 36,626 unique participants. In total, the HUNT2-3 and Tromsø4-7 surveys included 115,585 unique participants, aged 19-100 years. The attendance rate was high in both surveys (55-77% of the invited populations). After excluding participants with a history of VTE and/or cancer diagnosis prior to the inclusion in the cohorts (n=4,384), as well as those who moved before the date of inclusion (n=82), 111,119 participants were eligible for this study and included in the final analytical sample (35,142 participants from Tromsø and 75,977 from HUNT). The study was approved by the Regional Committee for Medical and Health Research Ethics in agreement with the Helsinki Declaration, and all participants provided written informed consent for participation and use of data for medical research.

Baseline characteristics

Baseline characteristics were collected through physical examination and self-administered questionnaires, as described in detail elsewhere.[3-5] Blood pressure and physical measures (e.g. height and weight) were recorded by trained personnel using standard methods. Hypertension was defined as either a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported hypertension, or the current use of antihypertensives.

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Information on baseline smoking, education level and history of diabetes and arterial cardiovascular disease (CVD) (angina pectoris, myocardial infarction, and stroke) was collected through the self-administered questionnaires. Education level was defined as primary (up to 10 years of education), high school (11-13 years of education), and college/university (1 or more years of education after 13 years). Education information was not available for those only attending HUNT3 (n=16,600). Smoking was defined as current daily smoking of cigarettes, cigars or pipes (yes/no).

Exposures and outcome

The exposure variables were VTE and cancer. Long-term follow-up on objectively confirmed, symptomatic incident VTE was conducted in both HUNT and Tromsø cohorts until December 31, 2019. All potential incident VTE events were identified by searching the hospital discharge diagnosis registry at the University Hospital of North Norway (UNN), Levanger Hospital, Namsos Hospital, and St. Olav's Hospital, in addition to the autopsy registry and the radiology procedure registry at the UNN. These four hospitals cover the catchment areas of Tromsø (UNN) and HUNT (Levanger, Namsos, and St. Olav hospitals) participants. Trained healthcare professionals reviewed the medical records for each potential VTE case. An episode of VTE was validated when clinical signs and symptoms of DVT or PE were combined with objective confirmation by radiological procedures and resulted in a VTE diagnosis requiring treatment (anticoagulant or thrombolytic therapy). VTEs were classified as DVT or PE, and participants with simultaneous DVT and PE were classified as PE. Superficial vein thrombosis and incidentally detected DVTs and PEs were not included in the present study.

Information on the date of cancer diagnosis, primary cancer site, stage, and histological grade was obtained by linkage to the Cancer Registry of Norway. The Cancer Registry of Norway is considered a valid registry with 98.8% completeness and 94% of the cases being histologically verified.[6] Cancer site was defined according to the International Classification of Diseases (ICD) codes (**ICD10 codes: C00-C97**). Individuals with non-melanoma skin cancer (**ICD10 code: C44**) were regarded as being cancer-free. The stage was assessed at cancer diagnosis and classified as localized, local spread, distant metastasis, and unknown. Information on cancer and VTE treatment was not available in the HUNT and Tromsø studies.

The outcome was all-cause mortality. The date of death was obtained from the Norwegian Population Registry.

Definition of active cancer period

A previous study using data from the Scandinavian Thrombosis and Cancer (STAC) cohort reported that the risk of VTE was already increased in the year before the cancer diagnosis and remained increased within 2 years after the cancer diagnosis.[7] Therefore, we defined an active cancer period as the time from 1 year before the date of a cancer diagnosis until 2 years after this date (i.e., for a total of 3 years). If a VTE occurred within the active cancer period, it was regarded as a cancer-related VTE.

Statistical analysis

Statistical analyses were performed with STATA version 18.0 (Stata Corporation, College Station, Texas, USA). Participants were followed from the date of inclusion in the surveys until the date of death, migration, or end of the study period (December 31, 2019), whichever came first. Person-time from all participants was distributed based on the exposures, which

defined four possible groups of observational periods: ‘disease-free’, ‘VTE’, ‘cancer’, and ‘cancer-related VTE’. VTE and cancer were treated as time-dependent exposure variables in all analyses. As illustrated in **Figure 1** (**Manuscript Figure**), the period from inclusion in the survey until the date of VTE diagnosis or cancer diagnosis was classified as disease-free observational period, and thereafter as VTE-exposed (**Figure 1B**) or cancer-exposed (**Figure 1C**) observational periods, respectively. The observational period was classified as cancer-related VTE if a VTE was diagnosed within 1 year before the date of cancer diagnosis until 2 years after the date of cancer diagnosis. Thus, participants who developed cancer-related VTE during follow-up contributed to three distinctive observational periods: disease-free, cancer, and cancer-related VTE if VTE was diagnosed until 2 years after cancer diagnosis (**Figure 1D**), or disease-free, VTE and cancer-related VTE if VTE was diagnosed within 1 year before cancer diagnosis (**Figure 1E**). This way, the contribution in terms of person-time of cancer-related VTE during follow-up only started when participants met the criteria of cancer-related VTE. In the main analysis, VTEs diagnosed outside the active cancer period were not regarded as cancer-related.

Because the definition of cancer-related VTE may vary across studies,[8-10] we performed sensitivity analyses for overall VTE considering three different scenarios to define cancer-related VTE: (i) VTEs occurring within 1 year before the date of cancer diagnosis until 5 years after the date of cancer diagnosis, (ii) only VTEs occurring within 2 years after the date of cancer diagnosis, (iii) only VTEs occurring within 5 years after the date of cancer diagnosis.

All analyses were stratified according to three time intervals: 1994-2002, 2003-2011, and 2012-2019. Participants who were not disease-free at the start of a new interval were removed from the analysis (e.g., participants who developed cancer and/or VTE in the interval from 2003 to 2011 would not be included in the analysis of the next interval from

2012 to 2019). Thus, only incident cancer and VTE events were assessed in each time interval. Means (±standard deviation) and proportions of baseline characteristics were calculated using descriptive statistics. We calculated the incidence rates (IRs) for mortality with 95% confidence intervals (CIs) by dividing the number of events (deaths) by the total accrued person-time for each of the four groups and expressed as number of events per 1,000 person-years. Cox proportional hazard regression models with cancer and VTE as time-dependent variables were used to calculate hazard ratios (HRs) for mortality with 95% CIs, creating models with the disease-free group or the cancer group as references. Two models were used to adjust for potential confounding factors: model 1 was adjusted for age and sex, and model 2 was adjusted for age, sex, as well as BMI (continuous variable), smoking, and comorbidities (arterial CVD, hypertension, and diabetes) assessed at baseline. In addition, we performed subgroup analyses according to cancer stage (non-metastatic cancer and metastatic cancer) and VTE subtype (DVT and PE). Kaplan-Meier curves were used to visualize survival over time in the cancer and cancer-related VTE groups in each time interval (1994-2002, 2003-2011, and 2012-2019). Finally, the survival analysis over time using the Kaplan-Meier approach was also carried out with the time intervals having the same length of follow-up (i.e., 1996-2003, 2004-2011, 2012-2019) for sensitivity purposes.

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Supplementary Tables

Supplementary Table S1 Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period (1994-2002, 2003-2011, 2012-2019) with cancer-related VTE defined as VTE occurring within 1 year before and 5 years after a cancer diagnosis

Exposure	PY, n (years)	Events, n	IR (95% CI), events per 1000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571654	3846	6.7 (6.5 - 6.9)	1 (reference)	1 (reference)
VTE	1796	134	74.6 (63.0 - 88.4)	3.5 (3.0 - 4.2)	3.7 (3.1 - 4.4)
Cancer	7420	1381	186.1 (176.6 - 196.2)	9.5 (8.9 - 10.1)	9.8 (9.2 - 10.5)
Cancer-related VTE	137	94	687.0 (561.3 - 840.9)	26.6 (21.7 - 32.7)	30.0 (24.4 - 36.9)
Cancer	7420	1381	186.1 (176.6 - 196.2)	1 (reference)	1 (reference)
Cancer-related VTE	137	94	687.0 (561.3 - 840.9)	3.1 (2.5 - 3.9)	3.3 (2.7 - 4.1)
2003-2011					
Disease-free	693550	6166	8.9 (8.7 - 9.1)	1 (reference)	1 (reference)
VTE	3107	225	72.4 (63.5 - 82.5)	2.9 (2.5 - 3.3)	2.9 (2.6 - 3.4)
Cancer	15365	2121	138.0 (132.3 - 144.0)	7.2 (6.8 - 7.5)	7.1 (6.8 - 7.5)
Cancer-related VTE	375	176	469.2 (404.7 - 543.9)	21.7 (18.7 - 25.2)	20.8 (17.8 - 24.2)
Cancer	15365	2121	138.0 (132.3 - 144.0)	1 (reference)	1 (reference)
Cancer-related VTE	375	176	469.2 (404.7 - 543.9)	3.3 (2.8 - 3.8)	3.3 (2.8 - 3.8)
2012-2019					
Disease-free	585345	5600	9.6 (9.3 - 9.8)	1 (reference)	1 (reference)
VTE	2676	160	59.8 (51.2 - 69.8)	2.6 (2.2 - 3.0)	2.5 (2.1 - 2.9)
Cancer	17727	1830	103.2 (98.6 - 108.1)	6.4 (6.1 - 6.8)	6.3 (6.0 - 6.7)
Cancer-related VTE	496	165	332.6 (285.5 - 387.4)	18.5 (15.8 - 21.6)	17.7 (15.2 - 20.7)
Cancer	17727	1830	103.2 (98.6 - 108.1)	1 (reference)	1 (reference)
Cancer-related VTE	496	165	332.6 (285.5 - 387.4)	3.0 (2.6 - 3.6)	2.9 (2.5 - 3.4)

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person years; VTE, venous thromboembolism.
Model 1: Adjusted for age and sex.
Model 2: Adjusted for age, sex, and baseline body mass index, smoking, and comorbidities (arterial cardiovascular disease, hypertension, diabetes).

Supplementary Table S2 Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period (1994-2002, 2003-2011, 2012-2019) with cancer-related VTE defined as VTE occurring within 2 years after a cancer diagnosis

Exposure	PY, n (years)	Events, n	IR (95% CI), events per 1000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571654	3846	6.7 (6.5 - 6.9)	1 (reference)	1 (reference)
VTE	1802	141	78.2 (66.3 - 92.3)	3.7 (3.1 - 4.4)	3.9 (3.3 - 4.6)
Cancer	7456	1403	188.2 (178.6 - 198.3)	9.5 (8.9 - 10.1)	9.9 (9.3 - 10.5)
Cancer-related VTE	94	65	690.3 (541.3 - 880.3)	34.3 (26.8 - 43.8)	38.8 (30.3 - 49.6)
Cancer	7456	1403	188.2 (178.6 - 198.3)	1 (reference)	1 (reference)
Cancer-related VTE	94	65	690.3 (541.3 - 880.3)	3.6 (2.8 - 4.7)	3.7 (2.9 - 4.8)
2003-2011					
Disease-free	693550	6166	8.9 (8.7 - 9.1)	1 (reference)	1 (reference)
VTE	3168	252	79.5 (70.3 - 90.0)	3.2 (2.8 - 3.6)	3.2 (2.8 - 3.7)
Cancer	15445	2157	139.7 (133.9 - 145.7)	7.3 (6.9 - 7.6)	7.2 (6.8 - 7.6)
Cancer-related VTE	234	113	483.2 (401.8 - 581.0)	21.3 (17.7 - 25.7)	21.4 (17.7 - 25.8)
Cancer	15445	2157	139.7 (133.9 - 145.7)	1 (reference)	1 (reference)
Cancer-related VTE	234	113	483.2 (401.8 - 581.0)	3.2 (2.7 - 3.9)	3.4 (2.8 - 4.1)
2012-2019					
Disease-free	585345	5600	9.6 (9.3 - 9.8)	1 (reference)	1 (reference)
VTE	2727	185	67.8 (58.7 - 78.4)	2.9 (2.5 - 3.4)	2.9 (2.5 - 3.3)
Cancer	17825	1862	104.5 (99.8 - 109.3)	6.5 (6.2 - 6.9)	6.4 (6.1 - 6.8)
Cancer-related VTE	348	108	310.5 (257.1 - 374.9)	16.0 (13.2 - 19.3)	15.3 (12.7 - 18.6)
Cancer	17825	1862	104.5 (99.8 - 109.3)	1 (reference)	1 (reference)
Cancer-related VTE	348	108	310.5 (257.1 - 374.9)	2.6 (2.2 - 3.2)	2.5 (2.1 - 3.1)

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person years; VTE, venous thromboembolism.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, and baseline body mass index, smoking, and comorbidities (arterial cardiovascular disease, hypertension, diabetes).

Supplementary Table S3 Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period (1994-2002, 2003-2011, 2012-2019) with cancer-related VTE defined as VTE occurring within 5 years after a cancer diagnosis

Exposure	PY, n (years)	Events, n	IR (95% CI), events per 1000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571654	3846	6.7 (6.5 - 6.9)	1 (reference)	1 (reference)
VTE	1796	134	74.6 (63.0 - 88.4)	3.5 (3.0 - 4.2)	3.7 (3.1 - 4.4)
Cancer	7456	1403	188.2 (178.6 - 198.3)	9.5 (8.9 - 10.1)	9.9 (9.3 - 10.5)
Cancer-related VTE	100	72	719.4 (571.0 - 906.3)	36.2 (28.6 - 45.7)	40.7 (32.2 - 51.5)
Cancer	7456	1403	188.2 (178.6 - 198.3)	1 (reference)	1 (reference)
Cancer-related VTE	100	72	719.4 (571.0 - 906.3)	3.8 (3.0 - 4.9)	3.9 (3.1 - 5.0)
2003-2011					
Disease-free	693550	6166	8.9 (8.7 - 9.1)	1 (reference)	1 (reference)
VTE	3107	225	72.4 (63.5 - 82.5)	2.9 (2.5 - 3.3)	2.9 (2.6 - 3.4)
Cancer	15445	2157	139.7 (133.9 - 145.7)	7.3 (6.9 - 7.6)	7.2 (6.8 - 7.6)
Cancer-related VTE	295	140	474.4 (402.0 - 559.9)	20.5 (17.3 - 24.3)	19.9 (16.8 - 23.6)
Cancer	15445	2157	139.7 (133.9 - 145.7)	1 (reference)	1 (reference)
Cancer-related VTE	295	140	474.4 (402.0 - 559.9)	3.2 (2.7 - 3.7)	3.2 (2.7 - 3.8)
2012-2019					
Disease-free	585345	5600	9.6 (9.3 - 9.8)	1 (reference)	1 (reference)
VTE	2676	160	59.8 (51.2 - 69.8)	2.6 (2.2 - 3.0)	2.5 (2.1 - 2.9)
Cancer	17825	1862	104.5 (99.8 - 109.3)	6.5 (6.2 - 6.9)	6.4 (6.1 - 6.8)
Cancer-related VTE	399	133	333.3 (281.2 - 395.1)	17.9 (15.1 - 21.3)	17.2 (14.5 - 20.5)
Cancer	17825	1862	104.5 (99.8 - 109.3)	1 (reference)	1 (reference)
Cancer-related VTE	399	133	333.3 (281.2 - 395.1)	2.9 (2.5 - 3.5)	2.8 (2.4 - 3.4)

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person years; VTE, venous thromboembolism.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, and baseline body mass index, smoking, and comorbidities (arterial cardiovascular disease, hypertension, diabetes).

Supplementary Figure

Supplementary Figure S1. Kaplan-Meier curve showing the 30-day survival probability of cancer-related VTE exposed group, stratified by time period (1994-2002, 2003-2011, 2012-2019). VTE, venous thromboembolism; CRVTE, cancer-related VTE.