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Gade, Inger Lise

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Dissertation submitted:	October, 2018
PhD supervisor:	Associate Prof., MD, Ph.D. Marianne Tang Severinsen Aalborg University
Assistant PhD supervisor:	Prof., MD, DMSc Søren Risom Kristensen Aalborg University
PhD committee:	Associate Professor Svend Eggert Jensen (chairman) Aalborg University
	Dr Alexander T. Cohen King´s College London
	Clinical Professor Henrik Frederiksen Odense Universitetshospital
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Clinical Medicine

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ENGLISH SUMMARY

Venous thromboembolism (VTE) is a collective name for blood clots formed and located in the deep veins of the body, and pulmonary embolism. Pulmonary embolism designates blood clots formed in the deep veins that detach from the breeding ground to flow with the venous blood and eventually settle in the arteries of the lungs. Even though VTE is a preventable disease, it remains a frequent complication that contributes considerably to morbidity and mortality in cancer patients. Prevention of VTE can be achieved by prophylactic anticoagulation treatment, however, prophylaxis is associated with adverse events of which bleeding is the most substantial. Cancer patients are at higher risk of both VTE and bleeding than the background population. Thus, it is important to identify the subgroups of cancer patients with a particularly high risk of VTE and, furthermore, to narrow down their cancer-associated time interval with highest risk of VTE. In this way, prophylactic anticoagulation treatment can be offered in proper time to the cancer patients with highest benefit of prophylaxis.

This thesis is based on four epidemiological studies where associations between cancer specific factors and VTE were investigated in different groups of cancer patietns. Study 1 showed that for some cancer types the degree of metastasis is associated with the risk of VTE in the sense that regional and/or distant metastasis increases the risk of VTE compared with localized disease, while for other cancer types the risk is high even in localized disease or conversely low regardless of stage. Study 3 showed that the risk of VTE in cancer patients who survive the acute effects of cancer, associated treatments and hospitalizations without VTE decrease to the level of the background population, except for patients with hematological cancer. Study 2 showed that especially myeloma patietns and chronic lymphocytic leukemia patients have a higher risk of VTE than the background population years after the diagnosis of hematological cancer. In study 4, the association between chronic lymphocytic leukemia and VTE was further investigated. Patients with chronic lymphocytic leukemia had a higher risk of VTE mostly because of additional cancer after the diagnosis, but biological markers of the prognosis of chronic lymphocytic leukemia were also associated with the risk of VTE.

In their entirety, the studies in this Ph.D. dissertation contributes to a more detailed understanding of when and which cancer patients are at highest risk of VTE. With other scientific contributions, the presented studies can aid in development of more personalized efforts against cancer-associated VTE in order to minimize premature, preventable death and morbidity in both patients with active cancer and those who survive the acute effects of cancer.

DANSK RESUME

Venøs thromboemboli (VTE) er en samlebetegnelse for blodpropper dannet i kroppens dybe vener og lungeemboli, som betegner en blodprop dannet i kroppens vener, som har løsrevet sig fra arnestedet og sætter sig fast i lungernes arterier. VTE er en hyppig sygdom som bidrager betragteligt til dødelighed og reduceret livskvalitet hos cancerpatienter, også selvom blodfortyndende behandling kan forebygge VTE. Blodfortyndende behandling er forbundet med bivirkninger, hvoraf blødning er den væsentligste. Cancerpatienter har højere risiko for både blødninger og VTE end baggrundsbefolkningen, og det er derfor vigtigt at identificere de patienter, som er i særlig høj risiko for at få VTE samt at finde ud af hvornår deres risiko er højest således at den forebyggende blodfortyndende behandling kan gives i de rigtige tidsintervaller til de patienter som har mest gavn af det.

Denne afhandling bygger på fire epidemiologiske studier, hvor sammenhænge mellem cancer specifikke faktorer og VTE er blevet belyst i forskellige grupper af cancer patienter. Studie 1 viste at graden af spredning (metastasering) i nogle cancer typer har betydning for risikoen for VTE forstået på den måde at regional spredning og/eller fjern matestaser øger risikoen for VTE sammenlignet med lokal sygdom, mens graden af spredning for andre cancer typer ikke har nævneværdig betydning – enten fordi risikoen for VTE er høj ligegyldigt hvor meget canceren har spredt sig eller fordi den er ditto lav. Studie 3 viste at risikoen for VTE hos patienter som overlever de akutte effekter af cancer, associerede behandlinger og indlæggelser uden VTE falder til baggrundsbefolkningens niveau, med undtagelse af de hæmatologiske cancer typer. Studie 2 viste at der blandt de hæmatologiske cancer typer var stor forskel på risikoen for VTE. Patienter med aggressive lymfomer, myelomatose og kronisk lymfatisk leukæmi havde højere risiko for VTE end baggrundsbefolkningen. For de to sidstnævnte typer også mange år efter diagnosen af den hæmatologiske cancer. Studie 4 undersøgte forekomsten af VTE hos patietner med kronisk lymfatisk leukæmi mere detaljeret. Særligt patienter som fik diagnosticeret en cancer mere havde høj forekomst af VTE, men biologiske markører for dårlig prognose for kronisk lymfatisk leukæmi var også associeret med øget forekomst af VTE.

Alt i alt bidrager resultaterne omtalt i ph.d. afhandlingen til en mere nuanceret forståelse af hvornår hvilke cancer patienter er i højest risiko for VTE. Sammen med andre videnskabelige bidrag kan de danne grundlag for en mere skræddersyet forebyggende indsats mod VTE og dermed minimere forebyggelig forringelse af livskvalitet eller dødsfald både hos patienter med aktiv cancer og blandt dem som overlever de akutte effekter af cancer.

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Inger Lise Gade, Aalborg, October 2018.

LIST OF PAPERS IN THE THESIS

The thesis is based on the following four papers:

I.
The Impact of Initial Cancer Stage on the Incidence of Venous Thromboembolism: The Scandinavian Thrombosis and Cancer (STAC) Cohort
Gade, I. L.; Braekkan, S. K; Næss, I. A.; Hansen, J-B; Cannegieter, S. C; Overvad, K; Jensvoll , H; Hammerstrøm, J; Blix, K; Tjønneland, A.; Kristensen, S. R.; Severinsen, M T.
Journal of Thrombosis and Haemostasis, Vol. 15, Nr. 8, (2017) 1567-1575.

II.
Epidemiology of Venous Thromboembolism in Hematological Cancers: The Scandinavian Thrombosis and Cancer (STAC) cohort
Gade, I. L.; Brækkan, S. K.; Næss, I. A.; Hansen, J.-B.; Rosendaal, F.; Cannegieter, S. C.; Overvad, K.; Jensvoll, H.; Hammerstrøm, J.; Blix, K.; Gran, O.V.; Tjønneland, A., Kristensen, S. R.; Severinsen, M.T.
Thrombosis Research 158 (2017) 157–160.

III.
Long-term Incidence of Venous Thromboembolism in Cancer: The Scandinavian Thrombosis and Cancer (STAC) cohort
Gade, I.L.; Brækkan, S.K; Næss, I.A.; Hansen, J.-B.; Cannegieter, S.C.; Rosendaal, F.; Overvad, K.; Hindberg, K.; Hammerstrøm, J.; Gran, O.V.; Tjønneland, A.; Severinsen, M.T.; Kristensen, S.R.
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IV.
Venous Thromboembolism in Chronic Lymphocytic Leukemia; a Danish Nationwide Cohort Study
Gade, I.L.; Riddersholm, S.J.; Christiansen, I.; Rewes, A.; Frederiksen, M.; Enggaard, L.; Poulsen, C.B.; Bergmann, O.J.; Gillström, D.B.; Pedersen, R.S.; Nielsen, L.; Eriksen, H.H.; Torp-Pedersen, C.T.; Kristensen, S.R.; Severinsen, M.T.
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ABBREVIATIONS

CI: Confidence interval

CLL: Chronic lymphocytic leukemia

DCH: Diet, Cancer and Health Study

DNPR: Danish National Patient Registry

HAS-BLED: The Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or alcohol use

HR: Hazard ratio

HUNT: The second Nord-Trøndelag Health Study

INR: International Normalized Ratio

IR: Incidence rate

IRD: Incidence rate difference

IRR: Incidence rate ratio

OR: Odds ratio

PY: Person years

ISTH: International Society of Thrombosis and Haemostasis

SHR: Sub-distributional hazard ratio

STAC: Scandinavian Thrombosis and Cancer (cohort)

Tromsø: The fourth survey of the Tromsø Study

VTE: Venous thromboembolism

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INTRODUCTION

> *"It frightened the life out of me; I was more scared of that than the cancer. You know blood clots can kill you like that - cancer you've got a little bit of chance, you know."*

Quote from a Welsh cancer patient with venous thromboembolism.[1]

Venous thromboembolism (VTE) is a collective term for blood clots formed in the deep veins (i.e. deep vein thrombosis) and pulmonary embolism, where a blood clot formed in the deep veins dislodges to the arteries of the lungs. VTE secondary to cancer is prevalent and associated with serious personal and societal outcomes; for the individual patient in forms of shortened life expectancy, physical and mental morbidity and prolonged hospitalization leading to increased health care costs for society.[2-4] VTE is potentially preventable by use of thromboprophylactic medication, which is however, associated with a risk of bleeding. Cancer patients are prone to bleeding even without thromboprophylactic treatment, which is therefore optimally restricted to cancer patietns with the highest risk of VTE in periods with some risk of VTE. The studies in this thesis investigated the etiology and epidemiology of cancer-associated VTE, which is important for future reduction of the mortality and morbidity caused hereby, by either aggressive thromboprophylaxis or modification of important risk factors.

BACKGROUND

VTE is among the most common cardiovascular diseases worldwide and is one of the leading causes of preventable in-hospital mortality and morbidity induced by adverse events in relation to hospitalization.[5-9] Post thrombotic complications or recurrence of VTE impair the quality of life in 20 - 30% of VTE patients.[10-14] Up to 50% of VTEs in the population occur under hospitalization or within the first three months after discharge.[15,16] Underuse or insufficient dosing of thromboprophylaxis contributes to this even though VTE is a known preventable disease.[17,18] Particularly medically ill hospitalized patients do not receive proper anticoagulation.[19] A recent meta-analysis of 11 randomized controlled trials showed that 21% more hospitalized patients received thromboprophylaxis and that the relative rate of VTE associated with hospitalization was decreased by 36% when medical health care professionals received alerts concerning VTE risk.[20] However, thromboprophylaxis comes at a price both in the literal, economic meaning and in terms of adverse medical events where bleeding represents the most common.

Cancer patients have a higher risk of both bleeding and VTE than the cancer free subjects.[21,22] The latter association was already described in French case reports 150 years ago and is since repeatedly demonstrated in large population based studies.[23-29] International guidelines recommend thromboprophylaxis for cancer patients undergoing cancer surgery or elective surgery, hospitalized cancer patients admitted with an acute medical condition and high-risk ambulatory cancer patients including myeloma patients treated with combinations of thalidomide.[30-32] Only a few of these patient categories are well defined and considerations about thromboprophylactic therapy in cancer patients thus remain complex. A recent Cochrane review concludes that prophylaxis with low molecular weight heparins reduced the relative risk of VTE by 46% compared with no administration of thromboprophylaxis in ambulatory cancer patients with even larger effect in ambulatory myeloma patients.[33] On the other hand, a review and pooled analysis of three randomized trials concluded that the evidence to support thromboprophylaxis in hospitalized cancer patients is debatable.[34]

Several risk stratification models have been proposed to aid the clinical decision about thromboprophylaxis in cancer patients, but their external validity is not impressive.[35] This may have several explanations including lack of comparability in cancer populations, but moreover the impact of items included in the models change over time and more influential risk factors not included in the models may occur. These challenges for the risk assessment models appear increasingly relevant in the years to come, where accelerated cancer-diagnosing programs and successively improved cancer treatments increases the proportions of patients living with chronic cancer,[36] even long enough to have second primary cancers.

This thesis is based on four studies that contributes to improved understanding of the impact of cancer stage, cancer type, time since cancer diagnosis and second primary

cancer on the risk of VTE. The following section outlines the epidemiology of VTE followed by a review of risk factors for VTE and the final section of this chapter summarizes risk assessment models for cancer-associated VTE.

EPIDEMIOLOGY

VENOUS THROMBOEMBOLISM (VTE) IN THE GENERAL POPULATION

Overall, two circumstances draw estimates of the VTE burden in the population in opposite directions thereby challenging precise estimation. On the one hand, some VTEs are never diagnosed. Asymptomatic presentation of VTE or initial symptoms mimicking other diseases is common in VTE.[37-39] The unspecific symptomatology can hinder the diagnosing of VTE. Furthermore, fatal VTE events are underestimated due to low autopsy rates.[7,40] On the other hand, the positive predictive value of VTE diagnosis codes used in register based studies is around 75%.[41] This could lead to overestimation of the VTE incidence in studies based on register data. Incidence rates (IR) of VTE, however, ranges from 1.1 per 1000 person years (PY) to 1.8 per 1000 PY in large population based studies from the most recent years.[6,14,42-44]

Several factors increase the risk of VTE, some of which are intrinsic to the patients (e.g. age and sex), while others are acquired (e.g. surgery, cancer). A VTE can be classified as provoked in case an acquired risk factor was present in temporal association with the VTE, whereas in cases with no obvious adequate acquired risk factor at the time of VTE, the event can be classified as unprovoked regardless of presence of intrinsic risk factors. Classification of a VTE event as either provoked or unprovoked is important, as it has implications for length of treatment and for the risk of recurrent VTE. For patients with VTE provoked by a transient risk factor (e.g. surgery), the annual risk of recurrence is 3- 4%, while for VTE patients with unprovoked VTEs it is 7-8%.[45] In patients with VTEs provoked by a persistent, provoking factor (e.g. cancer), the 12-month recurrence risk is around 20%.[21] Previous inconsistent definitions of provoked/unprovoked VTE is one of the reasons why the proportion of unprovoked VTE ranges from 11% to 50% in earlier studies.[6,14,46,47] The question whether a VTE was truly unprovoked is not revisited in large population based studies after the International Society of Thrombosis and Haemostasis (ISTH) Scientific Subcommittees of "Control of Anticoagulation and Predictive and Diagnostic Variables in Thrombotic Disease" proposed consistent categorization of VTE as provoked and unprovoked in a guideline from 2016.[48] In an observational study of 331 patients with pulmonary embolism from 2018, it was found that 67% of the events were provoked by acquired risk factors.[49]

Hospitalization is a proxy for many of the intrinsic and acquired risk factors. In an epidemiological model, it was estimated that 762 000 symptomatic VTEs occurred in France, Germany, Italy, Spain, Sweden and the UK in 2004, and 63% of these cases were related to hospitalization.[7] A recent Australian study found an IR of

hospitalization associated VTE of 9.3 per 1000 hospital admissions. The majority was diagnosed within the first three months after the discharge date.[50] VTE in association with hospitalization is prevalent in all parts of the world. In a study based on previously published data from both high and low-income countries, the annual IR of VTE was around 3 per 100 hospital admissions for both high-income and low-income countries.[5] VTE is one of the leading preventable causes of disability and premature death after hospitalization worldwide with 7.7 million lost disability-adjusted life-years, thereby surpassing both falls in the hospital, nosocomial infections, adverse drug events and decubitus ulcers.[5]

Mortality and morbidity following VTE in the general population

VTE is a serious condition that increases mortality and morbidity in affected individuals. In the model based on data from six European countries, it was estimated that 12% of all deaths is due to VTE.[7] Population based studies have shown that 20 - 30 % of patients with VTE die within the first year after VTE diagnosis.[6,14,51] In a Danish nationwide follow-up study, it was shown that the 30-day mortality in subjects with VTE was 33-fold higher compared with age and gender matched controls.[52] Mortality remains about 2-fold higher in subjects with VTE compared with reference subjects for as long as 30 years after a VTE diagnosis.[52-54]

Morbidity after VTE is frequent in case of both deep vein thrombosis and pulmonary embolism. After a pulmonary embolism, more than one-third of the patients have at least mild functional impairment, both related to persistent right ventricular dysfunction and general deconditioning.[55,56] Particularly dyspnea and reduced walking distance lowers the quality of life in survivors of pulmonary embolism.[57]Chronic thrombotic pulmonary hypertension is seen in 4 – 5% of patients who survive pulmonary embolism and these patients have severely reduced quality of life and high mortality. [10,58-61] After a deep vein thrombosis, up to 50% of patients are burdened by post thrombotic syndrome, which is a condition caused by chronic venous valve insufficiency and persistent obstruction in the deep veins after deep vein thrombosis.[11,12,62-65] Pain, edema, venous ulcers and phlebitis in the affected leg and hereby-impaired daily activity lowers the quality of life in patients with severe post thrombotic syndrome to levels comparable to patients with congestive heart failure, cancer or angina.[62]

Besides the post thrombotic complications, patients with VTE are at risk of recurrent VTE, which probably further adds to morbidity and mortality. Most recurrences occur within the first year after initial VTE diagnosis. Incidence rates of recurrent VTE of 11 per 100 PY were found in both the Tromsø study and in the UK.[14,51] In both studies, the IR of recurrent VTE fell to around 2 per 100 PY after the first year.

VTE IN CANCER PATIENTS

Around 20% of all VTEs occur in subjects with cancer at the time of VTE diagnosis.[16,25,42,66,67] The risk of VTE is increased by 4-5 - fold in cancer patients compared with the general population and even more if restricted to periods with active cancer.[24-27] Several studies have reported increasing proportions of VTE in cancer patients over the last 2-3 decades. Suggested explanations include increased awareness of VTE risk in cancer patients, better diagnostic tools, improved survival of cancer patients and use of more thrombogenic anti-cancer treatments to later stage patients over time.[26,68-70] It is thus not evident that the observed increased incidence of VTE in cancer patients is not merely a result of under-diagnosing of VTE in the past. Offhand, reports of the incidence of VTE in cancer populations might seem a straightforward task. However, several factors influence the effect estimates. First, the markedly higher mortality of cancer patients compared with other subjects in the population can have a remarkable effect on the risk estimates. Second, the risk of VTE differs widely with time since cancer diagnosis and reported effect estimates are highly dependent of this. Furthermore, there are many different definitions of VTE and reasons for exclusion of events in existing literature.

These methodological aspects of estimating the VTE risk in cancer populations are elaborated below, followed by a review of the consequences of VTE in cancer patients.

The competing risk of death and definition of VTE

Cancer patients have a higher mortality than the background population.[71] In a multinational study based on population-based cancer registry data, the age-standardized 1-year survival in breast cancer was between 88.6% and 97.6% while it was between 23.0% and 41.7% for lung cancer patients.[72] The considerable although variable mortality in cancer populations constitutes a problem in time-to-event analysis where the assumption of non-informative censoring must not be violated.[73] For the fulfillment of this assumption in studies of VTE in cancer populations, cancer patients who are censored in the analysis because of death would need to have the same risk of VTE as those still left for follow-up. Since this is unlikely (i.e. those who die would assumably have a higher risk of VTE than those still left in the study) it is necessary to take the competing risk of death into consideration when estimating the risk of VTE in cancer populations.[74,75] Since this focus has just recently emerged, only a minor fraction of studies concerning VTE in cancer populations investigated the risk of VTE with methods that allow for the competing risk of death (Table 1).[24,27,75]

The first prospective study that compared the risk of VTE in cancer patients with the background population treating death as competing risk, found a 1-year cumulative incidence of VTE of 1.4% in cancer patietns.[24] This study by Cronin-Fenton et al. only included cases hospitalized for the VTE and excluded VTE diagnosed solely in emergency departments because of low predictive value.[41] Moreover, a considerable

proportion of the cancer patients in the study had breast and prostate cancer, which are associated with lower mortality than other cancer types. Thus, the effect of treating death as competing risk and the definition of VTE events (leading to exclusion of events) both explain why the estimates do not differ markedly from previously published studies not accounting for the competing risk of death (Table 1).[28,68,76] However, the overall incidence rate of VTE was also lower in the study by Cronin-Fenton than in a study based on data from four registers in the UK by Walker et al.[26] The resulting cohort encompassed 83 203 cancer patients followed from the date of cancer diagnosis for a median of 2 years reaching an overall IR of VTE of 13.9 per 1000 PY including non-hospitalized VTE cases, contrary to the study by Cronin-Fenton et al. In a cohort of prospectively followed patients with either a newly diagnosed cancer or progression of cancer after remission, Ay et al. found a 1-year cumulative incidence of VTE of 7.6% treating death as competing risk, which is considerably higher than the cumulative incidence reported by Cronin-Fenton et al. (Table 1).[24,75] Presumably, some of the difference is caused by a broader definition of VTE and a much larger proportion of patients with brain tumors in the study by Ay et al. Brain tumors are consistently described as associated with very high risk of VTE with 1-year incidences of around 20%, and more than 10-fold increased risk of VTE compared with the general population.[77-79] Hence, even minor differences in proportions of patients with brain tumors in studies concerning VTE may lead to considerable differences in observed absolute estimates of VTE risk. Furthermore, Ay et al. excluded patients with prostate cancer from the analysis because of few events in this group. However, burden of VTE in the total population is to some degree attributable to prostate cancer as this is one of the most frequent cancer types.[27,80,81]

Time since cancer diagnosis

Time since cancer diagnosis has a major influence on occurence and effect estimates. Studies consistently report that most cancer-associated VTEs occur within the first few months after cancer diagnosis.[24-26,76] In a recent study by Cohen et al., the epidemiology of VTE in periods with active cancer in UK residents was investigated. Active cancer was defined as the 90 days preceding a hospital discharge diagnosis of primary cancer or cancer treatment encompassing bone marrow transplant, radiation or chemotherapy during hospitalization plus the subsequent 90 days here after.[25] The IR of VTE in periods with active cancer was 58 per 1000 PY. Walker et al. reported similar high IR of VTE during the first three months in the study (IR VTE 0-3 months after cancer diagnosis was 47 per 1000 PY).[26] Blix et al. specifically investigated the impact of time since cancer diagnosis in a study based on data from the Scandinavian Thrombosis and Cancer (STAC) cohort.[27] Cancer was treated as a time varying exposure, death was treated as competing risk and median follow-up was 2.3 years. The IR of VTE ranged from 2.9 per 1000 PY in the 12 - 6 months before cancer diagnosis to 31.4 per 1000 PY within the first six months after the cancer diagnosis, IR fell with successive time since cancer diagnosis but remained higher than the 12-6 months before cancer diagnosis. Both hazard ratios (HR) and sub-distributional HRs (SHR) were calculated

Table 1. Studies on the risk of VTE in cancer patients.

Author, year	Study population and design	Absolute risk estimate of VTE in cancer	Relative risk of VTE compared with cancer free population	Was death treated as competing risk in the study?
Ay, 2014[75]	1542 ambulatory cancer patients followed prospectively 2003-2014 (CATS)	6-month cumulative incidence 5.5% 1-year cumulative incidence 7.6%	-	Yes
Blix, 2018[27]	144 952 Scandinavians followed 1993-2012 (STAC)	2-year cumulative incidence 1 - 4% IR 0-6 months after cancer diagnosis 31.4 per 1000 PY IR 12-18 months after cancer diagnosis 8.6 per 1000 PY	HR 4.9 SHR 2.6	Yes
Blom, 2005[28]	66 329 cancer patients from Leiden, NL diagnosed between 1986-2006	6-month cumulative incidence 1.2%	-	No
Chew, 2006[76]	235 149 Californian cancer patients diagnosed between 1993-1995	2-year cumulative incidence 1.6%	-	No
Cohen, 2017[25]	UK residents with active cancer periods 2001-2011, in total 112 738 PY.	58 per 1000 PY (confined to period with active cancer)	54-times higher risk in periods with active cancer compared with non-cancer.	Yes
Cronin-Fenton, 2010[24]	Danish nationwide register study, 83 203 cancer patients and 577 207 controls (1997-2006)	1-year cumulative incidence 1.4% Over all IR 8.0 per 1000 PY (median FU 1.23 years)	HR 4.7	Yes
Stein, 2006[68]	~ 40 mio. Hospitalized US cancer patients (1979-1999)	2% of cancer patients	Odds ratio 2.0	No
Walker, 2013[26]	Case-non-case study,83 203 cancer and 577 207 age matched controls, UK 1987-2010	Over all IR 13.9 per 1000 PY (median FU 2 years) IR 0-3 months after cancer diagnosis 47 per 1000 PY IR 6 months after cancer diagnosis 29 per 1000 PY IR >12 months after cancer diagnosis 8 per 1000 PY	HR 4.7	No

in order to illuminate the importance of competing risk of death, which is particularly distinct in the first months after the cancer diagnosis.[27] Incidence rates of VTE with increasing time since cancer diagnosis were similar to what Walker et al. reported: Around 30 per 1000 PY for the first 6 months after cancer diagnosis and about 8 per 1000 PY >12 months after cancer diagnosis (Table 1).[26]

Consequences of VTE in cancer patients

Mortality

Venous thromboembolism affects survival in general and particularly in cancer patients. Despite variation in study populations and designs, several studies report that mortality in cancer patients with VTE is about two fold higher than in VTE free cancer patients, however with some variation due to cancer type.[2,29,67,76,82] Even asymptomatic deep vein thrombosis and superficial vein thrombosis were associated with a 2.4-fold increased risk of death in a prospective study where 150 VTE patients were followed for nine months in an outpatient clinic.[83] Based on data from the Tromsø study,[84] Timp et al. calculated age and gender adjusted HRs of death in case of VTE, cancer only and cancer plus VTE compared with subjects neither exposed to cancer nor VTE. They found VTE alone was associated with a 2.6 - fold increased risk of death and subjects with cancer only had a 7.4 - fold higher risk of death, while those with both cancer and VTE had a 31.2 - fold higher risk of death compared with subjects free of VTE and cancer.[85] Several studies of VTE in single types of cancer report higher mortality in case of VTE. For lung cancer patients, the risk of death was around 50% higher for those exposed to VTE in two large population based cohorts where VTE was included as a time varying exposure in the regression models.[86,87] Large studies based on data from the US found higher mortality for cancer patients with local or regional spread cancer and VTE compared with patients with same cancer stage and no VTE, whereas the impact of VTE on survival was weaker or even absent in patients with distant metastasis.[87-90]

Recurrence of VTE

Recurrent VTE is more frequent among cancer patients than in cancer free subjects. In the RIETE study, 4.5% of cancer exposed subjects had recurrent VTE, while 1.4% had recurrent VTE in the cancer free subset of the population. The HR of recurrence for cancer patients with metastases compared with study subjects without cancer was 5.6 (95% CI, 3.7-8.4), for cancer without metastases the HR was 2.6 (95% CI, 1.8-3.8).[67,91] Similar differences were observed in a single center, prospective cohort of 842 patients with DVT. The 12-month cumulative incidence of recurrent VTE was 20.7% in patients with cancer, while the 12-month cumulative incidence of recurrence was 6.8% in VTE patietns without cancer.[21] Death was however not treated as competing risk in this study, which would tend to increase the difference in recurrence rates in the two groups, as the mortality is probably not similar in the two groups.[92] In a study

based on data from a randomized clinical trial, Parpia et al. found a 180-day cumulative incidence of recurrent VTE of 6-12% treating death as competing risk in cancer patients treated for VTE. The risk of recurrence was 2.7-fold higher in case of metastasis compared with no metastasis.[93]

The mortality of cancer patients is probably further increased in cases of recurrent VTE. In a cohort of Olmsted, US residents diagnosed with cancer-associated VTE between 1966-2000, the 10-year cumulative incidence of recurrent VTE was 29% treating death as competing risk. Recurrent cases encompassed thrombus extension ≥ 24 hours after the initial VTE diagnosis (i.e. new or worsening symptoms of VTE). Patients with active cancer had higher recurrence rates than those with previously active cancer, particularly lung, brain, ovarian cancer, advanced cancer stage or cancer stage progression and myeloproliferative and myelodysplastic syndromes were associated with increased risk of recurrent VTE. In a univariate Cox model including recurrent VTE as a time-dependent predictor, the HR of death was 2.9 (95% CI ,2.3-3.6) for those with recurrent VTE compared with those with no VTE recurrence. No confounders were however added to the model, possibly due to statistical power and study aims.[94] In the study by Cohen and colleages,[25] the overall incidence rate of recurrent VTE was 9.6 per 100 PY (95% CI, 8.8-10.4), however markedly higher within the first six month after the initial VTE diagnosis in cancer patients (IR of recurrent VTE < 180 days was 22.1 per 100 PY [95% CI, 19.9-24.4]). The 10-year cumulative incidences of recurrent VTE were lower than observed in the Olmsted cohort[94], probably partly due to different definitions of recurrent VTE.

Side effects of antithrombotic treatment

Treatment for VTE is associated with adverse events of which bleeding is the most important. The risk of bleeding after anticoagulation treatment for VTE is higher in cancer patients than in cancer free VTE patients.[21] The Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile International Normalized Ratio (INR), Elderly, Drugs or alcohol use (HAS-BLED) score was developed to assess bleeding risk and net benefit of anticoagulation in patients with atrial fibrillation.[95] Recently, the HAS-BLED score was validated in a US cohort of 132 280 VTE patients of whom 19% had cancer. In this population-based cohort, 3.6% of the patients experienced bleeding, and 39% of these were classified as major bleeds. The cumulative incidence of bleeding was higher in cancer patients than in subjects without cancer, and cancer patients had a 2-fold increased risk of bleeding compared with non-cancer subjects.[22] In the Hokusai VTE-cancer study, 1050 patients with cancer-associated VTE was randomized to treatment with either a low molecular weight heparin or a non-vitamin K oral anticoagulant.[96] Major bleeding as defined by the ISTH[97] was observed in 3-6 % of the patients during a median anticoagulation treatment period of 184 days.[98] However, not only bleeding episodes defined as major are burdensome for the patients, and it is thus relevant to include non-major bleedings when assessing the risk of bleeding.[99] Non-major bleeds were included in analysis of data from the CATCH trial where the efficacy and safety

of low molecular weight heparin and vitamin K antagonist treatment of acute VTE in patients with active cancer was investigated.[100] In total, 15% of the study participants experienced clinically relevant bleeding episodes.[101]

Psychological and physical consequences for the patients

The opening quote from the Welsh cancer patient with VTE is one of many in recent studies that have assessed the qualitative aspects of cancer-associated VTE. As clearly stated, cancer patients with VTE experience psychological stress, not only in association with symptoms of VTE, but also in the diagnostic process and treatment of VTE.[1,3,102-105] Physical symptoms related to the VTE and related treatment also negatively affect the quality of life of patients with cancer-associated VTE, but treatment does improve both the physical and mental health over time.[105]

Health-economic consequences

The expenses for cancer patients with VTE are considerably higher compared with cancer patients without VTE. In a US study, 912 patients with VTE were matched on age and gender to 2736 cancer patients without VTE. After adjustment for cancer type, demographic factors and clinical confounders, VTE increased the economic cost by 30%.[4] The main contributor to this was longer duration of hospitalization due to complications and recurrences, which is also observed in other studies.[106-108]

In summary, the risk of VTE in cancer patients is considerable despite methodological challenges in estimating the precise burden of cancer-associated VTE in the population. It is evident that cancer patients with VTE have reduced survival compared with VTE free cancer patients, and that cancer patients exposed to VTE have a considerable risk of recurrent events despite treatment, which is associated with clinically relevant bleeding for a substantial proportion of the patients. Cancer-associated VTE is burdensome for both the health economy, and not least for the patients. A recent literature review concluded that the high incidence of VTE in cancer patients and subsequent economic and personal burden of cancer-associated VTE necessitate evidence based prevention of VTE in cancer patients.[109]This prevention is already sought, but the etiology of VTE in cancer patients is complex. Prediction of the VTE risk in cancer patients is challenged by this fact and by influence from non-cancer related risk factors for VTE at a person level. General and cancer-associated risk factors for VTE are reviewed in the following section.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Several factors are related to the risk of VTE at person level. Some risk factors are intrinsic qualities of the patient (e.g. genetic risk factors, age, sex) while others are acquired, provoking factors (e.g. hospitalization, cancer, surgery). All factors that influence the risk of VTE do so by disturbing the balance between three causes known

as Virchow's triad: [110]

I. The endothelial layer of the blood vessels is injured/dysfunctional
II. Blood flow is compromised
III. Blood composition changes to hypercoagulability net

Multiple factors can compromise each of these three causes and thereby increase the risk of VTE. In the general population, intrinsic risk factors often trigger VTE in co-occurrence with either persistent or temporary provoking risk factors, although for about 50% of patients provoking factors are not identified.[111-113] Genetic and intrinsic factors associated with VTE (not classifying events as provoked) are discussed first followed by a review of provoking factors.

GENETIC RISK FACTORS FOR VTE

Various factors in the blood are important for thrombogenicity. Dysfunction or deficiency of one of the important plasma coagulation inhibitors (loss-of-function mechanisms) have large effects on the risk of VTE but are relatively rare in the population. Inherited insensitivity to endogenous anticoagulation mechanisms or increased levels of circulating prothrombotic factors (gain-of-function mechanisms) increases the risk of VTE more moderately but are more prevalent in the population.[114]

In the general population

Loss-of-function mechanisms

Antithrombin is a potent endogenous anticoagulant with inhibitory effect on thrombin as well as other coagulation factors.[115] Antithrombin deficiency is associated with a more than 10-fold increased risk of VTE.[116] Protein C and Protein S are vitamin K-dependent endogenous anticoagulants, which inactivates coagulation factors V and VIII thereby reducing thrombin generation, Protein S works as a co-factor to Protein C.[117] Protein C and Protein S deficiencies increase the risk of VTE by 7-8 - fold compared with subjects with no coagulation defect.[118] These loss-of function thrombophilias are however rare in the general population. The incidence of Protein C deficiency is 14-50 per 10 000 persons while Protein S and Antithrombin deficiency is seen in around 10 per 10 000 persons. In VTE populations, about 1-3% have a loss-of-function thrombophilia.[114]

Gain-of-function mechanisms

The most frequent gain-of-function mechanism in the general population is non-O-blood type, which is found in more than half of the population.[119] Individuals with non-O blood type have higher levels of von Willebrand factor and coagulation factor VIII[120] which is believed to be one of the reasons for their 1.5-2.5 - fold higher risk of

VTE compared with subjects with blood type O. Other factors must however contribute because the association with non-O blood type remains after adjustment for von Willebrand factor and factor VIII levels.[119,121,122] In addition, the ABO locus is associated with levels of inflammatory molecules, which may also contribute to the effect of blood type on the risk of VTE.[123]

Coagulation factor V is a co-factor to factor activated factor X. This complex facilitates the activation of prothrombin to thrombin. Furthermore, factor V acts with Protein C and Protein S on the degradation of activated factor VIII.[124] Different variations in the gene encoding factor V, of which the factor V Leiden mutation is the most common, results in a lower rate of degradation of factor V and abnormal degradation of factor VIII.[114,124] The factor V Leiden mutation is present in populations of European ancestry, where the prevalence is 5-10%.[125,126] The risk of VTE is increased by 10-80 - fold in case of homozygosity, while the risk of VTE is increased by 2-5 - fold in the more common case of heterozygosity compared with subjects free of the factor V Leiden mutation.[119,126,127] Among VTE patients, 18% have the factor V Leiden allele.[114]

Prothrombin is the inactive precursor of thrombin, which is responsible for the conversion of fibrinogen to insoluble fibrin. Mutation in the untranslated part of the prothrombin gene (G20210A) results in increased levels of circulating prothrombin.[128] The G20210A mutation in the prothrombin gene is seen in 1-3% of the general population of European ancestry. The age and sex adjusted HR of VTE is 1.5 for heterozygote subjects, while in the very rare occasion of homozygosity the HR of VTE is 10 compared with subjects without the mutation.[119] The mutation is present in 6% of patients with VTE.[114]

Few individuals carry more than one prothrombotic mutation. In a study of 2310 VTE patients and 3204 controls, double heterozygosity was found in 2.2% of the cases, whose odds ratio (OR) for VTE was 20 (95% CI, 11.1-36.1).[127]

In cancer patients

Even though cancer is a tremendous provoking factor, genetic factors may not be a negligible in the assessment VTE risk in cancer patients. Several studies have shown that cancer patients with inherited thrombophilia (the vast majority being the factor V Leiden mutation) have a 2-7 - fold increased risk of VTE compared with cancer patients without thrombophilia.[129-133] Few studies have assessed if ABO blood group have an effect on the risk of VTE in cancer patients. A single center study of 130 glioma patients found 3-9 - fold higher risk of VTE in patients with non-O blood type.[134] In a study of 670 patients with pancreatic cancer, the OR of VTE in subjects with non-O blood type was 1.74 (95% CI, 1.07-2.84) in a multivariable model.[135]

INTRINSIC RISK FACTORS FOR VTE

Besides the genetic factors described above, several characteristics of the patients are related to their risk of VTE. These intrinsic factors are reviewed below for both the general population and cancer patients.

In the general population

The risk of VTE differs by **sex and age** in the general population, the association is however not simple. Overall, the risk of VTE increases by increasing age. In a population-based study from the US, incidence rates of VTE were 7-10 - fold higher in age groups above 75 years compared with those below 55 years. In the STAC cohort, the IR of VTE among subjects aged 20-29 years was 0.3 per 1000 PY, while it was 6.4 per 1000 PY in subjects above 80 years.[66] The increasing risk of VTE with higher age is not merely due to more cancers in the elderly population. In the Tromsø study, cancer was regarded a time-varying exposure. The HR of VTE in cancer patients <50 years was 20.5 compared with cancer free subjects after adjustment for cardiovascular risk factors, while in cancer patients ≥70 years the HR of VTE was 3.2 compared with cancer free subjects. The proportion of VTE that would not occur if cancer was eliminated in the population (i.e. the population attributable risk fraction) was however similar in the young and elderly age groups (14% and 18%, respectively).[136]

In the general population, the effect of **sex** on the risk of VTE is dependent of age. In a French population based study, IRs of VTE increased with increasing age, however women had a higher IR of VTE than men when younger than 40 years of age and older than 75.[44] In a population based VTE cohort from the UK, similar age dependent increase in the IR of VTE was observed, and with higher IRs of VTE in the youngest and oldest women compared with men.[14] Increased risk of VTE among users of **oral contraceptives** contributes to these observations. A recent Cochrane review found the use of combined oral contraceptives associated with a relative risk of VTE of 3.5% (95% CI, 2.9-4.3).[137] Pregnancies and puerperium also plays a role in the higher risk of VTE in younger women, and this is further elaborated in the section "Provoking, transient risk factors (non-cancer)" below. Among post-menopausal women, the use of **hormone replacement therapy** is associated with a doubling of the risk of VTE, however varying by type of hormone and route of administration.[138-140] Regarding the middle-aged, (around 50-70 years of age) men seem to have an increased risk of VTE compared with women[6,44,141] This association was explained by the effect of increasing **heigh**t on the risk of VTE in one of the studies as the association disappeared after adjustment for body height.[141] In the Tromsø study, a HR of VTE of 1.3 was observed per 10 cm increase in body height for men.[84] A recent meta-analysis of three cohorts also observed a 30-40% increased risk of VTE per 10 cm increase in height. The association remained after adjustment for genetic variants related to body height. Possible explanations could be combinations of higher resting venous pressure and thereby more damages in the vessels and a larger venous surface including more and larger venous valves, where the venous thrombosis can form. [142] **Obesity** (body mass index 30 > kg/m^2) has been associated with 2-3 - fold increased risk of VTE in population based

studies.[54,143,144] Potential confounding by cardio metabolic consequences of obesity on the risk of VTE was investigated in the Tromsø study.[145] No such confounding was observed, and the authors speculate that the increased risk of VTE in obese subjects could be due to obesity induced stasis or circulating adipokines.

In a meta-analysis of prospectively collected data from nine population based studies with 5000 validated VTE events among 245 000 subjects, **modifiable classical cardiovascular** risk factors were not associated with the risk of VTE except for **smoking**, whose effect could be mediated through cancer.[146]

A **history of VTE** is one of the strongest risk factors for VTE. The OR for a new VTE was 15.6 (95%CI, 6.8-35.9) in subjects with a history of VTE in a multi-center case control study with prospectively collected data from of 636 non-hospitalized DVT patients and 636 controls matched on age and gender.[147] It is not clearly understood why previous VTE predisposes to new VTEs, but it is established that elevated D-dimer can be used as a predictor of recurrence in patients with pulmonary embolism.[148]

In cancer patients

The association with **age** remains in cancer populations. Several studies have reported that the risk of VTE is higher in cancer patients above 60-65 years than in younger cancer patients.[25,26,69]

Several large studies assessed the impact of **sex** on the risk of VTE in cancer populations and found no effect.[24,87,88,132,149-151] In a few studies, female gender was associated with 14-40% higher risk of VTE compared with male.[69,90,152] None of these observations were however further explained.

Obese breast cancer patients are at higher risk of VTE than those with ideal body weight. Among 13 202 breast cancer patients in the UK, the HR of VTE increased with increasing body mass index after adjustment for age, comorbidities, cancer specific factors and associated treatments. Highest HR of VTE was observed on morbidly obese patients compared with ideal weight (HR 3.0, 95% CI, 2.1-4.4).[153] The same tendency towards a "dose dependent" increase in the risk of VTE was observed in a cohort of colorectal cancer patients from the UK, where the HR of VTE in morbidly obese patients compared with ideal weight was 2.0 (95% CI, 1.2-3.2).[154] Also in a study including 516 stage II and III colorectal cancer patients, an increase in the body mass index of 5 kg/m^2 was associated with a SHR for VTE of 1.6 (95% CI, 1.2-2.0).[155]

Smoking has been investigated as a possible risk factor for VTE in a few cancer populations. In colorectal cancer the HR of VTE in smokers/ex-smokers was 1.7 (95% CI, 0.4–6.7) compared with never smokers.[155] Among 422 lymphoma patients exposed to chemotherapy at the MD Anderson Cancer Center in 2003, former smoking was not associated with VTE.[156] In lung cancer patients, smoking was not associated with the

risk of VTE after controlling for age, body mass index, comorbidities, cancer specific factors and associated treatments (HR 1.2, 95% CI, 0.9-1.5).[86]

Several studies found no effect of **comorbidities** or performance status of cancer patients' risk of VTE.[86,132,150,153-155,157-159] This might however differ according to cancer type in the sense that the effect of cancer on the risk of VTE exceeds that of comorbidities in aggressive cancer types, whereas in less aggressive cancer types the effect of comorbidities on the risk of VTE is on par with or even exceeds that of the cancer. A study of 16 755 Californian lymphoma patients found that increasing number of comorbidities was a strong predictor for VTE in low grade lymphomas, whereas comorbidities did not affect the risk of VTE in high grade lymphomas.[151] A nationwide study of all Danish prostate cancer patients diagnosed between 1995-2011 showed a considerable interaction between prostate cancer and comorbidity levels after cancer diagnosis accounting for 30% of all VTEs among prostate cancer patietns.[81]

A history of VTE is one of the strongest risk factors for a new VTE in association with cancer. The risk of VTE after the cancer diagnosis was increased by 12-15 - fold in case of previous VTE in recently published studies.[160,161] The competing risk of death was accounted for in a study of VTE among 2730 lymphoma patients in the Veteran's Administration Cancer Registry; the SHR of VTE was 4.73 (95% CI, 2.5-9.0) in case of a history of VTE.[162]

In summary, genetic and intrinsic factors that do not classify VTE as a provoked event have substantial impact on the risk of VTE in both the general population and in cancer patients. A history of VTE is one of the strongest risk factors for a new VTE in both the general population and cancer populations. Older age, obesity and genetic thrombophilias are also risk factors for VTE in both cancer populations and in the general population.

PROVOKING, TRANSIENT RISK FACTORS (NON-CANCER)

Hospitalization, surgery and trauma

Hospitalization increases the risk of VTE dramatically in the general population. In a study based on review of medical records from residents of Olmsted County with VTE, the average age and sex adjusted IR of in-hospital VTE was 96 per 1000 PY while the IR of community acquired VTE was 0.7 per 1000 PY.[163] Hospitalization likewise increases the risk of VTE in cancer patients. In a case-control study including 570 cases with active cancer associated VTE and 604 controls with cancer, the OR of VTE in case of hospitalization was 7.9 (95%CI, 4.4-14.1).[164]

Approximately 200 000 VTE-related deaths occur annually in the US, one-third of these follow **surgery**.[165] About 50% of in total 68 183 hospitalized patients were at risk of VTE in a multinational cross-sectional study on hospitalizations in 358 sites during the

last five months of 2006. Forty-two percent of medical patients were at risk of VTE, while 64% of surgical patients were. However, only 59% of the surgical patients at risk of VTE received guideline-recommended thromboprophylaxis.[19] The risk of VTE differs according to type of surgery. The 3-month risk of hospitalization for VTE is highest among patients undergoing neurosurgery, total hip arthroplasty, cystectomy and major vascular surgery.[166] In a recent study of 12 388 patients undergoing colectomy, the overall IR of VTE within the first year after surgery was 30 per 1000 PY. The risk of VTE was 2.2-fold higher for patients undergoing acute colectomy compared with elective procedures. Interestingly, the risk of VTE in the first month after surgery was similar in cancer and non-cancer patients undergoing emergency colectomy.[167] Even despite thromboprophylaxis in the immediate postoperative period, the 3-month cumulative incidence of VTE following surgery was 2-3%.[168]

Trauma patients have a high risk of VTE. Among 349 trauma patients who did not receive thromboprophylaxis, DVT was diagnosed in nearly 60% by contrast venography 1-3 weeks after the admission.[169] In a recently published study of trauma patients expected to be admitted to an intensive care unit for more than 48 hours and given protocol-driven thromboprophylaxis,VTE was found by repeated screening in 31% of the study subjects during a median follow-up of 7 days.[170]

Infection

Infections transiently increase the risk of VTE in both hospitalized and non-hospitalized patients. In the Tromsø study it was recently observed that hospitalization due to **infection** lead to a 15-fold increased risk of VTE after adjustment for immobilization while in mobile patients hospitalized for infection, the risk of VTE was 20-fold increased compared with control periods.[171] The incidence rate ratio (IRR) of VTE within three months after hospital diagnosed infection was 3.3 (95% CI, 2.9-3.8) after adjustment for cancer, pregnancy, surgery and trauma in a Danish population based case-control study. For infections diagnosed and handled in the primary sector, the adjusted IRR of VTE was 2.6 (95% CI, 2.5-2.8).[172] The impact of infections in the community on the risk of VTE was also demonstrated in a self-controlled study of 11 033 VTE patients. The risk of VTE was significantly higher up to 26 weeks after a urinary or respiratory tract infection compared with before infection. Age adjusted IRs for VTE in the first two weeks after infection were 2 for both urinary tract and respiratory tract infections but fell with successive time since infection reaching the initial risk one year after the infection.[173]

Immobilization

Voluntary or involuntary transient immobilization reduces the blood flow in the venous system, which results in markedly increased risk of VTE in these settings or conditions. Immobilization increases the risk of VTE in the background population (OR 6.2 [95% CI, 5.4-7.0]) and even more among patients with major illnesses as liver and

kidney diseases, heart failure or arterial thrombosis (OR 10.4 [95% CI, 7.5-14.4]).[174] In a cohort of 8 755 employees of international organizations, the IR of VTE in association with air travel of more than four hours duration was 3.2 per 1000 PY, which was 3.2-fold higher compared with individuals not exposed to air travel. Concomitant use of oral contraceptives, repeated exposure to air travel, longer duration of air travels, and overweight were all associated with further increased risk of VTE during air travel.[175] In a study of 197 cases with VTE and 197 controls with other thrombotic diseases, the OR of VTE was 2.8 (95% CI, 1.2-6.1) if exposed to prolonged sitting in association with work or use of computers.[176] Below-knee cast immobilization increases the risk of VTE by 8-fold, with higher risks in those with traumatic indications for cast immobilization.[177]

Pregnancy and puerperium

Pregnancy and puerperium increases the risk of VTE by 4-6 - fold compared with non-pregnant women, especially obese women, those having cesarean delivery, preeclampsia or infections postpartum are at risk of VTE.[178-180]

PROVOKING, PERSISTENT RISK FACTORS (NON-CANCER)

Several non-malignant, chronic conditions increase the risk of VTE considerably. Chronic inflammatory bowel disease increases the risk of VTE by 3-9-fold dependent of disease activity.[181] Chronic renal diseases are associated with increased risk of VTE. In a recently published study of 3564 Taiwan patients with end-stage renal disease and controls matched on age, sex and index-year, the HR of DVT in the end-stage renal disease group was 13.9 after adjustment for comorbidities.[182] Even decreases in the estimated glomerular filtration rate in the normal spectrum was independently associated with VTE in a pooled analysis of data from five large population based cohorts.[183] Neurological diseases resulting in extremity paresis is associated with a high risk of VTE.[184] In a prospective study of 94 patients with spinal cord injury who all received thromboprophylaxis, 23% had a VTE within a median follow-up of 36 months. Previous VTE and paraplegia were associated with a 5-6-fold higher risk of VTE in this population.[185]

CANCER SPECIFIC RISK FACTORS

Active cancer is regarded a provoking, persistent risk factor for VTE in the definition proposed by ISTH.[48] Uncured cancer and ongoing curative treatment is considered active cancer in this classification. Cancer is no longer considered a provoking factor if cured. The time interval from last treatment to certainty of cure is, however, not easily standardized, and it is dependent of both cancer specific factors and treatment type. The impact of cancer characteristics, cancer relapse or additional cancer and cancer related treatments on the risk of VTE is reviewed below.

Cancer type

Population based studies including multiple cancer types do consistently report large variation in the risk of VTE according to cancer type, typically with lower risk in less aggressive cancer types as breast and prostate cancer, and higher risks in cancer types with a more aggressive phenotype such as pancreas, brain, ovary and bone cancer.[25,26,28,68,69,76,149,186] A large meta-analysis from 2012 based on data from 38 studies reporting VTE risks for both single and multiple types of cancer showed that the IR of VTE in prostate and breast cancer were around 10 per 1000 PY, while in brain and pancreas cancer the IR was more than 50 per 1000 PY(Figure 1).[79] A recent study based on data from the STAC cohort highlights the importance of inclusion of mortality rate when estimating the risk of VTE in cancer populations.[27] In the standard 1-KM approach, the 2-year cumulative incidence of VTE ranged from 1% in breast cancer to 10 % in pancreas cancer, while the range narrowed to 1 - 4% when taking the competing risk of death into account. This means that the effect of cancer type remains in analysis taking the competing risk of death into account, but it suggests that previously observed dramatic effects of cancer type might be overestimated due to considerable mortality in some cancer types, leading to informative right censoring.

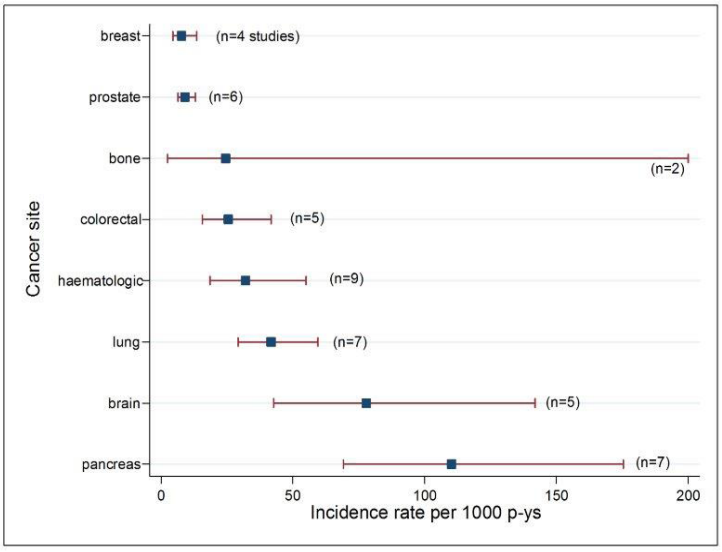

Figure 1. Figure S1 from Horsted et al. [79] showing pooled IRs of VTE for several cancer types based on data from studies where follow-up commenced at the cancer diagnosis. Number of studies contributing to each estimate are given in the brackets.

Estimates of VTE occurrence in recently published studies concerning single cancer types with study entry at cancer diagnosis are summarized in Table 2. Despite the same time of start of follow-up (i.e. at the time of cancer diagnosis) in these studies,

the provided VTE risk estimates can be difficult to compare due to different definitions of VTE, study methods and lengths of follow-up. The risk estimates do however reflect the findings from the aforementioned studies encompassing multiple cancer types and the meta-analysis, with 2-year risks of 1-2 % in breast and prostate cancer while higher estimates are seen in endometrial, ovarian, hematological, lung and colorectal cancer. The majority of studies provide cumulative risk estimates including events in close proximity to the cancer diagnosis with no or limited detailed information about risks of VTE beyond the period in closest proximity to the cancer diagnosis (Table 2).[80,81,153,154,157,158,160,187-189] In the study by Walker et al., the cumulative 2-year risk of VTE was 4.9%, but 58% (135 out of 232) of the events that contributed to this occurred within the first 6 months after cancer diagnosis.[154] Similarly, in the study by Rodriguez et al., the 2 - year cumulative incidence of VTE was 2.7%, however, 44% of the VTEs included in this estimate occurred within the first three month after the cancer diagnosis.[188] Given the large impact of time since cancer diagnosis actually described in most of these studies, it is relevant to provide estimates based on events occurring in different time intervals since cancer diagnosis in addition to estimates based on events that occurred within the first months after the cancer diagnosis. Fewer studies had this focus, and estimates based on total study time from the cancer diagnosis and onwards are consistently higher than the estimates restricted to 6-12 months after the cancer diagnosis and onward (Table 2).[86-88,90,150-152,162] This shows that the typically reported 2-year risk estimates are not only possibly high due to the competing risk of death in some cancer types, but also due to inclusion of events in close proximity to the cancer diagnosis. When focusing on estimates of VTE within the first few months after cancer diagnosis, the risk however still differs markedly with cancer type, from 2.5% in breast cancer, 7.2% in lung cancer to 19.2% in leukemia and possibly higher in lymphoma (Table 2). However, some of the studies in Table 2 probably overestimate the risk of VTE to some degree as only few of them treated death as competing risk when estimating cumulative incidences.[81,150,162]

Cancer stage

Several studies encompassing many cancer types, have reported that the risk of VTE is 2-19 - fold higher in distant metastasis compared with the general population[24] or localized disease.[28,129,190] However one study reported varying effects of cancer stage on the risk according to cancer type with highest effect in melanoma and bladder cancer and lower in lymphoma and prostate cancer.[76] Regional stage is associated with a 1.1-3.7 - fold higher risk of VTE compared with the general population or localized disease,[24,190] also varying by cancer type.[76] Different definitions of cancer stage complicates comparison of effect estimates in these studies, however there seems to be a consistent and "dose dependent" effect of cancer stage on the risk of VTE.

In the studies of single cancer types in Table 2, the consistency and "dose dependency" is however not confirmed for all cancer types: In breast cancer Chew et al.[187] found considerable effect of regional spread (HR 2.1 [95% CI, 1.8-2.3]) and even higher of

distant metastasis (HR 6.3 [95% CI, 5.3-7.5]) on the risk of VTE, while the effect of extent of breast cancer was more moderate in the studies by Walker et al. and Brand et al.[153,160] Similarly, in lung cancer the HR of VTE in regional stage was 2-fold higher in regional stage and 4-fold higher in distant metastasis compared with localized disease in the study by Chew et al., while the effect estimates were more modest and more similar in regional stage and distant metastatic lung cancer in the study by Walker et al.[86] High stage in colorectal cancer was associated with a 3-fold increased risk of VTE, while moderate disease extension was associated with a 2- fold increased risk of VTE compared with localized disease in both UK and US study populations.[88,154] For lymphoma and prostate cancer, the effect of disease extension is more moderate in all the studies in Table 2.

The competing risk of death may to some degree explain the dramatic effects of distant metastasis on the risk of VTE in some of the referred studies. The mortality for cancer patients with distant metastasis is higher than for those with localized disease, and this would introduce informative right censoring if death is not treated as competing risk. The absolute risk of VTE in case of distant metastasis was higher in studies not accounting for the competing risk of death.[86-88,90,154,187-189] However, both Lund et al. and Sanfilippo et al. found lymphoma stage associated with a higher risk of VTE treating death as competing risk in absolute and relative association measures; stage III/IV compared with stage I/II was associated with a 1.1 -1.5 - fold increased risk of VTE (Table 2)[150,162]

In summary, the reviewed literature shows that cancer stage has an impact on the risk of VTE, which is, however, however also influenced by the cancer type despite possible overestimation due to the competing risk of death.

Differentiation or histology of cancer cells

Several authors have speculated that the main contributor to VTE in cancer could be the aggressiveness of the cancer.[24,85,88,190,191] The degree of differentiation (tumor grade) and the histology are important markers for the aggressiveness of the tumor.[192] For this reason, Ahlbrecth et al. investigated the impact of tumor grade on the risk of VTE in cancer patients based on data from the CATS study, and found high grade tumors associated with a 2-fold higher risk of VTE compared with low grade tumors.[193] The absolute risk of VTE was however high for both high grade tumors and low grade tumors after 6-months (8.2% and 4.0%, respectively), and possibly overestimated because the competing risk of death was ignored.

Many of the studies in Table 2 investigated the effect of tumor grade or histology on the risk of VTE. The risk of VTE was higher in case of aggressive histology or poor differentiation of cancer cells in lung cancer, uterine cancers and lymphoma. Lund et al. and Sanfilippo et al. both found histology associated with VTE treating death as competing risk. In the study by Sanfilippo et al., the SHR of VTE in diffuse large B-cell

lymphoma was 1.5 (95% CI, 1.0-2.4) compared with follicular lymphoma, which was quite similar to the SHR of VTE in diffuse large B-cell lymphoma versus follicular lymphoma in the study by Lund et al. (1.8 (95% CI, 1.3-2.4).[150,162] Tumor grade and/or histology was not associated with the risk of VTE in either of the studies concerning leukemia, bladder, colorectal and breast cancer (Table 2).

Table 2. Incidences of VTE and effect of risk factors related to cancer on the risk of VTE categorized by cancer type.

Type	Author, Publication year number of study subjects	Design, data source	Inclusion period	Absolute risk of VTE	Effect of cancer stage	Effect of histology/grade	Effect of cancer related treatment
Bladder	Sandhu [90] 2010 N = 24 861	Population based, Californian cancer registry+Californian discharge registry	1993-95 + 1997-99	*0-6-month rate:* 2.5 per 100 PY *7-12 month rate:* 1.0 per 100 PY *2-year 1-KM:* 1.9%	Vs. local: Regional: HR 3.8 (3.0-4.8) Remote: HR 6.4 (4.8-8.7)	Vs. transitional: Small cell: HR 1.1 (0.4-2.9) Other epithelial: HR1.1 (0.8-1.6)	Major surgery (cystectomy). vs no surgery: HR 2.1 (1.6-2.7)
	Ording [157] 2016 N = 13 809	Danish nationwide bladder cancer cohort	1995-2011	*3-month risk:* 6.6 per 1000 persons *1-year risk:* 18 per 1000 pers.	NA	NA	3-month IR of VTE after (any type of) surgery: 5.8 per 1000 PY
Breast	Chew [187] 2007 N = 108 255	Population based, Californian cancer registry+Californian discharge registry	1993-95 + 1997-99	*1-year 1-KM:* 0.9% *2-year 1-KM:* 1.2%	Vs. local: Regional: HR 2.1 (1.8-2.3) Remote: HR 6.3 (5.3-7.5)	Vs. adenocarcinoma: Lobular, unspecified carcinoma, mucinous, tubular medullary and papillary: HR ~1	Breast related surgery vs no surgery: HR 0.6 (0.5-0.7)
	Brand [160] 2016 N = 8338	Regional, Swedish population based study.	2001-2008	*1-year 1-KM:* 2.0% *2-year 1-KM:* 2.5% (broad definition of VTE)	Vs no lymph spread: 1-4 nodes: HR 1 (0.8-1.3) >4 nodes: HR 1.7 (1.2-2.5)	Vs. low grade: Moderate: HR 0.95 (0.65-1.38) High: HR 0.85 (0.56-1.31)	Breast conserving surgery vs mastectomy: HR 1.1 (0.8-1.5) Radio therapy vs no: HR 1.1 (0.8-1.5) Chemotherapy vs. no: HR 2.4 (1.2-4.7) Endocrine treatment vs no: HR 1.9 (0.9-3.7)
	Walker [153] 2016 N = 13 202	Linking of 4 UK health data sources.	1997-2006	IR 8.4 per 1000 PY	Vs. local: Regional: HR 1.2 (0.9-1.4) Distant: HR 1.5 (1.0-2.4)	Vs. well differentiated: Moderately: HR 1.1 (0.8-1.5) Poorly: HR 1.1 (0.8-1.4)	During chemotherapy vs no: HR 10.8 (8.2-14.4) During endocrine treatment vs no: HR 2.4 (1.7-3.4)
Colorectal	Alcalay [88] 2006 N = 68 142	Population based, Californian cancer registry+Californian discharge registry.	1993-95 + 1997-99	*6-month rate:* 5 per 100 PY *6-12 month rate:* 1.4 per 100 PY *12-24 month rate:* 0.6 per 100 PY *2-year 1-KM:* 3.1%	Vs. Local: Regional: HR 2.1 (1.8-2.4) Distant: HR 3.2 (2.8-3.8)	Vs. adenocarcinoma: Mucinous + undifferentiated: HR~1	Major surgery (abdominal). vs no: HR 0.4 (0.3-0.4)
	Walker [154] 2014 N = 10 309	Linking of 4 UK health data sources.	1997-2006	*0-6 month ci:* 2.5% *2 year ci:* 4.9%	Vs. Duke stage A: Duke B: HR 1.3 (0.9-2.0) Duke C: HR 2.1 (1.4-3.1) Duke D: HR 3.1 (2.0-4.8)	Vs well differentiated: Moderately: HR 1.1 (0.8-1.6) Poorly: HR 1.2 (0.8-1.8)	Emergency surgery vs elective: HR 1.4 (1.2-1.8) Chemotherapy vs. no: HR 1.4 (1.1-1.7)

Gynecological	Rauh-Hain [158] 2015 N = 23 122 (endometrial)	SEER (covers 26% of US population) linked to Medicare claim files (older than 66 years) .	1992-2009	*2-year rate:* 7.2 per 100 pers.	Vs. stage I: Stage II: HR 1.4 (1.1-1.7) Stage III: HR 2.0 (1.7-2.4) Stage IV: HR 2.5 (2.1-2.9)	Vs. low grade: High grade: HR 1.2 (1.1-1.4)	Radio therapy vs no: HR 1.1 (1.0-1.2) Chemotherapy vs. no: HR 1.7 (1.4-1.9)
	Rodriguez [188] 2011 N = 1 770 (uterine)	Population based, Californian cancer registry+Californian discharge registry.	1993-95 + 1997-99	2-year 1-KM: 2.7%	Vs. Local: Regional: HR 2.6 (1.9-3.1) Distant: HR 8.1 (6.4-10.2)	Vs. endometroid: Clear cell: HR 1.5 (1.2-2.0) Sarcoma: HR 1.5 (1.1-.1.9)	Major surgery vs no: HR: 1.7 (1.1-2.6)
	Rodriguez [189] 2007 N = 13 031 (ovarian)	Population based, Californian cancer registry+Californian discharge registry.	1993-95 + 1997-99	2-year 1-KM: 5.2%	Vs. Local: Regional: HR 1.7 (1.1-2.6) Distant: HR 3.0 (2.1-4.2)	Vs. carcinoma: Borderline: HR 0.3 (0.1-0.5) Germ cell: HR 0.8 (0.3-2.0) Sarcoma: HR 0.9 (0.6-1.5)	Major surgery vs no: HR: 0.7 (0.6-0.8)
Hematological	Lund[150] * 2015 N = 10 924 (lymphoma)	Danish national cohort, nested case-control.	2000-2010	*0-30day IR:* 62 per 1000 PY *31-60 day IR:* 55 per 1000 PY *61-90 day IR:* 55 per 1000 PY *>1 year IR:* 8 per 1000 PY *2-year ci:* 3.5%	Vs. stage I/II: Stage III/IV:SHR 1.1 (0.9-1.5)	Vs. indolent lymphoma: DLBCL: SHR 1.8 (1.3-2.4) Mb. Hodgkin: SHR 1.6 (1.1-2.5) Mantle cell: SHR 0.9 (0.5-1.8)	Chemotherapy vs no: OR 1.9 (0.9-2.3) Radiation vs no: OR 4.0 (0.4-13.1) Rituximab vs no: OR 2.2 (0.9-3.3)
	Mahajan [151] 2014 N = 16 755 (lymphoma)	Population based, Californian cancer registry+Californian discharge registry.	1991-1997	*0-1 year rate:* 4.7 per 100 PY *1-2 year rate:* 0.7 per 100 PY *2-year ci:* 4.0% (all types combined)	Vs. Local Regional: HR 1.5 (1.2-1.8) Extensive: HR 1.5 (1.2-1.7)	2-year ci of VTE in: Follicular lymphoma: 2.1% DLBCL: 4.8% Burkitt/lymphoblastic: 4.5%	NA
	Simkovic[132] 2015 N = 346 (CLL)	Czech single center study.	1999-2010	11% had VTE during a median follow-up of 72 months	NA	NA	CLL treatment vs no: HR 0.9 (0.4-2.2)
	Ku [152] 2009 N = 5394 (AML) + 2482 (ALL, including childhood ALL)	Population based, Californian cancer registry+Californian discharge registry.	1993-95	AML: *3-month rate:* 19.2 per 100 PY *1-2 year-rate:* 1.4 per 100 PY *Cum. 2-year:* 5.2 per 100 PY ALL: *3-month rate:* 11.2 per 100 PY *1-2 year-rate:* 0.6 per 100 PY *Cum. 2 year:* 4.5 per 100 PY	Vs. ALL Fab type L3: ALL L1: HR 0.8 (0.2-3.4) ALL L2: HR 0.7 (0.1-3.8)	Vs. AML, unspecified AML M3: HR 1.3 (0.7-2.3) AML M1/M2: HR 0.8 (0.3-1.7) AML M4/M5: HR 0.7 (0.3-1.6)	CVC vs no: HR 1.6 (1.1-2.3)
	Sanfilippo [162] * 2016 N = 2730 (lymphoma)	US Veteran's Administration Central Cancer Registry.	1998-2009	DLBCL: *0-30 days-IR:* 271 per 1000 PY *31-180 days IR:* 108 per 1000 PY 181-365 days-IR: *35 per 1000 PY* *366-730 days IR*: 17 per 1000 PY FL: *0-30 days-IR:* 140 per 1000 PY *31-180 days IR*: 55 per 1000 PY *181-365 days-IR:* 23 per 1000 PY *366-730 days IR:* 20 per 1000 PY	Vs. stage I/II: Stage III/IV: SHR 1.5 (1.1-2.1)	Vs. follicular lymphoma: DLBCL: SHR 1.5 (1.0-2.4)	Chemotherapy vs no: SHR 7.6 (4.7-12.3)

Lung	Chew [87] 2007 N = 91 933	Population based, Californian cancer registry+Californian discharge registry.	1993-95 + 1997-99	*0-6 month rate of VTE:* 7.2 per 100 pers. *7-12 month rate:*2.4 per 100 pers. *2-year ci:* 3.4 %	For non-small cell type: Vs localized: Regional: HR 1.9 (1.6-2.2) Metastatic: HR 4.0 (3.4-4.6)	Vs. squamous cell carcinoma: Adenocarcinoma: HR 1.9 (1.7-2.1) Large cell carcinoma: HR 1.2 (1.0-1.4) Unspecified: HR 1.2 (1.1-1.4)	Lung-related surgery vs no: HR 0.7 (0.6-0.8)
	Walker [86] 2016 N = 10 598	Linkage of three UK databases. (in case of surgery within 90 days before cancer diagnosis, person time commenced at date of surgery)	1997-2007	*0-6 month IR:* 76.7 per 1000PY *6-12 month IR:* 35.6 per 1000 PY *>12 months IR:* 15.8 per 100 PY	Vs. Local: Regional: HR 1.3 (0.7-2.3) Distant: HR 1.8 (1.1-2.9)	Vs. well differentiated: Moderately: HR 1.3 (0.6-2.9) Poorly: HR 1.6 (0.7-3.4)	Chemotherapy vs no: HR 2.4 (1.6-3.5) Radio therapy vs no: HR 0.9 (0.1-1.1)
Prostate	Ording [81] * 2015 N = 44 035	Danish nationwide prostate cancer study.	1995-2011	1-year ci: 0.7% 5-year ci: 2.2%	Vs. D'Amico low risk: D'Amico high risk: HR 1.6 (0.9-2.8)	NA	NA
	Hemelrijck [80] 2010 N = 76 600	Swedish nationwide prostate cancer cohort study.	1997-2007	Overall SIR of VTE in prostate cancer compared with general male population: 1.9%	*SIR of DVT in curative treated patients aged 65-74 vs. <u>general cohort:</u>* localized tumors: 1.3 (1.0-1.8) Intermediate tumors: 1.8 (1.1-3.0) Metastatic tumors: 3.9 (0.8-11.4)	*SIR of PE in curative treated patients <u>aged 65-74 vs. general cohort:</u>* localized tumors: 1.9 (1.6-2.4) Intermediate tumors: 2.3 (1.5-3.4) Metastatic tumors: 3.5 (0.7-10.2)	*Absolute risk difference in prostate cancer aged 65-74 compared with general male <u>cohort:</u>* Endocrine: 3.6(3.4-4.0) Curative: 0.8 (0.5-1.2) Surveillance: 0.25(-0.01-0.5)

Abbreviations: 1-KM; 1 - Kaplan-Meier estimate (death treated as censoring event); ci, cumulative incidence (death treated as competing risk); CVC, central venous catheter; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; IR, incidence rate; pers, persons; SHR, sub-distributional hazard ratio; SIR, standardized incidence ratio.
*indicates use of competing risk framework in both absolute and relative risk estimates.

Cancer recurrence or additional cancer

The risk of VTE in cancer patients who are diagnosed with a second primary cancer or have relapse of the first one is not investigated to the same extent as the association between the first cancer diagnosis and VTE. A few studies have reported some information regarding the incidence or impact of additional or recurrent cancer in studies of cancer-associated VTE.

In the study concerning ovarian cancer by Rodriguez et al., 5% of those with VTE had a second primary malignancy, while in the study by Simkovic et al. 24% of CLL patients with VTE were registered with a second malignancy.[132,189] Among 516 patients with colorectal cancer, the overall VTE risk was low, however the HR for VTE was 13.0 (95% CI 4.4-38.7) in case of colorectal cancer recurrence.[155]

Multiple active cancers is associated with higher risk of VTE recurrence. In a population of VTE patients, the HR of recurrent VTE in case of multiple cancer types was 5.1 (95% CI, 2.2-11.5) compared with cancer free VTE patients, while for cases with a single cancer the HR of recurrence was 2.6 (95% CI, 2.0-3.4).[194] Chee at al. investigated VTE recurrence predictors in a cohort of patients with cancer-associated VTE.[94] In a multivariate model, the HR of recurrence was 1.8 (95% CI, 0.9-3.6) in case of multiple active cancers.

These sparse observations indicate that cancer recurrence or exposure to secondary malignancy may be associated with the risk of VTE. However, this topic needs further investigation.

Biomarkers for cancer-associated VTE

Several biomarkers have been proposed for prediction of VTE in cancer patients, especially thrombocytosis, leukocytosis and anemia have been correlated to VTE in cancer populations.[195-197] However, many studies on single cancer types reported either similar distribution of hemoglobin, thrombocyte and leukocyte count in patients with VTE compared with patients without VTE[198,199] or no effect on relative estimates.[86,150,156,162] Furthermore, the effects of thrombocytosis, leukocytosis and anemia was surpassed by D-dimer levels and P-selectin in the Vienna CATS study.[190,200] Nationwide registries usually do not include continuous laboratory variables, and large population based studies concerning the role of laboratory parameters in cancer-associated VTE are thus lacking in the existing literature.

CANCER TREATMENT RELATED FACTORS

Cancer treatment encompass several modalities as surgery, radiation therapy, chemotherapy, endocrine treatment, immunomodulatory agents and combinations hereof – sometimes administered through indwelling catheters. Furthermore, supportive treatment with blood transfusion and use of erythropoiesis stimulating agents are provided

in some occasions. These factors can influence the risk of VTE in cancer patients.

Cancer patients exposed to **chemotherapy** have a 6-16 - fold higher risk of VTE compared with the background population,[24,201] while the risk is about 2-fold higher for cancer patietns not exposed to chemotheraphy.[28,69,149,186] The risk of VTE was 1.5-10 - fold higher for those exposed to chemotherapy compared with unexposed in most of the studies reviewed in Table 2.[86,150,153,154,158,160,162] In general, cancer patients with a **central venous catheter** have a 6-7% risk of VTE. The risk of VTE is 2-fold higher in case of peripherally inserted catheters compared with centrally inserted catheters.[202] The risk of VTE was a higher in AML patients with a central venous catheter for administration of chemotherapy than in those with no central venous catheter, particularly the risk of upper extremity thrombosis (HR 3.4 [95% CI, 1.8-6.5]).[152]

In the recently published study by Blix et al.,[27] the risk of VTE was similar in the 6 months before cancer diagnosis and in the initial 6 months after the cancer diagnosis when accounting for the competing risk of death in the regression analysis. Based on this observation, the authors speculate that the risk of VTE in cancer is more related to the cancer itself rather than chemotherapy and other factors related to diagnosis and treatment of cancer, however they were unable to demonstrate this due to lack of information about these factors. Other recent studies including information about chemotherapy showed either significantly lower risk of VTE during exposure to chemotherapy[203] or no association between chemotherapy and the risk of VTE.[132,155] These studies are small but nonetheless indicate that the effect of chemotherapy does not simply increase the risk of VTE in all cancer types.

Endocrine treatment increases the risk about 2-fold in breast cancer patients.[153,160] In the study by van Hemelrijck et al., the absolute risk of VTE was higher in prostate cancer patients compared with the general population, however only for prostate cancer patients on endocrine treatments (absolute risk difference for VTE was 3.7, 95% CI 3.0-4.3) while the difference in VTE risk for prostate cancer patients in surveillance and the general population was 0.3 (95%CI, -0.01-0.5).[80] This indicates that the disease does not contribute as much as the endocrine treatment to the risk of VTE in prostate cancer. Several studies have shown that myeloma patients treated with **immunomodulatory therapy** in combination with dexamethasone have a considerable risk of VTE, and routine thromboprophylaxis is therefore recommended for this group of patients. [204-206]

The effect of **radio therapy** on the risk of VTE is assessed in a few studies and there is no consistent, strong association with VTE,[28,200] which is also reflected in the varying effect estimates in Table 2.[28,86,150,158,160] Exposure to **erythropoietin** (OR 1.3-1.6)[161,207] and **blood transfusion** (OR 1.6-2.3)[161,208] is associated with increased risk of VTE in cancer patients.

Cancer patients have a 4-fold higher risk of fatal PE in association with general **surgery** compared with non-cancer surgical patients.[209] However, if confined to cancer

surgery (e.g. mastectomy in breast cancer), lower risk of VTE after surgery is seen in many studies (HRs 0.4 -0.7).[87,88,187,189] In these studies, cancer surgery is a proxy for less extensive cancers in typically younger patients with better performance status.

In summary cancer itself increases the risk of VTE, however the impact is difficult to separate from contributions from cancer treatment modalities and supportive care. Central venous catheters, endocrine and immunomodulatory treatments increased the risk of cancer-associated VTE most consistently in the reviewed literature.

PREDICTION OF VTE IN CANCER PATIENTS

The risk of VTE in cancer patients is influenced by intrinsic factors, provoking factors and cancer specific factors. Several models for assessment of the risk of VTE in single cancer types[210-212] and in non-hospitalized cancer patients have been developed during the last decade including a selection of these factors. The Khorana score[195] was the first risk assessment model upon which several subsequent risk assessment model have been built[213-216] (Table 3). The risk assessment models all include cancer specific factors. Definitions of "very high risk" and "high risk" cancer types vary by study population, but all models except the COMPASS-CAT[217] includes cancer type as an item. Also, biomarkers were included in all the models. The COMPASS-CAT[217], the TiC-Onco[218] and the simple Vienna CATS[219] included only one biomarker, and the remainder included more than one. All models but the simple Vienna CATS included intrinsic factors. A history of VTE was only included in ONCOTEV[216] and COMPASS-CAT.[217] Items related to the treatment of cancer were included in several of the models, however for the Khorana model and the models based hereon restricted to treatment with erythropoietin. Only two models included information about anti-cancer treatment (PROTECHT and COMPAS-CAT) [214,217] Time since cancer diagnosis was only included in the COMPASS-CAT model.

External validation of the risk assessment models can confirm their usefulness in the clinic and in trials, however many of the models perform sub optimally.[77,212,220-225] Recently, the Khorana score, the Vienna CATS, PROTECHT and CONKO models were validated in a prospective, multinational cohort study. [35] The latter three tested models are modifications of the Khorana score (Table 3). In brief, the validation study showed that all four models performed poorly, however the Vienna CATS and the PROTECHT models were useful for discriminating between cancer patients with high risk of VTE and cancer patients with low risk of VTE. In another recent validation study, however smaller, the Khorana score, PROTECHT, CONKO and COMPASS-CAT models were tested in a cohort of 118 lung cancer patients among whom 20 VTEs occurred. [224] The sensitivity of a high COMPASS-CAT was 100% while for the other three models it was 10%-55%.

Development of new or refinement of current risk assessment models will presumably continue. The risk of VTE in cancer differs markedly by both cancer specific factors,

cancer related treatments, intrinsic factors, time factors and events that occur after the cancer diagnosis, and the effect of these factors maybe even vary within narrow periods. This complexity will probably increase as we learn more and maybe reach an extent where one risk assessment model does not fit all cancer types.

Table 3. Models for risk assessment of cancer-associated VTE, included items categorized by source.

	Name of risk assessment models	Khorana score[195]	Vienna CATS[213]	PROTECHT[214]	CONKO[215]	ONCOTEV*[216]	COMPASS-CAT[217]	TiC-Onco[218]	Simple Vienna CATS[219]
	Publication year	2008	2010	2012	2013	2017	2017	2018	2018
Cancer specific	Very high risk cancer type (stomach, pancreas)	x		x	x	(x)		x	x
	Very high risk cancer type (stomach, pancreas, brain)		x						
	High risk cancer type (lung, lymphoma, bladder, testicular, gynecologic)	x		x	x	(x)		x	
	High risk cancer type (lung, lymphoma, bladder, testicular, gynecologic, myeloma, kidney)		x						
	High risk cancer type(lung colorectal, esophagus, kidney, lymphoma, bladder, uterus, ovary, other								x
	Intermediate/Low risk cancer type (breast, prostate, other)								x
	Cancer stage					x	x	x	
	Macroscopic vascular/lymphatic compression					x			
Biomarkers	Anemia (Hgb <100g/L)/ use of EPO	x	x	x	x	(x)			
	Thrombocyte count > $350*10^9$/L)	x	x	x	x	(x)	x		
	Leukocyte count > $11*10^9$/L)	x	x	x	x	(x)			
	Soluble P-selectin ≥ 53.1 ng/mL		x						
	D-dimer ≥ 1.44 µg/mL		x						
	Continuous concentration of D-dimer								x
	Genetic risk score							x	
Intrinsic factors	BMI ≥ 35 kg/m²	x	x	x		(x)			
	BMI ≥ 25 kg/m²							x	
	BMI ≥ 30 kg/m²						x		
	WHO-performance status ≥2				x				
	Family history of VTE							x	
	Previous VTE					x	x		
	Previous AMI/stroke						x		
	Cardiovascular risk factors						x		
	Recent hospitalization for acute medical illness						x		
Treatment	EPO	(x)	(x)	(x)	(x)	(x)			
	Platinum -based chemotherapy			x					
	Gemcitabine			x					
	Endocrine treatment (HRP breast cancer)						x		
	Anthracycline						x		
	Central venous catheter						x		
	Time since cancer diagnosis < 6 months						x		

Abbreviations: Hgb; hemoglobin, EPO; erythropoietin, BMI; body mass index, WHO; World health organization, AMI; acute myocardial infarction, HRP; hormone-receptor positive
*Khorana score > 2, indicated by (x) plus the items marked by x.

HYPOTHESES AND AIMS

The incidence of VTE according to cancer stage has been investigated in large population-based studies. However, the incidence of VTE has been assessed either for cancer stage with no regard to cancer type, or in single types of cancer per study. This leaves little or no opportunity to assess whether the impact of cancer stage might differ by cancer type. The null hypothesis of study 1 was that the risk of VTE was similar across initial cancer stage. The aim of study 1 was accordingly:

Study 1:
To investigate the incidence of VTE according to initial cancer stage in different types of solid cancer in a large population-based cohort.

The risk of VTE in hematological cancers have been investigated in studies combining the different types of hematological cancer in one group, or in studies concerning only one or a few similar types of hematological cancer. Current knowledge of which types of hematological cancers contributes to the overall high risk of VTE in the group of hematological cancer is sparse. The null-hypothesis of study 2 was that the risk of VTE was similar across subtypes of hematological cancers. The aim of study 2 was hence:

Study 2:
To investigate the incidence of VTE according to type of hematological cancer by comparison with cancer free reference subjects matched on age and gender in a population-based cohort.

The chronic nature of some cancer types and recent improvements in cancer treatments leads to increasing numbers of individuals who live with chronic cancer or survive acute cancer types. The risk of VTE in cancer patients has typically been investigated in close proximity to cancer diagnosis. The null-hypothesis of study 3 was that the risk of VTE attenuated to levels observed in the general population for all cancer types. The aim of study 3 was therefore:

Study 3:
To investigate the risk of VTE in cancer patients who survived to two years after cancer diagnosis without VTE compared with cancer-free reference subjects in a population-based cohort.

In study 2 we observed surprisingly high IR of VTE among CLL patients. Two small studies have also reported high risk of VTE in CLL, however the impact of CLL prognostic factors and treatments was not exhaustively investigated. No prior studies have assessed the validity of VTE diagnoses in CLL patients. The null hypothesis of study 4 was that the risk of VTE was similar in CLL patients with regard to both patient specific characteristics and CLL prognostic factors. The aims of study 4 were:

Study 4:
To assess the validity of VTE diagnoses among CLL patients and to investigate if the risk of VTE was associated with CLL treatment periods, patient specific and CLL prognostic factors, and if VTE was associated with the mortality of CLL patients.

METHODS

STUDY POPULATIONS

Study 1-3 were based on data from a large Danish-Norwegian population-based database - the STAC cohort. The main research question in study 4 was investigated based on data from all Danish CLL patients, while the validation of VTE diagnosis codes within study 4 was based on a local Danish CLL cohort. These three study populations and the sources of data herein are further described below.

THE SCANDINAVIAN THROMBOSIS AND CANCER (STAC) COHORT

Study 1-3 are based on data from the STAC cohort, which was established in 2011 with the main objective to investigate VTE in cancer patients. The STAC cohort consists of data collected in three large population-based cohorts established in the mid-1990's in order to investigate the epidemiology of cardiovascular and chronic diseases and health related lifestyle (Tromsø and HUNT) and associations between lifestyle factors and cancer plus chronic diseases (DCH) in the populations.[226-228] Inhabitants of the municipality of Tromsø and Nord-Trøndelag County (HUNT) in Norway, and urban areas of Aarhus and Copenhagen in Denmark (DCH), respectively, were invited to participate. The study entry periods and dates for complete follow-up varied a little in the three original cohort studies, as did the age of the invited participants (Table 4). The earliest study entry was December 1993 in the DCH study, and the most recent last date of follow-up was for VTE was December 2012 in the Tromsø study. Study participants with cancer or VTE before study entry in the three original cohorts were excluded before merging of the three original cohorts. The STAC cohort accordingly includes person-time data of 144 952 subjects with a median age at study inclusion of 53 years and a minor overweight of female participants (52.6%). Information about socio-economic conditions, health status and anthropometric measures were obtained at baseline in all three original cohorts. All VTEs were objectively confirmed, as described below. Further details of the STAC cohort are published.[66]

Table 4. Overview of the three cohorts contributing with data to the STAC cohort.

Original cohort	No. of participants	No. excluded from merging due to previous cancer or VTE	Age of participants at study entry (years)	Study enrollment	Last date of follow-up for		
					VTE	Cancer	Death or migration
DCH	57 053	1040	50 - 64	1993 – 1997	30.04.2008	30.04.2008	01.07.2013
Tromsø	27 158	1065	25 - 97	1994 – 1995	31.12.2012	31.12.2012	31.12.2012
HUNT	65 237	2391	19 – 103	1995 – 1997	31.12.2007	31.12.2009	31.12.2010

THE DANISH NATIONAL CHRONIC LYMPHOCYTIC LEUKEMIA REGISTRY

Study 4, concerning VTE in CLL patients was based on data from the Danish National CLL Registry where clinicopathological characteristics of all patients diagnosed with CLL in Denmark since 2008 have been registered. In addition to the date and ICD-10 diagnosis code, also the clinicopathologic features, date and type of first line treatment and response hereto is recorded. The CLL-treating hematologists in the nine hematology centers in Denmark prospectively collect these data.[229] The coverage of the CLL registry was >99.0% in the years 2012 – 2014, for 2015 it was 98.7%. The data completeness was 98.7%, 92.7%, 84.2% and 59.6% for patients registered in 2012, 2013, 2014 and 2015, respectively. Regular cross-referencing with the Danish National Patient Registry (DNPR) ensures continuous updates and ongoing improvement of the data completeness in the Danish National CLL Registry.[230]

The Danish National Patient Registry and the Civil Registration System

The Danish hospitals are tax-funded based on each patient contact and the diagnoses and procedures in association hereto. This information is gathered in the DNPR for this purpose.[231] The DNPR was established in 1977. Until 1995, person level data from each hospitalization was registered and from 1995, ambulatory contacts were included in addition. More than 99% of all contacts to the Danish health care system is captured in the DNPR.[232] Patients cannot have a contact with the Danish health care system without registration by the civil personal registration number in the DNPR. The civil personal registration number is a unique ten-digit numeral code assigned to every Danish resident at birth or immigration by the Danish Civil Registration System that keeps track of vital status, moving within Denmark as well as in and out of the country.[233] The civil personal registration number is used for linkage of informations from all Danish registries at a person level.

LOCAL DATASET FROM AALBORG UNIVERSITY HOSPITAL

The validation of VTE diagnosis codes among CLL patients was based on a local dataset containing the patients diagnosed with CLL from 2008 to 2016 at Aalborg University Hospital. The regional data protection agency approved the study (project id-number 2017-93). The treatment and care of CLL patients from the North Denmark Region have been centralized at the Department of Hematology at Aalborg University Hospital since 2008. The medical records, biochemical tests and diagnostic images plus other clinical and para-clinical information of all patients treated in the North Denmark Region are embedded in the electronic patients system Clinical Suite operated by CSC Scandihealth. In Clinical Suite, both action and secondary diagnoses plus procedures related to diagnostics and treatments at person level are registered by use of the civil registration number, and subsequently reported to the DNPR.[231]

SOURCES OF INFORMATION

CANCER DIAGNOSIS

In the STAC cohort (study 1-3), information about cancer type, morphology, stage and date of diagnosis were obtained by linkage to the National Norwegian Cancer Registry for study participants from the Tromsø and HUNT studies and from the Danish National Cancer Registry for subjects in the DCH study.

The Danish National Cancer Registry has collected data about cancer cases since 1943, but in 1987 registration of cancer became mandatory by law. The Danish National Cancer registry used the ICD-O-1 (International Classification of Diseases for Oncology, 1st edition) codes from 1978 to 2003. From 2003 and onwards, the ICD-O-3 (International Classification of Diseases for Oncology, 3rd edition, 1992) system was used for morphology and topography and the ICD-10 (International Classification of Diseases, 10th edition, 1990) codes was used for the disease classification. All the ICD-O-1 codes from previously registered cases were converted to ICD-O-3 and ICD-10 codes.[234]

The Norwegian National Cancer Registry has systematically collected data on cancer cases since 1953, where notification became mandatory by law. The morphology and topography of tumors has been coded by the ICD-O-2 (International Classification of Diseases for Oncology, 2nd edition, 1992) from 1993. The ICD-O-3 has been used for non-solid tumors since 2002.[235] Topography has been converted to ICD-10 terminology from 2005 and onwards. [236]

In summary, the National Norwegian and Danish Cancer registries both provide ICD-10 and ICD-O-3 codes.[234,236]

In study 4, we received information about the CLL diagnosis from the Danish National CLL Registry, which is cross-referred to the DNPR as described in the paragraph concerning the Danish National CLL Registry. The dataset from the Danish National CLL Registry was transferred to a server at Statistics Denmark for linkage to other national registries. Information about diagnosis date and type of cancer besides CLL (ICD-8: 140-209, except 173.x and ICD-10: CC00-96) was retrieved from the DNPR by linkage of the CLL patients' civil personal registration numbers.

CANCER STAGE

The exposure of interest was cancer stage (i.e. the extent to which the cancer has developed by spreading) in study 1. Cancer stage was described differently in the national Danish and Norwegian cancer registries: Two national principal systems including a "local", "regional", and "distant metastasis" nomenclature for description of cancer stage for solid tumors were used. In Norway, the Norwegian principal classification

system with 12 principal codes for disease extension was used throughout the study period for subjects in the STAC cohort.[237] In Denmark, the Danish principal classification system was used until 2004, except for the gynecological and colorectal cancers, where cancer stage has been coded by FIGO and Duke's classifications, respectively until 2004. In 2004, the TNM Classification of Malignant tumors was introduced in the Danish cancer registry.[238] Hence, in total five cancer stage classification systems had to be aligned in a common cancer stage variable in the STAC cohort in order to describe all cancer-exposed subjects by the "local", "regional", and "distant metastasis" nomenclature. Three algorithms for this alignment were defined, as listed in Appendix 1.

The International Cancer Benchmark Partnership was established in order to compare cancer survival in six high-income countries, proposing an algorithm for conversion of TNM, FIGO and Duke's cancer stages for colorectal, lung, breast, fallopian tube and ovary cancers.[239] We adapted to this algorithm for relevant solid tumors. Types of cancers not covered by International Cancer Benchmark Partnership were mapped to the nomenclature "local", "regional" and "distant metastasis" guided by recommendations from the American Cancer Society and National Cancer Institute (http://www.training.seer.cancer.gov/ and http://www.cancer.org/cancer/index). However, the stages we refer to in the STAC cohort should not be interpreted as Surveillance, Epidemiology and End Results Summary Staging 2000 (SEER SS2000) stages,[240] though they are comparable.

The Norwegian cancer stage data were mapped to the principal local, regional and distant metastasis nomenclature by Algorithm 1 (Figure 2).

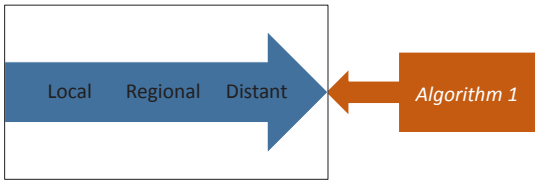

Figure 2. Norwegian cancer stages are classified by a Norwegian, principal system.

Cancer stages of Danish patients diagnosed before 2004 are described by codes 0-9, A and B, and the code covers the principal Danish classification plus FIGO and Duke's stages. Three variants of algorithm 2 was necessary since the same code for cancer stage could cover both FIGO, Duke and principal stages (Figure 3). Information on extent of cancer in cases after 2004 are coded in the TNM classification. Algorithm 3 hierarchically mapped the variables M, N and T for each type of solid cancer (Figure 3). For details of the algorithms, see Appendix 1.

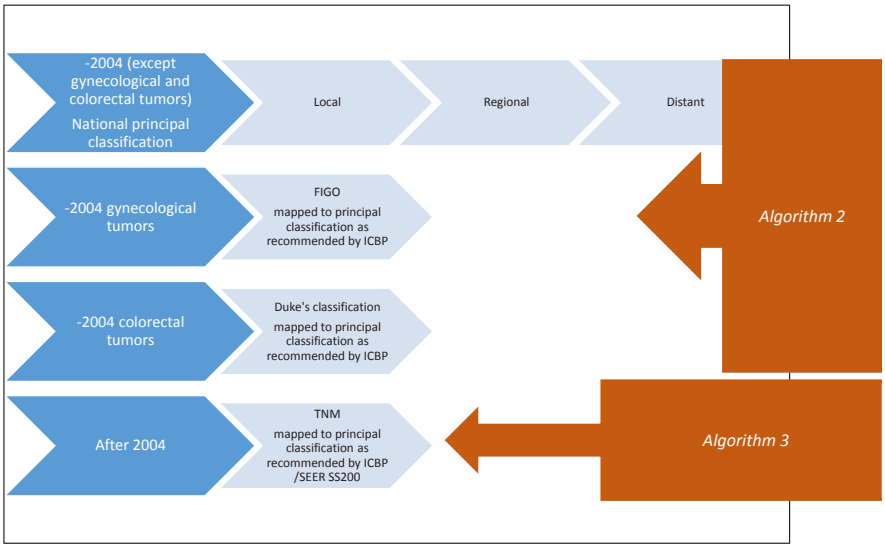

Figure 3. Danish cancer stages before and after 2004. ICBP, International Cancer Benchmark Partnership.[239]

SOURCES OF VTE INFORMATION

Information about VTE in study 4 and for the DCH subset of the STAC cohort (study 1-3) was retrieved from the DNPR. In the DCH, all VTE events registered in the DNPR were validated by systematic review of medical journals and diagnostic tests. Only VTEs associated with typical symptoms and confirmed by diagnostic tests were included in DCH and hence in the STAC cohort. Additionally, fatal events identified in the Danish National death Registry confirmed by autopsy were included.[41]

In the Norwegian part of the STAC cohort, VTEs were identified in local registries at the sites of the HUNT and the Tromsø study, respectively, and subsequently validated. In the HUNT study, information about VTE was retrieved from local discharge registries and radiology procedure registries at the three hospitals in Nord-Trondelag. Symptomatic VTEs that was confirmed by imaging diagnostics and treated were included in the HUNT study and thus in the STAC cohort.[6] In the Tromsø study, VTEs were identified in the discharge diagnosis registry, radiology procedure registry and autopsy registry at the University Hospital of North Norway. VTE was confirmed if a symptomatic VTE diagnosed by a physician was confirmed by diagnostic imaging and treated with either anticoagulation or vascular surgery.[241]

In study 4, the ICD-10 codes for VTE (I26, I80.1-I80.9) were identified by direct linkage to the CLL patients' civil personal registration numbers in the DNPR through Statistics Denmark. We subsequently excluded events solely coded in the emergency

departments in case neither subsequent anticoagulation medicine was prescribed nor subsequent ward or ambulatory VTE coding was registered.

Validation of VTE diagnoses in CLL patients

The positive predictive value and the sensitivity of VTE diagnosis among CLL patients was investigated by systematic review of the medical journals of all CLL patients treated at Aalborg University Hospital from 2008-2016. When clinical signs and diagnostic tests confirmed VTE, a registered VTE was considered valid, while VTE was ruled out in cases where accomplished diagnostic tests did not confirm the diagnosis. Medical records for the CLL patients without a registered VTE were systematically reviewed for unregistered valid VTEs. The positive predictive value was calculated as the proportion of validated VTE divided by the total number of VTEs registered in the DNPR. The sensitivity was calculated as the proportion of true positive VTEs registered in DNPR divided by the total number of validated VTE.

ANTICOAGULATION MEDICATION

Information about anticoagulation in study 4 was retrieved from the Danish National Prescription Registry. Expenses to medicine is to some extent reimbursed in Denmark, and the Danish National Prescription Registry holds information about ATC codes of prescribed and purchased medicine, doses and package sizes.[277] By use of the civil personal registration number, we identified which CLL patients were exposed to anticoagulation medication. In periods of hospitalization identified by linkage to the DNPR, we classified subjects exposed to anticoagulation in the immediate period before hospitalization as anticoagulated during hospitalization.

STATISTICS

STUDY 1

Study entry was the date of cancer diagnosis, and participants were followed until VTE, death, emigration or administrative censoring (i.e. last date of follow-up for VTE as described in Table 4). Incidence rates of VTE were calculated as number of VTEs per 1000 PY for localized disease, regional spread and distant metastasis in ten distinct solid cancer types. To assess the impact of initial cancer stage on the risk of VTE on an absolute scale, incidence rate differences (IRD) were calculated. The cumulative incidence of VTE according to initial cancer stage was depicted treating death as competing risk. Hazard ratios for VTE according to initial cancer stage were calculated in Cox proportional regression models with age and sex (in the gender unspecific cancer types) included as potential confounders.

STUDY 2 AND 3

Matching

The cancer exposed subjects in study 2 and 3 were matched on age, gender and original cohort to five reference subjects within the STAC cohort at the date of hematological cancer diagnosis and the 2-year anniversary for the cancer diagnosis, respectively. The latter matching criteria was due to different end of follow-up for VTE in the three original cohorts (Table 4). References were free of VTE and cancer at the index date and their chances for selection as reference were proportional to their contribution to person-time at risk (i.e. incidence density sampling). By incidence density sampling of reference subjects unexposed at the index date, references are time-matched to cases and the incidence rate ratio can be directly estimated. In other words, a sample of person-time rather than a set of persons acts as references. [242,243]

Follow-up and association measures

In study 2, subjects were followed from the hematological cancer diagnosis date/index date to VTE, death, emigration, last follow up for VTE and for reference subjects prospective first cancer diagnosis. IR and IRR of VTE were calculated for the total study period, for first year after study entry and for the period from one to five years after the study entry.

In study 3, subjects in the STAC cohort who had cancer after enrollment were matched to their reference subjects 730.50 days after the cancer diagnosis (if alive and free of VTE at this date). Follow-up commenced at this date and ended in case of VTE, end of follow-up for VTE, emigration or death. Additionally, for the reference subjects, a prospective first cancer diagnosis would terminate follow up, while a prospective second cancer diagnosis would for the cancer exposed subjects. In case the reference subjects got cancer after the index date and survived at least 730.50 days, they were included as cancer exposed subjects and 5 reference subjects were identified. IRs, IRDs and incidence rate ratios (IRR) were calculated for the entire follow-up (i.e. ≥ 2 years after the cancer diagnosis) and three years after study entry (i.e. ≥ 5 years after the cancer diagnosis).

STUDY 4

In study 4, the subjects were followed from the date of their CLL diagnosis until VTE, death, emigration or last follow-up for VTE (December 31, 2015). Prospective cancer after the CLL diagnosis was treated as a time-varying exposure. Cumulative incidences of VTE were calculated according to CLL prognostic factors and second primary cancer after the CLL diagnosis in analysis treating death and death plus second primary cancer after the CLL diagnosis as competing risks in order to illustrate the possible overestimation of VTE if second primary cancer was ignored as competing risk. In analysis of mortality, VTE was treated as a time-varying exposure and

also as competing risk for death among those not (yet) exposed to VTE. The impact of patient specific and CLL prognostic factors on the risk of VTE was investigated in multivariate Cox models.

ETHICS

The DCH, HUNT and Tromsø studies were approved by the respective National scientific ethics committees. Study participants gave informed written consent to linkage by their civil personal registration number to national health registries for research purposes.[226-228] The Danish and Norwegian Data Protection Agencies approved merging of the three original cohorts in the STAC cohort, further approval was hence not required for study 1, 2 and 3.[66] The use and linkage of data in study 4 was approved by the Danish Data Protection Agency (2008-58-0028, internal reference 2017-93).

RESULTS

STUDY 1: IMPACT OF INITIAL CANCER STAGE ON THE INCIDENCE OF VTE

Previous studies where the impact of cancer stage on the risk of VTE was investigated either combined several cancer types or investigated a single cancer type leaving little option to evaluate if the effect of cancer stage was similar in different cancer types. In study 1[244], the impact of initial cancer stage in different cancer types was investigated by comparing the risk of VTE in localized cancer with regional spread and distant metastasis in ten distinct cancer types based on data from the STAC cohort.

In total 10 583 participants in the STAC cohort were diagnosed with either lung, colorectal, upper gastrointestinal, pancreatic, breast, prostate, bladder, kidney, uterine or ovarian cancer. The cancer was localized at the time of diagnosis for 38% of the patients, for 30% it was regionally spread, 17% had distant metastasis while in 14% the initial cancer stage was actively coded "unknown" in the respective National Cancer Registries. Three hundred and thirty-five VTEs occurred in the study period, 54% within the first year after the cancer diagnosis.

The impact of initial cancer stage on the risk of VTE varied considerably by cancer type and time since cancer diagnosis. The IRD of VTE in distant metastatic cancer was larger than zero compared with localized disease in most cancer types in the first year after the cancer diagnosis (i.e. the IR of VTE was higher in distant metastasis compared with localized disease), but varied from 3.7 (95% CI, -7.0 to 15.2) more VTEs per 1000 PY in distant metastasis compared with localized disease in prostate cancer to 187.0 (95% CI -6.7 to 380.8) in pancreatic cancer. (Figure 4) The IRD of VTE in regional spread lung, colorectal, upper gastrointestinal, pancreatic, uterine and ovarian cancer was also larger than zero compared with localized disease in the first year after the cancer diagnosis, highest in uterine cancer (IRD 37.6, 95% CI -23.7 to 99.0). In breast however, the IRD was close to zero (i.e. the IR of VTE in regional spread and localized disease were similar). Most of the VTEs that contributed to the IRDs of VTE in regional spread and distant metastasis compared with localized disease in the 5-year period after the cancer diagnosis occurred during the first year after the cancer diagnosis.[244]

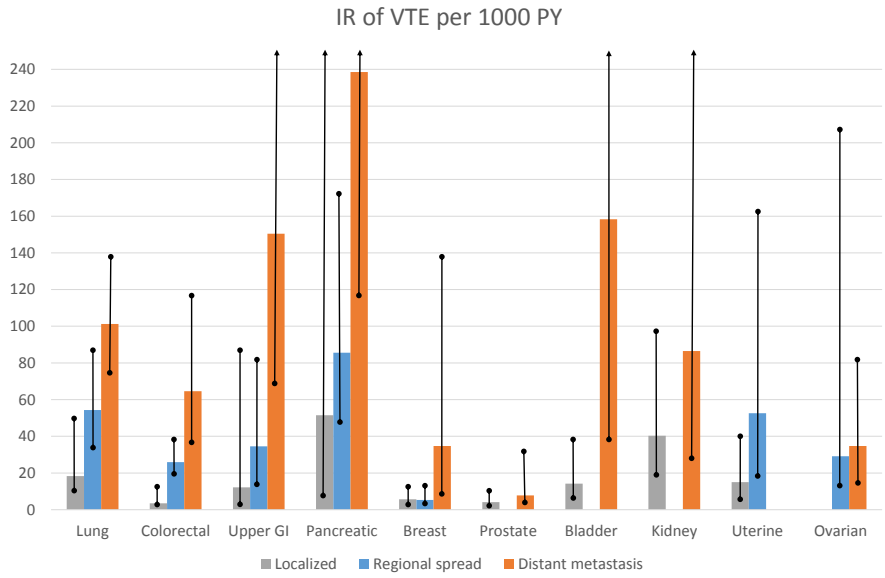

Figure 4. Incidence rates of VTE per 1000 PY according to initial cancer stage for ten cancer types 0-1 year after the cancer diagnosis.

Age and gender adjusted HR for VTE within the first year after cancer diagnosis in distant metastasis varied considerably by cancer type, lowest in prostate cancer (HR 1.5, 95% CI 0.3-8.3) and highest in colorectal cancer (HR 16.5, 95% CI 3.6 -74.6) (Table 5). The HRs of VTE were lower in general in regional spread cancer, lowest in breast cancer (HR 0.9, 95% CI, 0.3-3.1) and highest in colorectal cancer (HR 7.1, 95% CI 1.7-30.1).[244]

Table 5. Hazard ratios of VTE for regional spread cancer and distant metastasis compared with localized disease. Modified from [244].

	HR (95% CI) 0-1 year	HR (95% CI) 0-5 years
Regional spread vs. localized		
Lung	2.8 (0.9 - 8.3)	2.6 (1.1 - 6.2)
Colorectal	7.1 (1.7 - 30.1)	4.4 (1.8 - 10.4)
Upper GI	2.5 (0.3 - 21.2)	0.9 (0.2 - 4.0)
Pancreatic	1.4 (0.2 - 11.2)	1.7 (0.2 - 13.4)
Breast	0.9 (0.2 - 3.1)	1.4 (0.6 - 3.2)
Prostate	-	1.0 (0.3 - 3.6)
Bladder	-	2.0 (0.5 - 7.3)
Uterus	3.3 (0.7 – 15.1)	4.9 (1.4 - 17.2)
Ovary	-	1.5 (0.1 - 25.2)
Distant metastasis vs. localized		
Lung	4.8 (1.7 - 13.7)	4.1 (1.8 - 9.4)
Colorectal	16.5 (3.6 – 74.6)	10.5 (4.0 - 27.8)
Upper GI	9.1 (1.1 - 78.8)	4.0 (0.9 - 17.3)
Pancreatic	4.3 (0.5 - 35.7)	4.9 (0.6 - 40.6)
Breast	5.4 (1.1 - 27.1)	9.9 (3.4 - 29.0)
Prostate	1.5 (0.3 - 8.3)	2.1 (0.9 - 5.0)
Bladder	7.6 (1.3 – 46.0)	14.9 (2.5 - 90.0)
Kidney	1.7 (0.4 - 7.4)	3.1 (0.9 - 10.9)
Uterus	-	6.5 (0.7 - 57.9)
Ovary	-	4.5 (0.5 - 37.5)

STUDY 2: EPIDEMIOLOGY OF VTE IN HEMATOLOGICAL CANCERS

Previous studies concerning VTE in hematological cancer covered either several types combined in one group or one or a few similar types of hematological cancer. In order to compare the associations with VTE for various types of hematological cancer, patients with six distinct types of hematological cancer were matched on age, sex and original cohort to reference subjects free of cancer in the STAC cohort in study 2.[245]

Selected references could get solid or hematological cancer along the study period, in which case they were either censored (n= 395) or shifted to contribute with person-time at risk in the hematological cancer exposed group (n=26) at time of cancer diagnosis.

During follow up, 30 VTEs were observed among 838 subjects exposed to hematological cancer in total. Twenty-one VTEs occurred among the 4190 references. In CLL, myeloma and aggressive lymphoma the IRs of VTE were considerably higher than in

reference subjects. In aggressive lymphomas the IR was however mainly higher in the first year after the diagnosis. The indolent lymphomas contributed to similar amount of person time at risk of VTE as the CLL patients. Despite this, only one VTE was observed in indolent lymphoma, resulting in an IR of VTE not significantly different from the reference subjects (Figure 5).

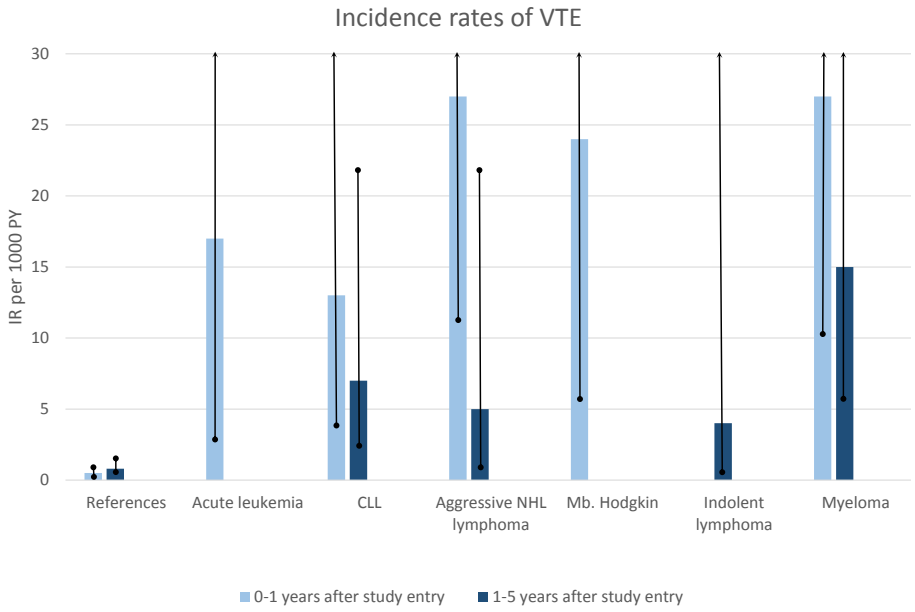

Figure 5. Incidence rates of VTE for by type of hematological cancer and associated 95% confidence intervals 0-1 year after the cancer diagnosis and 1-5 years after the cancer diagnosis.

STUDY 3: LONG-TERM INCIDENCE OF VTE IN CANCER

The risk of VTE in close temporal association with the cancer diagnosis has been extensively studied while the risk of VTE after possible attenuation of effects from cancer and associated treatments is sparsely investigated. In study 3,[246] we compared the incidences of VTE in cancer survivors (i.e. subjects alive and free of VTE two years after a cancer diagnosis) and reference subjects free of VTE and cancer at the index date based on data from the STAC cohort.

In total 7645 subjects were alive and free of VTE two years after their cancer diagnosis, where they entered this study. In total 110 VTEs occurred among the cancer exposed subjects, 44 of them were diagnosed later than five years after the cancer diagnosis.

Cancer exposed subjects had a higher IR of VTE than references, both in the entire study period and also when restricted to the VTEs that occurred later than five years after the cancer diagnosis. This was mainly caused by a sustained higher IR of VTE in the hematological cancers compared with reference subjects. For survivors of solid cancer types as prostate and colorectal cancer, the risk of VTE resembled the references subjects (Figure 6). In the solid cancer types, initial distant metastasis was associated with a 6-fold higher IR of VTE more than two years after the cancer diagnosis.[246]

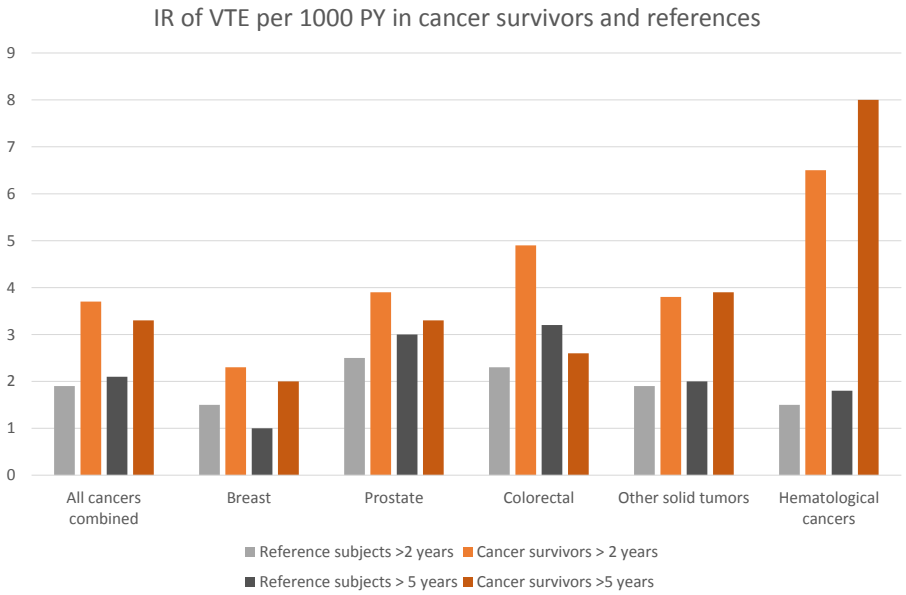

Figure 6. Incidence rates of VTE in cancer survivors and reference subjects by successive time from cancer diagnosis.

STUDY 4: VTE IN CHRONIC LYMPHOCYTIC LEUKEMIA

The etiology of VTE in CLL patients has not been thoroughly investigated, however a few studies indicated that the risk of VTE could be noticeably higher than in the background population. Some studies indicated that CLL patients had a considerable risk of second primary cancers, but it was not investigated if this was associated with the risk of VTE. In study 4,[247] we investigated the epidemiology of VTE in a Danish, national CLL cohort diagnosed in 2008-2015. Information concerning second primary cancers was included. The VTE diagnoses were validated in a local dataset covering 10% of the total study population.

VALIDITY OF THE VTE DIAGNOSES IN CLL PATIENTS

Medical journals from 469 CLL patients were systematically reviewed in the validation study. Thirty-two VTEs were coded in the DNPR. During the validation process, six additional VTEs were identified. Fifteen percent of the registered VTEs were not confirmed after review of medical journals and diagnostic tests. In five cases, VTE was classified as probable and in 28 cases, VTEs were confirmed. Fourteen were pulmonary embolisms and 22 deep vein thromboses, and in three of the cases, the deep vein thrombosis and pulmonary embolism were concurrent. Four (12.1%) of the validated VTEs were asymptomatic (i.e. diagnosed coincidentally because a CT scan was performed), three of which were registered in the DNPR. The positive predictive value of VTE diagnosis codes in DNPR was 84.4 % (95% CI, 67.2 - 97.4) while the sensitivity was 81.8% (95% CI, 64.5 - 93.0). In order to assess if a diagnosis of CLL influenced the validity of VTE diagnoses, we calculated the positive predictive value and sensitivity of VTEs that occurred after the CLL diagnosis. Twenty-two of the 33 validated VTEs occurred after the CLL diagnosis, the positive predictive value was 84.2% (95% CI, 60.4 – 96.6) and the sensitivity was 76.2% (95% CI, 52.8 - 91.8).

VTE IN THE DANISH CLL PATIENTS

We followed 3609 CLL patients for a median of 2.6 years. In total, 102 of the CLL patients had a VTE diagnosis registered after the CLL diagnosis. For ten of these, however, no subsequent ambulatory or ward coding of VTE was done, and no anticoagulation treatment was prescribed. These ten events were not included in the analysis due to questionable validity of the diagnosis. A considerable proportion of the CLL patients died during follow-up (20%) and 13% were diagnosed with a second primary cancer after the CLL diagnosis.

Sixteen of the 92 VTEs were diagnosed at or after a diagnosis of second primary cancer, and six of the 92 VTEs were diagnosed before a diagnosis of second primary cancer. Fifteen of the 92 CLL patients with VTE after the CLL diagnosis had a history of VTE. Three of the 15 VTEs preceding the CLL diagnosis could be the same as the one after the diagnosis of CLL because the time interval between the first registered VTE and the second was less than 30 days.

Exposure to VTE before the CLL diagnosis was associated with the highest risk of VTE followed by exposure to second primary cancer. A second primary cancer among CLL patients exposed to VTE before the CLL confounded this association, HR of VTE in previous VTE compared with no previous VTE however remained the highest observed in the study (Table 6).

Table 6. Hazard ratios of VTE by patients related factors and CLL specific markers. Modified from [247].

	HR, crude (95% CI)	HR, model 1 (95% CI)	HR, model 2 (95% CI)
Patient related factors			
Previous VTE			
No	Reference	Reference	Reference
Yes	5.79 (3.27 - 10.26)	5.29 (2.93-9.57)	5.09 (2.82 - 9.17)
Second primary cancer			
No	Reference	Reference	NA
Yes	3.72 (2.15 – 6.34)	3.65 (2.10-6.35)	NA
Anticoagulation*			
No	Reference	Reference	Reference
Yes	1.35 (0.65 – 2.08)	0.92 (0.43 – 1.95)	0.92 (0.44 – 1.95)
CLL prognostic markers			
IgHV mutational status			
Mutated	Reference	Reference	Reference
Unmutated	1.63 (1.06 - 2.54)	1.65 (1.07-2.57)	1.63 (1.05 - 2.53)
Not assessed	ND	ND	ND
FISH			
Deletion 13q14	Reference	Reference	Reference
Normal FISH	1.15 (0.61 - 2.14)	1.13 (0.60-2.13)	1.10 (0.59 - 2.06)
Trisomi 12	2.69 (1.42 - 5.10)	2.44 (1.26-4.72)	2.37 (1.23 - 4.59)
Deletion 11q / 17p	3.09 (1.67 - 5.72)	2.63 (1.28-5.40)	2.44 (1.20 - 4.99)
β_2-microglobulin, mg/L			
< 4	Reference	Reference	Reference
≥ 4	2.60 (1.55 - 4.37)	1.88 (1.08-3.27)	1.97 (1.14 - 3.41)
Not assessed	ND	ND	ND

Model 1: Adjusted for anti-coagulation treatment, WHO-PF, previous VTE, sex and age
Model 2: Adjusted for anti-coagulation treatment, WHO-PF, previous VTE, sex age and second primary cancer
*Adjusted for previous VTE, age and sex in model 1 and previous VTE, age, sex and second primary cancer in model 2

In interaction analysis, we found markedly higher effect of previous VTE on the risk of VTE after the CLL diagnosis in age groups >60 - ≤70 years, >70 - ≤80 and >80 years compared with ≤ 60 years. In analysis of previous VTE stratified by age, HR for VTE after CLL was 0.83 (0.10 – 6.69) in subjects ≤65 years of age exposed to previous VTE compared with subjects free of previous VTE, while for those > 65 years the HR was 6.34 (3.37 – 11.91) if exposed to previous VTE (Table 7). In other words, age was not strongly related to the risk of VTE unless exposed to VTE before the CLL diagnosis.

Table 7. Age stratified analysis of the effect of previous VTE on VTE after the CLL diagnosis.

	PY	IR (95% CI)	HR, crude (95% CI)	HR, adjusted* (95% CI)
≤ 65 years, previous VTE				
No	4 257	6.3 (4.3 – 9.2)	Reference	Reference
Yes	71	14.0 (2.0 – 99.3)	2.03 (0.27 – 14.95)	0.97 (0.12 – 7.88)
> 65 years, previous VTE				
No	6 637	7.5 (5.7 – 9.9)	Reference	Reference
Yes	234	59.7 (35.4 – 100.9)	6.62 (3.59 – 12.20)	6.68 (3.57 – 12.49)

*Adjusted for anti-coagulation treatment, WHO-PF, previous VTE, sex and second primary cancer.

Regarding CLL prognostic markers, the risk of VTE was highest in CLL patients with β_2-microglobulin levels above 4 mg/L and unmutated IgHV genes (Figure 7). These associations were not confounded by second primary cancer. (Table 6). Trisomy 12, Del11q and del17p were also correlated to the risk of VTE, while normal FISH did not increase the risk of VTE significantly compared with Del 13, which is a favorable prognostic marker in CLL[248] (Table 6, Figure 7).

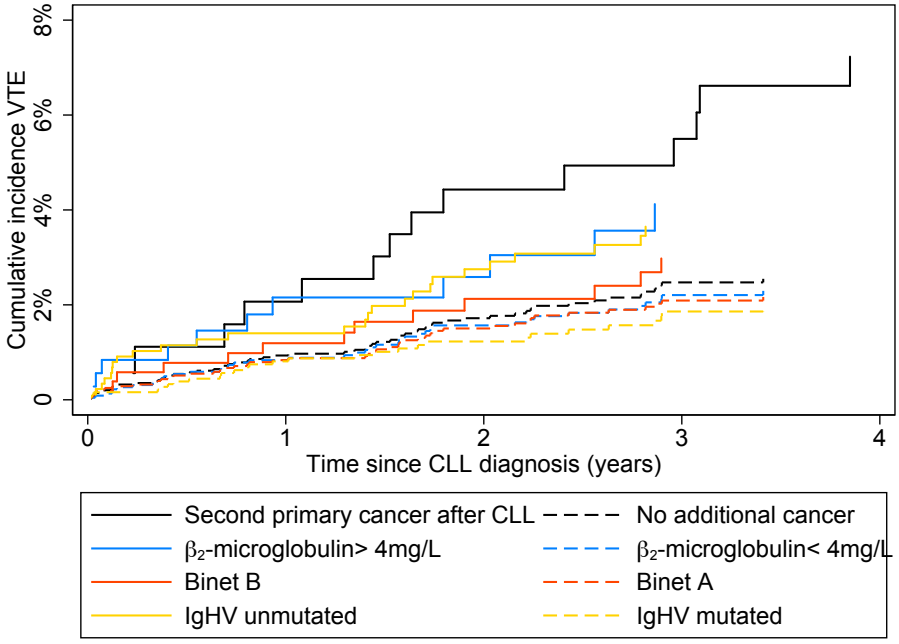

Figure 7. Cumulative incidences of VTE according to CLL prognostic factors, modified from [247].

Exposure to CLL treatment increased the risk of VTE (HR 2.40, 95% CI, 0.91-6.30). Several types of chemotherapy and immunotherapy and combinations hereof were represented among the CLL patients who were diagnosed with VTE during CLL treatment.

The mortality of CLL patients with VTE was marginally higher than in CLL patients without VTE after the CLL diagnosis (Figure 8). WHO performance status, age, sex, CLL risk profile and second primary cancer did not influence this association (crude and adjusted HRs 2.20 [95% CI, 1.43 – 3.37] and 2.13 [95% CI, 1.39 – 3.27], respectively).

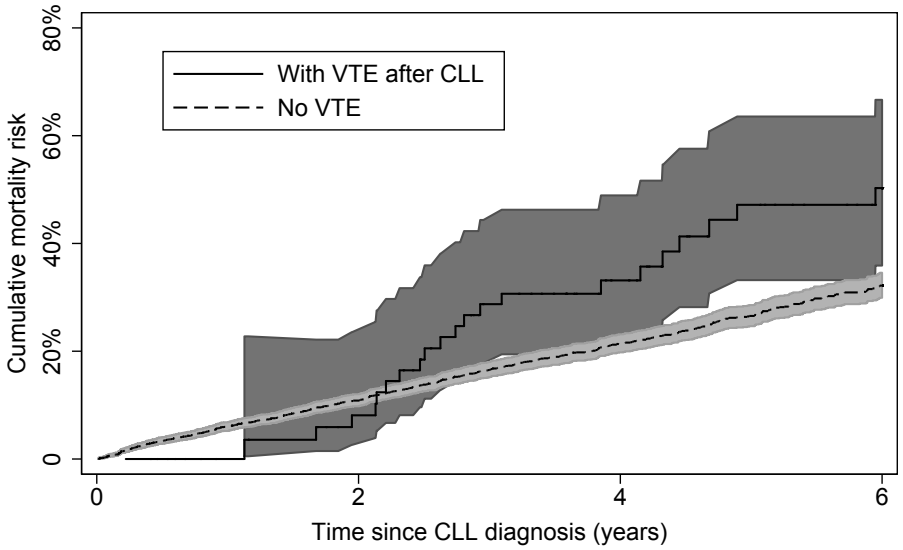

Figure 8. Cumulative mortality and associated 95% confidence intervals of CLL patients according to VTE after the CLL diagnosis. Modified from [247].

GENERAL DISCUSSION

Research aims to describe the real world by models applied to some sample, i.e. a small part of the real world. This will, however, always result in approximations for several reasons. First and foremost, the generalizability of observations in the sample of the real world depends on the degree of systematic errors within the sample. Furthermore, the applied models will always be approximations of the real world as they are too "small" to contain all aspects of the real world in the same way that a toy-car is too small to contain all the functional parts that make a real car.

The studies within this thesis aimed at describing several aspects of the epidemiology of cancer-associated VTE based on register data. None of the data sources were designed specifically for these studies. However, all data have been prospectively collected, which entail benefits as well as limitations discussed in this chapter. Furthermore, medical statistics continuously evolves and facilitates statistical models that bring estimates to a new level of complexity. The statistical methods used in the presented studies will be discussed along with new methods for data quality improvement and models for effect estimation.

METHODOLOGICAL CONSIDERATIONS

PRECISION AND POWER

Random error will always be some part of the explanation of estimates based on data from a sample. The extent of random error depends mainly on the sample size (i.e. number of observations) and precision of measurements in the sample. The width of confidence intervals of an estimate indicates its precision, where the true value of the investigated parameter will be inside the margins of the 95% confidence intervals 95 times if the study was repeated 100 times. Estimates from repeated studies will more frequently be close to the center of the confidence interval. The effect estimates in study 1-3 lacked precision as the sample size was small when divided into cancer types and stages. Hence, there was a lower probability of effect estimates being statistically significant if a true association actually existed (i.e. lack of power).[249] The results from these studies nevertheless indicate associations, but what the studies lack in precision and power, they do to some degree gain in validity, which is discussed below.

BIASES

Systematic errors in data can introduce biased results by three overall mechanisms. In case of **confounding**, measures of the association between exposure and outcome can become biased due to influence from a factor (confounder) that is both predictive of the outcome and also associated with the exposure.[242] Confounders are inherent in the real world population as well as in the studied sample, and thus a condition that needs attention in all study designs. Matching on confounder variables is the most common

method to control the effect of confounders in the study design phase. Additional methods can estimate the impact of the confounders on the effect estimate in the analysis phase, most simply by stratifying on the confounding variable or by inclusion of confounders in regression models.

Selection bias arises in the process of selection of the study sample if recruited and/or retained study subjects systematically differs from the real world.[242] This type of bias is not a problem in cohort studies with complete follow-up, as for instance the subjects in study 4, but might be present in the original studies in the STAC cohort.[66] All adult inhabitants in the geographical areas covered by the three cohorts were invited to participate. Attendance rates varied from 35% in the DCH study to 77% in the Tromsø study. This selection bias can affect the external validity, as participants in health surveys tend to be healthier and have higher socio-economic status than non-attendants.[250]

Information bias arise after selection of the study sample because of systematic errors with respect to the classification of the study subjects' exposure, outcome and confounder variables.[242] Information bias is diminished by use of high quality register data in study 1-4, and, additionally, use of validated outcomes in study 1-3. Ascertainment bias or medical surveillance bias is a type of information bias caused by more frequent medical examinations of exposed than unexposed subjects leading to systematically higher proportions of detected outcome (VTE) among exposed subjects. However, this bias is probably minor in studies 1-3 because solely symptomatic VTEs were included. Different methods for assessment of and handling biases are discussed below.

DATA QUALITY

Measures of data quality

Danish health care data was used in all four studies where cancer was the main exposure and VTE was the main outcome. Danish residents have income-independent access to universal tax-funded health care. Linkage of data from various registries is possible by use of the civil personal registration number providing extensive long- term tracking of individuals and cradle-to-grave follow-up at a national level. However, despite this ideal constellation for researchers within the field of clinical epidemiology, possible misclassification should be taken into consideration when findings based on health care data are interpreted. Human error does occasionally result in misclassification; non-diseased subjects receiving a diagnosis code classifying them as diseased, while in other occasions diseased patients are not registered and thus classified as non-diseased.

The validity of the main exposure in studies 1-3 has been evaluated by several methods encompassing the number of data sources per case, the proportion of cases only verified from death certificates, and the number of cases with unknown cancer type but microscopically verified cancer diagnoses are warranted. The proportion of microscopically verified diagnoses in Danish Cancer Registry has not been evaluated since

1992, where 93% were confirmed.[238] Study 1 – 3 additionally included information from the Norwegian Cancer Registry, where 94% of cancers registered in 2001-2005 were microscopically verified.[235]

For the main outcome in all four studies, the optimal estimation of misclassification of diagnoses would be assessment of sensitivity and specificity, however calculation of the positive predictive value and assessment of data completeness are more feasible measures of data quality, as described below.

In Table 8, A denotes diseased subjects with a (VTE) diagnosis in the register (true positive), B denotes subjects registered with disease but in reality non-diseased (false positive), C denotes diseased subjects without a registered diagnosis (false negative) and D denotes non-diseased, unregistered subjects (true negative).

Table 8. Validity of data, modified from Szklo et al.[242]

In the register	**The truth**		
	Diseased	Non-diseased	
Diseased	A	B	A+B
Non-diseased	C	D	C+D
	A+C	B+D	total

The validity of a diagnosis is optimally characterized by its sensitivity (the proportion of diseased subjects who are registered, i.e. A/A+C) and specificity (the proportion of non-diseased not registered with the disease, i.e. D/B+D).

The sensitivity and specificity of registered diagnoses can be measured by systematic review of medical journals of a sample of *both* diseased *and* non-diseased individuals in a cohort, as described in the validation of VTE diagnoses codes in study 4 and similarly in Danish prostate cancer patients.[251] The sensitivity and specificity (of a diagnosis code) depend on the "true diseased" (A+C) and "true non-diseased" (B+D), and these indices of validity are hence theoretically not related to the disease prevalence.[242] The specificity will be close to 1 for relatively rare diseases in a large population, while the data completeness e.g. in a local discharge registry is an estimate for the sensitivity when evaluated by comparing data from "the gold standard registry": [252]

$$\frac{\text{diseased registered in both "gold standard registry" and diseased registered in alternative register}}{\text{number of diseased registered in "gold standard registry"}}$$

The positive predictive value (proportion of true positive among all subjects registered with the disease, A/A+B) and the data completeness can be estimated by comparison of data from two registries or by review of medical journals from patients registered with the disease (A+B).[41,251,253,254] Both of these methods are more feasible than direct measurement of specificity and sensitivity, however, the two methods hinder direct comparison of measures of data validity between studies.

All potential VTEs included in the DCH, Tromsø and HUNT studies and hence in the STAC cohort were identified by linkage to local (Tromsø and HUNT) or national registries (DCH) followed by objective confirmation by review of medical journals. The positive predictive value of a registered VTE was not reported for the Tromsø and HUNT studies.[6,241] However, 740 out of 1526 (48%) possible VTEs identified in the discharge registry were objectively confirmed in HUNT study.[6] For participants in the DCH, the positive predictive value of a VTE discharge diagnosis in the DNPR was 75% if restricted to wards, while for discharge diagnoses from emergency departments it was 31%.[41] Thus, the inclusion of solely objectively confirmed VTE events in the STAC cohort is fundamental for its high quality of VTE data.

In study 4, the VTE events among CLL patients were identified in the DNPR, follow-up was from 2008 -2015, which was after last follow-up for the VTE in DCH.[41] The validity of VTE data in the total local CLL population was assessed in forms of systematic review allowing for estimation of sensitivity and specificity of VTE diagnosis in the DNPR.[247] For VTEs that occurred after a CLL diagnosis, the positive predictive value was 84.2%, while sensitivity and specificity were 76.2% and 99.3%, respectively. The positive predictive value was similar in a recent Danish study that assessed the validity of VTE diagnoses by review of medical journals of a sample of 100 VTE patients (88%).[254] The sensitivity of VTE diagnosis codes was assessed among Danish prostate cancer patients (1995-2012) by review of medical journals of all subjects with a VTE diagnosis in the DNPR (n=120) plus review of medical journals in a sample of prostate cancer patients with no VTE diagnosis code in the DNPR (n=120).[251] The sensitivity of VTE diagnosis codes was higher compared with our study (98% vs. 76.2%), while corresponding positive predictive value was similar to what we observed (86.1% vs. 84.2%).[251] As the assessment methods differed, the estimates from study 4 are, however, not directly comparable to the estimates from Drljevic et al.[251] Nevertheless, it indicates that the true validity behind apparent similar positive predictive values might differ considerably. For practical reasons, however, the positive predictive value will probably remain the preferred measure of register data validity.

Missing data

Missing data is a problem, although variable in all data sources. Estimates based on datasets with missing data can be biased if the reason for missing is associated with observed information (i.e. missing at random) or non-observed information (i.e. missing not at random). Estimates will not be biased if data are missing completely at

random, which is however, unusual. Several methods for dealing with missing data exists. They are developed in order to maintain the study sample size and thus statistical power and precision, and to assess the impact of the missing data on the estimates. In single value imputation, the missing values are replaced with one value. The single value can be obtained by replacing the missing value with the mean of the observed values, or by the last measured value. Another way to handle missing data is worst and best-case sensitivity analysis where the missing values are replaced by the extreme values. These single value methods provide one full copy of the dataset and hereby no consideration of the uncertainty the imputed value carry forward into the analysis. Possibly, these methods provide significant associations because standard errors will be falsely narrow. Moreover, results from this from of dataset is not really useful in case the estimate differ from the complete case analysis. Alternatively, missing data can be handled by use of other variables in the dataset. Multiple imputation is the most recognized method within this category. Multiple imputation allows for the inherent uncertainty of missing/imputed values by creation of several plausible datasets by use of predefined variables in the dataset and finally combining the results from all of these data sets taking uncertainty of the imputed datasets into accunt.[255,256]

In study 1, less than 1% of cancer stages were actually missing, i.e. had no value in the variables for cancer stages in the registries, while 14% were actively coded "unknown" stage. A code for "unknown stage" was however not per se equal to "unknown". For some subjects - especially early in the study period - it could have meant "missing".[235] The authors of a recent study on Norwegian breast cancer patients chose to treat the patients with actively coded "unknown" cancer stage as missing data.[257] The impact of the actively coded "unknown" cancer stages was assessed both in worst and best-case sensitivity analyses, and by multiple imputation of the missing values based on age, survival and calendar period of the cancer diagnosis. The estimates did however not change markedly in either of the datasets with replacement of missing data, hence there is no reason to believe that missing data did bias the estimates in the initial complete case analysis even though data were not missing completely at random. This lead to post-publication speculations about use of multiple imputation in study 1. Table 9 shows that actively coded "unknown" cancer stage is more frequent in the earliest calendar period and among subjects that were older at the time of cancer diagnosis. Furthermore, the distribution varied by cancer type.[244] The missing data were associated with observed information and multiple imputation would thus have been an option however unlikely to have affected our results.

Table 9. Missing and actively coded "unknown" cancer stage in study 1.

	Localized, regional or distant metastasis	Actively coded "unknown" cancer stage	Missing value in stage variable
Age groups			
20-62	89.5%	10.4%	0.1%
62-68	88.7%	11.2%	0.2%
68-74	84.7%	15.2%	0.1%
74-99	75.8%	24.2%	0.0%
Calendar period			
1993-2001	82.4%	17.4%	0.1%
2001-2005	83.5%	16.3%	0.2%
2005-2008	86.0%	13.9%	0.1%
2008-2011	88.0%	12.0%	0.0%

In study 4, very few data were actually missing. Binet stage was the only complete prognostic variable while 14%-25% of the other CLL prognostic markers had a value for "Not assessed" in the dataset. The CLL patients with "not assessed" values were typically older than 60 years of age at the CLL diagnosis and 75% had Binet stage A disease.[244] Furthermore, if one prognostic variable was not assessed, there was a higher proportion of other prognostic variables being unassessed (Table 10). This means that for the most optimal variables for multiple imputation, data would be missing as well.

Table 10. Proportion of "not assessed" IgHV values in study 4 (n=806).

	Normal FISH	Abnormal FISH	FISH "not assessed"
β_2 –microglobulin			
> 4 mg/L	15 (1.2%)	37 (4.6%)	39 (4.8%)
< 4mg/L	68 (8.4%)	171 (21.2%)	172 (21.3%)
Not assessed	44 (5.5%)	113 (14.0%)	147 (18.2%)

The actual pattern of missing data is as important as the proportion of missing values.[258] Missing values in prognostic variables in study 4 was associated with being older and having a normal bone marrow function. This pattern indicates that estimates in a sensitivity analysis in a best-case scenario would not change markedly.

SELECTION OF REFERENCE SUBJECTS IN MATCHED STUDIES

In principle, two different methods for sampling of controls within a defined cohort gives rise to two different study designs, or types of nested case-controls designs: By incidence density sampling of reference subjects unexposed at the index date, incidence rate ratio can be directly estimated. If, on the other hand, reference subjects are sampled from the total cohort including exposed subjects all with the same chance of being selected as reference subjects, the risk ratio can be directly estimated.[242,243] Person time-data is however not used in the latter design, but it enables use of the same control group for several outcomes. Since we were interested in using the available person-time data in the STAC cohort in study 2 and 3, we chose the incidence density sampling method for selection of references.

SHARED FRAILTY WITHIN MATCHES

Latent effects common within the group of the case and its selected reference subjects could lead to shared proneness (frailty) for VTE within matches and thereby lead to biased effect estimates.[278] Shared frailty models could have been included in study 2 and 3. However, adjustment for shared frailty was done in a preliminary dataset in study 2, where shared frailty within matches did not change estimates markedly (crude HR for VTE in hematological cancer compared with reference subjects: 5.05, 95% CI 2.94-8.67, HR adjusted for shared frailty: 5.40, 95% CI 3.12-9.31). In study 2, crude incidence rate ratios were reported, no further adjustment for age, gender or shared frailty was done in the final study. Due to few events, a regression model would be restricted to include very few parameters,[259] in this regard age and sex could probably not have been ignored, as discussed below.

ADJUSTMENT FOR MATCHING VARIABLES

Study 2 and 3 were matched cohort studies, where matching variables were age, sex and original cohort. In this study design, the matching variables can be ignored as long as no adjustment for other confounders take place. However, if regression models are constructed, they should include the matching variables along with the non-matching confounders of interest.[260,261] Since reasonable regression models should include at least age and sex in addition to other possible confounders, we chose not to do any regression analysis because they would be too complex for the sample size in study 2. In study 3, we used Poisson regression to adjust for ageing since cancer diagnosis and sex.[246]

CAUSALITY

While appraisal of associations observed in an individual study is based on evaluation of random and systematic errors in the particular study as described above, inference of causality is based on all available evidence.[242,249] Bradford Hill proposed nine criteria for evaluation of causality, however not all are relevant or applicable for the studies in this thesis.[262] First of all, causality necessitate temporality; the exposure must precede the outcome. Second, strong associations are more likely causal as the alternative explanations for the association are less likely. Relative risks above 3 are suggested to characterize a strong association, but relative risks closer to 1.0 does not preclude causality.[263] Third, consistent findings of the association in other studies with different study designs and samples indicate a causal association. Last, a biological gradient (i.e. dose-response relationship) and biological plausibility also indicates that an association is causal.

A single exposure seldomly causes the outcome alone. Most often, the exposure is a part of a combination of causes sufficient for the outcome (Figure 9).[264]

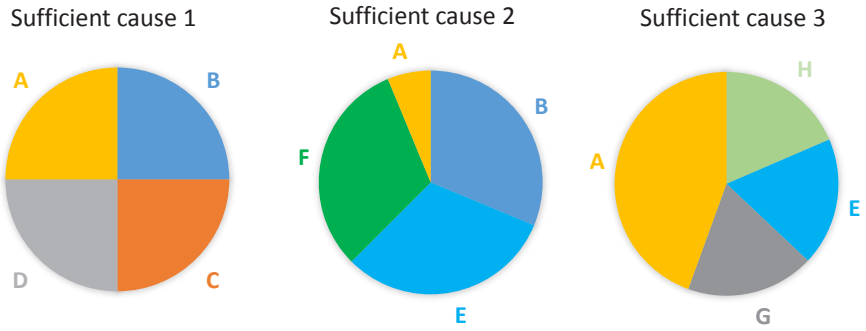

Figure 9. Three sufficient causes of an outcome. Modified figure from Rothman[264].

ASSOCIATION MEASURES

Estimates of occurrence and effect (i.e. strength of an association) would ideally be calculated by comparing the same person with itself in exposed and unexposed condition without time lag. This is obviously a hypothetical situation and the best approximation to this utopian ideal is to design scientific studies to resemble. Three general principles to bear in mind in the analysis phase of studies were recently formulated.[265]

1: Do not condition on the future.
2: Do not regard individuals at risk after they have died.
3: Stick to this world.

Although simple, these principles are nonetheless relevant in the following discussion of association measures.

Occurrence measures

The development of VTE over time (i.e. incidence) was investigated in all four studies in this thesis by use of two measures of occurrence: incidence rates and cumulative incidence (proportion). Both measures have the number of new events in the sample in the numerator. The denominator of incidence rates is the *person-time* at risk of VTE, whereas in the cumulative incidence the denominator is *number of study subjects* at risk at the beginning of the time unit.[268] For estimated cumulative incidences to be generalizable to the real population, one basic assumption needs to be met: The sample must be representative for the population at any given time in the study (not restricted to study entry), hence those who leave the study sample due to censoring should be representative of the study population at any given time. This is referred to as independent right censoring or non-informative censoring.[279] In our studies, cancer patients who die (and therefore become censored) are obviously not comparable to subjects still contributing to person-time at risk for VTE in the study as dead precludes the occurrence of VTE. In study 4, we additionally noted that CLL patients who became exposed to an additional cancer in the study period had a fundamentally altered probability of VTE occurrence. This was handled by treating death and in study 4 also second primary cancer as competing risks in calculation of the cumulative incidence of VTE by use of the Aalen-Johansen estimator.[266] This method differs from the traditional Kaplan-Meier method by taking into account the risk of VTE *and* the risk of death and, additionally, in study 4, the risk of second primary cancer, while the Kaplan-Meier estimate would describe the risk of VTE assuming that patients who had a second primary cancer had the same risk of VTE as those still in the study (i.e. violation of the assumption of independent right censoring). Furthermore, the Kaplan-Meier estimate treating all other events as censored assumes that censored subjects could later experience a VTE (i.e. those who die can experience a VTE) and estimates the occurrence of VTE as if VTE was the only possible outcome.[92] Hereby, the Kaplan-Meier estimator regards individuals at risk after they died and does not stick to this world as alternative outcomes are obviously possible.

We used the cumulative incidences to depict the time-dependency of VTE risks from the date of cancer diagnosis (study 1,2 and 4) and the two-year anniversary of cancer diagnosis (study 3). Additionally, we could have used the cumulative incidences as measures of occurrence of VTE by time since cancer diagnosis, if we had started the study entry with successive time since cancer diagnosis.[267] Instead, we calculated IRs of VTE in different time intervals since cancer diagnosis. In calculation of IRs, study subjects contribute to person-time at risk from study entry until VTE, administrative censoring or competing events.[242] Hence, when study subjects are no longer at risk of VTE, they do not contribute to person-time at risk meaning that the IR does stick to the real world and does not regard subjects at risk after they are dead. The precision of

estimates of IR depends on the number of events and not sample size (i.e. person-time at risk),[268] and the associated confidence intervals were thus generally broad in study 1 and 2 despite considerable amounts of person time at risk. More VTEs were studied in the compared groups in study 3 and 4 leading to generally better precision of estimates of the IR in these studies.

Effect measures

The absolute measures of outcome described above indicates whether and to which extent the association with the studied exposure is present but does not take confounding into account. Measures of the strength of the association (i.e. effect size) can be calculated in several ways. We used incidence rate differences in studies 1 and 3, which describes the strength of the association on the additive scale, however this method is also unable to control for confounding. As described above, an association can arise both because of a true relationship between the exposure and outcome but also due to confounding. The strength of an association is therefore a function of the relative prevalence of the causes, both the studied exposure and confounders, which result in the outcome. Estimates of the effect can be obtained from regression models accounting for known confounders. We used Cox proportional hazards models in studies 1 and 4. In study 1, we controlled for age and sex, and in study 4, we were also able to include time-varying covariates. In study 3, we considered calculating sub-distributional hazard ratios using the Fine-Gray regression model. [269] This model takes into account the competing risks, but the estimate is hard to interpret in a clinically meaningful way as it gives information about the instantaneous risk of the studied event among those who did not yet have the event, but also among those who experienced the competing event(s).[270,271] Hence, the Fine-Gray model violates the second principle. Furthermore, it is recommended to use the Fine- Gray model in studies of prediction while in etiological studies the reporting of rates are recommended.[270-272] We therefore used Poisson regression for assessment of effects in study 3.

A measure of the absolute risk difference or risk ratio with associated confidence intervals would be a preferable way to report clinically meaningful effects. This is possible both for estimates of survival as well as for events with competing risk by use of the pseudo values approach where transformation of the cumulative incidences/Kaplan-Meier estimates enables regression.[273] However, the pseudo value method requires a certain amount of events and was therefore not applicable in our studies.[274]

DISCUSSION OF THE MAIN RESULTS

STUDY 1: IMPACT OF INITIAL CANCER STAGE ON THE INCIDENCE OF VTE

The results from study 1 should be interpreted bearing the limited precision and power in mind, however the study does contribute to a more detailed understanding of the impact of cancer stage on the risk of VTE compared with studies combining all cancer types. [24,129,190] The effect of regional spread and distant metastasis did vary considerably according to cancer type indicating that cancer stage does not contribute with equal proportions to the sufficient cause of VTE in all cancer types. Given the very different biology and phenotypes of the ten investigated cancer types, it does seem biologically plausible that the effect of cancer stage could vary. The observations from study 1 are furthermore consistent with results from the studies of single types of cancer listed in Table 2. These estimates are however not directly comparable due to different classifications of cancer stage, study designs and populations, unlike the estimated effects of cancer stage on the risk of VTE in different cancer types in study 1.[244]

STUDY 2: EPIDEMIOLOGY OF VTE IN HEMATOLOGICAL CANCERS

The small groups and limited number of events led to imprecise estimates in study 2, however no studies previously compared the risk of VTE in distinct hematological cancer types to the background population. Study 2, therefore, for the first time, gives an opportunity to assess the association with VTE in distinct types of hematological caner. This gives a more detailed understanding of the epidemiology of VTE for each type of the hematological cancers. With the exception of indolent lymphomas, patients with both acute and chronic hematological cancers had markedly higher incidence rates of VTE compared with the reference subjects within the first year after cancer diagnosis. For patients with CLL and myeloma, the IR of VTE was still markedly higher years after the cancer diagnosis, which seems plausible as these cancer types are incurable with intermittent disease activity and associated with anticancer treatments at these occasions.[245]

STUDY 3: LONG-TERM INCIDENCE OF VTE IN CANCER

Estimates were more precise in study 3, however many types of cancer were combined in one large group of “other solid tumors”. The possible selection bias in the STAC cohort could lead to bias in study 3, because cancer survivors are socially marginalized to a higher degree and have more comorbidities than the non-cancer population.[275] Given that the STAC participants represent the most healthy and socially wealthy part of the background population, it is possible that the cancer survivors in the STAC cohort are generally better off than cancer survivors in the population, probably resulting in estimates biased towards the null hypothesis. We could have included social status, education, and health as confounders to partly correct for this selection bias and

increase the external validity of the study.

The observed prolonged increased risk of VTE in some groups of cancer survivors was confirmed by a few previous studies, where the five-year cumulative risk of VTE was 2-5-fold higher compared with the background population.[157,160] These studies, however, included events that occurred within the first few months after the cancer diagnosis in these calculations. In order tell cancer survivors whether or not their risk of VTE is reduced to that of their healthy friends, only events that occur after successive event free survival should be included in the calculations, as exemplified in study 3.[246]

STUDY 4: VTE IN CHRONIC LYMPHOCYTIC LEUKEMIA

The study population in study 4 was for all practical purposes the total population of Danish residents diagnosed with CLL in 2008-2015. Unlike the outcome in studies 1-3, only 10% of VTEs were objectively confirmed in this study. Furthermore, the events included both symptomatic VTE and incidental findings possibly resulting in ascertainment bias. This might particularly be the case for CLL patients with second primary cancers, as they would tend to undergo more imaging diagnostics than CLL patients with no second primary cancer. Nevertheless, the effect of second primary cancer on the risk of VTE was considerable, and it is furthermore biologically plausible that the observed association is causal.[247] The observed increased risk of VTE during CLL treatment, in the case of previous VTE and with increasing extent of the disease correlates with findings in previous studies.[85,132,160-162]

SUMMARY DISCUSSION OF THE FOUR STUDIES

Associations between several cancer specific factors and VTE were investigated in the studies in this thesis. Consistent association between **cancer type** and the risk of VTE was observed in studies 1-3. [244-246] In study 1, the risk of VTE did vary by **cancer stage**, but the magnitude of the effect varied dramatically with cancer type. [244] After adjustment for cancer type, initial distant metastasis was associated with a higher long-term risk of VTE in solid cancers in study 3. Furthermore, the Binet stage of CLL was associated with the risk of VTE in study 4. [247] The possibility of confounding must be taken into account in the interpretation of the impact of cancer specific factors on the risk of VTE. The lack of information about chemotherapy and hospitalizations must be taken into account when interpreting the results from study 1-3. Some of the observed effect of distant metastasis and regional spread on the risk of VTE may be attributable to these confounders, however they are unlikely to explain the entire effect, as other studies found considerably higher risk of VTE in advanced stage cancers after adjustment for chemotheraphy.[86,153,154,158,160,190] Similarly, the observed prolonged increased risk of VTE in hematological cancer patients in study 3 may also be confounded by repeated treatments, but **disease activity** in itself may also contribute. This is also indicated in other studies where the risk of VTE in cancer patients was high even before administration of anticancer treatment.[27,203] Additionally, we observed higher risk of

VTE in subjects with β_2-microglobulin levels above 4 mg/L indicating that the activity of CLL is associated with the risk of VTE. [247]

The effect of **time since cancer diagnosis** was a theme in all four studies. The cumulative incidence curves of VTE inclined steeply within the first year after cancer diagnosis in study 1, most pronounced for those with distant metastasis. For localized cancer types with typically good prognosis (i.e. colorectal, breast and prostate cancer), the incidence was however more constant throughout follow-up. [244] This observation is in line with the role of disease activity in the etiology of VTE discussed above, and also with observations from study 2: The acute, aggressive hematological cancer types were associated with high risks of VTE within the first year after the cancer diagnosis compared with references unlike the incurable hematological cancer types that were associated with higher risk of VTE both in close proximity to the cancer diagnosis and after several years. Some of the cancer survivors in study 3 presumably lived with incurable/chronic cancer while others were cured. The risk of VTE for (previous) colorectal cancer patients alive five years after the cancer diagnosis was similar to the reference population, whereas patients with (probably chronic) hematological cancer types had considerably higher long-term risk of VTE than the references. The cumulative incidence of VTE after a CLL diagnosis accordingly increased rather linearly throughout follow-up in study 4 if restricted to CLL patients without second primary cancers.[247] However, **second primary cancer** was strongly associated with the risk of VTE in study 4. The cumulative incidence of second primary cancer increased steeply within the first few months after the CLL diagnosis.[247]

CONCLUSION OF THE THESIS

The studies included in the thesis were based on data from high quality registers. Outcome, i.e. VTE in study 1-3 were objectively confirmed, as was outcome for 10% of subjects in study 4. The studies were in general not suitable for significance testing but did nonetheless suggest rejection of the four null hypotheses.

Study 1: The effect of distant metastatic and regional spread cancer varied considerably with cancer type. For some cancer types, the risk increased in a "dose-dependent" manner with more extensive cancer, while the risk of VTE was quite high or rather low regardless of cancer stage in other cancer types. [244]

Study 2: The risk of VTE was higher in aggressive lymphoma, CLL and myeloma patients compared with references –for the latter two types even several years after the diagnosis of hematological cancer.[245]

Study 3: The IR of VTE was generally higher in cancer survivors compared with reference subjects, highest in the hematological cancers with a 5-fold higher risk of VTE even later than five years after the diagnosis of cancer. However, the risk of VTE in survivors of some solid cancer types attenuated to levels similar to the reference population.[246]

Study 4: Exposure to second primary cancer after the CLL diagnosis and a history of VTE before the CLL diagnosis was associated with a 4-5 - fold higher risk of VTE, while the risk of VTE varied less according to CLL prognostic markers. Ignoring the competing risk of second primary cancer lead to an overestimation of the cumulative incidence of VTE.[247]

The studies overall indicate that the type, extent and activity of cancer are all part of the etiology of cancer-associated VTE, and that the impact of the cancer specific factors vary by time since cancer diagnosis and cancer type. It is always important to evaluate the risk of VTE with regard to time since cancer diagnosis, however not only in the sense that the risk of VTE is uniformly high in the first period after cancer diagnosis. For cancer survivors and generally also those with less aggressive types, the long-term incidence of VTE may actually be more relevant because it can be markedly higher than the background population. Second primary cancers increases the risk of VTE considerably and must be taken into account even in studies of cancer-associated VTE with short follow-up.

PERSPECTIVES

The presented studies contributes to a more detailed understanding of the epidemiology of cancer-associated VTE. The authors of the ISTH guideline on classification of VTE discuss when cancer is no longer a risk factor for VTE. [48] Based on the observations in the presented studies it should depend on cancer specific factors, though the long-term incidence of VTE needs further investigation. Second primary cancers or relapses are important competing risks for cancer-associated VTE, probably also in studies with shorter follow-up.

Cancer specific factors play complex roles in the etiology of VTE. This implies that future studies in the field of cancer-associated VTE should preferably be very detailed regarding cancer specific factors. Furthermore, patient related factors and possible additional cancers contributes to the complexity. The interplay between all these causes changes by time since cancer diagnosis leaving much etiology of cancer-associated VTE yet to be learned. Bearing this in mind, condensing all relevant knowledge into one common model for prediction of VTE in cancer patients seems an insuperable task.

In a just published survey concerning cancer patients' awareness of thrombosis, 72% of the 1344 respondents did not know that cancer entailed an increased risk of VTE.[276] This means that the patients represent an unexploited option for early diagnosis and treatment of cancer-associated VTE. If we educate cancer patients in signs and symptoms of VTE in the same breath as we teach them about neutropene febrilia, they might report these rather than just thinking of the cough, chest pain, leg tenderness or dizziness as a part of their cancer journey, as mentioned in the study by Noble et al.[3] Hence, my final remark is an invitation to policy makers, colleagues and patient organizations to corporate on bringing awareness of VTE into the public.

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APPENDIX

APPENDIX

APPENDIX 1. ALGORITHMS FOR MAPPING OF CANCER STAGE

ALGORITHM 1: ALL NORWEGIAN CANCER STAGES

The algorithm for mapping all Norwegian cancer exposed to the principal classification: Cases with stage code"3" is moved to regional spread as the description translated from Norwegian is" organ metastasis to same part of the body". Local spread to neighbor organs is not per se classified as distant metastasis. The Danish data coded in TNM is mapped to the principal classification according to international standards and ICBP. We have made this decision in order to harmonize Danish and Norwegian in the most precise manner, concerning international terminology.

- localized cancer; stage ==0 (original Norwegian code 0 and 8)
- regional spread, stage ==1 (original Norwegian code A, D, 1, 3, 5, 6)
- distant metastasis; stage ==2 (original Norwegian code B,C, 2,4,7)
- stage unknown; stage==3 (original Norwegian code 9)

A minor part of Norwegian colorectal – and gynecological cancers could have metastasis codes in the Duke's respective FIGO systems, this variable is not included in the merged cohort. Is this variable available in the Tromsø and HUNT databases before merging?

Breast cancer does have a TNM –based code in the Norwegian cancer registry – variable name: Stadium. Further more the code Stadium_B excists in the Norwegian cancer registry, it is identical to Stadium for all values of Stadium except: "ukjent (999)". In case of "ukjent (999)"the value from the variable "Metastase" is added. The "Metastase" code is based on TNM classification from 1986 *(https://www.kreftregisteret.no/Registrene/Datautlevering/Opplysninger-i-databasen/Ovrige-variable-i-Kreftregisterets-insidensregister/)*. For all other solid tumors 40-50% have TNM data in the national cancer registry.

ALGORITHM 2 (A, B AND C): CANCER STAGES IN DCH BEFORE 2004

Supplementary table 1. The variable C_UDBRED values 1, 2, 3 and 4 covers both FIGO and Duke's.

c_udbred	v_meaning
A	Unspecified: By coding
B	Not applied: Not cancer
0	Stadium 0, dysplasia, carcinoma in situ (gyn. tumors)
1	Stadium I (gyn. tumor)/Dukes A
2	Stadium II (gyn. tumor)/Dukes B
3	Stadium III (gyn. tumor)/Dukes C
4	Stadium IV (gyn. tumor) /Dukes D
5	localized (incl. Pre-ankroses outside uterus and benign tumors)
6	Regional spread
7	Distant metastaser
9	Unspecified by coding

(http://www.esundhed.dk/dokumentation/Registre/Sider/Register.aspx?rp:A_Register=23&rp:Visning=3&)

Algorithm for breast[239], prostate[80], bladder, kidney, colorectal [239], pancreas, lung[239] and upper gastrointestinal (GI) cancer:

- localized cancer; stage ==0 (original code in C_UDBRED 0, 1, 2 and 5)
- regional spread; stage ==1 (original code in C_UDBRED 3 and 6,
- distant metastasis; stage ==2 (original code in C_UDBRED 4 and 7)
- stage unknown; stage ==3(original code in C_UDBRED 9, A)
- Exposed with the code "B" in C_UDBRED are excluded as the translation of this code is: Not applied: Non-cancer.

Algorithm for ovary cancer[239]

- localized cancer; stage==0 (original code in C_UDBRED 0, 1 and 5)
- regional spread; stage==1 (original code in C_UDBRED 2 and 6)
- distant metastasis; stage==2 (original code in C_UDBRED 3, 4 and 7)
- stage unknown; stage==3(original code in C_UDBRED 9, A)
- Exposed with the code "B" in C_UDBRED are excluded as the translation of this code is: Not applied: Non-cancer

Algorithm for uterus and cervix cancer

- localized cancer; stage ==0 (original code in C_UDBRED 0, 1 and 5)
- regional spread; stage ==1 (original code in C_UDBRED 2, 3 og 6)
- distant metastasis; stage ==2 (original code in C_UDBRED 4 og 7)
- stage unknown; stage ==3 (original code in C_UDBRED 9, A)
- Exposed with the code ”B” in C_UDBRED are excluded as the translation of this code is: Not applied: Non-cancer

ALGORITHM 3: CANCER STAGES IN DCH *AFTER* JANUARY 1ST 2004

BEFORE RUNNING ALGORITHM 3: SET CANCER STAGE TO UNKNOWN ==3 BY DEFAULT, map to relevant stages by this algorithm:

Participants in the DHC diagnosed with cancer from 2004 and forwards have to be mapped to the principal classification ”local”, ”regional”, and ”distant metastasis” based on the TNM classification. “T” refers to extension/size of primary tumor, “N” refers to lymph node involvement and ”M” to metastasis to other organs. The variable M outweigh N and T, and N outweights T. The algorithm therefore is build hierarchically and takes M into account before N, which is taken into account before T.

Due to inconsistency between solid tumors on when lymph node affection (N) and extent of primary tumor (T) draws the principal label ”regional spread” – and even ”distant metastasis” we have to work with different versions of algorithm 3. All algorithms are designed according to / adapted from references 6 and 7 when no other are mentioned.

The variable ”M”

At first we look into metastasis to other organs (M0 = no metastasis, M1= yes). M0 has the code AZCD40x, M1 has the code AZCD41x. If ”M” is unknown it is coded AZCD49x. This step is equal for all solid tumors.

All with TNM AZCD41x are mapped to stage==2. (i.e. ”replace stage=2” if a TNM code corresponding to AZCD41x exists)

All with TNM AZCD40x are mapped to stage==0; if stage==3

(If TNM code is AZCD49x stage==3 is maintained)

The variable "N"

Now we look into lymph node involvement in the TNM classification. It is divided into four categories: N0, N1, N2 and N3 and unknown. N0 has the code AZCD3.0x. N1 has the code AZCD31x. N2 has the code AZCD32x. N3 has the code AZCD33x. If unknown lymph node affection, the code is AZCD39x. Not all types of solid tumors are classified by all four N-categories.

For prostate[80], pancreas, cervix, ovary[239] and kidney cancer:

- All with TMN AZCD32x is mapped to stage==2
- All with TNM AZCD33x is mapped to stage==2
- All with TNM AZCD31x is mapped to stage==1 if not already stage==2
- All with TNM AZCD30x is mapped to stage==0 if stage==3

For lung[239] og uterus cancer:

- All with TNM AZCD33x is mapped to stage==2
- All with TMN AZCD32x is mapped to stage==1 if not already stage==2
- All with TNM AZCD31x is mapped to stage==1 if not already stage==2
- All with TNM AZCD30x is mapped to stage==0; if stage==3

For breast[239], upper GI, bladder and colorectal cancer[239]:

- All with TNM AZCD33x is mapped to stage==1 if not already stage==2
- All with TMN AZCD32x is mapped to stage==1 if not already stage ==2
- All with TNM AZCD31x is mapped to stage==1 if not already stage==2
- All with TNM AZCD30x is mapped to stage==0; if stage==3

The variable "T"

At last we look into extension of primary tumor. As for "N" varying levels of "T" triggers mapping to "regional" in different tumors. The AZCD codes for T is the following:

T0: AZCD10x
Ta:AZCD11x
Tis:AZCD12x
T1:AXCD13x
    T1a: AZCD13A
    T1b: AZCD13B
    T1c: AZCD13C
T2.AZCD14x

T3:AZCD15x
T4:AZCD16x
T unknown:AZCD19x

About T0: we chose to include this as it is an option to have metastatic cancer without detected primary tumor.

Algorithms:

For lung[239], pancreas, prostate[80], bladder and kidney:

- AZCD10x is mapped to stage==0; if stage==3
- AZCD11x is mapped to stage==0; if stage==3
- AZCD12x is mapped to stage==0; if stage==3
- AXCD13x is mapped to stage==0; if stage==3
- AZCD14x is mapped to stage==0; if stage==3
- AZCD15x is mapped to stage==1; if stage==0 or stage==3
- AZCD16x is mapped to stage==1; if stage==0 or stage==3
- AZCD19x does not give rise to alteration of stage

For upper GI, colorectal[239] and breast cancer[239]:

- AZCD10x is mapped to stage ==0; if stage ==3
- AZCD11x is mapped to stage ==0; if stage ==3
- AZCD12x is mapped to stage ==0; if stage ==3
- AXCD13x is mapped to stage ==0; if stage ==3
- AZCD14x is mapped to stage ==0; if stage ==3
- AZCD15x is mapped to stage ==0; if stage ==3
- AZCD16x is mapped to stage ==1; if stage ==0 or stage==3
- AZCD19x does not give rise to alteration of stage

For uterus and cervix:

- AZCD10x AZCD11x, AZCD12x are excluded as these codes covers carcinoma in situ (CIS), which is not coded as cancer.
- AXCD13x is mapped to stage ==0; if stage==3
- AZCD14x is mapped to stage ==1; if stage ==0 or stage ==3
- AZCD15x is mapped to stage ==1; if stage ==0 or stage ==3
- AZCD16x is mapped to stage ==1; if stage ==0 or stage ==3
- AZCD19x does not give rise to alteration of stage

For ovary[239]**:**

- AZCD10x is mapped to stage ==0; if stage ==3
- AZCD11x is mapped to stage ==0; if stage ==3
- AZCD12x is mapped to stage ==0; if stage ==3
- AZCD131 is mapped to stage ==0; if stage ==3
- AZCD13A is mapped to stage ==0; if stage ==3
- AZCD13B is mapped to stage ==0; if stage ==3
- AZCD13C is mapped to stage ==1; if stage ==0 or stage ==3
- AZCD14x is mapped to stage ==1; if stage ==0 or stage ==3
- AZCD15x is mapped to stage ==2; if stage ==0 or stage ==1 or stage ==3
- AZCD16x is mapped to stage ==2; if stage ==0 or stage ==1 or stage ==3
- AZCD19x does not give rise to alteration of stage

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