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

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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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There are no conflicts of interest by any of the authors.

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 (HRs) with 95% confidence intervals (CIs) for all-cause mortality using Cox regression with cancer and VTE as time-dependent exposures, and one-year cumulative incidence of mortality after CRVTE. Analyses were performed for three time-periods (1994-2002, 2003-2011, 2012-2019). The age- and sex-adjusted HRs 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 HRs for mortality after CRVTE versus cancer-group remained stable (about 3-fold higher) along the three time-periods. Similar estimates were obtained after further adjustments for comorbidities. The one-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.

Keywords: cancer; venous thromboembolism; venous thrombosis; mortality; cohort.

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 (CVDs) 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 nine-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 one-year all-cause mortality rate was 88% in patients with cancer diagnosed at the same time of a VTE event compared with 64% in cancer patients without VTE.[15] More recent data, albeit improved, still show a high one-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 PEs 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 to investigate 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 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 Helsinki Declaration, 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 DVTs and PEs 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 1 year before the date of cancer diagnosis until 2 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 Norwegian 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', as illustrated in Figures 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 (HRs) for mortality with 95% confidence intervals (CIs), 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, 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 methods is available in the Supplementary Data.

RESULTS

Demographics, lifestyle factors and clinical characteristics of the study population

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

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 HRs 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 HRs 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 (Supplementary Figure S1). The one-year cumulative incidence of mortality after cancer-related VTE also decreased over time as depicted in Figure 2, 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. The one-year cumulative 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, as shown in Table 3 and Figure 3. The age- and sex-adjusted HRs 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 HRs of metastatic cancer-related VTE increased over time, though estimates were imprecise with wide 95% CIs (Table 3).

The HRs for mortality after cancer-related DVT compared 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 HRs 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 HRs 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 (Supplementary Tables S1-S3). However, when cancer-related VTE comprised only VTEs occurring within 2 or within 5 years after the date of a cancer diagnosis, respectively (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. Further, 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 one-year cumulative incidence of mortality after cancer-related VTE and cancer displayed a similar trend as the main analysis (data not

shown). Of note, the main results remained essentially the same when adding education level as a covariate 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 one-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 VTEs and cancer-related DVTs. 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 registries.[16,17] In two nationwide cohorts from Denmark, the one-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 one-year cumulative incidence of mortality was lower (45%). Regardless of the definition of cancer-related VTE, the authors found a decline in the one- and five-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 1 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 one-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 1 year before a cancer diagnosis,[31] and not considering VTEs occurring shortly before a cancer diagnosis or including VTEs 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 as compared with our findings, which could be particularly due to differences in the definitions of cancer-related VTE; for instance, in the RIETE registry, patients with VTEs occurring shortly before a cancer diagnosis were not included. A study conducted in the Scandinavian Thrombosis and Cancer (STAC) cohort, which included data from Tromsø4, HUNT2, and Diet, Cancer and Health Study,[33] found HRs 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 clinics, 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 low molecular weight heparin,[36] whereas the current guidelines also suggest the use of direct oral anticoagulants (DOACs) for the treatment of VTE in cancer.[37,38] It is important to address 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 DOACs is considered for the management of VTE in patients with cancer.[37,38] Although we cannot rule out the off-label use of DOACs 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 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 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 (about 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, potentially 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 VTEs were not included in the present analysis, and therefore an increase in their detection cannot explain our finding of a declining mortality in cancer-related VTE. CT-pulmonary angiography introduced in the 1990s has shown improved sensitivity for detecting subsegmental PEs with potentially better prognosis,[41] which could be an explanation for the decreasing mortality after cancer-related VTE over the decades. Nonetheless, in light of our findings this is unlikely since the decrease in mortality was essentially driven by cancer-related DVTs, 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 6 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 one-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 hematological 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 the health systems. Future research should pursue a more comprehensive understanding of factors that have been contributing to keep 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 VTEs. We acknowledge that currently there is a substantial proportion of VTEs 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 both HUNT and 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 done 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 maintain the high mortality rates after cancer-related VTE.

REFERENCES

1. Schulman S, Lindmarker P, Holmstrom M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. J Thromb Haemost. 2006;4(4):734-742.
2. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev. 2014;28(6):221-226.
3. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet. 2021;398(10294):64-77.
4. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen M-L, Njølstad I, Mathiesen EB. Declining Incidence of Ischemic Stroke. Stroke. 2017;48(3):544-550.
5. Mannsverk J, Wilsgaard T, Mathiesen EB, et al. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016;133(1):74-81.
6. Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017;32(4):299-305.
7. Munster AM, Rasmussen TB, Falstie-Jensen AM, et al. A changing landscape: Temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006-2015. Thromb Res. 2019;176:46-53.
8. Heit JA, Ashrani A, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thromb Haemost. 2017;117(2):390-400.
9. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
10. Trousseau A. Clinique Medicale de l'Hotel-Dieu de Paris (Lectures on Clinical Medicine at the Hotel-Dieu, Paris). 1872.
11. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021;137(14):1959-1969.
12. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-1723.
13. Fernandes CJ, Morinaga LTK, Alves JLJ, et al. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019;28(151):180119.
14. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5(3):632-634.
15. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med. 2000;343(25):1846-1850.
16. Ording AG, Skjøth F, Søgaard M, et al. Increasing Incidence and Declining Mortality After Cancer-Associated Venous Thromboembolism: A Nationwide Cohort Study. Am J Med. 2021;134(7):868-876.e5.
17. Sorensen HT, Pedersen L, van Es N, Buller HR, Horvath-Puho E. Impact of venous thromboembolism on the mortality in patients with cancer: a population-based cohort study. Lancet Reg Health Eur. 2023;34:100739.
18. Mahajan A, Brunson A, Adesina O, Keegan THM, Wun T. The incidence of cancer-associated thrombosis is increasing over time. Blood Adv. 2022;6(1):307-320.
19. Shapiro CL. Cancer Survivorship. N Engl J Med. 2018;379(25):2438-2450.
20. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: a population-based study. Lancet. 2015;385(9974):1206-1218.
21. Hashim D, Boffetta P, La Vecchia C, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol. 2016;27(5):926-933.

22. Campia U, Moslehi JJ, Amiri-Kordestani L, et al. Cardio-Oncology: Vascular and Metabolic Perspectives: A Scientific Statement From the American Heart Association. Circulation. 2019;139(13):e579-e602.
23. Liu B, Zhou H, Tan L, Siu KTH, Guan XY. Exploring treatment options in cancer: Tumor treatment strategies. Signal Transduct Target Ther. 2024;9(1):175.
24. Stevenson M. Ageing and Health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. Published 2022. Accessed 20.02, 2024.
25. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-967.
26. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-977.
27. Åsvold BO, Langhammer A, Rehn TA, et al. Cohort Profile Update: The HUNT Study, Norway. Int J Epidemiol. 2023;52(1):e80-e91.
28. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. J Am Coll Cardiol. 2014;63(11):1071-1078.
29. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol. 2010;171(10):1109-1115.
30. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-1231.
31. Blix K, Gran OV, Severinsen MT, et al. Impact of time since diagnosis and mortality rate on cancer-associated venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort. J Thromb Haemost. 2018;16(7):1327-1335.
32. Bertoletti L, Madridano O, Jiménez D, et al. Cancer-Associated Thrombosis: Trends in Clinical Features, Treatment, and Outcomes From 2001 to 2020. JACC CardioOncol. 2023;5(6):758-772.
33. Crobach MJT, Anijs RJS, Brækkan SK, et al. Survival after cancer-related venous thrombosis: the Scandinavian Thrombosis and Cancer Study. Blood Adv. 2023;7(15):4072-4079.
34. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med. 2005;353(2):172-187.
35. Zhou Z, Li M. Targeted therapies for cancer. BMC Med. 2022;20(1):90.
36. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):401S-428S.
37. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021;5(4):927-974.
38. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Guideline Update. J Clin Oncol. 2023;41(16):3063-3071.
39. Schunemann HJ, Ventresca M, Crowther M, et al. Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. Lancet Haematol. 2020;7(10):e746-e755.
40. Bosch FTM, Mulder FI, Kamphuisen PW, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. Blood Adv. 2020;4(20):5215-5225.
41. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011;171(9):831-837.
42. Madsen SF, Christensen DM, Strange JE, et al. Short- and Long-Term Mortality for Patients With and Without a Cancer Diagnosis Following Pulmonary Embolism in Denmark, 2000 to 2020: A Nationwide Study. J Am Heart Assoc. 2023;12(23):e030191.
43. Ward MP, Kane LE, Norris LA, et al. Platelets, immune cells and the coagulation cascade; friend or foe of the circulating tumour cell? Mol Cancer. 2021;20(1):59.

44. Falanga A, Marchetti M. Cancer-associated thrombosis: enhanced awareness and pathophysiologic complexity. J Thromb Haemost. 2023;21(6):1397-1408.
45. Wacholder S, Hartge P, Lubin JH, Dosemeci M. Non-differential misclassification and bias towards the null: a clarification. Occup Environ Med. 1995;52(8):557-558.
46. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(5):452-467.

Tables

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	89294	92927	83842
Male, n (%)	42272 (47.3%)	43410 (46.7%)	38911 (46.4%)
Age (years), mean (SD)	46.4 (16.6)	50.8 (16.7)	56.0 (14.9)
BMI (kg/m²), mean (SD)	25.8 (4.0)	25.9 (4.1)	25.9 (4.1)
Current daily smoking, n (%)	28928 (32.4%)	28312 (30.5%)	24463 (29.2%)
Highest level of education, n (%)			
Primary school	29403 (32.9%)	24670 (26.5%)	18571 (22.1%)
High school	35366 (39.6%)	32661 (35.1%)	29975 (35.8%)
College/university	21023 (23.5%)	19656 (21.2%)	21310 (25.4%)
Comorbidities, n (%)			
Arterial CVD	8572 (9.6%)	6801 (7.3%)	4315 (5.1%)
Hypertension	46633 (52.2%)	43485 (46.8%)	34960 (41.7%)
Diabetes	4607 (5.2%)	4260 (4.6%)	3373 (4.0%)
Exposures, n (%)			
VTE	785 (0.9%)	1179 (1.3%)	1093 (1.3%)
Cancer	3533 (4.0%)	5664 (6.1%)	6378 (7.6%)
Cancer-related VTE	116 (0.1%)	217 (0.2%)	235 (0.3%)
VTE type, n (% of VTEs)			
Deep vein thrombosis	511/785 (65.1%)	585/1179 (49.6%)	528/1093 (48.3%)
Pulmonary embolism	274/785 (34.9%)	594/1179 (50.4%)	565/1093 (51.7%)
Cancer stage, n (% of cancers)			
Localized	1002/3533 (28.4%)	1972/5664 (34.8%)	2643/6378 (41.4%)
Regional metastasis	738/3533 (20.9%)	1386/5664 (24.5%)	1572/6378 (24.6%)
Distant metastasis	687/3533 (19.4%)	1056/5664 (18.6%)	907/6378 (14.2%)
Unknown	1106/3533 (31.3%)	1250/5664 (22.1%)	1256/6378 (19.7%)
Cancer site, n (% of cancers)			
Colorectal	592/3533 (16.8%)	919/5664 (16.2%)	971/6378 (15.2%)
Pancreatic	113/3533 (3.2%)	165/5664 (2.9%)	168/6378 (2.6%)
Lung	347/3533 (9.8%)	584/5664 (10.3%)	580/6378 (9.1%)
Breast*	430/1688 (25.5%)	700/2663 (26.3%)	773/2956 (26.2%)
Gynecological*	240/1688 (14.2%)	331/2663 (12.4%)	328/2956 (11.1%)
Prostate†	563/1845 (30.5%)	1065/3001 (35.5%)	1249/3422 (36.5%)
Urological	225/3533 (6.4%)	321/5664 (5.7%)	458/6378 (7.2%)
Central nervous system	80/3533 (2.3%)	148/5664 (2.6%)	156/6378 (2.4%)
Hematological	292/3533 (8.3%)	434/5664 (7.7%)	532/6378 (8.3%)
Upper gastrointestinal	220/3533 (6.2%)	325/5664 (5.7%)	355/6378 (5.6%)
Others	431/3533 (12.2%)	672/5664 (11.9%)	808/6378 (12.7%)

BMI, body mass index; CVD, cardiovascular disease (angina pectoris, myocardial infarction, and stroke); SD, standard deviation; VTE, venous thromboembolism.
Participants not disease-free at the start of each time period were excluded.
Participants with 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.

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 (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	7420	1381	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	7420	1381	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	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	15365	2121	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	15365	2121	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	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	17727	1830	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	17727	1830	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)

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).

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 metastasis status

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 - 4.3)	3.8 (3.2 - 4.6)
Non-metastatic cancer	6842	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 - 1349.1)	44.2 (31.4 - 62.4)	55.6 (39.4 - 78.4)
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 - 3.6)
Non-metastatic cancer	14262	1332	93.4 (88.5 - 98.5)	4.9 (4.6 - 5.2)	4.8 (4.6 - 5.1)
Metastatic cancer	1102	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	1315.7 (1033.7 - 1674.7)	90.8 (71.2 - 115.8)	102.5 (80.1 - 131.0)
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)	2.8 (2.5 - 3.3)
Non-metastatic cancer	16596	1214	73.2 (69.1 - 77.4)	4.6 (4.3 - 4.9)	4.5 (4.2 - 4.8)
Metastatic cancer	1132	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	1158.1 (889.1 - 1508.4)	131.5 (100.6 - 171.9)	125.8 (96.2 - 164.6)

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

Unknown metastasis 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).

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 (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)
DVT	1206	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	7420	1381	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 - 1013.5)	20.0 (13.8 - 29.0)	24.8 (17.1 - 36.0)
2003-2011					
Disease-free	693550	6166	8.9 (8.7 - 9.1)	1 (reference)	1 (reference)
DVT	1753	116	66.2 (55.2 - 79.4)	2.6 (2.1 - 3.1)	2.6 (2.1 - 3.1)
PE	1415	136	96.1 (81.2 - 113.7)	4.0 (3.4 - 4.8)	4.1 (3.5 - 4.9)
Cancer	15365	2121	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	585345	5600	9.6 (9.3 - 9.8)	1 (reference)	1 (reference)
DVT	1442	87	60.3 (48.9 - 74.4)	2.7 (2.2 - 3.3)	2.7 (2.1 - 3.3)
PE	1285	98	76.3 (62.6 - 93.0)	3.2 (2.6 - 3.9)	3.1 (2.5 - 3.7)
Cancer	17727	1830	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)

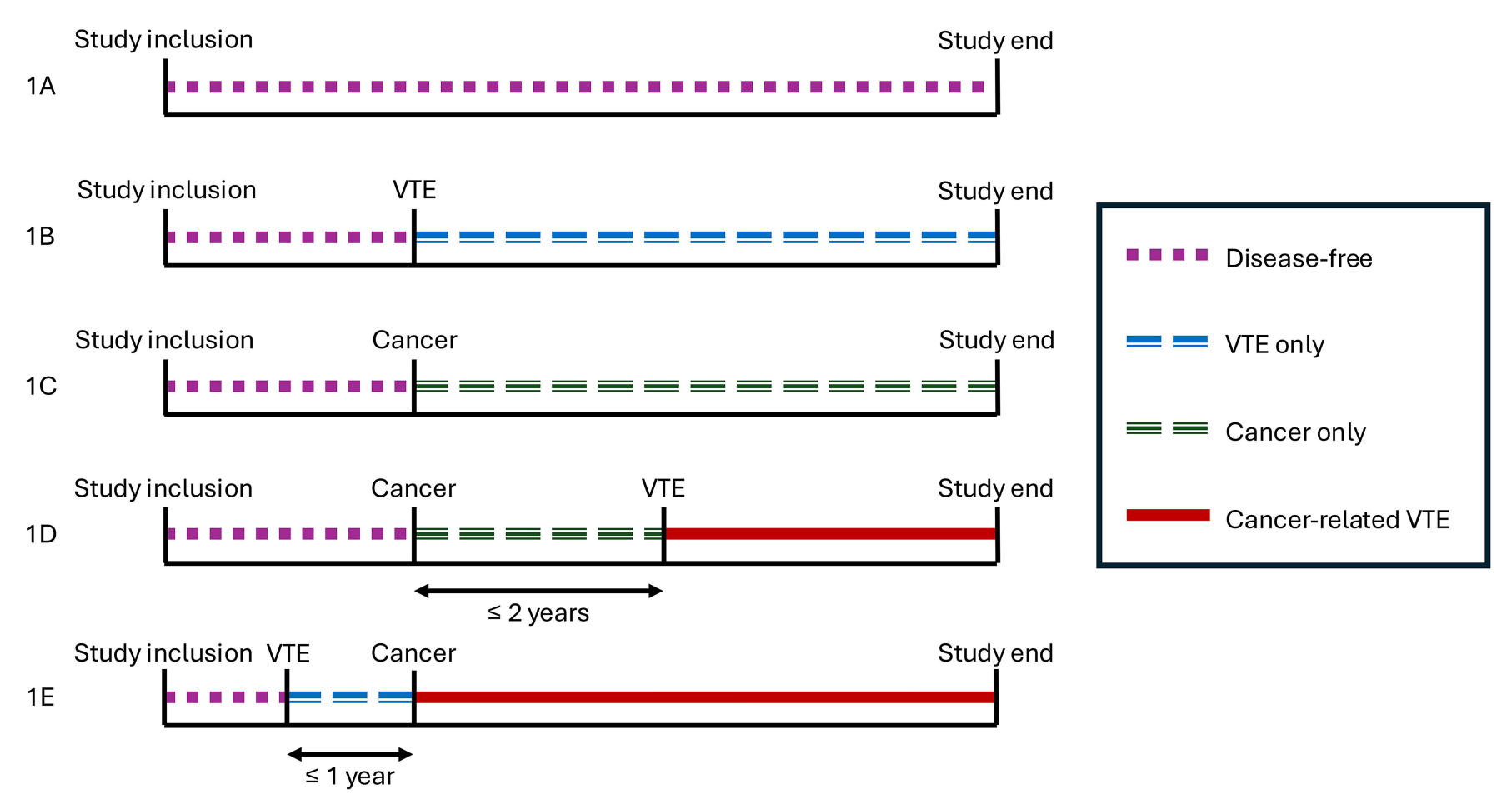
CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; IR, incidence rate; PY, person years; PE, pulmonary embolism.
Model 1: Adjusted for age and sex.
Model 2: Adjusted for age, sex, and baseline body mass index, smoking, and comorbidities (arterial cardiovascular disease, hypertension, diabetes).

Figure legends

Figure 1. Graphical illustration of distinctive groups of observational periods based on the exposure to cancer, venous thromboembolism (VTE), or cancer-related VTE during study follow-up. Figure 1A shows participants exposed to neither cancer nor VTE from the study inclusion to the study end (disease-free group). Figures 1B and 1C show 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 (Figure 1B) or cancer-exposed (Figure 1C) person-time, respectively. Figure 1D shows 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. Figure 1E shows 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. As depicted in Figures 1D and 1E, 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.

Figure 2. Kaplan-Meier curves showing survival probability over time of cancer exposed group and cancer-related VTE 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 VTE. Because 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). VTE, venous thromboembolism; CRVTE, cancer-related VTE.

Figure 3. Kaplan-Meier curves showing survival probability of non-metastatic and metastatic cancer-related VTE 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 VTE (3A) or metastatic cancer-related VTE (3B). VTE, venous thromboembolism; CRVTE, cancer-related VTE.


Study inclusion
Study end
1A
Study inclusion
VTE
Study end
1B
Study inclusion
Cancer
Study end
1C
Study inclusion
Cancer
VTE
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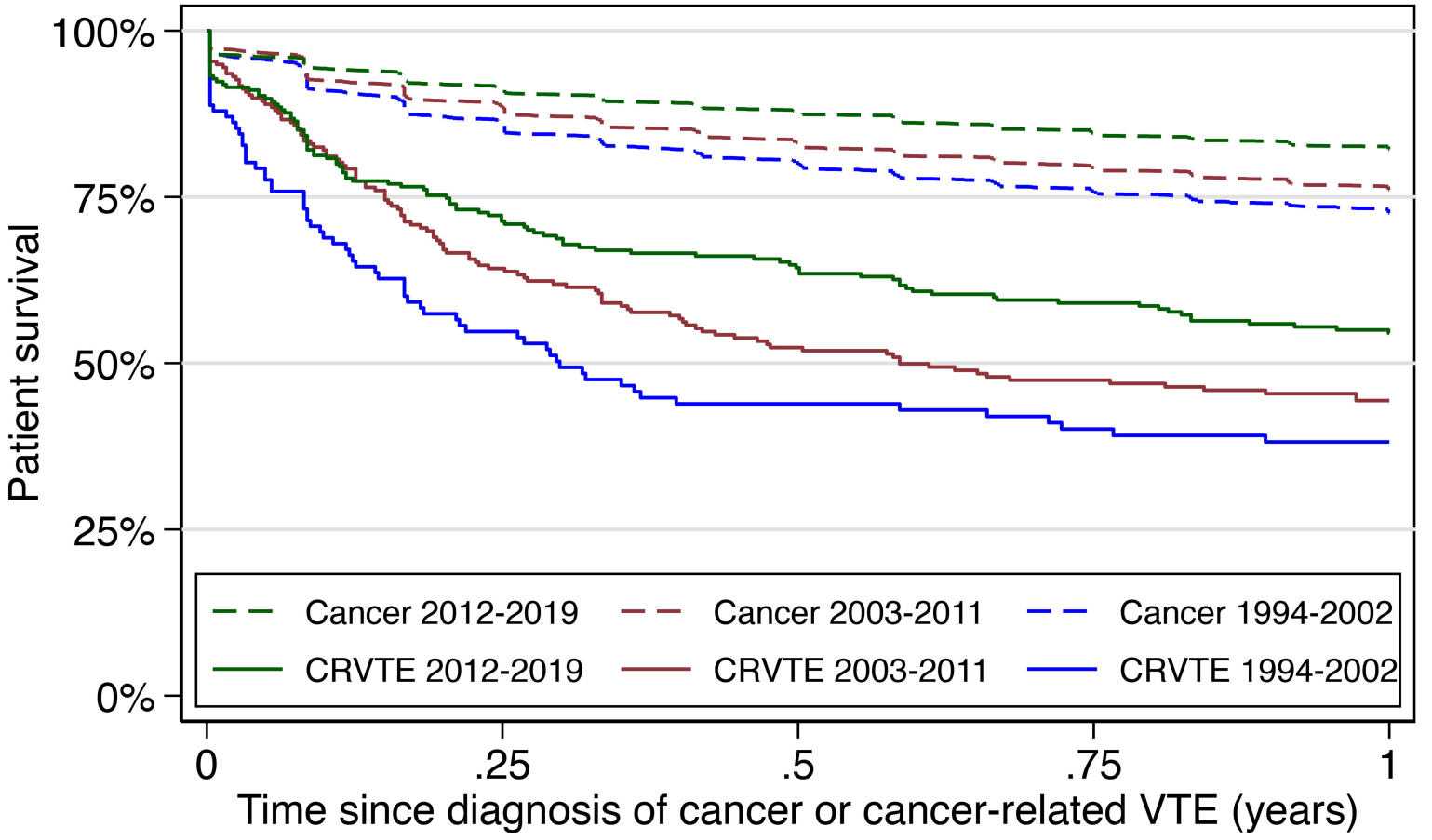
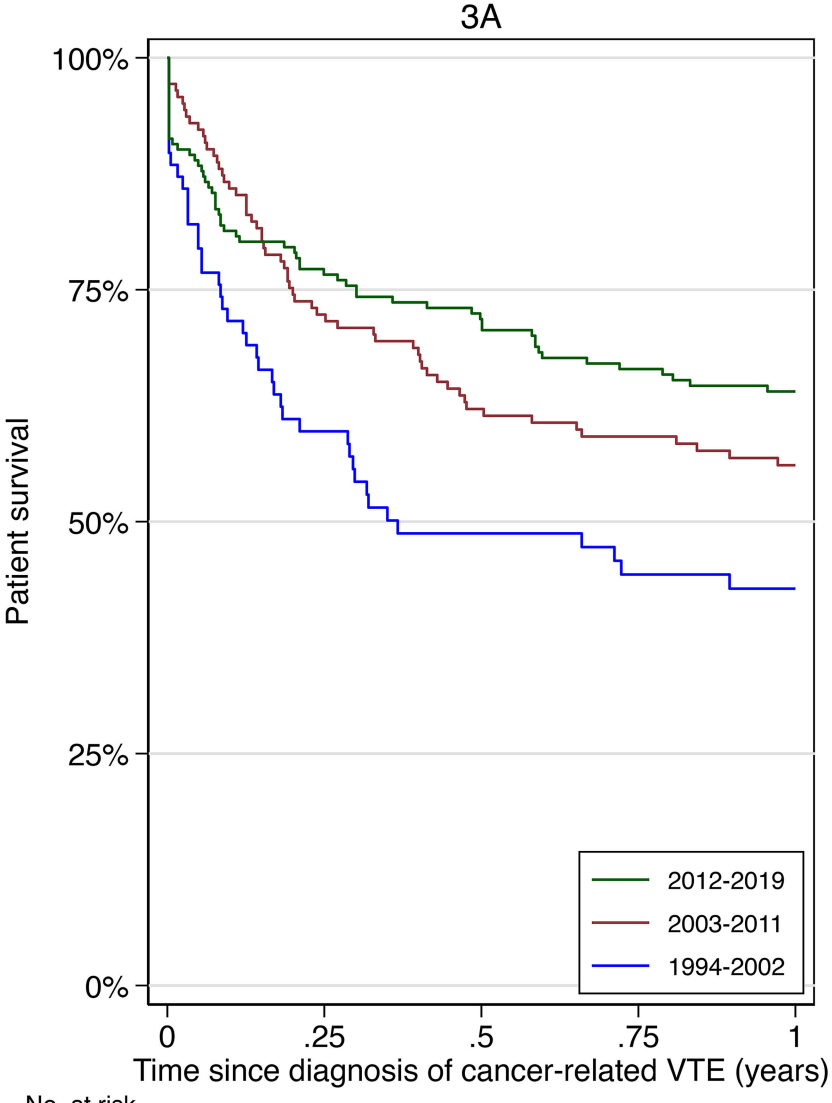
1D
≤ 2 years
Study inclusion
VTE
Cancer
Study end
1E
≤ 1 year
Disease-free
VTE only
Cancer only
Cancer-related VTE

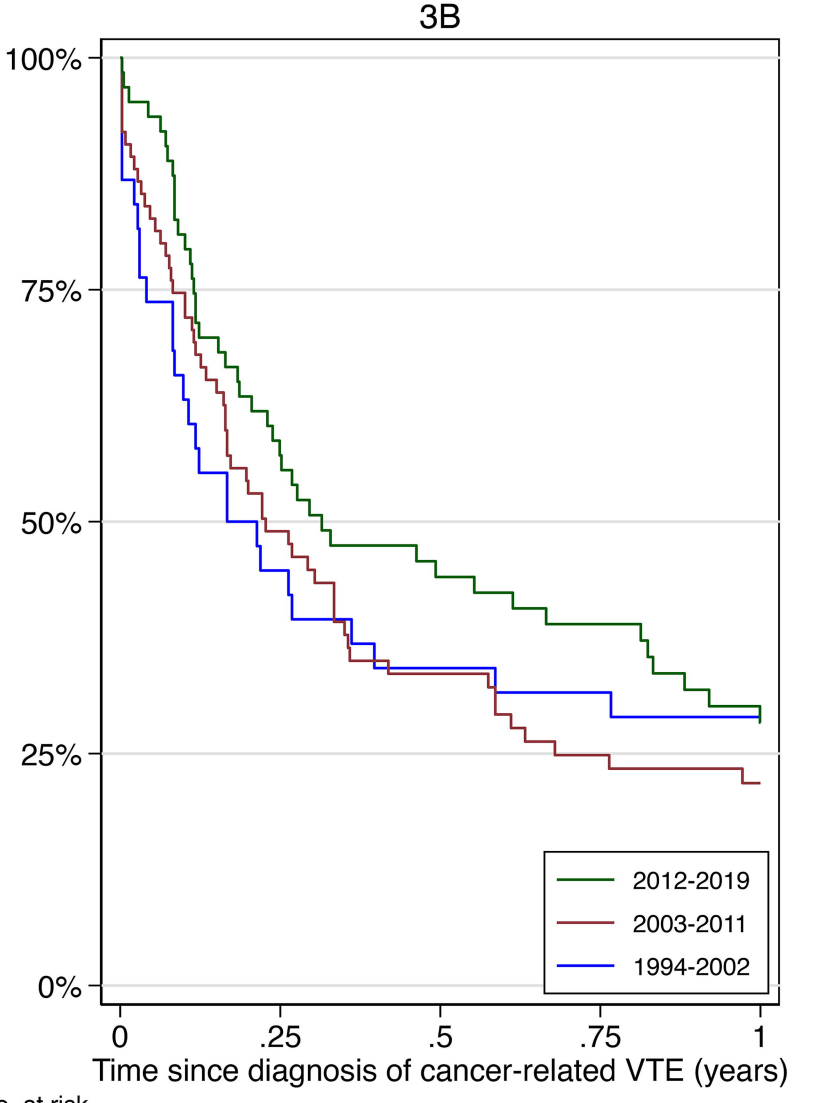


No. at risk					
CRVTE 2012-2019	235	164	146	133	118
CRVTE 2003-2011	217	137	109	95	86
CRVTE 1994-2002	116	61	48	42	37
Cancer 2012-2019	6319	5508	5112	4747	4419
Cancer 2003-2011	5608	4726	4277	3933	3610
Cancer 1994-2002	3500	2849	2530	2292	2091



No. at risk

2012-2019	172	128	120	111	102
2003-2011	142	101	85	78	72
1994-2002	78	44	35	30	26



No. at risk

2012-2019	63	36	26	22	16
2003-2011	75	36	24	17	14
1994-2002	38	17	13	12	11

SUPPLEMENTARY DATA

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

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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.

References

1. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41(4):961-967.
2. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-977.
3. Åsvold BO, Langhammer A, Rehn TA, et al. Cohort Profile Update: The HUNT Study, Norway. Int J Epidemiol. 2023;52(1):e80-e91.
4. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. J Am Coll Cardiol. 2014;63(11):1071-1078.
5. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol. 2010;171(10):1109-1115.
6. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-1231.
7. Blix K, Gran OV, Severinsen MT, et al. Impact of time since diagnosis and mortality rate on cancer-associated venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort. J Thromb Haemost. 2018;16(7):1327-1335.
8. Ording AG, Skjøth F, Søgaard M, et al. Increasing Incidence and Declining Mortality After Cancer-Associated Venous Thromboembolism: A Nationwide Cohort Study. Am J Med. 2021;134(7):868-876.
9. Sorensen HT, Pedersen L, van Es N, Buller HR, Horvath-Puho E. Impact of venous thromboembolism on the mortality in patients with cancer: a population-based cohort study. Lancet Reg Health Eur. 2023;34:100739.
10. Crobach MJT, Anijs RJS, Brækkan SK, et al. Survival after cancer-related venous thrombosis: the Scandinavian Thrombosis and Cancer Study. Blood Adv. 2023;7(15):4072-4079.

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.