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

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Abstract

Venous thromboembolism (VTE) is a common and serious condition among cancer patients. The diagnostic and therapeutic strategies for cancer and VTE have improved during the last three decades. It remains unclear whether mortality after cancer-related VTE (CRVTE) has decreased in this period. Therefore, we investigated the mortality risk after CRVTE over the last three decades in a population-based cohort. In total, 111,119 participants from Tromsø4-7 (1994-2016) and HUNT2-3 (1995-2008) surveys were followed through 2019, and all first-lifetime cancer and VTE events were recorded. CRVTE patients were compared with participants neither exposed to cancer nor VTE (disease-free group), and those with cancer. We estimated hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality using Cox regression with cancer and VTE as time-dependent exposures, and 1-year cumulative incidence of mortality after CRVTE. Analyses were performed for three time periods: 1994-2002, 2003-2011, and 2012-2019. The age- and sex-adjusted HR for mortality after CRVTE *versus* disease-free group decreased from 25.3 (95% CI: 20.5-31.3) in 1994-2002 to 22.6 (95% CI: 19.2-26.6) in 2003-2011, and 16.9 (95% CI: 14.3-20.0) in 2012-2019. The HR for mortality after CRVTE *versus* cancer group remained stable (approx. 3-fold higher) along the three time periods. Similar estimates were obtained after further adjustments for comorbidities. The 1-year cumulative incidence of mortality after CRVTE decreased from 61.8% (95% CI: 52.9-70.8%) in 1994-2002 to 55.6% (95% CI: 49.0-62.4%) in 2003-2011, and 45.5% (95% CI: 39.3-52.1%) in 2012-2019. Our results indicate a decrease in mortality risk after CRVTE over the last three decades, which might be mainly the result of considerable advances in cancer management.

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease associated with severe short- and long-term complications, including recurrence, post-thrombotic syndrome, post-PE syndrome, and death.[1-3] In contrast to the declining incidence of arterial cardiovascular diseases (CVD) in recent decades,[4,5] the incidence of VTE has remained stable or even slightly increased during the same period.[6-8] It is expected that the incidence of VTE will continue to rise with the increasing prevalence of major VTE risk factors, among which cancer is one of the most relevant from a public health perspective.[8,9]

The association between cancer and VTE has been known for over 150 years.[10] The risk of VTE in cancer patients is reported to be almost 9-fold higher compared with the general population,[11] and approximately 25% of all first-lifetime VTE events are cancer-related.[12] The risk of VTE in cancer has a multicausal nature and can be attributed to factors related to the patient (e.g., age, comorbidities, prior history of VTE, and inherited prothrombotic conditions), cancer site and stage, cancer treatment, as well as exposure to hospitalization and prolonged immobilization.[12,13] Notably,

the development of VTE in cancer patients is associated with a poor prognosis, with VTE being an important cause of death in these patients.[14] In a landmark study conducted in Denmark with data from 1977 to the early 1990s, the 1-year all-cause mortality rate was 88% in patients with cancer diagnosed at the same time as a VTE event compared with 64% in cancer patients without VTE.[15] More recent data, albeit improved, still show a high 1-year mortality rate in cancer-related VTE, with estimates ranging from 45% to 68%,[16,17] depending on the criteria used to define cancer-related VTE.

The incidence of cancer-related VTE has increased in recent years.[11,18] Multiple factors may have contributed to this increase, including a rising incidence of cancer worldwide and improved overall cancer survival,[9,19-21] a higher detection of incidental and subsegmental PE due to more frequent use of high-resolution computed tomography (CT) scanning,[11] and the introduction of targeted therapy (e.g., protein kinase inhibitors, and immunotherapy), which has been reported to have prothrombotic properties.[13,22] However, whether the increase in cancer-related VTE incidence in the general population has impacted patient prognosis remains unclear. Improved diagnostic strategies for cancer and VTE, as well as changes in the therapy of both diseases, along with an aging population worldwide living with an increasing burden of comorbidities may have affected the mortality after cancer-related VTE.[3,23,24] While previous data suggest an improved prognosis of cancer-related VTE,[16,17] further population-based studies with extended follow-up are warranted to clarify whether and to what extent mortality has changed during recent decades.

Therefore, in the present study, we used data from two large population-based cohorts with validated assessments of both VTE and cancer with the aim of investigating time trends in mortality after cancer-related VTE over the last three decades.

Methods

Study population and design

This cohort study used data from the Trøndelag Health Study (HUNT) and the Tromsø Study.[25-27] A total of 115,585 unique participants, aged 19-100 years, from the Tromsø4-7 (1994-2016) and HUNT2-3 (1995-2008) surveys were included. After excluding participants with VTE and/or cancer history prior to cohort inclusion (N=4,384) and those who moved before the inclusion date (N=82), 111,119 participants were included in the final analytical sample. Baseline characteristics were collected through physical examination and self-administered questionnaires.[27-29] The study was approved by the Regional Committee for Medical and Health Research Ethics in agreement with the Declaration of Helsinki, and all participants provided written informed consent for participation and use of data for medical research.

Exposures and outcome

The exposures were VTE and cancer. Follow-up on symptomatic incident VTE was conducted until December 31, 2019. VTE validation required signs and symptoms of DVT or PE combined with objective confirmation by radiological procedures, resulting in a VTE diagnosis requiring treatment. Simultaneous DVT and PE were classified as PE. Superficial vein thrombosis and incidentally detected DVT and PE were not included. The date of cancer diagnosis, primary cancer site, stage, and histological grade were obtained by linkage to the Cancer Registry of Norway.[30] In line with a previous report,[31] an active cancer period was defined as the time from one year before the date of cancer diagnosis until two years after this date. If a VTE occurred within the active cancer period, it was regarded as cancer-related VTE. 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 National Population Registry.

Statistical analysis

Participants were followed from the date of cohort inclusion until the date of death, migration, or end of the study (December 31, 2019), whichever came first. Person-time was distributed according to exposures, which defined four groups of observational periods: 'disease-free', 'VTE', 'cancer', and 'cancer-related VTE' (Figure 1A-E), with VTE and cancer treated as time-dependent exposure variables.

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. Thus, only incident cancer and VTE events were assessed in each time interval. Cox proportional hazards regression models with cancer and VTE as time-dependent variables were used to calculate hazard ratios (HR) for mortality with 95% confidence intervals (CI), with disease-free or cancer groups as references. Cox models were adjusted for potential confounding: Model 1 was adjusted for age and sex, and Model 2 was additionally adjusted for body mass index (BMI), smoking, and comorbidities (arterial CVD, hypertension, and diabetes) assessed at baseline. We performed subgroup analyses according to cancer stage (non-metastatic cancer and metastatic cancer) and VTE subtype (DVT/PE). Kaplan-Meier curves were used to visualize survival over time in the cancer and cancer-related VTE groups in each time interval.

A detailed description of the methods is available in the *Online Supplementary Appendix*.

Results

Demographics, lifestyle factors, and clinical characteristics of the study population

The median follow-up time was 22.7 years among the 111,119

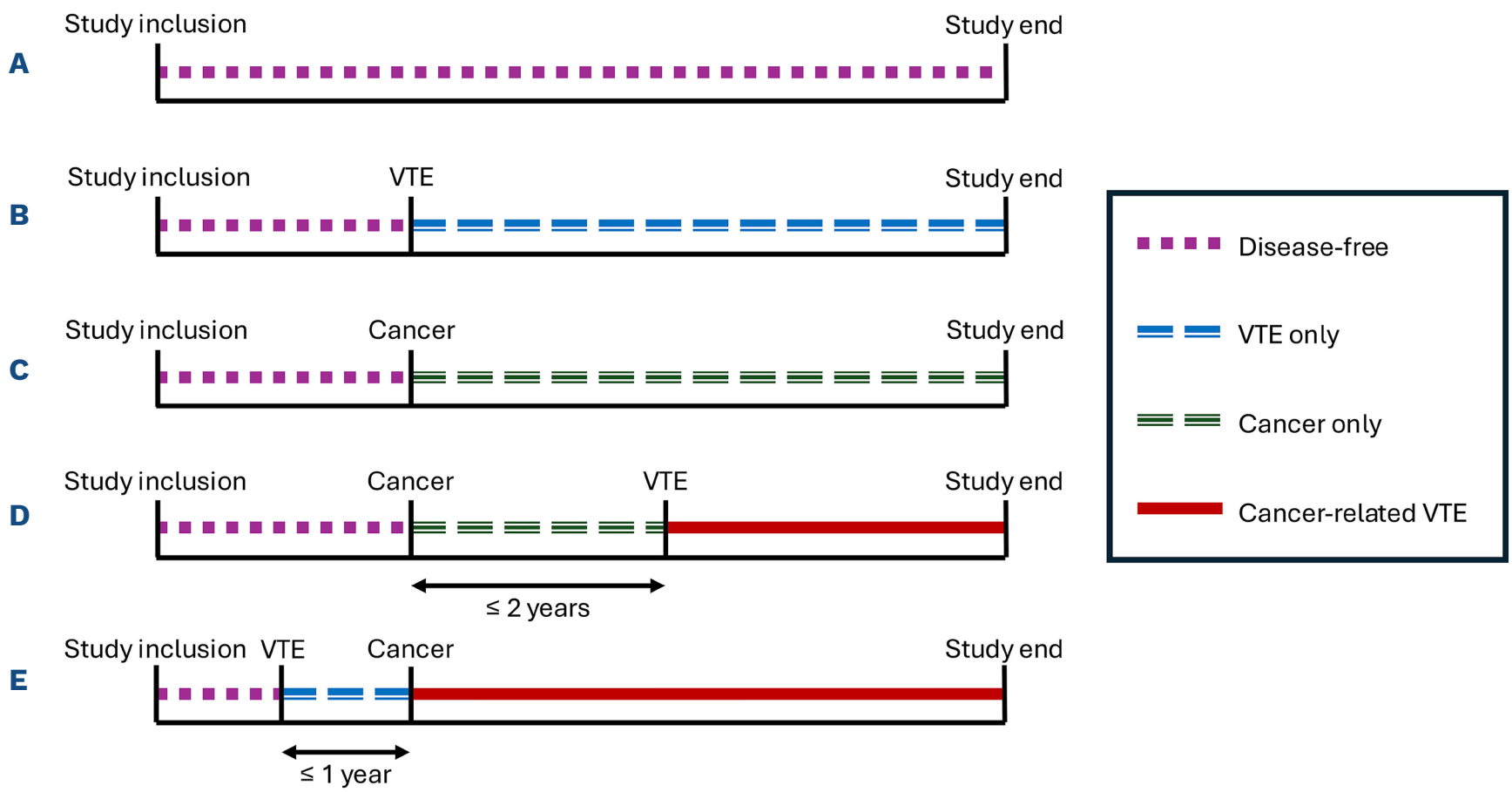


Figure 1. Distinctive groups of observational periods based on the exposure to cancer, venous thromboembolism, or cancer-related venous thromboembolism during study follow-up. (A) Participants exposed to neither cancer nor venous thromboembolism (VTE) from study inclusion to study end (disease-free group). (B and C) Participants exposed to only VTE or cancer during follow-up, respectively. These participants contribute to person-time in the disease-free group from the study inclusion until the date of a VTE diagnosis or a cancer diagnosis, and thereafter as VTE-exposed (B) or cancer-exposed (C) person-time, respectively. (D) Participants with a VTE event occurring ≤2 years after the date of a cancer diagnosis. These participants contribute during follow-up as disease-free person-time, then as cancer-exposed person-time, and lastly as cancer-related VTE-exposed person-time. (E) Participants with a VTE event occurring ≤1 year before the date of a cancer diagnosis. These participants contribute during follow-up as disease-free person-time, then as VTE-exposed person-time, and lastly as cancer-related VTE-exposed person-time. (D and E) Contribution in terms of person-time of cancer-related VTE during follow-up only started when participants met the criteria of cancer-related VTE.

participants free of cancer and VTE at inclusion. Demographics, lifestyle factors, and clinical characteristics are presented according to time-stratified analysis in Table 1. There were 3,057 VTE events, among which 568 were classified as cancer-related. Over the decades, the mean age increased from 46.4 years in 1994-2002 to 50.8 years in 2003-2011 and 56.0 years in 2012-2019, as most participants were followed for multiple periods. The proportion of individuals with arterial CVD, hypertension and diabetes decreased over time, whereas the proportion of those with cancer increased (from 4.0% in 1994-2002 to 7.6% in 2012-2019). The proportion of individuals with distant metastasis at cancer diagnosis decreased from 19.4% in 1994-2002 to 14.2% in 2012-2019, with the proportion of localized cancer stage increasing in the same period. The most common cancer sites were prostate, breast, and colorectal, regardless of the time period. Of note, the proportion of VTE diagnoses classified as PE increased from 34.9% in 1994-2002 to 51.7% in 2012-2019.

Time trends in mortality risk after cancer-related venous thromboembolism

During the three time periods (i.e., 1994-2002, 2003-2011, and 2012-2019), 21,898 participants died. In comparison with the disease-free group, the relative risk estimates for mortality after cancer-related VTE decreased over time (Table 2), with age- and sex-adjusted HR of 25.3 (95% CI: 20.5-31.3) in 1994-2002, 22.6 (95% CI: 19.2-26.6) in 2003-2011, and 16.9 (95% CI: 14.3-20.0) in 2012-2019. Additional adjustments for BMI, smoking, hypertension, diabetes, and arterial CVD in Model 2 had minor impact on these risk estimates. The HR for mortality were about 3-fold higher in cancer-related VTE compared with cancer and remained stable over the three time periods in models adjusted for age and sex as well as in the fully adjusted analyses (Table 2).

The 30-day cumulative incidence of mortality after cancer-related VTE decreased from 26.8% (95% CI: 19.7-35.9%) in 1994-2002 to 16.6% (95% CI: 12.3-22.2%) in 2003-2011 and 15.8% (95% CI: 11.7-21.1%) in 2012-2019 (*Online Supplementary Figure S1*). The 1-year cumulative incidence of mortality after cancer-related VTE also decreased over time from 61.8% (95% CI: 52.9-70.8%) in 1994-2002 to 55.6% (95% CI: 49.0-62.4%) in 2003-2011, and further to 45.5% (95% CI: 39.3-52.1%) in 2012-2019 (Figure 2). The 1-year cumulative

Table 1. Distribution of demographics, lifestyle factors, and clinical characteristics of the study population according to time period: 1994-2002, 2003-2011, 2012-2019.

	1994-2002	2003-2011	2012-2019
Total, N	89,294	92,927	83,842
Male, N (%)	42,272 (47.3)	43,410 (46.7)	38,911 (46.4)
Mean age in years (SD)	46.4 (16.6)	50.8 (16.7)	56.0 (14.9)
Mean BMI, kg/m² (SD)	25.8 (4.0)	25.9 (4.1)	25.9 (4.1)
Current daily smoking, N (%)	28,928 (32.4)	28,312 (30.5)	24,463 (29.2)
Highest level of education, N (%)			
Primary school	29,403 (32.9)	24,670 (26.5)	18,571 (22.1)
High school	35,366 (39.6)	32,661 (35.1)	29,975 (35.8)
College/university	21,023 (23.5)	19,656 (21.2)	21,310 (25.4)
Comorbidities, N (%)			
Arterial CVD	8,572 (9.6)	6,801 (7.3)	4,315 (5.1)
Hypertension	46,633 (52.2)	43,485 (46.8)	34,960 (41.7)
Diabetes	4,607 (5.2)	4,260 (4.6)	3,373 (4.0)
Exposures, N (%)			
VTE	785 (0.9)	1,179 (1.3)	1,093 (1.3)
Cancer	3,533 (4.0)	5,664 (6.1)	6,378 (7.6)
Cancer-related VTE	116 (0.1)	217 (0.2)	235 (0.3)
VTE type, N (% of VTE)			
Deep vein thrombosis	511/785 (65.1)	585/1,179 (49.6)	528/1,093 (48.3)
Pulmonary embolism	274/785 (34.9)	594/1,179 (50.4)	565/1,093 (51.7)
Cancer stage, N (% of cancers)			
Localized	1,002/3,533 (28.4)	1,972/5,664 (34.8)	2,643/6,378 (41.4)
Regional metastasis	738/3,533 (20.9)	1,386/5,664 (24.5)	1,572/6,378 (24.6)
Distant metastasis	687/3,533 (19.4)	1,056/5,664 (18.6)	907/6,378 (14.2)
Unknown	1,106/3,533 (31.3)	1,250/5,664 (22.1)	1,256/6,378 (19.7)
Cancer site, N (% of cancers)			
Colorectal	592/3,533 (16.8)	919/5,664 (16.2)	971/6,378 (15.2)
Pancreatic	113/3,533 (3.2)	165/5,664 (2.9)	168/6,378 (2.6)
Lung	347/3,533 (9.8)	584/5,664 (10.3)	580/6,378 (9.1)
Breast*	430/1,688 (25.5)	700/2,663 (26.3)	773/2,956 (26.2)
Gynecological*	240/1,688 (14.2)	331/2,663 (12.4)	328/2,956 (11.1)
Prostate†	563/1,845 (30.5)	1,065/3,001 (35.5)	1,249/3,422 (36.5)
Urological	225/3,533 (6.4)	321/5,664 (5.7)	458/6,378 (7.2)
Central nervous system	80/3,533 (2.3)	148/5,664 (2.6)	156/6,378 (2.4)
Hematologic	292/3,533 (8.3)	434/5,664 (7.7)	532/6,378 (8.3)
Upper gastrointestinal	220/3,533 (6.2)	325/5,664 (5.7)	355/6,378 (5.6)
Others	431/3,533 (12.2)	672/5,664 (11.9)	808/6,378 (12.7)

Participants not disease-free at the start of each time period were excluded. Participants with venous thromboembolism (VTE) include those exposed to VTE only and cancer-related VTE. Participants with cancer include those exposed to cancer only and cancer-related VTE. Data for education are missing for HUNT3 participants (N=16,600). *Percentage based on women only. †Percentage based on men only. Others: ear/nose/throat cancers, melanoma, endocrinological cancers, sarcomas (bone/connective tissue), eye cancer, penis/testis cancers, thymus/heart/mediastinum/pleura cancers, mesothelioma/Kaposi sarcoma, unknown origin. BMI: body mass index; CVD: cardiovascular disease (angina pectoris, myocardial infarction, and stroke); N: number; SD: standard deviation.

incidence of mortality for the cancer group was 27.4% (95% CI: 25.9-29.0%) in 1994-2002 and decreased to 23.9% (95% CI: 22.8-25.1%) in 2003-2011 and 17.8% (95% CI: 16.9-18.8%) in 2012-2019 (Figure 2).

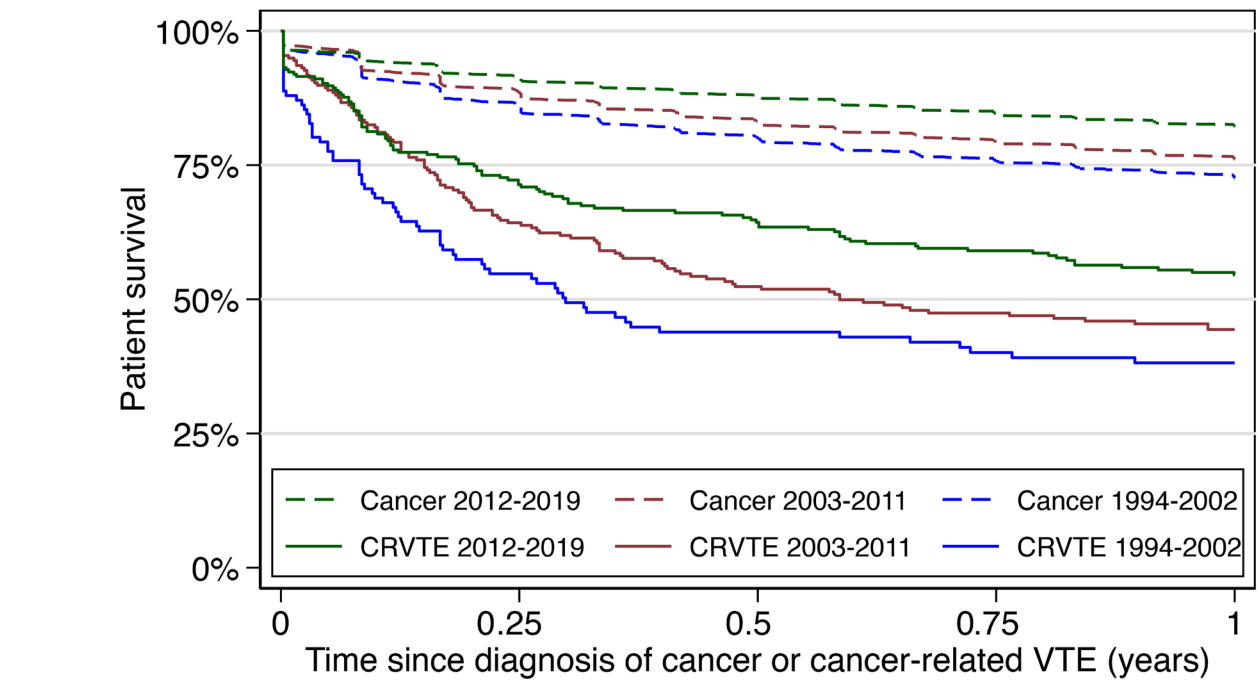
The decrease in mortality over time was clearly noticeable after non-metastatic cancer-related VTE (Table 3, Figure 3). The age- and sex-adjusted HR for mortality in the non-metastatic cancer-related VTE group *versus* the disease-free group decreased from 20.0 (95% CI: 15.2-26.1) in 1994-2002 to 14.0 (95% CI: 11.3-17.5) in 2003-2011, and further to 10.7 (95% CI: 8.6-13.2) in 2012-2019, with similar results obtained in the fully adjusted analyses. In contrast, the corresponding HR of metastatic cancer-related VTE increased over time, though estimates were imprecise, with wide 95% CI (Table 3).

The HR for mortality after cancer-related DVT compared

Table 2. Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period: 1994-2002, 2003-2011, 2012-2019.

Exposure	PY N	Events N	IR (95% CI) events per 1,000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571,654	3,846	6.7 (6.5-6.9)	1 (reference)	1 (reference)
VTE	1,802	141	78.2 (66.3-92.3)	3.7 (3.1-4.4)	3.9 (3.3-4.6)
Cancer	7,420	1,381	186.1 (176.6-196.2)	9.5 (8.9-10.1)	9.8 (9.2-10.5)
Cancer-related VTE	131	87	664.6 (538.7-820.1)	25.3 (20.5-31.3)	28.6 (23.1-35.5)
Cancer	7,420	1,381	186.1 (176.6-196.2)	1 (reference)	1 (reference)
Cancer-related VTE	131	87	664.6 (538.7-820.1)	3.0 (2.4-3.7)	3.2 (2.5-3.9)
2003-2011					
Disease-free	693,550	6,166	8.9 (8.7-9.1)	1 (reference)	1 (reference)
VTE	3,168	252	79.5 (70.3-90.0)	3.2 (2.8-3.6)	3.2 (2.8-3.7)
Cancer	15,365	2,121	138.0 (132.3-144.0)	7.2 (6.8-7.5)	7.1 (6.7-7.5)
Cancer-related VTE	314	149	474.7 (404.3-557.4)	22.6 (19.2-26.6)	22.1 (18.7-26.0)
Cancer	15,365	2,121	138.0 (132.3-144.0)	1 (reference)	1 (reference)
Cancer-related VTE	314	149	474.7 (404.3-557.4)	3.3 (2.8-3.9)	3.4 (2.9-4.0)
2012-2019					
Disease-free	585,345	5,600	9.6 (9.3-9.8)	1 (reference)	1 (reference)
VTE	2,727	185	67.8 (58.7-78.4)	2.9 (2.5-3.4)	2.9 (2.5-3.3)
Cancer	17,727	1,830	103.2 (98.6-108.1)	6.4 (6.1-6.8)	6.3 (6.0-6.7)
Cancer-related VTE	445	140	314.6 (266.6-371.3)	16.9 (14.3-20.0)	16.2 (13.7-19.2)
Cancer	17,727	1,830	103.2 (98.6-108.1)	1 (reference)	1 (reference)
Cancer-related VTE	445	140	314.6 (266.6-371.3)	2.8 (2.3-3.3)	2.7 (2.2-3.2)

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). CI: confidence interval; HR: hazard ratio; IR: incidence rate; N: number; PY: person years; VTE: venous thromboembolism.



N at risk					
CRVTE 2012-2019	235	164	146	133	118
CRVTE 2003-2011	217	137	109	95	86
CRVTE 1994-2002	116	61	48	42	37
Cancer 2012-2019	6,319	5,508	5,112	4,747	4,419
Cancer 2003-2011	5,608	4,726	4,277	3,933	3,610
Cancer 1994-2002	3,500	2,849	2,530	2,292	2,091

Figure 2. Kaplan-Meier curves showing survival probability over time of cancer exposed group and cancer-related venous thromboembolism exposed group stratified by time period: 1994-2002, 2003-2011, and 2012-2019. Follow-up started at the date of diagnosis of cancer or cancer-related venous thromboembolism (VTE). Since participants with VTE occurring within one year before the date of cancer diagnosis were never exposed to cancer only, they were excluded from the analysis of the cancer exposed group (N=33 in 1994-2002, N=56 in 2003-2011, N=59 in 2012-2019). CRVTE: cancer-related VTE; N: number.

Table 3. Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period (1994-2002, 2003-2011, 2012-2019) and metastatic status.

Exposure	PY N	Events N	IR (95% CI) events per 1,000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571,654	3,846	6.7 (6.5-6.9)	1 (reference)	1 (reference)
VTE	1,802	141	78.2 (66.3-92.3)	3.7 (3.1-4.3)	3.8 (3.2-4.6)
Non-metastatic cancer	6,842	861	125.8 (117.7-134.5)	6.4 (5.9-6.9)	6.5 (6.1-7.1)
Metastatic cancer	577	520	900.8 (826.6-981.7)	46.5 (42.4-51.0)	50.8 (46.2-55.8)
Non-metastatic CRVTE	96	54	559.6 (428.6-730.7)	20.0 (15.2-26.1)	22.0 (16.8-28.8)
Metastatic CRVTE	34	33	959.1 (681.9-1,349.1)	44.2 (31.4-62.4)	55.6 (39.4-78.4)
2003-2011					
Disease-free	693,550	6,166	8.9 (8.7-9.1)	1 (reference)	1 (reference)
VTE	3,168	252	79.5 (70.3-90.0)	3.2 (2.8-3.6)	3.2 (2.8-3.6)
Non-metastatic cancer	14,262	1,332	93.4 (88.5-98.5)	4.9 (4.6-5.2)	4.8 (4.6-5.1)
Metastatic cancer	1,102	789	715.7 (667.5-767.5)	32.3 (30.0-34.8)	31.9 (29.6-34.4)
Non-metastatic CRVTE	264	83	314.7 (253.8-390.2)	14.0 (11.3-17.5)	13.6 (10.9-16.9)
Metastatic CRVTE	50	66	1,315.7 (1,033.7-1,674.7)	90.8 (71.2-115.8)	102.5 (80.1-131.0)
2012-2019					
Disease-free	585,345	5,600	9.6 (9.3-9.8)	1 (reference)	1 (reference)
VTE	2,727	185	67.8 (58.7-78.4)	2.9 (2.5-3.4)	2.8 (2.5-3.3)
Non-metastatic cancer	16,596	1,214	73.2 (69.1-77.4)	4.6 (4.3-4.9)	4.5 (4.2-4.8)
Metastatic cancer	1,132	616	544.4 (503.0-589.1)	29.8 (27.4-32.5)	28.5 (26.1-31.0)
Non-metastatic CRVTE	397	85	213.9 (172.9-264.5)	10.7 (8.6-13.2)	10.3 (8.3-12.8)
Metastatic CRVTE	47	55	1,158.1 (889.1-1,508.4)	131.5 (100.6-171.9)	125.8 (96.2-164.6)

Unknown metastatic status is regarded as non-metastatic. 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). CI: confidence interval; CRVTE: cancer-related venous thromboembolism (VTE); HR: hazard ratio; IR: incidence rate; N: number; PY: person years.

with the disease-free group clearly decreased from the two early periods to the most recent one in 2012-2019 (Table 4). In the fully adjusted analyses, the HR for mortality after cancer-related DVT were 30.9 (95% CI: 23.9-40.0) in 1994-2002 and decreased to 11.1 (95% CI: 8.5-14.4) in 2012-2019. For cancer-related PE, the risk of mortality compared with the disease-free group did not substantially change, with HR of 24.8 (95% CI: 17.1-36.0) in 1994-2002 and 23.2 (95% CI: 18.7-28.9) in 2012-2019.

Results from sensitivity analyses, when different definitions of cancer-related VTE were applied, were similar to those obtained in the main analysis, with the risk of mortality decreasing over time (*Online Supplementary Tables S1-S3*). However, when cancer-related VTE comprised only VTE occurring within two or within five years after the date of a cancer diagnosis, respectively (*Online Supplementary Tables S2 and S3*), the decline in mortality after cancer-related VTE *versus* the disease-free group was somewhat more pronounced between the first and the two most recent periods in comparison with the main analysis. Furthermore, in the sensitivity analysis in which the three time intervals had the same length of follow-up (i.e., 1996-2003, 2004-2011, 2012-2019), the decline in the 1-year cumulative incidence of mortality after cancer-related VTE and cancer displayed a similar trend to the main analysis (*data not shown*). Of note, the main results remained essentially the same when adding education level as a co-variate in the adjustment models (*data not shown*).

Discussion

In this study, we investigated the trends in mortality after cancer-related VTE over the past three decades, using data from two large Norwegian population-based cohorts. Our results revealed a substantial reduction in the 1-year cumulative incidence of mortality after cancer-related VTE, declining from 62% in 1994-2002 to 46% in 2012-2019. In comparison with the disease-free group, the cancer-related VTE group had a 25-fold higher risk of mortality in 1994-2002 but estimates declined over time and were about 17-fold higher in 2012-2019. This favorable trend seemed to be driven by mortality reductions after non-metastatic cancer-related VTE and cancer-related DVT. It is worth noting that the mortality risk after cancer-related VTE compared with the cancer group remained stable (about 3-fold higher) over time during the study period. Our findings suggest an improved prognosis of cancer-related VTE during the past three decades, a period during which important advances have also occurred in cancer and VTE management.

Data on time trends in mortality rates after cancer-related VTE are scarce and mainly derived from the Danish health

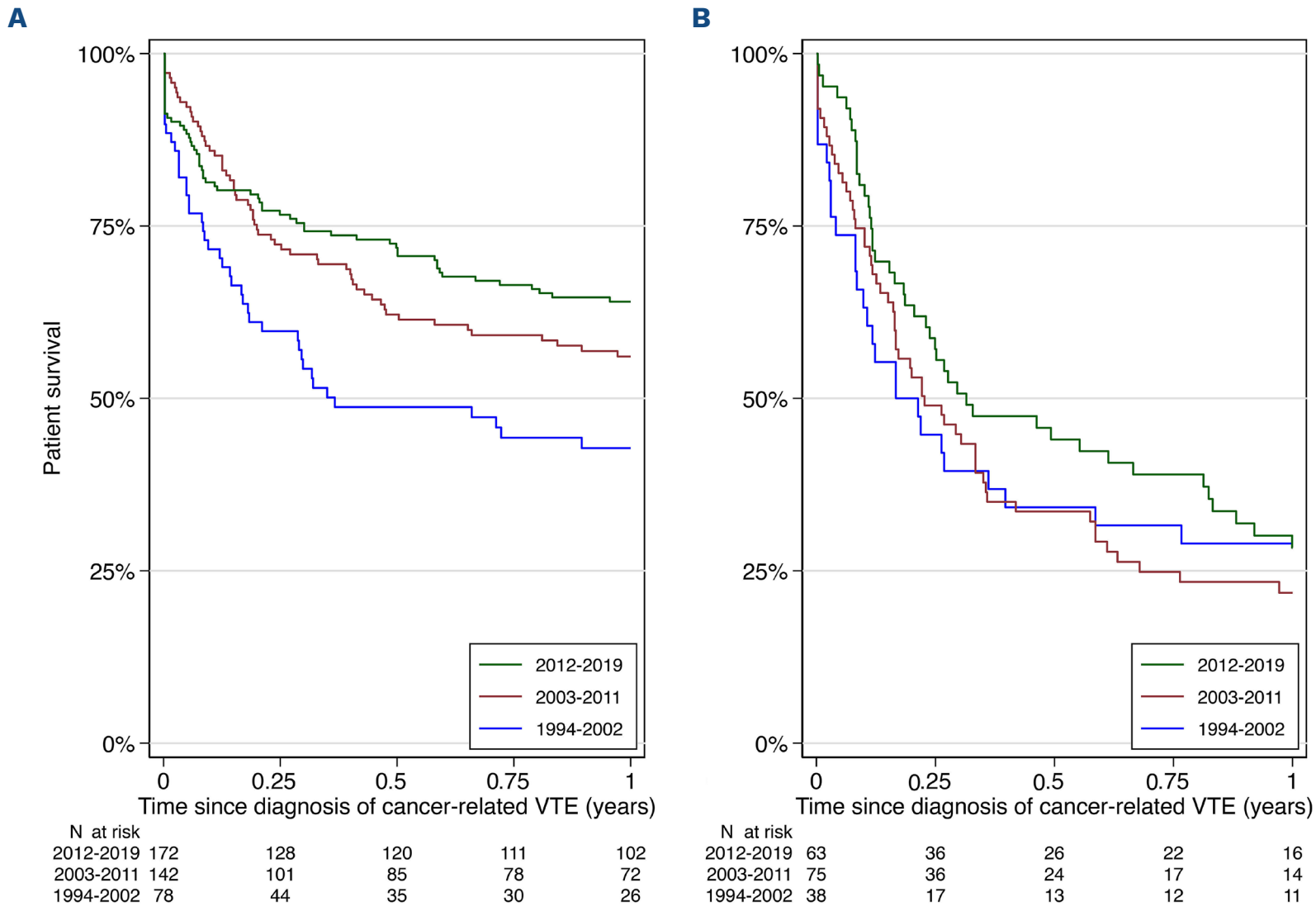


Figure 3. Kaplan-Meier curves showing survival probability of non-metastatic and metastatic cancer-related venous thromboembolism exposed groups stratified by time period: 1994-2002, 2003-2011, and 2012-2019. Follow-up started at the date of diagnosis of non-metastatic cancer-related thromboembolism (VTE) (A) or metastatic cancer-related VTE (B). CRVTE: cancer-related VTE; N: number.

registries.[16,17] In two nationwide cohorts from Denmark, the 1-year cumulative incidence of mortality in patients with VTE diagnosed concurrently with cancer was 88% in the report using data until the early 1990s[15] and decreased to 68% when applying more recent data (1995-2018).[17] In the latter study, patients with a VTE occurring at any time after cancer diagnosis were also classified as having cancer-related VTE (median time between cancer diagnosis and VTE was 2.6 years),[17] and in this scenario, the 1-year cumulative incidence of mortality was lower (45%). Regardless of the definition of cancer-related VTE, the authors found a decline in the 1- and 5-year cumulative incidence of mortality over time (1995-2018), which was less pronounced for patients with VTE diagnosed concurrently with cancer.[17] Ording *et al*. also conducted a study using the Danish health registries (time-frame 2006-2017) and defined cancer-related VTE as a VTE event occurring within one year after the cancer diagnosis.[16] The authors found a trend of decreasing mortality similar to ours, despite a shorter follow-up time, with the 1-year mortality decreasing from 52.4% in 2006-2008 to 45.8% in 2015-2017.[16] Overall, our results on time trends in mortality rates after cancer-related VTE are in line with the most contemporary data derived from the Danish health registries.[16,17] However, some key differences between our study and the Danish reports should be addressed. In the above-mentioned studies,[15-17] authors used the International Classification of Diseases (ICD) codes to assess the VTE diagnosis, which could have led to some degree of misclassification of VTE events, whereas in our study VTE was based on objectively validated diagnosis. In addition, the risk of VTE was reported to be already elevated one year before a cancer diagnosis,[31] and not considering VTE occurring shortly before a cancer diagnosis or including VTE occurring several years after cancer might underestimate the mortality rates of cancer-related VTE.

In a recently published cohort study involving 17,271 patients with cancer-related VTE derived from the RIETE registry, Bertoletti *et al*. found a reduction in all-cause mortality at the 30-day follow-up from 11.9% in 2001-2005 to 8.4% in 2016-2020.[32] Although the decline in mortality over time is in line with our results, the 30-day death rates from the RIETE registry are somewhat lower than our findings, which could be due to differences in the definitions of cancer-related VTE; for instance, in the RIETE registry, patients with VTE occurring shortly before a cancer diagnosis were not included. A study conducted in the Scandinavian Thrombosis and Cancer (STAC) cohort, which included data from the Tromsø4, HUNT2, and Diet, Cancer and Health studies,[33]

Table 4. Crude incidence rates and hazard ratios with 95% confidence intervals for mortality stratified by time period (1994-2002, 2003-2011, 2012-2019) and type of venous thromboembolism.

Exposure	PY N	Events N	IR (95% CI) events per 1,000 PY	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1994-2002					
Disease-free	571,654	3,846	6.7 (6.5-6.9)	1 (reference)	1 (reference)
DVT	1,206	84	69.6 (56.2-86.2)	3.4 (2.8-4.3)	3.7 (3.0-4.6)
PE	596	57	95.6 (73.8-124.0)	4.2 (3.2-5.5)	4.2 (3.2-5.5)
Cancer	7,420	1,381	186.1 (176.6-196.2)	9.5 (8.9-10.1)	9.8 (9.2-10.5)
Cancer-related DVT	91	59	649.2 (503.0-837.9)	29.0 (22.4-37.5)	30.9 (23.9-40.0)
Cancer-related PE	40	28	699.8 (483.2-1,013.5)	20.0 (13.8-29.0)	24.8 (17.1-36.0)
2003-2011					
Disease-free	693,550	6,166	8.9 (8.7-9.1)	1 (reference)	1 (reference)
DVT	1,753	116	66.2 (55.2-79.4)	2.6 (2.1-3.1)	2.6 (2.1-3.1)
PE	1,415	136	96.1 (81.2-113.7)	4.0 (3.4-4.8)	4.1 (3.5-4.9)
Cancer	15,365	2,121	138.0 (132.3-144.0)	7.2 (6.8-7.5)	7.1 (6.7-7.5)
Cancer-related DVT	135	81	598.0 (481.0-743.5)	32.7 (26.3-40.7)	31.4 (25.2-39.2)
Cancer-related PE	178	68	381.1 (300.5-483.3)	16.5 (13.0-21.0)	16.3 (12.9-20.8)
2012-2019					
Disease-free	585,345	5,600	9.6 (9.3-9.8)	1 (reference)	1 (reference)
DVT	1,442	87	60.3 (48.9-74.4)	2.7 (2.2-3.3)	2.7 (2.1-3.3)
PE	1,285	98	76.3 (62.6-93.0)	3.2 (2.6-3.9)	3.1 (2.5-3.7)
Cancer	17,727	1,830	103.2 (98.6-108.1)	6.4 (6.1-6.8)	6.3 (6.0-6.7)
Cancer-related DVT	208	56	269.8 (207.6-350.6)	12.6 (9.6-16.4)	11.1 (8.5-14.4)
Cancer-related PE	237	84	353.8 (285.7-438.2)	21.9 (17.7-27.2)	23.2 (18.7-28.9)

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). CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; IR: incidence rate; N: number; PE:pulmonary embolism; PY: person years.

found HR for mortality of cancer-related VTE compared with disease-free or cancer groups similar to our estimates, mainly from the early period from 1994 to 2002. Because there is some degree of overlap of the study population between the STAC cohort and our study, similar findings may be expected. However, the STAC cohort study did not investigate potential change in mortality over time and the follow-up was until 2012.

Our findings on the declining mortality after cancer-related VTE over time occurred in parallel with major advances in cancer management. Indeed, cancer treatment has made great breakthroughs in recent decades, contributing to increasing cancer survival.[19] For instance, by targeting specific signaling pathways in cancer, targeted therapies have resulted in the introduction of precision medicine in the clinic, changing the natural history of some cancer types, and improving patient outcomes.[34,35] The treatment of cancer-related VTE has also evolved during the past decades, with guidelines from the mid-2000s recommending the use of low molecular weight heparin,[36] whereas the current guidelines also suggest the use of direct oral anticoagulants (DOAC) for the treatment of VTE in cancer.[37,38] It is important to address the fact that the follow-up of the present study ended in 2019; thus, the study period did not include implementation of the contemporary guidelines, where the use of DOAC is considered for the management of VTE in patients with cancer.[37,38] Although we cannot rule out the off-label use of DOAC for the treatment of cancer-related VTE in the most recent period (2012-2019), this would only apply for a small proportion of patients with cancer-related VTE and would presumably have negligible impact on the mortality rate over time in the present study. In addition, the current guidelines suggest the use of primary pharmacological thromboprophylaxis for ambulatory cancer patients at high VTE risk receiving systemic therapy.[37,38] However, despite being effective at preventing VTE in ambulatory patients with cancer when compared with placebo or standard care, primary thromboprophylaxis has not been associated with a significant reduction in mortality.[39,40] Moreover, primary thromboprophylaxis was rarely used in Norway during the study period.

In the present study, the mortality risk of patients with cancer-related VTE compared with those with cancer remained relatively stable during the three time periods (approx. 3-fold higher). It is reasonable to assume that patients with cancer-related VTE and those with cancer without VTE would have experienced the benefits of the advances in cancer treatment in a similar way over the past three decades, and that the VTE treatment would have been a major difference between the two groups, poten-

tially affecting survival among those with cancer-related VTE. However, because the mortality risk did not reveal any substantial changes during the past decades when comparing the cancer-related VTE group *versus* the cancer group, one might speculate that changes in the management of cancer and not of VTE would be the main driving factors for reducing mortality over time.

Incidental VTE were not included in the present analysis, and therefore an increase in their detection cannot explain our finding of a declining mortality rate in cancer-related VTE. CT-pulmonary angiography introduced in the 1990s has shown improved sensitivity for detecting subsegmental PE with potentially better prognosis,[41] which could be an explanation for the decreasing mortality rates after cancer-related VTE over the decades. Nonetheless, in the light of our findings, this is unlikely since the decrease in mortality was essentially driven by cancer-related DVT, particularly when comparing the first two periods (1994-2002 and 2003-2011) with the most recent one (2012-2019). Consistent with our findings, a Danish nationwide cohort comprising only PE patients showed that the overall 31- to 365-day mortality for patients with a diagnosis of cancer registered within six months before the PE diagnosis remained stable from 2000 to 2020.[42] Finally, the proportion of participants with localized cancer at diagnosis increased over time (28% in 1994-2002, 35% in 2003-2011, and 41% in 2012-2019), and localized cancer is associated with improved survival, which may partially explain our finding of a decrease in mortality after cancer-related VTE during the study period. It is noteworthy that a decline in mortality over time was only observed among those with non-metastatic cancer-related VTE, which may be due to the detection of cancer at increasingly early stages, facilitating earlier treatment with subsequently improved life expectancy.

Despite declining estimates over the last decades, the risk of death in cancer-related VTE was still high, with a 1-year cumulative incidence of mortality in the most recent period (2012-2019) of 46%. Moreover, the risk of death was about 3-fold higher in cancer-related VTE compared with cancer without VTE, even after adjustment for several comorbidities. The mechanism by which cancer-related VTE is linked to increased mortality has probably a multifactorial nature. The VTE risk is reported to be particularly high in biologically aggressive cancer types (e.g., pancreas, brain, ovarian, lung, and some hematologic malignancies) and in the presence of advanced stage,[11,12] which are factors associated with poor prognosis. Furthermore, the activation of some pathways of the hemostatic system in cancer-related VTE may facilitate tumor progression.[43,44] Notably, clinical factors such as the delay or interruption of cancer therapy in patients who develop VTE along with complications associated with VTE treatment, including bleeding, may also have a detrimental impact on survival in cancer-related VTE.

Cancer is a major risk factor for VTE in the general population,[11,12] and the still substantial risk of death in cancer-related VTE represents a burden for the affected individuals, their families, and health systems. Future research should pursue a more comprehensive understanding of factors that have been contributing to maintaining the high mortality rates in cancer-related VTE as well as strategies to mitigate them.

The main strengths of this study include a long follow-up, with the opportunity to investigate long-term changes in mortality in cancer-related VTE. The Tromsø and the HUNT studies are large cohort studies representative of the general population, with comparable baseline measurements of several demographics and clinical characteristics. The VTE events in our study were validated using objective diagnostic criteria, in contrast to earlier studies that relied on ICD codes.[15-17] The use of health registry data may lead to misclassification, which would tend to be non-differential with regards to mortality (outcome), likely resulting in an underestimation of the true associations.[45]

Some study limitations also merit attention. The limited statistical power did not allow the analysis of mortality stratified by cancer sites over the different time periods. The lack of information on treatment precluded the assessment of novel cancer and VTE treatments as potential explanations for the decreased mortality in cancer-related VTE. Given the criteria used to validate a VTE event, our study does not include data on incidental VTE. We acknowledge that currently there is a substantial proportion of VTE in cancer patients that are considered incidental,[46] and future research aimed at assessing the changes in mortality risk over time after incidental VTE in cancer should be designed. The assessment of cancer-specific mortality would likely provide a better understanding of the main factors behind the decreasing mortality after cancer-related VTE over the past three decades. Unfortunately, data on cancer-specific mortality were not available in either the HUNT or the Tromsø studies. The generalizability of the study findings may be limited, as most of the participants were of European ethnicity, and extrapolation of our findings to other races or ethnicities should be made with caution.

In conclusion, our results indicate that the mortality rate after cancer-related VTE has decreased over the last three decades, which might be mainly the result of considerable advances in cancer management. Despite a favorable temporal trend, the most contemporary estimates still show substantially high mortality rates. Our findings may form the basis for future research aimed at investigating the driving factors that contribute to maintaining the high mortality rates after cancer-related VTE.

Disclosures

No conflicts of interest to disclose.

Contributions

JBH and VMM are responsible for study concept and design.

KH, SKB and JBH are responsible for data collection. NHE, FBR and SKB are responsible for statistical analysis. NHE, CL, FBR, NvE, KH, SKB, JBH and VMM are responsible for data interpretation. NHE and VMM drafted the manuscript. NHE, CL, FBR, NvE, KH, SKB, JBH and VMM critically revised the manuscript. All co-authors reviewed and approved the final version.

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Data-sharing statement

Access to data from the HUNT and Tromsø studies can be obtained by application to the administration of HUNT (https://www.ntnu.edu/hunt/data) and Tromsø (https://uit.no/research/tromsostudy/project?pid=709148&p_document_id=708030) studies.

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