UiT
THE ARCTIC
UNIVERSITY
OF NORWAY

Faculty of Health Sciences

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Cancer-related venous thromboembolism

Epidemiology and risk factors

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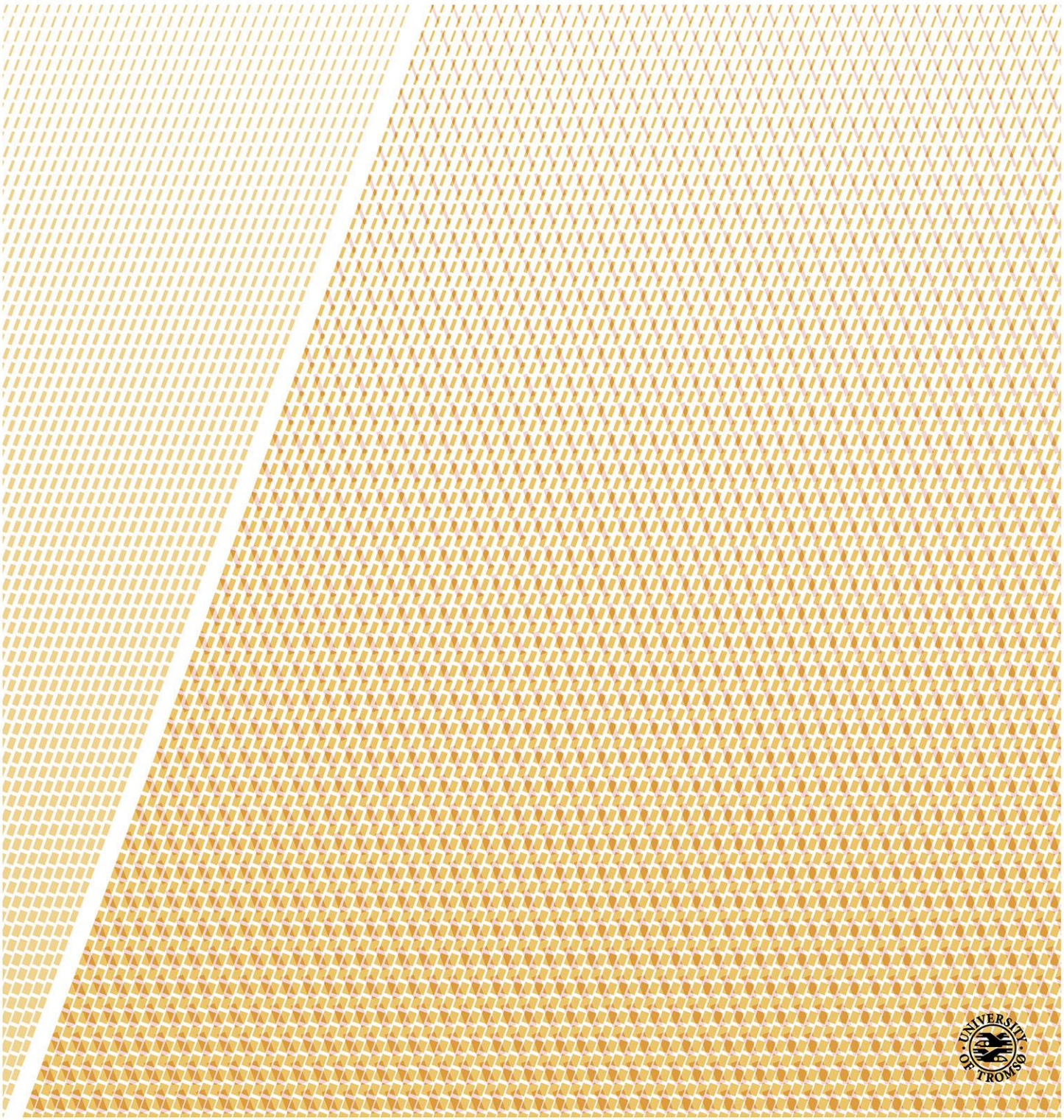
A dissertation for the degree of Philosophiae Doctor – August 2014



CONTENTS

ACKNOWLEDGEMENTS

The work of this thesis was carried out in the Hematological Research Group (HERG), Department of Clinical Medicine at the University of Tromsø between August 2010 and July 2014. The first three years were supported by a student scholarship from the Tom Wilhelmsen Foundation and was carried out during the final years of medical school (2010-2013). The last year was spent as a fulltime PhD-student, financed by the Northern Norway Regional Health Authority.

I would like to express my deepest gratitude to Professor John-Bjarne Hansen. You have been a wonderful and dedicated supervisor ever since the beginning of this work. Your professional skills and hard work never stopped to impress me, and our meetings and coffee breaks were always inspiring. However ungrateful at the time, I am truly thankful for your firm deadlines and honest critiques, without which this thesis would not be possible. Future supervisors and colleagues certainly have large shoes to fill. I hope you can forgive my urban escape, and allow me to continue the work with you and the group in the future.

I am also enormously grateful to my second supervisor Sigrid Kufaas Brækkan. Thank you for sharing your knowledge and for teaching me nearly all I know with great patience. I always admired your epidemiological talents, structure and efficiency, and your scientific contributions to all four papers have been invaluable. I also want to direct a special thanks to my closest colleague throughout this work, Hilde Jensvoll. It has been a pleasure to get to know you and work closely with you on several papers in this thesis. We have not only shared desk downstairs in F1.216, but a number of scientific and non-scientific frustrations during these last years. You have been a great support, and it is no exaggeration that this thesis only was possible thanks to your dedicated work and friendship. I also wish to acknowledge the contributions of my other co-authors Finn-Egil Skjeldestad, Saskia le Cessie, Suzanne C. Cannegieter and the STAC-investigators. Thanks to my good friend Ingrid Nagell for always finding time for English support, however inconvenient in your schedule.

Membership in HERG has gone hand in hand with a wide range of challenges, including heights, hot tubs and freezing ocean waters at Sommarøy, exotic gastronomy in Japan, balcony standing long jumps and endless disappointments of the Friday afternoon lottery. Lessons learned include written documentation of all betting rules and that no HERG/TREC-bets are too reckless - as they usually remain unsettled. To date I only count one exception. I want to thank all current and previous HERG/TREC members (Erin Mathiesen Hald, Trond Børvik, Lars Daae Horvei, Trond Isaksen, Gunhild Lerstad, Caroline Lind, Trygve Sølberg Ellingsen, Jostein Lappegård, Kristin Fjeldstad Enga, Ida J. Hansen-Krone, Knut Borch, Helle Jørgensen, Cathrine Ramberg, Simin Jamalay, Nadezhda Latysheva, Irina Starikova, Mikhail Sovershaev, Elena Egorina, Timofey Sovershaev, Ellen Brodin, Anders Vik, Tove Skjeldbakken, Jan Brox, Bjarne Østerud, Birgit Svendsson and Arne Nordøy) for creating a great scientific environment and for making the PhD-life very joyful.

I also want to thank the Tom Wilhelmsen Foundation and Professor Rolf Seljelid for their generosity and efforts. I am truly grateful for the many and unpredicted opportunities that have followed the student scholarship.

I would like to express my thanks to the staff and participants of the Tromsø Study as well as the Cancer Registry of Norway, for making this research possible.

Finally, I want to thank my family and friends for their patience and encouragement during these last years. I wish to direct a special thanks to my sister who always amuses me, and to my parents for their love and support.

Kristine
Oslo, August 2014

SUMMARY

The association between cancer and venous thromboembolism (VTE) was described already in the 19th century and cancer has later been acknowledged as one of the most important risk factors for VTE. Population-based studies on the subject with information about confounders and validated endpoints are lacking. The first aim of this thesis was to estimate the frequency of VTE among cancer patients in a population-based cohort study and assess the risk among cancer patients compared to a cancer-free reference population. Secondly, we wanted to investigate whether the level of leukocytes and platelets at inclusion influenced the future risk of VTE in cancer patients and in those who remained cancer-free.

The fourth survey of the Tromsø study (Tromsø IV) was applied in all four papers of this thesis. The Tromsø Study is a prospective study of adult inhabitants of Tromsø. In Tromsø IV (1994-95), information from more than 27 000 subjects were collected by physical examination, self-administrated questionnaires and blood tests, and VTE events were registered throughout 2010. Information about cancer was provided by the Cancer Registry of Norway. In paper II, the Tromsø IV cohort was merged with two additional Scandinavian cohorts (i.e. HUNTII and DCH) and 137 000 subjects were included in the study.

VTE occurred among 3-5 % of the cancer patients. Malignancy accounted for 20-25 % of the VTE events in the population, and the proportion was highest among middle-aged where cancer explained almost 30 % of the events. Patients with malignancy exhibited an overall 5-fold increased risk of VTE. The risk was highest during the initial 6 months after diagnosis (i.e. 17-fold increased) and declined thereafter. Patients with certain cancers, such as pancreatic-, lung- and brain cancers, had a particularly high risk of VTE. However, most cancers exhibited a high risk during the initial 6 months after diagnosis with incidence rates ranging from 30-90 cases per 1000 person-years for all sites, except for breast- and prostate cancers which had substantially lower risks. Despite the strong association between high age and VTE in the general population, the risk of VTE was similar across age-categories within the first year after a cancer diagnosis.

We found that WBC- and platelet count were associated with VTE in cancer patients. Baseline leukocyte- or platelet count above the 80th percentile provided doubled risk of VTE compared to the 40th percentile, and the combined effect of the parameters was synergistic. The association was confined to subjects diagnosed with cancer, and the results suggest that platelet- and white blood cell counts have impact on the risk of cancer-related VTE.

SAMMENDRAG

Sammenhengen mellom kreft og venøs blodpropp (i.e. VTE) ble beskrevet allerede på 1800-tallet, og i dag er kreft en av de viktigste risikofaktorene for VTE vi kjenner til. Store befolkningsstudier med informasjon om tilleggsfaktorer og validerte diagnoser har manglet i kunnskapsbildet. Vi ønsket å undersøke forekomsten av kreft-relatert VTE i en stor, prospektiv kohort studie, og estimere den relative risikoen for VTE blant kreftpasienter sammenliknet med en kreftfri populasjon. Videre ville vi se om antall hvite blodceller og blodplater hadde innvirkning på VTE-risikoen hos de som utviklet kreft og hos de som forble kreftfri gjennom studieperioden.

Data fra den fjerde Tromsøundersøkelsen gjennomført i 1994-95 (Tromsø IV) er brukt i alle fire artiklene i avhandlingen. Alle innbyggere i Tromsø kommune som var fylt 25 år ble invitert, og 27 000 personer deltok (77% av de inviterte). Informasjon om deltakerne ble innhentet ved hjelp av klinisk undersøkelse, spørreskjemaer og blodprøver, og kreftdiagnoser ble registrert ved kobling til Kreftregisteret. VTE hendelser blant deltakerne ble registrert fra inklusjon til 2010. Artikkel II er basert på en sammenslått populasjon bestående av Tromsø IV og to andre Skandinaviske befolkningsstudier (HUNTII og DCH), og 137 000 deltakere inngikk i den studien.

VTE ble diagnostisert hos 3-5% av kreftpasientene gjennom oppfølgingstiden. Kreft kunne forklare hele 20-25% av VTE-tilfellene i befolkningen, og andelen var høyest blant middelaldrende der nærmere 30 % av tilfellene var forklart av kreft. Sammenliknet med kreftfrie deltakere hadde de som utviklet kreft 5 ganger høyere risiko for VTE. Risikoen var høyest i de første 6 månedene etter diagnosen og falt deretter. Enkelte krefttyper som bukspyttkjertelkreft, lungekreft og hjernesvulster var assosiert med høyest risiko, men alle krefttyper ga høy risiko i den første tiden etter diagnosen. Høy alder, som vanligvis er en sterk disponerende faktor for VTE, var bare svakt assosiert med VTE i det første året etter en kreftdiagnose.

Konsentrasjonen av hvite blodceller og blodplater i blodet målt før kreftutvikling påvirket VTE-risikoen hos de som utviklet kreft. Begge parameterne ga hver for seg en dobling i risiko når 80-persentilen ble sammenliknet med 40-persentilen, og den kombinerte effekten av høye konsentrasjoner av hvite blodceller og blodplater var synergistisk. Resultatene tyder på at basalnivået at hvite blodceller og blodplater bidrar til utvikling av blodpropp hos kreftpasienter.

LIST OF PAPERS

The thesis is based on the following papers:

I. The increased risk of venous thromboembolism by advancing age cannot be attributed to the higher incidence of cancer in the elderly: the Tromsø study
Blix K, Brækkan SK, le Cessie S, Skjeldestad FE, Cannegieter SC, Hansen JB.
Eur J Epidemiol. 2014; 29(4):277-84.

II. Cancer-associated venous thromboembolism in a general population – the Scandinavian Thrombosis and Cancer (STAC) Study
Blix K, Severinsen MT, Brækkan SK, Jensvoll H, Dziewiecka O, Kristensen SR, Overvad K, Tjønneland A, Næss IA, Hammerstrøm J, Rosendaal FR, Cannegieter SC, Hansen JB.
Manuscript

III. White blood cell count measured prior to cancer development is associated with future risk of venous thromboembolism – the Tromsø Study
Blix K, Jensvoll H, Brækkan S, Hansen JB.
PloS One. 2013; 8(9):e73447.

IV. Platelet count measured prior to cancer development is a risk factor for future symptomatic venous thromboembolism: the Tromso Study
Jensvoll H, Blix K, Brækkan S, Hansen JB
PloS One. 2014; 9(3):e92011.

ABBREVIATIONS

ADP	adenosine diphosphate
ANC	Awareness of Neutropenia in Chemotherapy
APC	activated protein C
AR %	attributable risk fraction (i.e. proportion of cases among exposed that can be attributed to the exposure)
AT	antithrombin
BMI	body mass index
CATS-study	the Vienna Cancer and Thrombosis study
CI	confidence interval
CLOT-trial	The randomized Comparison of Low-molecular-weight heparin versus Oral anticoagulant therapy for the prevention of recurrent venous Thromboembolism in patients with cancer-trial
CRN	Cancer Registry of Norway
CRP	C-reactive protein
DCH-study	Diet, cancer and health-study
DCO	death certificate only
DNA	deoxyribonucleic acid
DOACs	direct oral anticoagulants
DVT	deep vein thrombosis
EDTA	ethylene-diamineteraacetic acid
eGFR	estimated glomerular filtration rate
EPCR	endothelial protein C receptor
ESAs	erythropoiesis-stimulating agents
FII	factor II (prothrombin)
FIIa	factor IIa (thrombin)
FIXa	activated factor IX
FVIIa	activated factor VII
FVIII	factor VIII
FVL	factor V Leiden

FX	factor X
FXa	activated factor X
FXa	activated factor X
FXI	factor XI
GP	glycoprotein
HR	hazard ratio
HUNT-study	Health Survey in Nord-Trøndelag (*Helseundersøkelsen i Nord-Trøndelag)*
ICD	International Classification of Diseases
IR	incidence rate
LITE-study	Longitudinal Investigation of Thromboembolism Etiology-study
LMWH	low molecular weight heparin
MAR	missing at random
MCAR	missing completely at random
MEGA-study	Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis-study
MMP	matrix metalloproteinase
MPs	microparticles
MPV	mean platelet volume
NETs	neutrophil extracellular traps
NMAR	not missing at random
NNT	number needed to treat
OR	odds ratio
PAR %	population attributable risk fraction (i.e. proportion of cases in the population that can be attributed to the exposure)
PE	pulmonary embolism
PS	phosphatidylserine
PY	person-years
RAM	risk assessment model
RCT	randomized controlled trial
RIETE	Registro Informatizado de la Enfermedad Trombo Embólica
STAC-study	Scandinavian Thrombosis and Cancer-study

TCIPA	tumor cell induced platelet aggregation
TF	tissue factor
TF+ MPs	tissue-factor-bearing microparticles
VTE	venous thromboembolism
vWF	von Willebrand factor
WBC count	white blood cell count
WC	waist circumference

1 INTRODUCTION

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is development of a blood clot in the deep veins, primarily of the lower extremities, that prohibits normal venous blood flow back towards the heart. The condition leads to pain, redness and swelling of the affected extremity. Pulmonary embolism is traditionally understood as a complication of DVT where a part of the clot, an *embolus*, breaks free from its origin and is carried with the blood-stream to the arterial circulation of the lungs. Where the vessel narrows, the clot is fixed and may obstruct the blood flow of the respective pulmonary artery. However, the origin of the pulmonary emboli remains undetected in up to 50 % of PE patients (1, 2). This may be due to evaporation or dislodging of the entire DVT, but novel origins such as cardiac thrombi and *de novo* thrombus formation in the lung arteries may also be possible. Classical signs and symptoms of pulmonary embolism are dyspnea, tachypnea and pleuritic chest pain. Depending on the size of the embolus, the clinical course of a pulmonary embolism ranges from asymptomatic to fatal circulatory collapse (3, 4). Patients diagnosed with VTE are treated with anticoagulants, and the standard treatment consists of concomitant low molecular weight heparin (LMWH) and a vitamin K antagonist (VKA) in the initial phase, followed by VKA monotherapy in the long-term treatment (5). Direct oral anticoagulants (DOACs) are now being implemented in the standard treatment of VTE patients.

The association between cancer and venous thrombosis was described already in the 19th century, and has been termed the Trousseau syndrome after one of the early discoverers (6, 7). The link between cancer and VTE has later been convincingly demonstrated in a number of publications, and today cancer is acknowledged as one of the most important risk factors for venous thromboembolism in the population. However, the

pathophysiology of these thrombi is not fully understood, and large variations in risk have been demonstrated with regard to cancer- and patient-related characteristics.

In the past decades attention has been addressed towards identification of patients at risk for appropriate use of prophylaxis and improved antithrombotic treatment in patients with cancer. The CLOT Trial from 2003 detected lower rates of recurrent VTE in cancer patients treated with LMWH compared to VKA, and is the basis for the current recommendation of LMWH monotherapy in cancer-associated VTE (8, 9). The DOACs have not been tested in appropriate trials of cancer patients or compared to long-term treatment with LMWH, and the role of these agents in cancer-associated VTE is not established (10, 11).

1.1 **Epidemiology**

1.1.1 *Venous thromboembolism in the general population*

Venous thromboembolism occurs in 1-2 per 1000 adults in Western countries annually, and is the third most common cardiovascular disease after myocardial infarction and stroke (12). The clinical presentation as deep vein thrombosis is more common than pulmonary embolism, and occurs approximately at a 2:1 ratio (3, 13, 14). The two conditions are often present at the same time. Silent pulmonary embolisms have been observed in 50-80 % of the patients with acute DVT (15), and compression ultrasonography or venography in patients with pulmonary embolism revealed DVT in about 50 % of the patients (1, 2, 16).

A VTE event is classified as provoked or unprovoked (idiopathic), based on the presence or absence of provoking factors. Provoking factors are transient conditions or situations which are associated with VTE and include hospitalization, acute medical illness, malignancy, surgery, trauma, plaster-cast and long-haul travel. The concept may also

comprise certain lasting conditions such as paralysis and wheel-chair use. In general, the presence of provoking factors is associated with lower recurrence rates (17) and justifies a shortened long-term treatment (5). Population-based studies estimate that 50-60 % of the VTE events are associated with provoking factors (13, 14, 18, 19).

VTE is a disease with serious short-and long-term consequences. One-month case-fatality rates of 10-15 % for PE and of 5-10 % for DVT have been reported (3, 13, 19). Additionally, sudden deaths caused by unsuspected PE are often misinterpreted as myocardial infarction (20), and was the single diagnosis most often missed by clinicians (21). However, it has also been emphasized that only a low proportion of deaths that follow PE are attributable to the PE itself (22-24). Major bleeding during treatment, defined as fatal bleeding, bleed into critical sites, fall of ≥ 2 g/dl hemoglobin or requirement for transfusion of two or more units of blood, have been reported in 1-2 % of the patients in recent clinical trials (25). Despite appropriate therapy, recurrence is common and occurs in 10-30 % of patients with unprovoked VTE within five years (26-28), and tends to have the same location (PE/DVT) as the initial event (27, 29, 30). Recurrence more often follows DVT than PE (27, 29), and is more common in men than women (26, 31). Post-thrombotic syndrome, characterized by chronic pain, swelling, stasis dermatitis and in severe cases leg ulcers and intractable edema, develops in 20-50 % of the DVT-patients (32, 33).

1.1.2 Venous thromboembolism in cancer patients

Malignant diseases are present in 15-25 % of all venous thrombotic events in a general population, and recent literature suggests that cancer is associated with an overall 4-7 fold increased risk of venous thrombosis compared to subjects without cancer (34-36). However, the risk-estimates for cancer-associated VTE rely on many cancer- and patient

characteristics, as well as methodological aspects such as duration of follow-up, patient selection and the identification of the VTE events (Table 1). Clinical trials of thromboprophylaxis in hospitalized medical patients with cancer and in oncology patients attending out-patient clinics have reported rates of VTE of 4-20 % (37) and 3-4 % (38, 39) in the respective placebo groups. Corresponding observational studies have observed cumulative risks of 2-7 % (40-43) (Table 1).

Although the above-mentioned studies provide relevant risk-estimates during high-risk settings, population-based studies and general cancer cohorts are important in terms of estimating the disease burden at population level. In epidemiological studies where the cancer diagnoses are obtained from cancer-registries and encompass all sites and stages, the rates of VTE are fairly low, and reported rates range from 0.8 % per year to 1.2 % within the first 6 months (34, 44, 45). In these studies, the observation-time is not confined to specific exposures such as active treatment, hospitalizations or progression of the disease, and show a clear trend of decreased risk from the date of the cancer diagnosis throughout follow-up. Blom and co-workers investigated site- and stage-specific incidence rates of VTE and assessed the impact of treatment modalities in a population based cancer cohort (44). Incident cancers between 1986 and 2002 were obtained from the Dutch cancer registry, and VTE events were collected from two outpatient anticoagulation clinics. The 6-month cumulative risk varied across cancer sites and ranged from 1-6 %. A limitation of the study was the detection of VTE diagnosis at outpatient clinics, which did not capture severe cases with poor prognosis that were managed in-hospital only or patients who died before registration at the anticoagulation clinics. A similar study by Chew and colleagues obtained cancer-diagnoses from the Californian Cancer Registry between 1993 and 1995 and reported VTE rates by linkage to the state registry of discharge diagnoses (45). The highest rate was

observed in patients with remote pancreatic cancer where 5.4 % developed VTE within 2 years, and a clear trend from localized to advanced disease was observed in each cancer site.

Concurrent with the beginning of this project, Cronin-Fenton and colleagues published the first prospective study to investigate the risk of VTE in patients with cancer compared to the general population (34). This Danish registry-based study of 57 600 patients with cancer and 287 500 controls reported that risk of VTE in cancer-patients was increased almost 5-fold (HR 4.7), and found an incidence rate of 1.4 % in the first year after a diagnosis of cancer. However, the study was confined to hospitalized cases. This might be problematic because the risk estimates (i) might have been influenced by a differential bias in the outcome assessment (i.e. different hospitalization rate for VTE-patients with and without cancer) and (ii) did not capture the total VTE burden in the population. Furthermore, similar to the study by Chew and colleagues, the VTE events were retrieved from a national diagnosis registry without validation. The estimated positive predictive value of a VTE-diagnosis in a sub-cohort was only 75 % (46). A study of discharge diagnosis from France found that the sensitivity of ICD-10 codes was better for PE than DVT, and that VTEs that developed during hospitalization or after surgery often were missed (47).

Study population	*Authors, year*	*Study design*	*Number of participants*	*Relative risk*	*Absolute risk*
Population based cancer cohorts	Levitan et al, 1999 (48)	(1988-1990)	1 200 000 cancer patients	-	0.6 %
	Blom et al, 2005 (35)	Case-control study (MEGA)	3220 VTE patients	6.7 (OR)	-
	Blom et al, 2006 (44)	Registry-based cohort study	66 329 cancer patients	-	12 per 1000 (6-months cumulative risk)
	Chew et al, 2006 (45)	Registry-based cohort study	235 149 cancer patients	-	1.6 % (2-year cumulative risk)
	Cronin-Fenton et al, 2010 (34)*	Population based cohort study (registry based)	57 591 cancer patients 287 476 controls	4.7 (HR)	1.4 % (1-year incidence)
	Walker et al, 2013 (49)*	Population based cohort study (registry based)	83 203 cancer patients 577 207 controls	4.7 (HR)	14 per 1000 person-years (total follow-up)
Hospitalized cancer patients	Khorana et al,2006 (40)	Multicenter registry-based cohort (1995-2002)	66 106 hospitalized neutropenic cancer patients	-	6.5 % (cumulative risk during all hospitalizations)
	Stein et al,2006 (41)	Nationwide registry-based cohort (1979-1999)	40 787 000 patients hospitalized with cancer	2.0 (OR)	2 %
Outpatients with cancer	Khorana et al, 2008 (42)	Prospective cohort study (ANC Study Group Registry) (2002-2005)	4 066 ambulatory cancer patients	-	2 % (cumulative risk after a median of 2.5 months)
	Ay et al, 2010 (43)	Prospective cohort study(CATS) (2003-2008)	819 ambulatory cancer patients	-	7.4 % (cumulative risk after a median of 2 years)
Pharmaceutical trials	Agnelli et al, 2009 (38)	Trial of VTE prophylaxis in outpatients with cancer (Protecht)	769 nadroparin 381 placebo	-	3.2 % (cumulative risk within 150 days in the placebo group)
	Agnelli et al, 2012 (39)	Trial of VTE prophylaxis in outpatients with cancer (Save-Onco)	1608 semuloparin 1604 placebo	-	3.4 % (cumulative risk after a median of 3.5 months in the placebo group)
	Samama et al, 1999 (50)	Trial of VTE prophylaxis in hospitalized medical patients (Medenox)	41 enoxaparin (cancer) 31 placebo (cancer)	-	10 % VTE with prophylaxis 20 % VTE with placebo
	Leizorovicz, 2004 (51)	Trial of VTE prophylaxis in hospitalized medical patients (Prevent)	72 dalteparin (cancer) 65 placebo (cancer)	-	3 % VTE with prophylaxis 8 % VTE with placebo
	Cohen, 2006 (52)	Trial of VTE prophylaxis in hospitalized medical patients (Artemis)	51 fondaparinux (cancer) 47 placebo (cancer)	-	17 % VTE with prophylaxis 4 % VTE with placebo

Table 1. Risk of VTE in patients with cancer categorized by study population.
* Published during the work of this thesis

The relative importance of different exposures may be expressed as attributable proportions. A few studies have reported attributable risk of cancer in the etiology of VTE (53, 54). The most reliable estimates suggested that cancer was responsible for 15 % of the VTE events in young subjects, and 35 % among the elderly (54). However, the relative risks that were applied in the calculations were not age-specific, and the estimates are biased if the relative risk varies across age-groups. No study has previously assessed the attributable risk of cancer based on incidence rates of VTE among cancer and non-cancer subjects.

VTE is a serious disease in cancer patients. Fatal PE after an initial VTE event is higher among cancer patients compared to cancer-free patients (55, 56), and bleeding complications during anticoagulant treatment are more common than in cancer-free subjects. In the RIETE registry, major bleeding was registered among 4 % during the first three months of treatment (57) whereas the 1-year cumulative rate has been reported to be 10-15 % (58-60). Cancer has also been associated with several-fold increased risk of recurrent VTE (19, 48) which was detected among approximately 15-20 % within the first year (58-60). Other adverse effects of VTE in this patient group are interruption of chemotherapy and more frequent and prolonged hospitalizations (59, 61, 62). The frequency of post-thrombotic syndrome among patients who have suffered from cancer-associated VTE is not known, but is presumably high among survivors due to the high recurrence rate.

Sørensen and co-workers were the first to demonstrate that cancer patients who developed VTE had a poor prognosis compared to cancer patients without VTE (63). The study was based on three linked databases; the Danish National Registry of Patients, the Danish Cancer Registry and the Danish Mortality Files. They found that the patients with cancer and VTE had a two-fold increased risk of death and that the prevalence of distant metastasis was higher among the VTE-patients. However, the cancer stage was not

considered in the mortality estimates, and the study was therefore not able to discriminate between more aggressive cancers or the thrombotic event as the cause of increased mortality. Several studies have confirmed the findings of Sørensen et al. Chew and colleagues found that the mortality of cancer-related VTE remained increased after adjustment for age and cancer stage (45). A study of colorectal-cancer patients reported increased mortality after VTE in patients with localized and regional disease, but not among patients with distant metastasis (64). The authors suggested that the increased mortality among those with non-advanced cancers and VTE was due to more aggressive cancer in the VTE patients not captured by stage. Recent mortality estimates from the Tromsø cohort found that VTE patients without cancer had a crude death-rate of 5.1 per 100 person-years, as compared to 12.7 per 100 person-years for cancer only and 55 per 100 person-years for those with cancer-related VTE (65).

In a frequently cited paper from 2007 Khorana et al investigated the causes of death among outpatients who received chemotherapy (66). Among 4466 patients enrolled in the ANC (Awareness of Neutropenia in Chemotherapy) Study Group Registry, 141 deaths (3.1%) were registered during a median follow-up of 75 days. 71% of the deaths were assumed to be a result of cancer progression. Thromboembolic events, including arterial and venous thrombosis, were registered as cause of death in 9% of the cases, and venous thrombosis accounted for 3.5 %. Lethal infections were equally common as thrombosis altogether and were responsible for 9% of the cases. In this study, the causes of death were not verified by autopsy, but retrieved directly from the death certificate. As stated by the authors, autopsy studies have revealed higher rates of pulmonary embolism among cancer patients than the rates reported for symptomatic VTE. A Norwegian study of autopsies performed between 1960 and 1984 reported pulmonary embolism in 10.5% of the 6200 subjects with a

registered malignancy, and in 8.4 % of the 21 500 subjects without malignancy (67). Similarly, another autopsy study of subjects who died in hospital reported that fatal PE had occurred in 14 % of the patients with cancer and in 8 % among the cancer free subjects, and further stated that 60% of the patients who died from PE had localized or limited metastatic cancers without poor prognosis (68). A Swedish study from 1970-1982 found even higher rates of PE in cancer patients, where 23 % of the patients had PE, of which more than 40 % were considered fatal (69). The highest rate of PE was observed in patients with pancreatic cancer where PE was confirmed in more than 40 % of the patients. Thus, the finding that 3.5% of deaths were due to VTE in the ANC Study Group Registry was probably too low. Updated autopsy studies are needed to estimate the true impact of VTE on the mortality among cancer- and non-cancer patients.

Altogether, cancer associated thrombosis leads to substantial resource claims and health care costs (59). In a retrospective study, VTE and VTE-related complications occupied 6 % of the bed-capacity at an oncology department (70), and adjusted measures have suggested that the average economic burden attributable to VTE in patients with cancer was close to 10 000 USD per patient within the first year after the event (61).

An increasing incidence of VTE among cancer patients has been noted in several studies (40, 41). From 1979 to 1999, Stein and colleagues observed an increase in the VTE-rate from 1.5 % to 3.5 % among hospitalized patients with cancer, whereas no such trend was observed in patients without a cancer diagnosis (41). The increase was most prominent in the 1990s, and was primarily caused by an increased frequency of DVT. Khorana and co-workers reported a 36 % increased risk of VTE among neutropenic cancer patients in the period 1995 until 2002 (40). Improved survival among cancer patients, more aggressive cancer treatment as well as increased awareness of cancer-associated VTE have been

suggested as likely explanations. The notion that the PE rate has remained constant undermines that incidentally detected VTE is the primary cause.

However, due to improved imaging techniques, incidental VTE detected during the diagnostics work-up or staging in cancer patients is common, and has been reported in 4 % of cancer patients who undergo computed tomography of the chest for reasons other than suspected PE (71). Similar rates of recurrence and mortality has been noted in patients with symptomatic and asymptomatic cancer-related VTE (60), and guidelines suggest that incidental PE should be managed like symptomatic events (5, 72).

The risk of VTE is highly dependent on the **cancer site** and rates of VTE in various cancers have been reported in a number of studies (73). Due to methodological variations between studies, the comparison of VTE risk in different cancers should probably be based on studies where several sites are included and cancer sites can be compared directly. Chew and colleagues found that advanced cancers of pancreas, uterus and stomach were associated with the highest risk, and that pancreatic cancer provided a clearly higher risk among the localized cancers (45). High risk in pancreatic cancer has also been noted by others, along with brain and ovarian cancer (44, 48). Prostate and breast cancers have generally been associated with a low risk of VTE (73).

1.2 **Pathophysiology**

1.2.1 *General pathophysiology of venous thromboembolism*

Hemostasis is essential in the physiological management of vascular injury, but may cause severe disease when it propagates within the vasculature. This process is termed *thrombosis* and is typically described by two distinct, but interlinked pathways.

Blood platelets, which are derived from megakaryocytes in the bone marrow (74) and are the smallest among the circulating cells, are responsible for the initial seal at the site of injury (75). Several receptors and ligands influence the platelet function. The platelet glycoprotein (GP) Ibα-receptor adhere platelets to the subendothelial tissue by binding to von Willebrand Factor (vWF) (76, 77). Fibrinogen, vWF and other ligands enable platelet aggregation and activation by binding to the receptor GP IIb/IIIa. Platelets are activated by addenosine diphosphate (ADP), collagen and thrombin. Activated platelets release a number of substances that further enhance platelet activation and recruitment, including ADP and thromboxane A_2 (75). Aggregates of platelets cover the disrupted endothelium and form the primary platelet plug. Upon activation, platelets also undergo a conformational change which increases their surface area and adhesive properties. “Flip-flop” reactions within the platelet membrane translocate negatively charged phospholipids, such as phosphatidylserine (PS), to the outer leaf of the membrane (78). In the mid-nineties, Hoffmann and co-workers proposed a cell-based coagulation model, suggesting that the PS-rich surface facilitates assembly of coagulation factors and provides a catalytic surface for several steps of coagulation (79).

The coagulation system is a series of proteins that are activated in a cascade fashion that results in fibrin deposition (80). Subendothelial tissue exposed by injury express tissue factor (TF), a transmembrane protein recognized as the main trigger of coagulation in vivo (81). In complex with factor (F) VIIa, TF activates small amounts of FIX and FX (the extrinsic pathway of coagulation) (80). Activated FX (FXa) and its associated co-factor (FVa), also termed the *prothrombinase complex*, converts prothrombin (FII) to thrombin (IIa), and ultimately leads to fibrin deposition through a feed-forward mechanism (78, 80, 82). However, unlike arterial thrombosis where plaque rupture leads to exposure of

subendothelial ligands, venous thrombi are usually surrounded by intact endothelium (83, 84). Extensive mechanistic research has aimed to identify the triggers of hemostasis in venous thrombosis.

Today it is widely accepted that venous thrombi develop in the valvular sinuses of the venous valves (85, 86). In this particular area of the veins the blood tends to linger and is susceptible to desaturation. As the innermost layer of the vessel wall is supplied from the vessel lumen, low oxygen tension causes endothelial hypoxia that in turn induces a number of proinflammatory and procoagulant processes in endothelial cells as well as in circulating leukocytes and platelets (Figure 1). Down-regulation of anticoagulant proteins such as thrombomodulin and the endothelial protein C receptor (EPCR) reduce the anticoagulant activity, and increased expression of membrane-bound P-selectin and vWF recruits leukocytes and platelets to the hypoxic endothelium. Importantly, activated leukocytes and platelets bud off small phosphatidylserine-rich membrane vesicles (0.1-1 μm) known as microparticles (MPs) (87). MPs, and especially those derived from monocytes (88), may express TF (89). It has been suggested that TF-bearing (+) MPs are key triggers of venous thrombosis (90). However, the results are inconsistent (91-95) and the majority of studies are retrospective and susceptible to reversed causation (96). Thus, the role of MPs in non-cancer VTE remains to be established.

Leukocytes may further enhance thrombosis through surface expression of TF, recruitment of platelets and release of neutrophil extracellular traps (NETs). NETs were first described in 2004, and are webs of DNA containing histones and antibacterial proteins (97). NETs have previously been recognized as a part of the innate immune response towards bacterial infections, and have only recently been proposed as an important feature of neutrophil-driven coagulation (98, 99).

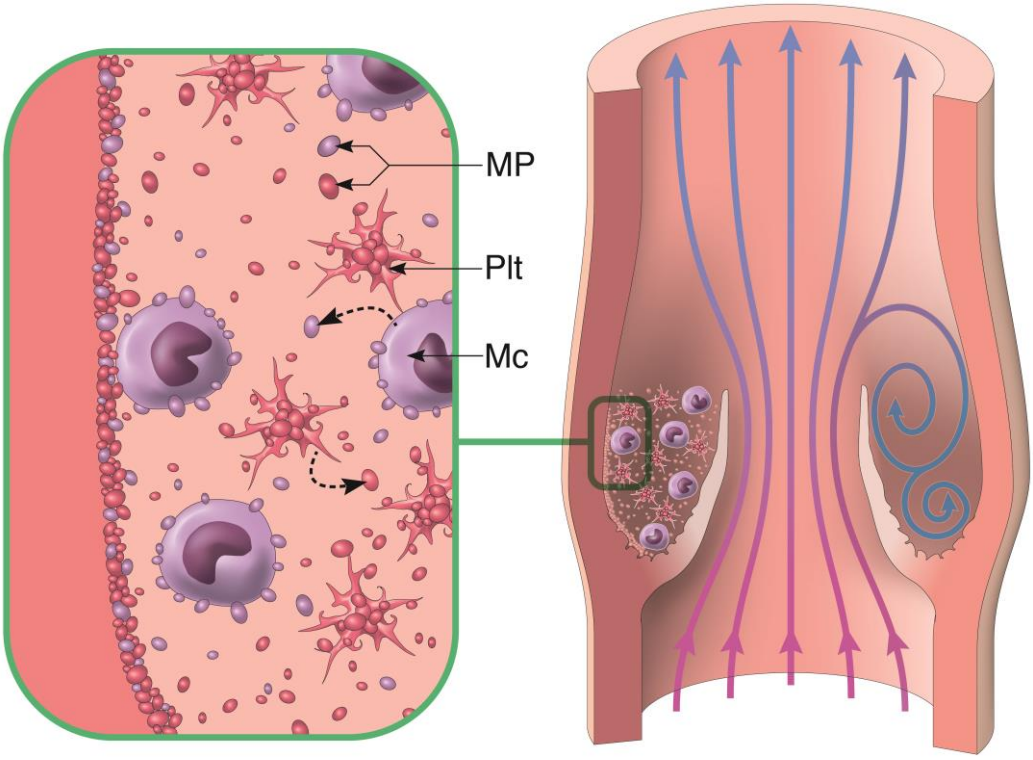


Figure 1. The pathophysiology of venous thromboembolism: blood is caught in a secondary vortex of the valve pockets and becomes desaturated. Hypoxia promotes proinflammatory and prothrombotic responses in endothelial cells, leukocytes and platelets (Plt). Endothelial P-selectin expression leads to docking of leukocytes to the endothelium. Activated platelets and leukocytes bud off procoagulant microparticles (MP). The MPs are procoagulant due to surface phosphatidylserine and in some cases expression tissue-factor (especially those derived from monocytes (Mc)).

1.2.2 *Pathophysiology of cancer-related venous thromboembolism*

Markers of ongoing coagulation such as D-dimer, thrombin-antithrombin complexes and pro-thrombin fragment 1+2 are elevated in patients with cancer compared to healthy controls (100-102), and a number of mechanisms for cancer-induced hypercoagulability have been proposed. The malignant environment may induce intrinsic changes in the hemostatic system, and veins can be compressed by solid tumors leading to stasis or the endothelium may be damaged by invasive growth in the vessel wall. In addition, patients with cancer are subjected to a number of VTE risk factors during the course of a malignant disease, such as major surgery, chemotherapy, hospitalization, infections and bed-rest.

A cysteine proteinase termed cancer procoagulant was isolated from animal carcinoma cells already in 1985 (103). The molecule was able to activate FX directly and has been emphasized as an important contributor to activation of coagulation in cancer (102). Cancer-induced deficiency of the vWF cleavage protein ADAMST-13, causing unusually large von Willebrand multimeres has also been described (104). Additionally, elevation in coagulation factors due to decreased hepatic clearance (100) and pro-coagulant endothelium caused by tumor derived cytokines as well as regulation of the fibrinolytic system (105) may be significant mediators of the pro-thrombotic state in cancer patients.

Recent publications emphasize the role of tumor derived microparticles in cancer-associated VTE (106, 107). Epithelial-derived malignant tissues often express TF (108-110), and together with monocytes, cancer cells are an important source of TF+MPs in the circulation (78, 106). TF-MP activity has been associated with more advanced cancer stage, higher tumor grade and decreased survival in patients with pancreatic cancers (111).

Finally, leukocytosis and thrombocytosis are common findings in patients with cancer and have been associated with increased risk of cancer-associated VTE (112-115). However, elevated levels of these blood cells are considered as epiphenomenon of an inflammatory state and are associated with advanced malignant disease. Epidemiological studies may therefore be confounded by the presence of other pro-thrombotic conditions, and a potential role of high leukocyte or platelet count is difficult to evaluate. It is therefore not known whether high levels of cells per se contribute the procoagulant state in cancer patients, or merely reflect associated risk factors.

1.3 **Risk factors**

1.3.1 *Non-cancer related risk factors*

During the past decades, epidemiological studies have identified a number of risk factors for venous thrombosis. The three major causes of thrombosis postulated by Rudolph Virchow in the mid-1800s still apply, and suggest that thrombosis results from altered blood flow, hypercoagulability or vessel wall injury. In the modern literature, these causes are usually categorized as acquired or inherited risk factors.

Acquired risk factors for VTE include high age, obesity, tall stature, immobility, medical illnesses, surgery, trauma, pregnancy, puerperium and female hormones, as well as cancer and cancer-associated factors addressed in the next section. **Increasing age** is the strongest and most consistent risk factor for VTE in the general population, and the annual risk is observed to increase exponentially from 0.1 per 1000 in adolescence to 6-10 per 1000 at high age (13, 14, 24, 116). The reason for increased risk of VTE by age is unknown, but thickening of the venous valves (117), decreased muscle tone and accumulation of co-morbidities including malignancy have been suggested as potential underlying causes (53). A higher risk has been observed in young women compared to men (13, 116), and has been attributed to reproduction-associated factors and the use of oral contraceptives in younger women (118, 119). In middle-aged and elderly, an increased risk has been noted in men (13, 116, 120). Interestingly, this **difference between genders** was eliminated when the risk estimate was adjusted for body height (120). Recently, it has also been emphasized that after taking reproduction-associated factors in women into account, men have a 2-fold higher risk also at young age (121). **Body height** has been demonstrated to be an independent risk factor for VTE (120, 122, 123), and 30 % higher risk of VTE per 10 cm increase in height has been noted in men (123). **Obesity**, measured by body mass index

(BMI) ≥ 30 kg/m^2, provides a 2-3 fold increased risk of VTE (122, 124-127). In the Tromsø study, waist circumference (WC) had the best ability to identify patients at risk of VTE, and WCs ≥ 85 cm in women and ≥95 in men were associated with 2- and 3-fold risks, respectively (127). Population-based studies that have investigated the association between **smoking** and VTE have reached diverging conclusions (125, 128, 129). A recent meta-analysis concluded that smoking is a weak but independent risk factor for VTE, and emphasized that studies that did not control for BMI tended to report lower estimates (130). However, in a previous report from the Tromsø Study, the 1.5 fold increased risk of VTE by heavy smoking (≥ 20 pack-years) disappeared when cancer and myocardial infarction were taken into account in a competing risk model (131). Thus, the risk of VTE by smoking remains controversial and should perhaps be further investigated in populations with and without these diseases.

It has been demonstrated that family history of VTE provides a 2-3 fold increased risk of VTE (132-136), and family studies have estimated that 50-60 % of the variation in susceptibility to develop VTE can be attributed to **inheritance** (137-139). Since the first discovery in 1965 (140), a number of inherited risk factors have been identified (141). *Thrombophilia* may be caused by increased function of natural procoagulants or impeded effect of the anticoagulants. So-called *gain of function* thrombophilia include **Factor V Leiden** (FVL), prothrombin G20210A and non-O blood groups. Heterozygote FVL is present in approximately 5 – 8 % of the population (128, 142, 143) and is more common in northern Europe. FVL is caused by a missense mutation of the Factor V gene which makes the cofactor insensitive to activated protein C (APC), and heterozygote carriers have a 2-5-fold increased risk of VTE compared to non-carriers (141, 144). **Prothrombin G20210A** is a polymorphism associated with increased levels of prothrombin and regulation of the anticoagulant pathway of APC. The variant is found in 1-2 % of the population (143, 145) and is associated with a

1.5-3 fold increased risk of VTE (144). The **non-O blood groups** are the most common inherited risk factors as they are found in ~ 60 % of the population (143). Due to decreased clearance of non-O vWF, subjects with these blood types have higher levels of vWF and FVIII (146) and a 1.5-2 fold higher risk of VTE compared to blood group O (141, 143). However, blood type remains an independent risk factor for VTE after adjustment for plasma levels of vWF and FVIII (147, 148), and implies that the thrombotic risk in subjects with non-o blood groups also may be mediated through additional unknown pathways. Protein C, -S and antithrombin deficiencies constitute the *loss of function* thrombophilia. These deficiencies are associated with higher risk, and are termed *severe thrombophilia*. **Antithrombin (AT) deficiency** was first described in a mother (39 years) and her son (13 years) from Skjervøy both experiencing VTE by the Norwegian physician Olav Egeberg in 1965 (140). AT is a potent inhibitor of several steps of the coagulation cascade (thrombin, FXa, FIXa), and is further enhanced by administration of heparins. Regardless of the high number of identified mutations (>340), AT deficiencies are rare (~0.02 %) and are associated with about 10-50 fold increased risk of VTE (144). **Protein C and S deficiencies**, discovered in the 80s (149, 150), provide risks of similar magnitude (~10-fold), however they too are rare and occur in only 1-5 per 1000 in the population (151).

Inherited risk factors can be modified by the presence of other genetic or environmental factors, and is referred to as gene-gene or gene-environment interactions. For instance, more excess cases were observed in obese carriers of FVL than in the non-obese (122, 128). The effect was described as an interaction on an additive scale. Similarly, smoking appears to provide higher excess risk among FVL carriers than non-carriers (128, 152). Positive gene-gene interactions are also common. One example is the high risk of VTE

noted in subjects with both FVL and prothrombin 20210A polymorphism, where a 20-fold increased risk has been demonstrated (153).

Despite increasing knowledge of the inherited risk factors, it has been estimated that known mutations only account for 5 % of the observed heritability (154). In coherence, family history remained an independent risk factor for VTE after consideration of common inherited risk factors (133). Epigenetics, unrecognized mutations and interactions may be underlying explanations. Genome-wide association studies have detected weak genetic mutations that are frequent in the population (e.g. single nucleotide polymorphisms; SNPs). Ongoing and future genomic studies will presumably increase the knowledge on genetics in thrombosis.

Venous thromboembolism is a multicausal disease, meaning that several risk factors need to be present for a thrombus to develop. The concept is well explained by the *potential model* for thrombosis (155), which illustrates how individual risk factors, such as high age and FV Leiden, alone may not be sufficient for formation of a thrombus. Under high-risk situations however, these intrinsic risk factors contribute to reach a threshold where the physiological anticoagulant properties are outweighed by the hypercoagulable state, resulting in thrombosis. The model also demonstrates the acute pathogenesis of VTE. Unlike arterial plaque formation which evolves throughout life, incident VTE occur when accumulation of factors leads to a sudden imbalance between the natural pro-and anticoagulants (Figure 2).

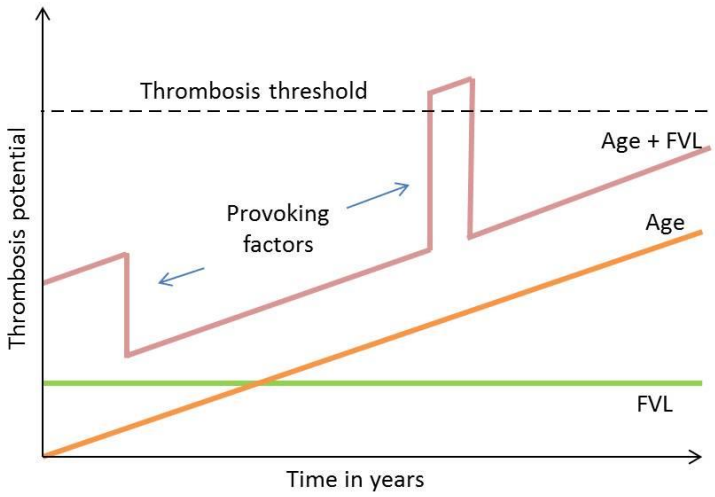


Figure 2. The thrombosis potential model. The green line represents an intrinsic risk factor such as factor V Leiden (FVL), and the red line represents the effect of age alone. The purple line demonstrates the effect of age and FVL, in combination with provoking factors early and late in life, respectively. The latter combination reaches the thrombosis threshold and the person develops symptomatic VTE.

1.3.2 *Cancer-related risk factors*

A number of cancer-specific factors may lead to the hypercoagulable state observed in cancer patients, and several factors are often present at the same time. Characteristics like cancer site, stage, treatment modality and age are highly correlated. Since all these factors also influence the risk of thrombosis, it can be difficult to determine the effect of the individual contributors.

Chemotherapy is a well-established risk factor for VTE (156). In a nested case-control study from the US (36), the risk for VTE by malignant disease was increased from 4-fold to 6.5-fold in patients who received chemotherapy, and in a large cohort of cancer patients from the Netherlands, chemotherapy was associated with a 2 fold increased risk of VTE (44). In a case cross-over study from the United States, chemotherapy was identified as an important trigger of hospitalization for VTE and was associated with a 6-fold increased risk (157). A randomized study showed high excessive risk of VTE in breast cancer patients who were assigned to 6 months of chemotherapy in addition to tamoxifen in comparison to treatment with tamoxifen alone (14 % and 2.6 %, respectively) (158). Khorana and co-

workers reported an absolute VTE risk of 2.2 % after a median follow-up of 2.5 months (range 5-364 days) in a study of 4066 outpatients included in ANC Study Group Registry (42). Two smaller studies found higher rates of VTE; 7 % during or within 3 months (159) and 8 % within 35 months after chemotherapy (114). Various chemotherapeutic agents affect the risk of VTE differently, and certain combination regimens are known as highly thrombogenic. Cisplatin-based agents provided higher risk for thrombosis than oxaliplatin (12 % and 6.5 % within one month after discontinuation, respectively) in a randomized trial of patients with gastro-esophageal cancers (160). Thalidomide with concomitant high-dose steroid therapy and/or chemotherapy in patients with multiple myeloma has been associated with particularly high risk of VTE (161-164). A meta-analysis showed 30 % increased risk of VTE in patients treated with the angiogenesis inhibitor bevacizumab (165).

Several potential mechanisms may explain the risk of VTE observed during chemotherapy. First, chemotherapeutic agents can cause endothelial injury. Lysis of tumor cells, endothelial cells or circulating blood cells may cause release of various cytokines with prothrombotic potential. Cell free DNA has been suggested as a novel procoagulant stimulus, and has been shown to rise 24 hours after administration of chemotherapy (166). Chemotherapy have also been proposed to activate blood platelets directly through the arachidonic acid pathway (167). Implanted ports, bed rest and reduced performance status as well as neutropenia and infections may further enhance the VTE risk during chemotherapy. Somewhat surprisingly, two studies have failed to demonstrate increased levels of circulating MPs in subjects with chemotherapy-related VTE (168, 169).

Several **acute infections** have been associated with a higher risk of VTE (170-172), and infection has been emphasized as an important risk factor for VTE in cancer patients (173). A particularly high risk of VTE was reported in a study of neutropenic cancer patients

(40), and multiple neutropenic episodes have been associated with increased risk of recurrent VTE in oncology patients (174). Neutropenia is closely related to infection, and abovementioned results might imply that infectious diseases in patients with malignancy exhibit a particular thrombotic risk.

VTE is a frequent complication of **surgery** in both cancer and non-cancer patients. Heit and colleagues reported that recent institutionalization with and without surgery were associated with 22- and 8-fold increased risks of VTE, respectively (36). A 2-3 fold higher risk of VTE and fatal PE following surgery for cancer compared to surgery in non-cancer patients (9, 175-177) and a 30-day cumulative risk of 1.6 % have been reported after cancer surgery (178). Surgeries for gastrointestinal, lung, prostate and gynecological cancers were high risk procedures, and the risk was particularly high in older patients, in those with congestive heart failure, obese patients or in patients with ascites, and in subjects with preoperative thrombocytosis. Operation time > 6 hours was associated with a 4-fold increased risk compared to a duration < 2 hours. A nationwide study from the UK reported an in-hospital VTE rate of 1.3 % after major cancer surgery (177). However, 30-60 % of postoperative VTE occur after hospital discharge (175, 178, 179). Extended LMWH prophylaxis beyond the hospital stay has been tested in several trials of cancer and non-cancer patients, and has been reported to reduce the risk of VTE without any substantial increase in bleeding complications (180). In the 9th edition of the American College of Chest Physicians guidelines for prevention of VTE, the recommendation for extended prophylaxis (4 weeks postoperatively) after cancer surgery was strengthened (Grade 1B in 2012 vs. 2A in 2008) (180).

Immobilization is a recognized provoking factor for venous thromboembolism (181). In a case-control study of cancer-free subjects aged > 70 years, immobility-related risk

factors (e.g. hospitalization, surgery, fractures, plaster cast use, minor injuries and transient immobility at home) accounted for 40% of the VTE events (182). A meta-analysis of 36 cohort studies and seven case-control studies found that immobilization was associated with an overall 2-fold risk of VTE (183), and in a case-crossover study from 2012, immobilization provided a 4-fold increased risk of hospitalization with venous thrombosis (157). Due to the non-randomized distribution of bed-rest among patients, the sole impact of immobilization is difficult to separate from the underlying cause of bed-confinement. However, the biological rationale for a true association is strong. In healthy individuals, the venous pressure decreases during exercise due to the muscle pump activity, and venous emptying is facilitated by high muscle mass (184). A supine position prohibits the use of the muscle-vein pump, and may induce stasis and vessel-wall hypoxia. Furthermore, muscle mass rapidly decreased during bed-rest. It is possible that this causes inadequate venous emptying also in the period after prolonged immobility. The increased risk of VTE observed after long-haul travel (185, 186) and in patients with stroke (187-189) further strengthens the evidence of a causal relationship between immobility and VTE. Immobilization is common in cancer patients, especially during active treatment and at end-stage disease, and may be responsible for a high proportion of cancer-associated VTE.

Venous ports and **indwelling central venous catheters** (CVC) for administration of chemotherapy are associated with an increased risk of upper-extremity DVT, and are often considered as a provoking factor (190). The frequency of upper limb DVT varies greatly between studies, and ranges from 4-40 % (191-196) . A recent Canadian study followed 400 cancer patients with newly implanted ports who did not receive thromboprophylaxis. Within a median of 12 months, 8.5 % were diagnosed with VTE. Men had a 2-fold increased risk compared to women, and PE was equally common as DVT (197).

The majority of studies of cancer-associated VTE are based on data from health registries. While cancer-associated factors such as cancer stage and treatment often are available in such registries, and co-morbidity data can be obtained by discharge diagnosis codes, other patient characteristics can normally not be provided. As a consequence, the impact of the **conventional VTE risk factors** observed in cohort-studies of the general population has only been evaluated in a few studies of cancer-associated VTE. Little is known about the joint effect of cancer and risk factors such as lifestyle habits and anthropometric measures, or whether the effect is constant across cancer sites. Prothrombotic mutations are probably also important determinants of cancer-associated VTE. Results from the MEGA study revealed that Factor V Leiden or prothrombin 20210A mutations further increased the VTE-risk in patients with cancer (35).

Several studies have evaluated the effect of **high age** on the risk of VTE. While the effect of increasing age at population-level is clear, the impact of high age in cancer-cohorts is inconclusive. A large study of hospitalized cancer patients found virtually similar rates of VTE among patients aged 40-59 years and 60-79 years (41). In the registry-based cohort study of cancer patients by Chew et al (45), they found an overall positive association between high age and VTE. However, the age-effect differed across cancer sites and the association was not positive for all cancer sites. Among cancer patients included in the Danish cohort by Cronin-Fenton et al (34), the overall effect of age was also positive. In this cohort, young and elderly patients had similar risk in the first year after cancer diagnosis, whereas the average risk during the entire follow-up was higher among the elderly. High age was noted as an important risk factor for cancer-associated thrombosis in a study of neutropenic cancer patients (40). However, the increased risk by age was mainly due to high risk of arterial thrombosis in the elderly, and age had little influence on the risk of VTE.

Finally, the ANC Study Group found that the risk of VTE was independent of age in their cohort of ambulatory cancer patients (42). Taken together, previous findings are inconsistent and it is not known whether high age should be emphasized as an independent risk factor for cancer-associated VTE.

1.4 **Risk stratification for cancer-related venous thromboembolism**

1.4.1 *Biomarkers*

A biomarker is a laboratory parameter with diagnostic or prognostic value. As opposed to a risk factor, which in the general sense is causally associated with the outcome, a biomarker can be causally or non-causally associated with the disease. A good biomarker has high sensitivity and specificity for the outcome of interest. Knowledge about biomarkers for cancer-associated VTE has mainly been provided by two prospective cohorts; namely the ANC Study Group Registry (42) and the Vienna Cancer and Thrombosis Study (CATS) (43). The ANC Study Group Registry includes approximately 4000 cancer patient followed through maximum four cycles of chemotherapy, with baseline measurements obtained prior to initiation of chemotherapy. Biomarkers for chemotherapy-associated VTE identified in this cohort were leukocytosis (> 11 x 10^9 /L), thrombocytosis (≥350 x 10^9/L) and anemia (hemoglobin < 10 g/dl). In CATS, 819 patients recently diagnosed with incident cancer or relapse were followed for a median of almost two years. Increased risk by elevated platelet count (above the 95th percentile) was confirmed in this cohort (112). Additionally, P-selectin, d-dimer, prothrombin fragment 1+2 and factor VIII level have been reported to further increase the VTE-risk among the CATS participants (198-200). Biomarkers for prediction of venous thrombosis in cancer patients have recently been summarized in a review by Pabinger and colleagues (201).

In agreement with the findings from the ANC Study Group Registry, leukocytosis was associated with VTE among patients enrolled in RIETE registry (202). The study revealed a 60 % increased risk of recurrent VTE among cancer patients with leukocytosis at the time of the acute VTE. Conversely, the association between leukocyte count and VTE, measured by a doubling in the white blood cell (WBC) count, could not be confirmed in CATS (112). However, the CATS study is a quite small study with only 62 VTE events, and the lack of association may be due to low power.

D-dimer is a degradation product of cross-linked fibrin, and is elevated during ongoing coagulation and fibrinolysis. Elevated d-dimer is a sensitive but non-specific marker of VTE (203, 204) that plays an important role in VTE diagnostics (205). D-dimer levels are increased in cancer patients compared to controls and have been found to predict VTE in patients with cancer. Since the predictive value of a negative test is inversely associated with the incidence, the negative predictive value will presumably be high in asymptomatic cancer-patients as compared to subjects admitted to hospital with typical signs and symptoms. The highest HR for VTE in patients with elevated d-dimer was demonstrated in lung cancer patients, with a HR of 11 (cut-off >1.5 μg/ml) (206), and several other studies have reported positive results (199, 207-209). The CATS study observed an almost doubled risk of VTE in patients with elevated d-dimer at inclusion (199).

The CATS study group also demonstrated that P-selectin above the 75th percentile was an independent risk factor for cancer-associated VTE with a HR of 2.6 (198). P-selectin is an adhesion molecule stored in α-granules of platelets and Weibel-Palade bodies of endothelial cells, and is a recognized marker of activated platelets and endothelial cells. P-selectin has also been associated with VTE in patients without cancer (210).

Other biomarkers suggested for cancer-associated VTE are TF+ MPs, factor VIII and estimated glomerular filtration rate (eGFR). In 2007, Tesselaar and co-workers observed an association between TF+ tumor-derived MPs (TMP) and VTE in a retrospective study of 40 patients with breast or pancreatic cancers (211). The majority of later studies have confirmed the finding, and prospective studies have indicated that the increased level of TF+ MP precedes the onset of thrombosis (106). Conversely, two prospective studies, including CATS, did not observe an association between TF+ MPs and VTE (212, 213). It has been hypothesized that an early collection of blood samples may explain the lack of association in these studies. CATS had a 2-year follow-up after the baseline blood sample, and would not capture a potential increase in TF+ MPs activity occurring closer to the thrombotic event (213). An ongoing study in patients with advanced cancers uses repeated blood samples and may clarify the predictive properties of TF+ MPs in cancer-associated VTE (106).

In coherence with the increased risk of bleeding in patients with factor VIII deficiency (i.e. hemophilia A), increased levels of factor VIII has been emphasized as an independent risk factor for VTE in several case-control studies (214-220). Factor VIII is bound to vWF in the circulation, and serves as a cofactor to factor IXa in the activation of factor X. Increased levels of factor VIII has been noted in various cancers (221-223). In the CATS population, high factor VIII levels showed an age-dependent association with VTE, which ranged from 2-fold in young to a non-significant 20 % increased risk in the elderly (224).

Recently, reduced eGFR was demonstrated to exhibit a 3-fold increased risk of subsequent VTE in cancer patients who underwent chemotherapy, and has been proposed as a cost-efficient tool for VTE prediction in cancer patients (225).

1.4.2 *Prediction models and prophylaxis*

Patients with cancer form a heterogeneous group and the risk of VTE varies accordingly. Risk stratification is needed to obtain an optimal risk-benefit strategy for pharmacological prevention of VTE. Hospitalization for medical illness, major cancer surgery and treatment with chemotherapy are the main high-risk situations were prophylaxis should be considered. Risk assessment models (RAMs) for various settings have been suggested and include the Khorana model and the Padua Prediction Score (Table 2a and b). The Khorana model (42) was developed and validated in an outpatient cohort who received chemotherapy. The model assigns points for five clinical and laboratory parameters, and high risk scores (≥ 3 points) and the absence of contraindications suggests that prophylaxis may be beneficial. Points are assigned for very-high and high risk cancer sites (2 and 1 point, respectively), pre-chemotherapy leukocyte-, platelet- and hemoglobin level (anemia or use of erythropoiesis-stimulating agents (ESAs)), as well as obesity measured by BMI ≥ 35 kg/m^2. Overall, 2 % developed VTE during the 2.5 months of follow-up. In the validation cohort (one third of the cohort), the model had a negative predictive value of 98.5%, while the absolute risk (positive predictive value) of VTE among patients with ≥ 3 points was 7 %. Patients with brain-, renal- and myeloma cancers were not included in sufficient numbers, and their allocation (i.e. *normal*, *high risk* or v*ery high risk*) could not be determined in the study. Performance status showed only a weak, non-significant association with VTE, but a small proportion of the cohort had poor performance status and the lack of a clear association could be due to low power. Age ≥ 65 years was not associated with VTE risk in the cohort.

Table 2

a)

The Khorana model (42) *Patient characteristics*	*Risk score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9/L$	1
Prechemotherapy hemoglobin level < 10 ***g/dL or ESA use***	1
Prechemotherapy leukocyte count $> 11 \times 10^9/L$	1
BMI $\geq 35\ kg/m^2$	1

b)

Padua Prediction score (226) *Patient characteristics*	*Risk score*
Active cancer	3
Previous VTE	3
Reduced mobility	3
Known thrombophilic condition	3
Recent (≤ 1 mo) trauma and/or surgery	2
Elderly age (≥ 70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
BMI $\geq 30\ kg/m^2$	1
Ongoing hormonal treatment	1

Ay and colleagues suggested that soluble P-selectin and d-dimer should be included in an extended version of the Khorana model (43). The cumulative risk at 6 months among patients with the two highest scores (score 4 and 5, capturing about 10% of the participants) was 25% and 35 %, respectively. When the original Khorana model was applied in this cohort, the risk was 18 % at 6 months. Thus, addition of the two biomarkers further increased the positive predictive value of the Khorana model, but the cost-effectiveness is unclear. The overall higher frequency of VTE in the latter cohort (7.4 % vs. 2.1 %) was probably due to prolonged follow-up, as well as the inclusion of more high-risk cancer sites, (such as pancreas, brain and gastric cancer).

A post hoc analysis of the participants of the Protecht-trial was performed to assess the impact of chemotherapy (cisplatin- or carboplatin-based, or gemcitabine) on VTE-risk (227). Based on the use of these agents together with the parameters of the Khorana model, patients were defined as low- or high-risk patients. More than 30 % of the patients were

termed as high-risk by the Protecht score (compared to 12 % by the Khorana model), and 67 % of the VTE events occurred in this group (compared to 33 % by the Khorana model).

VTE prediction among hospitalized cancer patients has been less thoroughly investigated. A comparison of three different RAMs for hospitalized patients (i.e. Kucher, Harinath and St. Johns) (228) found that the models had different accuracy according to department, and that the Kucher RAM (229), which is used in North-American hospitals, was superior in oncology patients. However, none of the RAMs for hospitalized patients were developed for cancer patients in particular, and high age was included in all of the models (> 40 in the Harinath and St. Johns, > 65 in Kucher, and > 70 in the Padua score). As previously emphasized, studies conclude differently with respect to age in cancer-associated VTE. For appropriate VTE prevention in cancer patients, it is important that the role of high age is established.

Current guidelines suggest prophylaxis for high risk out-patients and selected medical patients, and recommends extended prophylaxis in cancer patients who undergo major surgery. The effect of prophylaxis has been evaluated in clinical trials of outpatients with cancer, and was found to reduce the rate of VTE in these patients. However, the VTE rates in the trials were low, and the number needed to treat (NNT) to save one VTE event ranged from 50-100 (38, 39). Use of RAMs and targeted prophylaxis have not been formally tested, but will necessarily reduce over-prophylaxis. Application of the Khorana score and the Protecht score was estimated to reduce to NNT from 50 to less than 20 (227). The number of cancer-patients has been limited in trials of hospitalized patients, and the safety of prophylaxis in these settings has not been evaluated in cancer patients. Thus, the risks and benefits of pharmacological prophylaxis in hospitalized cancer patients are not known (230).

2 AIMS OF THE STUDY

Although cancer-associated VTE has been addressed in many studies, large population-based cancer cohorts with validated end-points and information about potential confounders have been lacking in the epidemiological description of the disease. Patients with cancer have a high-risk of VTE, and risk stratification and targeted pharmaceutical prevention is warranted. These aspects stress the importance of reliable estimates of the disease-burden as well as the impact of various cancer- and patient-related factors on cancer-associated VTE.

High levels of leukocytes and platelets are predictive of VTE in oncology patients. However, characteristics such as cancer stage and comorbidities may influence the cell counts, and it is therefore not known whether high levels of these cells are causally related to VTE or merely reflect concomitant risk-factors. Baseline measurements prior to cancer development may yield a better understanding of the role of blood-count parameters in cancer-associated VTE.

The aims of the study were:

1. To assess the incidence of cancer-associated VTE in age-groups, and determine whether the increased risk of VTE in the elderly could be attributed to cancer.
2. To assess the incidence of cancer-associated VTE and attributable risks by cancer-sites and age-groups in a large Scandinavian cohort with validated symptomatic VTE events.

3. To investigate the impact of pre-cancer leukocyte and neutrophil counts on the risk of VTE in subjects who subsequently develop cancer and in those who remain cancer free.
4. To investigate the impact of pre-cancer platelet count on the risk of VTE in subjects who subsequently develop cancer and in those who remain cancer free.

3 METHODS

3.1 **Study populations**

3.1.1 *The Tromsø Study*

The Tromsø Study is a prospective, population-based study with repeated health surveys of the adult population in Tromsø. Since the first survey in 1974, five surveys has been conducted, the most recent in 2007-2008 (231). The Institute of Community Medicine at the University of Tromsø is responsible for the study, and the seventh survey is now under planning. The study was originally conducted due to the high frequency of myocardial infarction in the northern Norway. Additional outcome registries, including the VTE registry, have been established subsequently.

The largest survey (Tromsø IV) was carried out in 1994-95. All inhabitants of the municipality of Tromsø aged > 24 years were invited to participate and 27 158 subjects participated (77 % of the invited population). Papers I, III and IV are based on Tromsø IV, whereas paper II includes two additional Scandinavian cohorts.

3.1.2 *The Scandinavian Thrombosis and Cancer Study*

The Scandinavian Thrombosis and Cancer (STAC) Study is a merged cohort which consists of three longitudinal cohort studies, namely the Tromsø IV (Norway), the Health Survey in Nord-Trøndelag (HUNT) (Norway) and the Diet, Cancer and Health (DCH) Study (Denmark). A detailed description of the study population is found in paper II. The HUNT study invited all adults aged > 19 years, whereas only middle-aged subjects (50-65 years) without a history of cancer were included in DCH. Enrollment of study participants took place between 1993 and 1997. The studies were approved by the respective ethical

committees in Tromsø and Trøndelag (Norway) and Copenhagen and Aarhus (Denmark), and subjects gave their informed written consent to participate. The individual populations counted 26 856 (Tromsø Study), 65 174 (HUNT II) and 56 014 (DCH), and after exclusion of subjects with a history of cancer or missing data, the merged cohort consisted of 137 273 subjects.

3.2 **Cancer ascertainment**

Information about cancer was obtained by linkage to the cancer registries in Norway and Denmark. The Cancer Registry of Norway (CRN) and the Danish Cancer Registry are similarly organized and receive notifications from several medical sources including hospital doctors, general practitioners, pathological laboratories and death certificates. The Danish Cancer Registry was linked to the national hospital discharge registry in 1987, and included outpatient diagnoses since 1995 for additional completeness. In Norway, discharge diagnoses for hospital- and outpatient care have only been included since 1998. Reporting has been mandatory since 1987 in Denmark (232) and 1952 in Norway (233). In Norway, physicians who fail to report a case (i.e. to send the clinical notification) within two months after a diagnosis has been reported from another source (e.g. pathologists, patient discharge records or mortality sources), will receive a reminder from the cancer registry. For each case, the cancer registries aim to provide the date of diagnosis, primary site (ICD-7/ICD-10), morphology, grade, disease stage and initial treatment (233).

3.3 **Baseline measurements**

Baseline measurements in Tromsø IV were applied as potential confounding variables in papers I and II, and provided the exposures of interest in papers III and IV. The information was obtained by physical examination, self-administered questionnaires and non-fasting blood samples. Anthropometric measures were obtained with subjects wearing light clothing and no shoes. Body mass index was calculated as the weight in kilograms divided by the squared height in meters (kg/m^2). Blood pressure was recorded by trained personnel using an automatic device (Dinamap Vital Signs Monitor). After 2 minutes of sitting rest, the blood pressure was recorded three times by 2-minute intervals, and the average of the two last readings was used in the analyses. Non-fasting blood samples were collected from the antecubital vein and analyzed by the Department of Clinical Chemistry. For mean platelet volume (MPV) and white blood cell-, neutrophil- and platelet counts 5 ml of blood were collected into Vacutainer tubes with EDTA as an anticoagulant (K_3-EDTA 40 µL, 0.37 mol/L per tube) and analyzed by an automated blood cell counter (Coulter Counter®, Coulter Electronics, Luton, UK) within 12 hours. Information about previous atherothrombotic diseases (i.e. myocardial infarction, angina and stroke), diabetes and current use of antihypertensive medicine were obtained from self-administered questionnaires. Smoking status, alcohol consumption and physical activity level were also collected. Smoking habits were assessed by current daily smoking of cigarettes, cigars or pipe (i.e. yes/no for each question), the number of daily cigarettes and years of daily smoking for former and current smokers, as well as the time since smoking cessation for former smokers. The English translation of the original questionnaires are presented in the Appendix.

Acquisition of baseline data in the HUNT study and the DCH study was similarly performed, and has been described in detail elsewhere (234, 235).

3.4 **Registration and validation of venous thromboembolism**

VTE events were similarly recorded and validated in the three cohorts, and symptomatic, first life time VTE events were included. In the Tromsø Study, VTE events were identified by searching the hospital discharge diagnoses registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway. Relevant International Classification of Diseases, revision 9 (ICD-9) codes for the period 1994-1998 were 325, 415.1, 452, 453, 671.3, 671.4 and 671.9, and ICD-10 codes for the period 1999-2010 were I26, I80, I81, I82, I67.6, O22.3, O22.5, O87.1 and O87.3. For the cases identified by discharge codes or the radiology registry, the VTE events were included when typical signs and symptoms of VTE were described in the medical record, objective diagnostic tests were performed (e.g. compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan and pulmonary angiography) and a diagnosis was made in the medical record. Unless contraindications were specified in the medical journal, treatment with anticoagulants, thrombolytics or vascular surgery was also required for verification. VTE events identified from the autopsy registry were included when VTE was described as the cause of death or a significant condition in the autopsy record.

In the Danish cohort, cases were identified by linkage to the Danish National Patient Registry and the Danish National Death Registry by use of the personal identification number (128). The events were validated by similar abovementioned confirmatory criteria in the patient medical records. In addition, echocardiography was among the confirmatory diagnostic tests for PE. Events that were identified through the cause of death statistics (i.e. National Death Registry) were included only if VTE was confirmed by autopsy.

VTE events in the HUNT study were identified from discharge codes from the two hospitals in the region and procedure codes from the respective radiology departments. Each case was verified by objective criteria described in detail elsewhere (13).

A VTE event was classified as either DVT or PE, and when they occurred concurrently the event was classified as PE. VTE cases were further classified as provoked or unprovoked. Provoking factors were defined slightly differently across the studies. In all the three studies provoking factors included cancer at the time of the VTE event, surgery, trauma, long haul travel, acute medical conditions, immobilization and other factors like central venous catheters prior to the event. Pregnancy/puerperium and oral contraceptive use were considered as provoking factors only in the HUNT study.

4 MAIN RESULTS

4.1 **Paper I**

THE INCREASED RISK OF VENOUS THROMBOEMBOLISM BY ADVANCING AGE CANNOT BE ATTRIBUTED TO THE HIGHER INCIDENCE OF CANCER IN THE ELDERLY: THE TROMSØ STUDY

It has been suggested that the increased risk of VTE in the elderly may be due to a higher frequency of cancer, but the statement has not been formally tested. We used a prospective population-based cohort with validated VTE events to assess the adjusted impact of cancer on the risk of VTE across age-strata, and to estimate the attributable proportions in young, middle-aged and elderly. Subjects were recruited from the fourth survey of the Tromsø Study, and cancer was treated as a time-dependent exposure counted from 1 year prior to the date of cancer diagnosis. Cancer was substantially more common at higher age, and the rates were 1.8 per 1000 person-years (PY) in those < 50 years and 22 per 1000 PY in those ≥ 70 years. VTE was recorded in 138 of the 2 290 subjects with cancer, whereas 393 events occurred among 26 094 unexposed subjects. The crude incidence rate (IR) for cancer-exposed subjects was 13 per 1000 person-years (PY), compared to 1.2 per 1000 PY among the cancer-free. The rate of VTE by overt cancer increased from 9 per 1000 PY in young to 15 per 1000 PY in the elderly. Despite the high frequency of cancer in the elderly, the attributable proportion was highest in middle-aged, where cancer explained 27 % of the events in the population. Corresponding proportions in young and elderly were 14 and 18 %, respectively. The hazard ratio (HR) for VTE by cancer was 5.5 for all ages combined, and declined from 26-fold in young to 3-fold in the elderly. Despite higher proportion of potential confounders in cancer patients, the HRs were not attenuated by inclusion of these variables in the multivariable Cox-model. Our results imply that cancer cannot explain the increased risk of VTE at higher age.

4.2 **Paper II**

CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM IN A GENERAL POPULATION – THE SCANDINAVIAN THROMBOSIS AND CANCER (STAC) STUDY

Previous population-based cancer cohorts are mainly based on registry data and risk estimates may be biased by incomplete outcome registration and lack of VTE validation. Potential confounders of the association between cancer and VTE such as smoking and body mass index have not previously been addressed in overall- and site-specific risk assessment. We performed one-level analyses of three population-based Scandinavian cohorts including a total of 137 273 subjects that were followed from inclusion (1993-1997) to 2010 at the most. Cancer exposure accrued from the date of diagnosis until VTE, death, migration or end of follow-up. Site-specific incidence rates (IRs) of cancer-associated VTE were assessed per 1000 person-years (PY), and hazard ratios were calculated by adjusted regression models with age as timescale and cancer-free subjects as reference. A total of 1.6 % developed VTE within the first year after cancer diagnosis. Close to 20 % of the VTEs in the population could be attributed to cancer, and cancer of the lungs, bowel and prostate were responsible for more than 40 % of the cancer-associated VTE events. The crude rate of VTE in the cancer cohort was 8.7 per 1000 PY corresponding to an adjusted HR for VTE by cancer of 4.9 (95 % CI; 4.4-5.5). However, there was a strong temporal relation between the cancer diagnosis and VTE, and IRs and HRs declined by increasing the duration of follow-up. This effect was most pronounced in cancers with low mortality. In conclusion, the adjusted HRs for cancer overall and within cancer sites were similar to those previously reported. However, risk estimates assessed from long-term follow-up appear to be influenced by site-specific mortality, and underestimate the risk in cancers with better prognosis.

4.3 **Paper III**

WHITE BLOOD CELL COUNT MEASURED PRIOR TO CANCER DEVELOPMENT IS ASSOCIATED WITH FUTURE RISK OF VENOUS THROMBOEMBOLISM – THE TROMSØ STUDY

An increased risk of VTE has been demonstrated in cancer patients with elevated leukocyte count. However, as inflammation due to aggressive cancer or concomitant infection is associated with leukocytosis as well as VTE, previous studies do not allow for causal inference. To investigate a potential causal relationship between high leukocyte count and VTE in malignancy, we used a prospective population-based study where WBC- and neutrophil counts were collected prior to cancer development. We assessed the risk of VTE by categories of WBC- and neutrophil count in subjects who developed cancer and in subjects who remained cancer-free. 24 304 initially cancer-free subjects were recruited from the fourth survey of the Tromsø Study. A total of 388 VTE events were recorded from inclusion to end of follow-up (September 1st 2007), of which 116 events occurred among the 1720 subjects who developed cancer. In the cancer cohort, baseline WBC count above the 80th percentile (≥8.6 x 10^{9} cells/L) provided a 2.4-fold increased risk of VTE compared to subjects with WBC count below the 40th percentile (HR 2.36, 95% CI:1.44-3.87). Similar findings were observed for neutrophil count. Conversely, no association was observed between WBC- or neutrophil count in the group of cancer-free subjects. Our results suggest that the elevated white blood cell count may play a causal role in development of cancer-associated VTE.

4.4 **Paper IV**

PLATELET COUNT MEASURED PRIOR TO CANCER DEVELOPMENT IS A RISK FACTOR FOR FUTURE SYMPTOMATIC VENOUS THROMBOEMBOLSIM: THE TROMSØ STUDU

Platelets are important components of the hemostatic system, and elevated platelet count has been associated with increased risk of VTE in cancer patients. Since thrombocytosis is associated with metastases and inflammation, it is not known whether elevated platelet count plays a causal role in development of cancer-associated VTE or merely reflect concomitant risk factors. We used a population-based cohort with platelet count measured prior to cancer development to investigate the impact of high platelet count on VTE risk among subjects who developed cancer and in those who remained cancer-free. Since we previously observed that pre-cancer WBC count predicted VTE in patients who developed cancer, we also investigated a potential interaction between high platelet and WBC counts. 25 160 subjects recruited from the fourth survey of the Tromsø study with baseline measurement of WBC and platelet count, and without history of cancer or VTE were included. There were 2082 subjects who developed cancer during follow-up, and 129 VTE events were recorded among these subjects. In the non-cancer population, 377 VTE events were registered. The VTE risk by platelet count above the 80th percentile, was increased 2-fold in subjects who developed cancer (HR 1.93 95 % CI: 1.18-3.16). The risk of VTE in subjects with high platelet and WBC counts were increased 3-fold (HR 2.96 95%CI:1.72-5.08), and exceeded the expected combined effect. In conclusion, a high baseline platelet count predicted the risk of VTE in patients who developed cancer, but not in those who remained cancer-free. The combined effect of high pre-cancer platelet and leukocyte count can be described as synergistic.

5 GENERAL DISCUSSION

5.1 **Methodological considerations**

5.1.1 *Study design*

The four papers in this thesis are based on results from the Tromsø Study, and paper II also incorporates two additional population-based cohorts that were merged with Tromsø IV. A prospective cohort study is characterized by collection of exposure data prior to development of disease with subsequent outcome surveillance. For the three cohorts included in this thesis, baseline examinations were performed in the years 1993-1997, and development of VTE were registered throughout 2010 at the most. Due to the closed design of the cohorts, events such as migration, death, development of VTE or cancer led to a progressive decrease in the cancer-free population throughout follow-up. Conversely, subjects with cancer at baseline were excluded from the study, and the cancer cohort was successively formed during the study period. The observation-time for cancer started at the diagnosis date in the national cancer registries, and cancer was treated as a time-dependent exposure.

Cohort studies have several advantages compared to other observational studies. Due to the temporal sequence of the exposure and outcome assessment, the presence or absence of disease do not influence the exposure status at inclusion. Misclassification of exposures in a cohort study therefore tends to be *non-differential*, and means that *recall bias* for self-reported exposures usually is a minor concern in the cohort design. Similarly, since laboratory parameters are collected prior to the outcome of interest, *reversed causation* is generally not an issue. These aspects reduce the chances of type I error (i.e. incorrectly rejecting the null-hypothesis) in a cohort study compared to a case-control design. However, the high number of subjects required and the prospective follow-up make

cohort studies both time consuming and expensive. The cohort study is therefore not suitable for rare diseases.

5.1.2 *Relative and absolute measures of effect*

The risk of an outcome can be expressed by absolute or relative risk estimates. Absolute risks can only be derived from cohort studies. They can be interpreted as probabilities and include incidence rates and cumulative risks. Both cumulative risks and incidence rates are calculated from the number of new cases in a defined population within a given time-frame. However, whereas the denominator of an incidence rate is the sum of in-study *person-time*, the denominator of a cumulative risk is the number of *subjects* at risk at the beginning of the study period. Therefore, when a significant proportion of the participants are followed for less than one year, as is often the case in oncology research, and the risk of an outcome declines throughout this year, the incidence within the first year and the 1-year cumulative risk will differ (i.e. the incidence is higher than the cumulative risk). Accordingly, the 1-year cumulative risk of VTE in cancer patients overall was 1.6 %, whereas the 1-year rate was 2.0 % in our study. For cancers with high mortality, the difference between the two estimates increases accordingly.

Relative effect measures, such as odds ratios, relative risks and hazard ratios, provide the risk among exposed subjects relative to the risk among unexposed. These measures are appropriate when evaluating the strength of a causal risk factor, but are highly dependent on the risk in the comparison group. The comparison group may represent only a minority of subjects at risk in the population, and can be misleading in the clinical setting. Furthermore, a relative effect measure is usually relatively low in high-risk populations, for instance among elderly, even though the exposure leads to a high absolute number of cases. The main

advantage of relative risk estimates is the possibility to adjust for potential confounding factors in multivariable regression models. Hazard ratios (HRs) are estimated by use of the *Cox proportional hazards model* (236), and can only be reported in prospective studies where time-to-event data is available. A hazard (*h(t)*) is defined as the instantaneous risk of a certain event, given that the subject is event-free at time *t*, and a HR is read as the ratio of the hazard among exposed and unexposed subjects. In contrast, ORs represent the odds of exposure among cases (exposed divided by non-exposed) relative to the odds of exposure among controls. Odds ratios are usually obtained from case-control studies by univariate analyses or logistic regression, and does not take survival-time into consideration. However, odds ratios are comparable to relative risks/hazard ratios when the outcome is rare (237).

Attributable proportions can be calculated from relative risks or incidence rates (238). However, when relative risks are applied, the prevalence of the exposure must also be known. The prevalence of a disease can be difficult to measure, as it is dependent on both incidence and duration. Therefore, attributable risks estimated from incidence rates among unexposed and exposed/total population, might be more accurate. Attributable risks were estimated in papers I and II, and can be understood as the proportion of a disease in the population (PAR%) or among the exposed (AR%) that is explained by the exposure. However, for multicausal diseases such as VTE, the interpretation of attributable proportions is not straight-forward. Many factors are required for development of disease, whereas elimination of one single factor may prevent the disease from occurring. The sum of single attributable proportions will therefore often exceed 100% (238, 239).

5.1.3 *Confounding and interaction*

When an association between an exposure and an outcome has been observed, several possibilities need to be considered before causality can be inferred; and include chance, bias and confounding. A *confounding factor* is associated with both the exposure and the outcome of interest, and is not an intermediate variable in the causal pathway. The exposure of interest and the confounding factor may be causally or non-causally associated, and leads to uneven distribution of the confounder among exposed and unexposed subjects. There are several approaches to investigate the presence of confounding, and the most common are stratification and adjustment in a multivariable model (240-242). If the observed crude effect disappears within strata of the supposed confounder or after adjustment, the crude risk estimate was likely to be explained by one (or several) confounding factors. Strong confounders may also turn the direction of the true association between the exposure and the outcome. *Propensity score models* is another method increasingly used to evaluate confounding by indication (242-244).The score can be obtained by multiple logistic regression, and accounts for differences between groups that may be predictors of the exposure status when allocation is not random.

Subjects who develop cancer might be different from the general population. Potential confounders of the association between cancer and VTE include common risk factors such as obesity and heavy smoking, comorbidities and cancer-related factors such as surgery, hospitalization and chemotherapy. However, cancer-related factors can also be regarded as intermediates of the causal pathway. In an analysis to assess the overall impact of malignancy in a population, adjusting for the latter factors may lead to over-adjustment, which would obscure the full impact of malignancy on VTE-risk. The multivariable models presented in paper I were adjusted for body mass index, smoking status, physical activity,

self-reported cardiovascular disease and diabetes. The risk estimates were similar to the sex-adjusted model, and suggested that confounding by these variables did not explain the increased VTE risk in the cancer cohort.

In paper IV, where we investigated the role of pre-cancer platelet count on the risk of VTE, we also observed a positive association between platelet count and cancer stage. Since advanced cancer is an acknowledged risk-factor for VTE, the association between pre-cancer platelet count and VTE was potentially confounded by higher cancer stage among those with high platelet count at baseline. However, including cancer stage in a multivariable model did not attenuate the risk estimate, and we inferred that the increased risk of VTE by pre-cancer platelet count was not mediated through higher cancer stage.

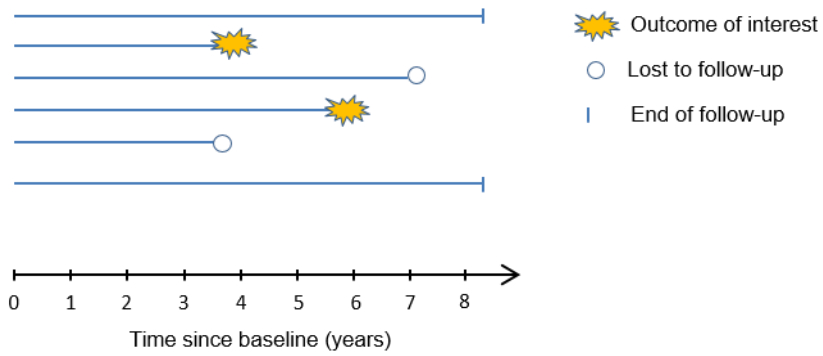
To ensure that observed associations are not mediated by dissimilar distribution of other risk factors, potential confounders must always be considered in observational studies. However, it cannot necessarily be assumed that confounding has been eliminated after adjustment for recognized confounders. Residual confounding due to large within-strata variations or poor assessment of the confounding variables as well as the presence of unrecognized confounders can usually not be ruled out. The gold standard for establishing causal relationships are experimental studies where the exposure of interest is randomly assigned to study participants, i.e. randomized clinical trials (RCT). However, although the role of recognized and unrecognized confounders is diminished in RCTs, confounding may still be present due to chance.

Age is an important confounder in epidemiologic research of many diseases and VTE is no exception. The widely used time-scale in Cox regression (Figure 3a) is the time-on-study scale, were at-risk subjects at event-time *t* are those who have not experienced an event or been censored before *t*. However, it has been argued that using age as timescale in the

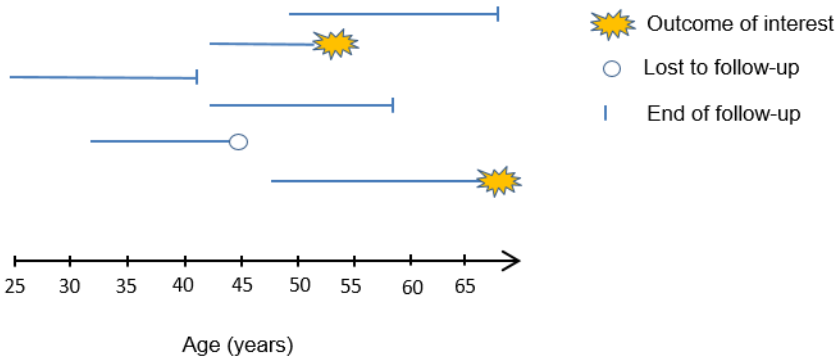
regression analyses is a more proper way of eliminating confounding by age than the standard age adjustment in a multivariable model (Figure 3b) (245, 246).

Figure 3. Different time-scales in Cox regression

(a) Time-on-study time-scale



(b) Age as time-scale



Instead of comparing those who are still in study at time *t* (counted from the date of inclusion), it may be more reasonable to compare the participants who have not experienced an event or been censored by age *a*. The main argument is that there probably is a greater variability with respect to the outcome-risk between subjects of different ages, than between subjects who have been under observation for different amount of time. Age

as time-scale was applied in papers I and II. This method also allowed for a dynamic and more accurate allocation to the age-strata, since subjects were able to switch age-category as they aged throughout follow-up.

When the effect of a risk factor on an outcome varies across another variable which is not the exposure of interest, this second variable is known as an *effect modifier*, and means that statistical *interaction* is present. As opposed to confounding, where the crude effect will be weakened or strengthened across all strata of the confounding variable, interaction will lead to variation in the risk estimates across the strata (247). Presence of statistical interaction can be evaluated on an additive (i.e. absolute risk difference) or multiplicative (i.e. relative risk difference) scale, and must be specified as they may reach diverging conclusions (248). This was observed in the first two papers of this thesis. In paper I, the relative risk of VTE by cancer showed large variation across age-groups (range from 26-fold to 3-fold increased risk), and suggested that higher age negatively modified the effect of cancer on the risk of VTE on a multiplicative scale. Although this is not surprising given the large discrepancy in the background risk, it follows that an overall relative risk estimate is not applicable to all age-groups, and is especially inaccurate for those aged far from the mean. The risk difference on the other hand was quite similar across age-groups, and implied that age was not an, or even a slightly positive, effect modifier of the effect of cancer on the risk of VTE on an additive scale.

Another example of interaction was observed in paper III and IV. The leukocyte and platelet counts were only associated with VTE among subjects who developed cancer, and not among the cancer-free, i.e. the parameters showed statistically different effect in the two strata of cancer exposure. This specific form of interaction is termed a *qualitative*

interaction, as opposed to quantitative interactions where the association is present but varies in strength across strata of the interacting variable (247).

In contrast to statistical interactions, there are no formal statistical tests for biological interactions. However, departure from additivity of individual effects may imply that risk factors interact with each other on a biological level. In paper IV, by use of Rothman's synergy index (249), we observed that the risk of VTE in subjects with high platelet- and leukocyte counts exceeded the expected combined effect of the two parameters. This effect was described as synergistic.

5.1.4 *Bias*

Bias is the term for systematic errors in epidemiologic research that is related to the study design or conduct (247). Bias may be introduced during the selection of study participants or during measurement of exposures, confounders or the study outcome. The two main categories are selection bias and information bias, but overlap exists. *Selection bias* occurs when exposure or outcome status of an individual influence the probability of participating in the study. In case-control studies, selection bias occurs when participation status is related to the exposure, and when this association is more pronounced in either cases or controls. In cohort studies, the relationship between exposure and outcome must be different among those who participate and those who do not participate in the study. Thus, selection bias may be important to consider in a case-control study, but rarely leads to erroneous associations in prospective studies. However, when a cohort study unintentionally consist of selected subjects, absolute effect measures (i.e. incidence rates, cumulative risks and attributable proportions) may not be representative of the source population.

Information bias is introduced when study participants are placed in the wrong exposure or outcome category, known as misclassification. *Non-differential* misclassification is common in prospective studies, and means that misclassification is equally distributed among cases and non-cases. Non-differential misclassification dilutes the true associations and may result in type II error (250). When the chance of exposure misclassification is affected by the outcome status, the misclassification is characterized as *differential*. Differential misclassification may lead to under- or over-estimation of effects and can thereby cause type I and type II errors. A classic example of differential misclassification is the *recall bias* in case-control studies, where cases more than controls are prone to over- or underestimate previous exposures, or vice versa. Misclassification of confounding variables in a study leads to poor control for confounding, potentially causing residual confounding (247, 250).

The exposure status may be related to the medical surveillance of study participants and thereby influence the detection of the outcome, and is termed *medical surveillance bias* or *detection bias*. This bias is often present when the exposure is a disease (such as diabetes or cancer) or a treatment (such as oral contraceptives) and the outcome is not systematically assessed (247). Since malignancy is a well-known risk factor for VTE and most cancer patients see doctors frequently, diagnostic work-up for VTE is probably performed more often among oncology patients than for other patient groups. Thus, detection bias should be kept in mind when evaluating the effect of cancer on the risk of VTE. In cohort studies, detection bias is categorized as a type of information bias. In case control studies the issue leads to selection bias. Regardless of study design, detection bias typically causes over-estimation of the effect.

5.1.5 *Missing data and loss to follow-up*

Missing data is often encountered in observational studies. There are several methods for handling missing values ranging from simple deletions to sophisticated imputation techniques (251). The selected approach depends on the volume of missing data and the missing data mechanism. These mechanisms generally fall under three categories: missing at random (MAR), missing completely at random (MCAR) and not missing at random (NMAR). When missing status is independent of the value itself, but related to other variables in the data set, such as age or sex, the mechanism is termed MAR. NMAR denotes that certain values for the variable itself are more likely to be missing, for instance when weight status is more often missing among obese subjects. Conversely, values that are MCAR are not related to the variable itself nor other variables in the data set, and may result from questionnaires lost in the mail or plotting errors performed by the researcher (252).

None of the main exposures in this thesis were self-reported (i.e. cancer, WBC- and platelet count) and missing values, assumed to be MAR or MCAR, were managed by pairwise and listwise deletions (252). *Pairwise deletions* were performed in papers III and IV, where subjects with missing values for the respective exposures (i.e. leukocyte- and platelet count) were deleted from the dataset (3-6 %), whereas subjects with missing data for other covariates only were excluded from the multivariable analyses. In paper II based on the STAC cohort, the proportion of missing data was high for certain self-reported covariates, and missing was more common among elderly (i.e. MAR). Initial pairwise deletions where subjects with missing values for covariates were excluded from the multivariate analyses only, provided higher HR compared to the age-and sex adjusted model. However, this was merely an effect of age-reduction. Thus, to ensure that the same subjects were included in the different regression models, listwise deletions were performed in paper II, meaning that

subjects with missing values for any of the covariates in the multivariable model were excluded from all analyses (also termed *complete case analysis*). A disadvantage of both listwise and pairwise deletions are reduced power with a higher probability of type II error (251).

Loss to follow-up in prospective studies is usually handled by *censoring*. An assumption to censored survival time is that these observations have the same risk of the event of interest as those who remain in the study (i.e. non-informative censoring). Thus, censoring is a reasonable approach when subjects are lost to follow-up due to migration. However, even though death from other causes necessarily prevents any future development of the study outcome (when the outcome is not all-cause mortality), death is often handled as a censored observation. It has been suggested that death from other causes than the disease of interest should be considered a competing event, after which subjects are no longer at risk (253). In study populations with low mortality such as population-based cohort studies, regular Kaplan-Meier survival analysis and the competing risk method provide similar results. In cancer- and thrombosis studies however, where a large proportion of the exposed population dies within the study period, there may be a considerable difference between censoring and competing risk analysis (i.e. overestimation of VTE risk when death is handled by censoring). Graphically the Kaplan-Meier- (survival) and the failure- (1-survival) curves cross and add up to > 1 (254). By use of the method proposed by Fine and Gray (255), death was considered a competing event to VTE in paper I. As expected the risk estimates were attenuated, and were most attenuated among the elderly where the mortality rates were higher.

5.1.6 *Data quality*

The main exposure throughout this thesis was a diagnosis of cancer obtained from the Danish or Norwegian cancer registries. Several measures have been used to assess the accuracy and completeness of the registries, including the share of microscopically confirmed diagnoses, the number of sources per case, the proportion of cases from death certificates only (DCO), and the number of cases with an unknown primary site or cancer stage. Morphological verification is warranted and has improved over the years. In Denmark the proportion of microscopically confirmed diagnoses increased from 55 % in 1943 to 93% in 1992, whereas the proportion of DCO cases decreased from 19 % to 0.7% during the same period (256). Correspondingly, 94 % of the cases in the Cancer Registry of Norway (CRN) were confirmed by microscopy in 2001-2005 (233). In this period, the average number of reporting sources per case was 3.2 in the CRN. Reporting from multiple sources can be used to assess the probability of missed cases by the *capture-recapture method*, either by assuming that the sources are independent or by taking dependence between sources into consideration (257, 258). The latter was performed by Larsen and colleagues to assess the completeness of the CRN (259). Weak, but positive dependencies were noted between clinical notifications and death certificates and clinical notifications and pathologists, and a negative dependence was observed between death certificates and pathologist. The authors estimated that 1.2 % of cancer diagnoses in Norway go undetected suggesting a completeness of 98.8%.

The VTE events included in the Tromsø Study were detected from the hospital discharge diagnosis registry, the radiology procedure registry and the autopsy registry. Both hospitalized and outpatient cases were registered, meaning that cases diagnosed during travel would be captured if the patient subsequently were followed at the hospital

outpatient clinic. The careful evaluation of each case by access to the patient's medical record limited the inclusion of false positive cases. Thus, we have reason to believe that the VTE registry in the Tromsø cohort has high completeness and validity.

VTE events in HUNT and DCH applied in paper II were also identified from more than one source and validated by objective criteria (13, 128). However, as indicated by previous publications (13, 14, 120), lower age-specific rates of VTE were noted in these cohorts compared to the Tromsø Study. Possible reasons for the lower rates include fewer sources of information (i.e. two not three for each registry), different coding routines and perhaps easier access to hospitals outside the study area, leading to missed cases. Theoretically, VTE may also be more common in the northern Norway.

5.1.7 *External validity*

If the findings are internally valid, i.e. not caused by chance, bias or confounding, the next step would be to evaluate the external validity or generalizability. These concepts denote that the findings are applicable to populations other than the population where the association was investigated. The Tromsø Study is a population-based study intended to reflect the general adult population in North Norway. All inhabitants of the municipality aged more than 24 years were invited to the fourth survey, and the participation rate was high (77 % of the eligible population). A lower participation rate was noted for men compared to women, as well as in subjects younger than 30 years and in those > 80 years (231). The participation rate in the Diet Cancer Health study in Denmark (Paper II) was lower than in Tromsø IV and HUNT2, and only 37 % of women and 34 % of men participated in the study. Comparison of socioeconomic factors obtained by central registries revealed large variations between participants and non-participants (260). Predictors of participation were

higher education, occupational status, housing conditions and marital status, where single men had the lowest participation rate.

Cancer patients in this thesis were health survey participants, and it can therefore be argued that the cancer cohort was more health-conscious than cancer-patients as a whole. Participants may for instance visit doctors more frequently and have an early diagnosis, and thereby have a lower risk of VTE. If the effect of cancer on VTE is modified by factors that are unevenly distributed among participants and non-participants, such as smoking habits or physical activity, the risk estimates may not be extrapolated to the general population. However, this is a highly theoretical selection bias, and is unlikely to have had any major impact on the results.

The relative distribution of cancer sites in papers I and II is in coherence with reports from the Nordic cancer registries (233, 261), and supports that the cancer cohorts applied in this thesis are representative for cancer in the general population. The benefit of such cohorts is the high degree of generalizability of the risk estimates. From a community perspective, populations representative for cancer patients as a whole are crucial to assess the overall significance of the disease in public health, which cannot be extrapolated from studies of high-risk patients. However, the studies do not include children, and is therefore not applicable to the risk of VTE amongst children with cancer. Furthermore, the vast majority of the population was of Caucasian ethnicity, thus the results may only be extrapolated to other Caucasian populations.

5.2 **Discussion of main results**

5.2.1 *Risk of cancer-associated VTE in the general population (Papers I and II)*

In papers I and II we found crude rates of cancer-associated VTE of 9-13 per 1000 person-years, and a 5-fold increased risk in comparison to the cancer-free population. Both the absolute and relative measures are in reasonable agreement with previous studies (Table 1). In a recent publication more than 80 000 cancer patients were identified from the UK cancer registry, and VTE rates were obtained by linkage to the nationwide discharge diagnosis registry and primary care registry. The crude rate of VTE among cancer patients was 14 per 1000 person-years, and the relative risk was 4.7 (49). A meta-analysis from 2012 also supports our findings (73). Based on the patient composition in the respective cohorts, the authors categorized relevant studies as average- or high-risk studies. Three general cancer cohorts similar to our own were categorized as average risk studies, and the overall VTE rate for this category was 13 per 1000 person-years. However, it should be kept in mind that the duration of follow-up was inconsistent between the studies, and the heterogeneity of the results is probably more pronounced than implied by the average incidence rate.

In comparison to previous studies and Paper I, the rate of cancer-associated VTE in the STAC cohort was lower than anticipated (IR 8.6 per 1000 PY) (Paper II). However, the cumulative risks at cut-offs up to 2 years after the diagnosis were not lower than previously reported (44, 45, 49). We therefore suggested that the overall lower rates were due to the long duration of follow-up in the STAC study compared to previous studies. As for the discrepancies within the STAC cohort, it appears that the Tromsø study exhibited somewhat higher rates than previously reported, rather than that the rates in the other two studies were particularly low.

We were not able to determine any important confounders of the association between cancer and VTE. Although there were some differences across baseline variables in cancer and non-cancer subjects, the HR for VTE by cancer was not attenuated by adjustment for these potential confounders. However, in paper I smoking was initially adjusted for by including a dichotomized variable (daily smoking yes or no) in the multivariable Cox-model, and it was suggested that residual confounding by smoking quantity could be present. Additional adjustment for pack-years for current and former smokers did not attenuate the risk estimate. In paper II, smoking was considered by including an ordinal variable (categories were never, former, < 15 cigarettes daily, 15-25 cigarettes daily and ≥ 25 cigarettes daily). Although the difference between these category intervals might not have been constant, the variable probably accounted for differences between smoking habits in cancer- and non-cancer subjects more accurately than a dichotomized variable. Either way, smoking did not appear to be a confounder of the association between cancer and VTE.

Additional risk factors among those who developed cancer may have been unevenly distributed throughout follow-up. For instance, many of the subjects who developed lung cancer probably also had chronic obstructive pulmonary disease (262). Other medical conditions such as heart failure, diabetes and renal disease may have been more common among those who developed cancer and are potential confounders. We did not have information about comorbidities during follow-up, and could not take this into consideration. Residual confounding by these factors would lead to over-estimation of the association between cancer and VTE. In the Danish registry study (34) comorbidity data from the Danish National Registry of Patients was included in the multivariable HR model, and provided an adjusted relative risk (HR) by cancer of 4.7. However, the authors did not report

the unadjusted risk estimates, and the potential role of these comorbidities cannot be read from the paper (34).

In the papers of this thesis, the stability of the risk estimates in multivariable models where baseline confounders were included, along with the clear temporal relation between the cancer diagnosis and the VTE events, suggest that the association is not heavily confounded.

An unconfounded association is necessary to obtain meaningful attributable proportions from incidence rates. The attributable proportions due to cancer in papers I and II (i.e. 23 % and 20 %, respectively) were based on crude rates in the respective populations and do not take confounding factors or interaction into consideration (263). Although no important confounders were identified in our studies, residual cofounding by unrecognized factors or unavailable data cannot be ruled out. Thus, the external validity of these estimates relies not only on a similar frequency of the exposure, but also on similar distribution of potential confounders and effect modifiers. Furthermore, if one wanted to predict the frequency of VTE if cancer was eliminated from the population (as is often attempted for modifiable risk factors), the total amount of person-time at risk of VTE would presumably increase, which might in fact result in a higher absolute number of cases in the population (264). Thus, attributable fractions cannot simply be understood as a preventable share of events a population. Nonetheless, with these limitations in mind, attributable proportions are useful to easily illustrate the relative importance of a risk factor at population level. The attributable proportions presented in this thesis confirm that cancer is one of the most important risk factors for VTE in a general population.

5.2.2 *Time since diagnosis, cancer sites and risk of VTE (Paper II)*

In paper II we conclude that the strongest predictor for VTE in patients with cancer is the proximity to cancer diagnosis. Altogether, more than 50 % of the cancer-related VTE events occurred in the one-year period between 6 months before and 6 months after the cancer diagnosis. In the 6 months before cancer, subjects exhibited a 7-fold increased risk of VTE compared to the cancer-free population. During the first 6 months after manifest disease patients had a 17-fold increased risk of VTE, which rapidly declined to a 5-fold increased risk within the following 6 months. The elevated risk prior to diagnosis underpins a direct impact of malignancy on the hemostatic system previously described in this thesis. The pronounced increase in the initial 6 months is probably explained by iatrogenic risk factors and comorbidities. This notion is supported by the high frequency of other provoking factors in patients with cancer-related VTE observed in paper I, where additional provoking factors including recent surgery, medical illness and central venous catheters, were noted in almost 50 % of those with cancer-related VTE. Notably, information about chemotherapy was not registered among provoking factors, suggesting that the true proportion with concomitant risk factors was substantially higher than 50 %.

The cancers that accounted for the largest proportions of the cancer-related VTE events were lung-, colorectal- and prostate cancers (18 %, 13 % and 9 %, respectively), whereas rare cancers like pancreatic and brain cancers each explained less than 5 % of the cancer-associated VTEs. To the best of our knowledge cancer-specific attributable proportions has not previously been estimated. However, the proportions presented in paper II are reasonable considering the incidence of these cancers along with the site-specific risk of thrombosis.

As previously demonstrated (34, 45, 49, 265), there were large variations in the risk of VTE across cancer sites when the entire follow-up was applied. The cancer sites that exhibited the highest relative risk during the study period were pancreas, lung, brain, kidney and ovaries. In addition, patients with stomach cancer had a high absolute risk of VTE. However, as already shown in previous publications (34, 44, 45), nearly all sites investigated in paper II provided high risks of VTE in the initial 6 to 12 months after the cancer diagnosis. As discussed in the manuscript, site-specific variations in VTE risk demonstrated during long-term follow-up may be partly explained by diverging degrees of exposure misclassification. For cancers with high mortality, such as pancreatic cancer, there was probably only a small proportion of patients who attained remission of the disease. Thus, the exposure status (i.e. cancer/non-cancer) presumably had high validity throughout the study period. Conversely, for cancers with better prognosis, a significant proportion of the person-time may have been accrued from cured individuals. Attenuated risk estimates due to misclassification and regression dilution bias can therefore not be ruled out, and would presumably be more pronounced for cancers with low mortality.

5.2.3 *Age as risk factor for cancer-associated VTE (Paper I+II)*

Guidelines in clinical practice are often age-restricted. This may be founded on age-dependent complication rates, utility measures (such as quality-adjusted life years) or risk of incident disease. High age is often included in VTE prediction models (226, 228, 229) based on the higher risk of incident VTE in the elderly. To date, there are no RAMs specifically developed for hospitalized oncology patients, and subjects with cancer are subjected to the RAMs for hospitalized patients overall.

Papers I and II present age-specific incidence rates and relative risks of VTE in cancer patients. In the Tromsø Study (Paper I), the incidence rate among cancer patients showed a clear gradient across the three age-categories with doubled rate in those aged ≥ 70 years compared to those younger than 50 years (7 and 15 per 1000 person-years, respectively). As expected from the low background risk in young subjects, the HR declined with increasing age.

The high number of participants in the merged cohort applied in paper II allowed for subgroup analyses, and we were able to calculate the site-specific impact of higher age. Interestingly, the effect of high age was small or absent in the groups of high-risk cancers during the first year after the diagnosis. Thus, for decisions on thromboprophylaxis among cancer patients, which primarily are warranted in this period, our results imply that high age should not be emphasized as an independent risk factor. Presumably, the risk of bleeding complications is also higher among elderly patients (266). Taken together, it appears unlikely that the risk-benefit ratio of prophylaxis is more beneficial among elderly cancer patients.

The main question in Paper I was whether cancer could explain the increased VTE risk in the elderly, and the answer is both yes and no. From calculations of attributable proportions in age groups, we concluded that cancer was not a major contributor to the increased risk of VTE by advancing age. The conclusion was based on the decline in attributable risk (PAR%) from 27 % in middle-aged to 18 % in elderly, which implied that other risk factors emerged or increased their influence more than cancer with ageing. However, cancer provided a higher number of excess cases among elderly, and thereby contributed to a higher incidence of VTE by age in the population.

5.2.4 *White blood cell count and cancer-associated VTE (Paper III)*

Total white blood cell count is a frequently used laboratory parameter in many clinical situations. Acute elevation of circulating leukocytes is a sensitive marker of infection and inflammatory diseases, and can usually be detected before other inflammation-markers such as C-reactive protein (CRP). The inter-individual variation of the normal white blood cell count is significant with a reference range of 4-11 x 10^9cells/L and is influenced by genetic and environmental factors (267, 268). The WBC count in healthy humans is mainly determined by the number of circulating neutrophils. Neutrophils are short-lived granulocytic blood cells (7-10 h in the circulation) important in the innate immune response towards bacterial infections. High levels of WBCs and neutrophils have been associated with all-cause mortality, cardiovascular mortality and cancer-associated mortality (269-272). Since low-grade inflammation is a recognized risk-factor for myocardial infarction as well as for cancer development, it is not known whether these relationships are causative or due to a pro-inflammatory state in subjects with high WBC count.

Leukocytosis (WBC count ≥ 11 x 10^9 cells/L) has recently been associated with VTE in several studies of ambulatory cancer patients (115, 202, 273, 274). In the present study, we observed an increased risk of VTE among subjects with high baseline WBC count who subsequently developed cancer, but not among those who remained cancer free.

It may be hypothesized that the positive association in the cancer cohort is due to a systemic inflammation, rather than the leukocytes per se. However, as opposed to atherosclerosis and cancer, the role of low-grade inflammation in the pathogenesis of VTE has been a subject of discussion. Case-control studies have demonstrated an association between inflammation markers and VTE in the acute phase, and a few prospective studies have found positive associations between CRP-levels and subsequent VTE (275, 276). Other

prospective studies have questioned these findings. CRP, fibrinogen and white blood cell count was not associated with VTE in the LITE study (277), pro-inflammatory cytokines did not provide excess risk of VTE in a nested case-cohort design of the HUNT study (278), and baseline high-sensitivity CRP level was not associated with future VTE in the Tromsø Study (279). In the CATS cohort, CRP was associated with an increased risk of VTE after one year, but the effect disappeared in the multivariable model adjusted for age, BMI, surgery, chemotherapy, radiotherapy and p-selectin (280). Altogether, the conflicting results indicate that low-grade inflammation is not an important contributor to development of VTE.

Conversely, acute inflammation is a well-established risk factor for venous thrombosis, and a high risk of VTE has been observed in inflammatory disorders (281-284) and acute infections (170-172). In the present study we did not have information about comorbidities such as autoimmune or infectious diseases. However, if the association was explained by underlying comorbidity in patients with high leukocyte count, a positive risk estimate would be expected also in the cancer-free cohort.

Leukocytes are recognized cellular components of venous thrombi. In a mouse model of DVT based on venous stasis, von Bruhl and colleagues demonstrated that leukocytes adhered to the endothelium early in the DVT formation, and that the majority of these leukocytes were neutrophils (285). They demonstrated that neutropenic mice developed significantly smaller thrombi, and further observed that TF played a key role in coagulation following depressed flow, and that the TF was derived from myeloid cells, not the vessel wall. Apart from TF provided by monocytes, the neutrophils contributed to coagulation by formation of NETs.

Since the baseline leukocyte count to a larger extent is determined by genetic factors and clearly is less influenced by emerging confounders during malignancy, the use of pre-

cancer WBC counts may be regarded as a proxy for *mendelian randomization*. By using WBC counts that were unbiased by the malignant disease, it can be argued that the present study provides reliable evidence for a causal relationship between WBC count and cancer-associated VTE. Although biological interactions cannot be established based on statistical effect modification, this notion is not unlikely. The observation that the association between WBC count and VTE was restricted to cancer patients supports that cancer-associated factors (i.e. the malignant microenvironment, chemotherapy, surgery, acute infections etc.) interact with leukocytes in a way that makes the number of circulating leukocytes to a determinant of venous thrombosis.

A recent publication by Demers and colleagues reported that the neutrophils in mice with solid or hematological cancers released more NETs upon stimulation than neutrophils in cancer free mice, and suggested that this pathway could be important in cancer-associated thrombosis (286). Chemotherapy has also been shown to promote the release of cell-free DNA (166). Further investigation is needed to establish other potential cancer-leukocyte interactions that may take part in the pathogenesis of cancer-related VTE.

5.2.5 *Platelet count and cancer-associated VTE (Paper IV)*

Blood platelets are crucial components of the hemostatic system and are acknowledged contributors in the development of thrombosis. Traditionally, their role in thrombus initiation has been emphasized for arterial thrombotic disease, and to a lesser extent in venous thrombosis. However, several studies suggest that antiplatelet therapy reduce the risk of VTE (287-289), and mean platelet volume (MPV), a marker of platelet activation, has previously been associated with VTE in the Tromsø study (290).

Elevated platelet count is a common finding in patients with cancer and is associated with a poor prognosis in many solid tumors (291, 292). Thrombocytosis has been found to predict VTE in ambulatory cancer patients (112-114), but has not been associated with VTE in prospective studies of the general population (125, 290, 293). In accordance, we observed that a baseline platelet count above the 80th percentile were associated with increased risk of VTE in subjects who developed cancer, but not in those who remained cancer free. The finding indicates that elevated platelet count is not only related to VTE as a marker of acute inflammation or advanced cancer, but may also play a direct role in development of VTE in cancer patients.

Activation of platelets in subjects with cancer is a potential explanation of the observed interaction. In contrast to the fairly limited knowledge about cancer-leukocyte interactions, the platelet-cancer interplay is well-established. The phenomenon has been termed t*umor cell induced platelet aggregation* (TCIPA) and has been described in several studies (294-296). A number of mechanisms may take part in the process (296). Both P-selectin and the fibrinogen-receptor GP IIb/IIIa have been noted as important mediators of platelet-cancer cell interactions through binding of adhesion molecules on cancer cells (297, 298). Generation of thrombin, a potent platelet activator, by lung and pancreatic cancer cell lines were demonstrated already in the mid-nineties (294, 295), and other platelet agonists such as ADP, thromboxane A and MMPs derived from cancer cells has also been suggested as potential mediators of TCIPA (299). In vivo studies have reported high levels of the platelet activation marker soluble P-selectin in cancer patients compared to healthy controls (300-302) and underpins that platelets are activated in these patients. Moreover, P-selectin on the platelet surface is also a mediator of platelet-leukocyte interactions (299) and platelets may thereby be important in DVT propagation by recruitment of leukocytes.

Other features than the malignant environment itself may also influence platelet activation in patients with cancer. In vitro studies have demonstrated that platelet aggregation can be induced directly by chemotherapy (167). Further on, thrombocytosis has been associated with VTE risk in hospitalized medical patients (303), in trauma patients (304, 305) and in patients who undergo cancer surgery (178). An increased risk of VTE has also been noted in patients with reactive thrombocytosis during the recovery phase of critical illness (306). Thus, there is convincing evidence that elevated platelet count is associated with the risk of future VTE in situations where the circulating platelets tend to be activated. In line with this notion, a protective effect of aspirin has been observed in high risk patients (287, 307, 308), whereas a trial of healthy women failed to demonstrate an effect (309).

The platelet count in our study was measured before the cancer diagnosis and it is not known how it is related to the platelet count during malignancy. Even though it is reasonable to assume that those with a baseline platelet count above the 80th percentile would be more prone to thrombocytosis during the period of active cancer, it is possible that the risk of VTE is mediated through other pathways. For instance, platelets are an important source of vascular endothelial growth factor (310), which is essential in angiogenesis (311, 312). It has been demonstrated that platelets are important in cancer development and metastasis (313). Interestingly, we observed that a platelet count in the upper clinical range was associated with a higher risk of distant metastases at the time of cancer diagnosis. Since the latter is also related to VTE, the increased risk of VTE in those with high pre-cancer platelet count were potentially mediated through a higher risk of metastasis. However, adjustment for cancer stage in the multivariable model did not attenuate the risk estimate. The latter observation undermines the hypothesis that risk of VTE was mediated primarily through more advanced cancers in those with high platelet count.

Altogether, mechanistic knowledge about the role of platelets in thrombosis along with the predictive properties of thrombocytosis and platelet activation markers noted in cancer patients provides solid biological and epidemiological grounds for our findings. Our own and other recent observations support a causal role of platelet count in cancer-associated VTE. Similar to our conclusion with respect to WBC- and neutrophil counts, our findings suggest that conditions such as malignancy are mandatory for the platelet count to influence the VTE-risk, probably due to altered platelet function.

6 CONCLUSIONS

Venous thromboembolism is common in patients with cancer and is diagnosed in approximately 3-5 % of all cancer patients. The highest rate was observed in the Tromsø Study (Paper I), where the overall incidence of cancer-associated VTE was 13 per 1000 person-years. The relative risk was substantially higher in the young, whereas the incidence was higher in the elderly. The proportion of VTE events in the population that was due to cancer (PAR %) altogether was 24 %, and declined from 27% in the middle-aged to 18 % in those aged more than 70 years. We therefore concluded that the high risk of VTE in the elderly not is mediated through a high frequency of malignancy at high age (Paper I).

Paper II had greater power compared to Paper I and we were able to apply more narrow age-groups (i.e. 10-year categories), perform site-specific analyses and time-restricted estimates. The study generally confirmed the findings of paper I, and suggested that 20 % of the VTE events were due to cancer. Although the VTE-rates were higher among elderly in the long-term follow-up, the rates between age-groups did not differ much in the first year after diagnosis. Since more than 50 % of the VTE events occurred within the 6 months before and 6 months after manifest cancer, proximity to the cancer diagnosis appeared to be the strongest risk factor for cancer-related VTE. There were large site-specific differences when all years of follow-up was applied in the calculations (e.g. high risk for pancreatic, lung- and brain cancers), but was less pronounced when analyses were restricted to the initial period after diagnosis (e.g. most cancers exhibited an initial high risk of VTE). We therefore suggest that the majority of cancers, with exception of breast and prostate cancer, are associated with a high initial risk of venous thrombosis.

In paper III and IV we found that high white blood cell count and platelet count (> 80th percentile) measured before development of cancer were risk factors for cancer-related

VTE. Increased levels of in these parameters have previously been identified as risk factors for VTE in cancer patients. Since the present measurements were unbiased by the severity of the malignant disease and associated comorbidities, our findings adds to current knowledge by suggesting a causal relationship between WBC- and platelet count and development of VTE in cancer patients. In agreement with previous studies, WBC- and platelet count were not associated with VTE in those who remained free of cancer throughout follow-up.

7 IMPLICATIONS OF RESULTS AND FUTURE PERSPECTIVES

Throughout this thesis we have demonstrated that most effect measures of the association between cancer and VTE are ambiguous and that interpretation and comparisons not are straight forward. Due to the pronounced decline in risk after diagnosis, both site-specific mortality and the duration of follow-up set by the researcher has implications on hazard ratios and incidence rates. Although sophisticated statistical methods may provide more accurate results, they may also become incomprehensible to the reader. Simple cumulative risks (i.e. the number of events divided by the number of subjects at risk) should not be underestimated as a useful effect measure in cancer-and thrombosis studies.

Close to 30 000 subjects are diagnosed with cancer each year in Norway (233) and make cancer-associated VTE an important health concern. In fact, by applying the 1-year cumulative risk of VTE demonstrated in the STAC cohort (i.e. 1.6 % in cancer patients), we estimate that approximately 500 subjects newly diagnosed with cancer will suffer from VTE in Norway each year. Similarly, given that the risk does not vary substantially between ethnicities, the world annual incidence of 14 million cancer diagnoses (314) suggests that more than 200 000 cancer-patients develop VTE each year world-wide.

Despite the high risk of VTE associated with malignant diseases, proper administration of prophylaxis during hospitalization has been especially poor in oncology patients (315-317). Important risk factors in the general population do not necessarily apply to these patients, and risk assessment tools such as the Padua prediction score may thereby be inaccurate, for instance by assigning higher scores to elderly subjects. To improve the targeted prophylaxis in cancer patients, we suggest that future studies continue to define risk prediction models for cancer outpatients and hospitalized oncology patients. To increase the awareness of VTE in oncology, the importance of thromboembolic complications should

perhaps be communicated in clinical departments where high risk patients are admitted, including divisions for lung-, gastroenterological- and neurological cancer patients.

The strong temporal relationship between the diagnosis of cancer and the VTE events points towards a significant contribution of treatment-related factors in the pathogenesis of cancer-related VTE. However, studies that have evaluated the risk of VTE by different treatment modalities are based on initial treatment reported to cancer registries (34, 44). To ensure appropriate timing of prophylactic treatment in patients with various cancers, future studies should aim to distinguish between the different treatments, clinical risk factors such as performance status as well as cancer biology as underlying causes for the VTE events. A case-crossover design might be useful to identify the triggers of VTE in oncology-patients.

Finally, the emerging knowledge about risk factors and biomarkers now available makes identification of patients with the highest risk feasible. However, an arising challenge for future trials and clinical practice will be to make decisions on the patients within an intermediate risk class. To determine the appropriate risk-level above which prevention is beneficial, more knowledge about the safety of prophylactic anticoagulation in various clinical settings in oncology is needed. Due to possible variations in bleeding rates within cancer sites and age-groups, age- and site-specific complication rates and corresponding risks of thrombosis should preferably be evaluated in future clinical trials.

8 REFERENCES

1. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Presence of lower limb deep vein thrombosis and prognosis in patients with symptomatic pulmonary embolism: preliminary report. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2009;37(2):225-31.
2. van Langevelde K, Sramek A, Vincken PW, van Rooden JK, Rosendaal FR, Cannegieter SC. Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique. Haematologica. 2013;98(2):309-15.
3. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I4-8.
4. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386-9.
5. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-94S.
6. Trousseau A. Phlemgmasia Alba Dolens: lectures on clinical medicine. London, England: The New Sydenham Society;1868:5:281-331.
7. Buller HR, van Doormaal FF, van Sluis GL, Kamphuisen PW. Cancer and thrombosis: from molecular mechanisms to clinical presentations. J Thromb Haemost. 2007;5 Suppl 1:246-54.
8. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53.
9. Brose KM, Lee AY. Cancer-associated thrombosis: prevention and treatment. Curr Oncol. 2008;15(Suppl 1):S58-67.
10. den Exter PL, Kooiman J, van der Hulle T, Huisman MV. New anticoagulants in the treatment of patients with cancer-associated venous thromboembolism. Best Pract Res Clin Haematol. 2013;26(2):163-9.
11. Wharin C, Tagalakis V. Management of venous thromboembolism in cancer patients and the role of the new oral anticoagulants. Blood Rev. 2014;28(1):1-8.
12. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005;162(10):975-82.
13. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692-9.
14. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso study. J Thromb Haemost. 2008;6(11):1851-7.
15. Buller HR, Sohne M, Middeldorp S. Treatment of venous thromboembolism. J Thromb Haemost. 2005;3(8):1554-60.
16. Girard P, Musset D, Parent F, Maitre S, Phlippoteau C, Simonneau G. High prevalence of detectable deep venous thrombosis in patients with acute pulmonary embolism. Chest. 1999;116(4):903-8.
17. Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med. 2010;170(19):1710-6.

18. Gaborit FS, Overvad K, Norgaard M, Kristensen SR, Tjonneland A, Severinsen MT. Alcohol intake and risk of venous thromboembolism. A Danish follow-up study. Thromb Haemost. 2013;110(1):39-45.
19. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117(1):19-25.
20. Tavora F, Crowder C, Kutys R, Burke A. Discrepancies in initial death certificate diagnoses in sudden unexpected out-of-hospital deaths: the role of cardiovascular autopsy. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology. 2008;17(3):178-82.
21. Tavora F, Crowder CD, Sun CC, Burke AP. Discrepancies between clinical and autopsy diagnoses: a comparison of university, community, and private autopsy practices. American journal of clinical pathology. 2008;129(1):102-9.
22. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. N Engl J Med. 1992;326(19):1240-5.
23. van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. Arch Intern Med. 1997;157(22):2593-8.
24. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991;151(5):933-8.
25. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. Bmj. 2012;345:e7498.
26. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350(25):2558-63.
27. Kovacs MJ, Kahn SR, Wells PS, Anderson DA, Chagnon I, G LEG, et al. Patients with a first symptomatic unprovoked deep vein thrombosis are at higher risk of recurrent venous thromboembolism than patients with a first unprovoked pulmonary embolism. J Thromb Haemost. 2010;8(9):1926-32.
28. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160(6):761-8.
29. Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost. 2010;8(11):2436-42.
30. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. Jama. 1998;279(6):458-62.
31. Douketis J, Tosetto A, Marcucci M, Baglin T, Cosmi B, Cushman M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. Bmj. 2011;342:d813.
32. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol. 2009;145(3):286-95.
33. Kahn SR. Post-thrombotic syndrome after deep venous thrombosis: risk factors, prevention, and therapeutic options. Clinical advances in hematology & oncology : H&O. 2009;7(7):433-5.

34. Cronin-Fenton DP, Sondergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer. 2010;103(7):947-53.
35. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. Jama. 2005;293(6):715-22.
36. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160(6):809-15.
37. Carrier M, Lee AY. Thromboprophylaxis in cancer patients. Semin Thromb Hemost. 2014;40(3):395-400.
38. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009;10(10):943-9.
39. Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med. 2012;366(7):601-9.
40. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol. 2006;24(3):484-90.
41. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60-8.
42. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902-7.
43. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. Blood. 2010;116(24):5377-82.
44. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost. 2006;4(3):529-35.
45. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458-64.
46. Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjonneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. Journal of clinical epidemiology. 2010;63(2):223-8.
47. Casez P, Labarere J, Sevestre MA, Haddouche M, Courtois X, Mercier S, et al. ICD-10 hospital discharge diagnosis codes were sensitive for identifying pulmonary embolism but not deep vein thrombosis. Journal of clinical epidemiology. 2010;63(7):790-7.
48. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine. 1999;78(5):285-91.
49. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer. 2013;49(6):1404-13.
50. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341(11):793-800.

51. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110(7):874-9.
52. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Bmj. 2006;332(7537):325-9.
53. Rosendaal FR, A VANHV, Doggen CJ. Venous thrombosis in the elderly. J Thromb Haemost. 2007;5 Suppl 1:310-7.
54. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010;8(10):2105-12.
55. Monreal M, Falga C, Valdes M, Suarez C, Gabriel F, Tolosa C, et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2006;4(9):1950-6.
56. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med. 1999;159(5):445-53.
57. Trujillo-Santos J, Nieto JA, Ruiz-Gamietea A, Lopez-Jimenez L, Garcia-Bragado F, Quintavalla R, et al. Bleeding complications associated with anticoagulant therapy in patients with cancer. Thromb Res. 2010;125 Suppl 2:S58-61.
58. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484-8.
59. Elting LS, Escalante CP, Cooksley C, Avritscher EB, Kurtin D, Hamblin L, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. Arch Intern Med. 2004;164(15):1653-61.
60. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. J Clin Oncol. 2011;29(17):2405-9.
61. Khorana AA, Dalal MR, Lin J, Connolly GC. Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. ClinicoEconomics and outcomes research : CEOR. 2013;5:101-8.
62. Shayne M, Culakova E, Poniewierski MS, Dale DC, Crawford J, Wogu AF, et al. Risk factors for in-hospital mortality and prolonged length of stay in older patients with solid tumor malignancies. Journal of geriatric oncology. 2013;4(4):310-8.
63. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med. 2000;343(25):1846-50.
64. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol. 2006;24(7):1112-8.
65. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-23.
66. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5(3):632-4.
67. Svendsen E, Karwinski B. Prevalence of pulmonary embolism at necropsy in patients with cancer. Journal of clinical pathology. 1989;42(8):805-9.
68. Shen VS, Pollak EW. Fatal pulmonary embolism in cancer patients: is heparin prophylaxis justified? Southern medical journal. 1980;73(7):841-3.

69. Ogren M, Bergqvist D, Wahlander K, Eriksson H, Sternby NH. Trousseau's syndrome - what is the evidence? A population-based autopsy study. Thromb Haemost. 2006;95(3):541-5.
70. Harrington KJ, Bateman AR, Syrigos KN, Rintoul R, Bhidayasiri R, McCormack M, et al. Cancer-related thromboembolic disease in patients with solid tumours: a retrospective analysis. Ann Oncol. 1997;8(7):669-73.
71. Browne AM, Cronin CG, English C, NiMhuircheartaigh J, Murphy JM, Bruzzi JF. Unsuspected pulmonary emboli in oncology patients undergoing routine computed tomography imaging. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010;5(6):798-803.
72. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(17):2189-204.
73. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
74. Italiano JE, Jr., Shivdasani RA. Megakaryocytes and beyond: the birth of platelets. J Thromb Haemost. 2003;1(6):1174-82.
75. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357(24):2482-94.
76. Andrews RK, Berndt MC. Adhesion-dependent signalling and the initiation of haemostasis and thrombosis. Histology and histopathology. 1998;13(3):837-44.
77. Brill A, Fuchs TA, Savchenko AS, Thomas GM, Martinod K, De Meyer SF, et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. J Thromb Haemost. 2012;10(1):136-44.
78. Owens AP, 3rd, Mackman N. Microparticles in hemostasis and thrombosis. Circ Res. 2011;108(10):1284-97.
79. Hoffman M, Monroe DM, Roberts HR. Cellular interactions in hemostasis. Haemostasis. 1996;26 Suppl 1:12-6.
80. Mackman N, Tilley RE, Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscler Thromb Vasc Biol. 2007;27(8):1687-93.
81. Tilley R, Mackman N. Tissue factor in hemostasis and thrombosis. Semin Thromb Hemost. 2006;32(1):5-10.
82. Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. Arterioscler Thromb Vasc Biol. 2003;23(1):17-25.
83. Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. Journal of clinical pathology. 1974;27(7):517-28.
84. Lund F, Diener L, Ericsson JL. Postmortem intraosseous phlebography as an aid in studies of venous thromboembolism. With application on a geriatric clientele. Angiology. 1969;20(3):155-76.
85. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. Blood Rev. 2009;23(5):225-9.
86. Bovill EG, van der Vliet A. Venous valvular stasis-associated hypoxia and thrombosis: what is the link? Annual review of physiology. 2011;73:527-45.
87. VanWijk MJ, VanBavel E, Sturk A, Nieuwland R. Microparticles in cardiovascular diseases. Cardiovascular research. 2003;59(2):277-87.
88. Manly DA, Boles J, Mackman N. Role of tissue factor in venous thrombosis. Annual review of physiology. 2011;73:515-25.

89. Aleman MM, Gardiner C, Harrison P, Wolberg AS. Differential contributions of monocyte- and platelet-derived microparticles towards thrombin generation and fibrin formation and stability. J Thromb Haemost. 2011;9(11):2251-61.
90. Mackman N. New insights into the mechanisms of venous thrombosis. J Clin Invest. 2012;122(7):2331-6.
91. Ay C, Freyssinet JM, Sailer T, Vormittag R, Pabinger I. Circulating procoagulant microparticles in patients with venous thromboembolism. Thromb Res. 2009;123(5):724-6.
92. Bucciarelli P, Martinelli I, Artoni A, Passamonti SM, Previtali E, Merati G, et al. Circulating microparticles and risk of venous thromboembolism. Thromb Res. 2012;129(5):591-7.
93. Dignat-George F, Camoin-Jau L, Sabatier F, Arnoux D, Anfosso F, Bardin N, et al. Endothelial microparticles: a potential contribution to the thrombotic complications of the antiphospholipid syndrome. Thromb Haemost. 2004;91(4):667-73.
94. Ye R, Ye C, Huang Y, Liu L, Wang S. Circulating tissue factor positive microparticles in patients with acute recurrent deep venous thrombosis. Thromb Res. 2012;130(2):253-8.
95. Chirinos JA, Heresi GA, Velasquez H, Jy W, Jimenez JJ, Ahn E, et al. Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. J Am Coll Cardiol. 2005;45(9):1467-71.
96. Lacroix R, Dubois C, Leroyer AS, Sabatier F, Dignat-George F. Revisited role of microparticles in arterial and venous thrombosis. J Thromb Haemost. 2013;11 Suppl 1:24-35.
97. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science. 2004;303(5663):1532-5.
98. Geddings JE, Mackman N. New players in haemostasis and thrombosis. Thromb Haemost. 2014;111(4):570-4.
99. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD, Jr., et al. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A. 2010;107(36):15880-5.
100. Hoffman R, Haim N, Brenner B. Cancer and thrombosis revisited. Blood Rev. 2001;15(2):61-7.
101. Kakkar AK, DeRuvo N, Chinswangwatanakul V, Tebbutt S, Williamson RC. Extrinsic-pathway activation in cancer with high factor VIIa and tissue factor. Lancet. 1995;346(8981):1004-5.
102. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102 Suppl 1:S2-9.
103. Falanga A, Gordon SG. Isolation and characterization of cancer procoagulant: a cysteine proteinase from malignant tissue. Biochemistry. 1985;24(20):5558-67.
104. Oleksowicz L, Bhagwati N, DeLeon-Fernandez M. Deficient activity of von Willebrand's factor-cleaving protease in patients with disseminated malignancies. Cancer research. 1999;59(9):2244-50.
105. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. Lancet Oncol. 2005;6(6):401-10.
106. Geddings JE, Mackman N. Tumor-derived tissue factor-positive microparticles and venous thrombosis in cancer patients. Blood. 2013;122(11):1873-80.
107. Rautou PE, Mackman N. Microvesicles as risk markers for venous thrombosis. Expert review of hematology. 2013;6(1):91-101.
108. Yu JL, May L, Lhotak V, Shahrzad S, Shirasawa S, Weitz JI, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. Blood. 2005;105(4):1734-41.

109. Khorana AA, Ahrendt SA, Ryan CK, Francis CW, Hruban RH, Hu YC, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res. 2007;13(10):2870-5.
110. Callander NS, Varki N, Rao LV. Immunohistochemical identification of tissue factor in solid tumors. Cancer. 1992;70(5):1194-201.
111. Thaler J, Ay C, Mackman N, Metz-Schimmerl S, Stift J, Kaider A, et al. Microparticle-associated tissue factor activity in patients with pancreatic cancer: correlation with clinicopathological features. European journal of clinical investigation. 2013;43(3):277-85.
112. Simanek R, Vormittag R, Ay C, Alguel G, Dunkler D, Schwarzinger I, et al. High platelet count associated with venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). J Thromb Haemost. 2010;8(1):114-20.
113. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer. 2005;104(12):2822-9.
114. Mandala M, Barni S, Prins M, Labianca R, Tondini C, Russo L, et al. Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial. Ann Oncol. 2010;21(4):871-6.
115. Ahmed S, Shahid RK, Bhatt H, Lee-Ying R, Lim J. Chemotherapy-Related Thrombocytosis: Does It Increase the Risk of Thromboembolism? Oncology. 2012;82(6):327-32.
116. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158(6):585-93.
117. van Langevelde K, Sramek A, Rosendaal FR. The effect of aging on venous valves. Arterioscler Thromb Vasc Biol. 2010;30(10):2075-80.
118. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008;6(4):632-7.
119. van Hylckama Vlieg A, Middeldorp S. Hormone therapies and venous thromboembolism: where are we now? J Thromb Haemost. 2011;9(2):257-66.
120. Severinsen MT, Johnsen SP, Tjonneland A, Overvad K, Dethlefsen C, Kristensen SR. Body height and sex-related differences in incidence of venous thromboembolism: a Danish follow-up study. European journal of internal medicine. 2010;21(4):268-72.
121. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S. Sex difference in risk of second but not of first venous thrombosis: paradox explained. Circulation. 2014;129(1):51-6.
122. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139(2):289-96.
123. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol. 2010;171(10):1109-15.
124. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. A prospective study of risk factors for pulmonary embolism in women. Jama. 1997;277(8):642-5.
125. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002;162(10):1182-9.

126. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80.
127. Borch KH, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, et al. Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol. 2010;30(1):121-7.
128. Severinsen MT, Overvad K, Johnsen SP, Dethlefsen C, Madsen PH, Tjonneland A, et al. Genetic susceptibility, smoking, obesity and risk of venous thromboembolism. Br J Haematol. 2010;149(2):273-9.
129. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121(17):1896-903.
130. Cheng YJ, Liu ZH, Yao FJ, Zeng WT, Zheng DD, Dong YG, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med. 2013;10(9):e1001515.
131. Enga KF, Braekkan SK, Hansen-Krone IJ, le Cessie S, Rosendaal FR, Hansen JB. Cigarette smoking and the risk of venous thromboembolism: the Tromso Study. J Thromb Haemost. 2012;10(10):2068-74.
132. Zoller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation. 2011;124(9):1012-20.
133. Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med. 2009;169(6):610-5.
134. Dowling NF, Austin H, Dilley A, Whitsett C, Evatt BL, Hooper WC. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. J Thromb Haemost. 2003;1(1):80-7.
135. Noboa S, Le Gal G, Lacut K, Mercier B, Leroyer C, Nowak E, et al. Family history as a risk factor for venous thromboembolism. Thromb Res. 2008;122(5):624-9.
136. Sorensen HT, Riis AH, Diaz LJ, Andersen EW, Baron JA, Andersen PK. Familial risk of venous thromboembolism: a nationwide cohort study. J Thromb Haemost. 2011;9(2):320-4.
137. Souto JC, Almasy L, Borrell M, Blanco-Vaca F, Mateo J, Soria JM, et al. Genetic susceptibility to thrombosis and its relationship to physiological risk factors: the GAIT study. Genetic Analysis of Idiopathic Thrombophilia. American journal of human genetics. 2000;67(6):1452-9.
138. Heit JA, Phelps MA, Ward SA, Slusser JP, Petterson TM, De Andrade M. Familial segregation of venous thromboembolism. J Thromb Haemost. 2004;2(5):731-6.
139. Larsen TB, Sorensen HT, Skytthe A, Johnsen SP, Vaupel JW, Christensen K. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. Epidemiology. 2003;14(3):328-32.
140. Egeberg O. Inherited Antithrombin Deficiency Causing Thrombophilia. Thrombosis et diathesis haemorrhagica. 1965;13:516-30.
141. Morange PE, Tregouet DA. Current knowledge on the genetics of incident venous thrombosis. J Thromb Haemost. 2013;11 Suppl 1:111-21.
142. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet. 1995;346(8983):1133-4.
143. Sode BF, Allin KH, Dahl M, Gyntelberg F, Nordestgaard BG. Risk of venous thromboembolism and myocardial infarction associated with factor V Leiden and prothrombin mutations and blood type. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(5):E229-37.

144. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med. 2001;344(16):1222-31.
145. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost. 1998;79(4):706-8.
146. Gallinaro L, Cattini MG, Sztukowska M, Padrini R, Sartorello F, Pontara E, et al. A shorter von Willebrand factor survival in O blood group subjects explains how ABO determinants influence plasma von Willebrand factor. Blood. 2008;111(7):3540-5.
147. Ohira T, Cushman M, Tsai MY, Zhang Y, Heckbert SR, Zakai NA, et al. ABO blood group, other risk factors and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost. 2007;5(7):1455-61.
148. Cohen W, Castelli C, Alessi MC, Aillaud MF, Bouvet S, Saut N, et al. ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. Arterioscler Thromb Vasc Biol. 2012;32(8):2021-8.
149. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. J Clin Invest. 1981;68(5):1370-3.
150. Comp PC, Nixon RR, Cooper MR, Esmon CT. Familial protein S deficiency is associated with recurrent thrombosis. J Clin Invest. 1984;74(6):2082-8.
151. Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nature reviews Cardiology. 2014.
152. Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008;83(2):97-102.
153. Emmerich J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost. 2001;86(3):809-16.
154. Germain M, Saut N, Greliche N, Dina C, Lambert JC, Perret C, et al. Genetics of venous thrombosis: insights from a new genome wide association study. PLoS One. 2011;6(9):e25581.
155. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353(9159):1167-73.
156. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thromb Res. 2006;118(5):555-68.
157. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. Circulation. 2012;125(17):2092-9.
158. Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. J Clin Oncol. 1996;14(10):2731-7.
159. Otten HM, Mathijssen J, ten Cate H, Soesan M, Inghels M, Richel DJ, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch Intern Med. 2004;164(2):190-4.
160. Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol. 2009;27(23):3786-93.

161. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood. 2001;98(5):1614-5.
162. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol. 2002;20(21):4319-23.
163. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR, Eastern Cooperative Oncology G. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24(3):431-6.
164. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22(2):414-23.
165. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. Jama. 2008;300(19):2277-85.
166. Swystun LL, Mukherjee S, Liaw PC. Breast cancer chemotherapy induces the release of cell-free DNA, a novel procoagulant stimulus. J Thromb Haemost. 2011;9(11):2313-21.
167. Togna GI, Togna AR, Franconi M, Caprino L. Cisplatin triggers platelet activation. Thromb Res. 2000;99(5):503-9.
168. Tesselaar ME, Romijn FP, van der Linden IK, Bertina RM, Osanto S. Microparticle-associated tissue factor activity in cancer patients with and without thrombosis. J Thromb Haemost. 2009;7(8):1421-3.
169. Mukherjee SD, Swystun LL, Mackman N, Wang JG, Pond G, Levine MN, et al. Impact of chemotherapy on thrombin generation and on the protein C pathway in breast cancer patients. Pathophysiology of haemostasis and thrombosis. 2010;37(2-4):88-97.
170. Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sorensen HT. Acute infections and venous thromboembolism. Journal of internal medicine. 2012;271(6):608-18.
171. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet. 2006;367(9516):1075-9.
172. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000;160(22):3415-20.
173. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007;110(10):2339-46.
174. Lin J, Proctor MC, Varma M, Greenfield LJ, Upchurch GR, Jr., Henke PK. Factors associated with recurrent venous thromboembolism in patients with malignant disease. J Vasc Surg. 2003;37(5):976-83.
175. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost. 2003;90(3):446-55.
176. Kakkar AK, Haas S, Wolf H, Encke A. Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy. Thromb Haemost. 2005;94(4):867-71.
177. Trinh VQ, Karakiewicz PI, Sammon J, Sun M, Sukumar S, Gervais MK, et al. Venous thromboembolism after major cancer surgery: temporal trends and patterns of care. JAMA surgery. 2014;149(1):43-9.
178. Merkow RP, Bilimoria KY, McCarter MD, Cohen ME, Barnett CC, Raval MV, et al. Post-discharge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis. Ann Surg. 2011;254(1):131-7.

179. Toledano TH, Kondal D, Kahn SR, Tagalakis V. The occurrence of venous thromboembolism in cancer patients following major surgery. Thromb Res. 2013;131(1):e1-5.
180. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-77S.
181. Gibbs NM. Venous thrombosis of the lower limbs with particular reference to bed-rest. The British journal of surgery. 1957;45(191):209-36.
182. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van Hylckama Vlieg A. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. J Thromb Haemost. 2014;12(3):290-6.
183. Pottier P, Hardouin JB, Lejeune S, Jolliet P, Gillet B, Planchon B. Immobilization and the risk of venous thromboembolism. A meta-analysis on epidemiological studies. Thromb Res. 2009;124(4):468-76.
184. Kugler C, Strunk M, Rudofsky G. Venous pressure dynamics of the healthy human leg. Role of muscle activity, joint mobility and anthropometric factors. Journal of vascular research. 2001;38(1):20-9.
185. Kraaijenhagen RA, Haverkamp D, Koopman MM, Prandoni P, Piovella F, Buller HR. Travel and risk of venous thrombosis. Lancet. 2000;356(9240):1492-3.
186. Kuipers S, Schreijer AJ, Cannegieter SC, Buller HR, Rosendaal FR, Middeldorp S. Travel and venous thrombosis: a systematic review. Journal of internal medicine. 2007;262(6):615-34.
187. Pongmoragot J, Rabinstein AA, Nilanont Y, Swartz RH, Zhou L, Saposnik G. Pulmonary embolism in ischemic stroke: clinical presentation, risk factors, and outcome. Journal of the American Heart Association. 2013;2(6):e000372.
188. Kelly J, Rudd A, Lewis RR, Coshall C, Moody A, Hunt BJ. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. Stroke; a journal of cerebral circulation. 2004;35(10):2320-5.
189. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009;373(9679):1958-65.
190. Zwicker J, Connolly G, Carrier M, Kamphuisen P, Lee A. Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2014.
191. Lee AY, Levine MN, Butler G, Webb C, Costantini L, Gu C, et al. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol. 2006;24(9):1404-8.
192. Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. J Clin Oncol. 2005;23(18):4057-62.
193. Bern MM, Lokich JJ, Wallach SR, Bothe A, Jr., Benotti PN, Arkin CF, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. Ann Intern Med. 1990;112(6):423-8.
194. Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol. 2005;23(18):4063-9.
195. Gaitini D, Beck-Razi N, Haim N, Brenner B. Prevalence of upper extremity deep venous thrombosis diagnosed by color Doppler duplex sonography in cancer patients with

central venous catheters. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2006;25(10):1297-303.
196. Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol. 2006;17(2):289-96.
197. Piran S, Ngo V, McDiarmid S, Le Gal G, Petrcich W, Carrier M. Incidence and risk factors of symptomatic venous thromboembolism related to implanted ports in cancer patients. Thromb Res. 2014;133(1):30-3.
198. Ay C, Simanek R, Vormittag R, Dunkler D, Alguel G, Koder S, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). Blood. 2008;112(7):2703-8.
199. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009;27(25):4124-9.
200. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C, et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol. 2009;29(12):2176-81.
201. Pabinger I, Thaler J, Ay C. Biomarkers for prediction of venous thromboembolism in cancer. Blood. 2013;122(12):2011-8.
202. Trujillo-Santos J, Di Micco P, Iannuzzo M, Lecumberri R, Guijarro R, Madridano O, et al. Elevated white blood cell count and outcome in cancer patients with venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost. 2008;100(5):905-11.
203. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med. 2004;140(8):589-602.
204. Di Nisio M, Squizzato A, Rutjes AW, Buller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007;5(2):296-304.
205. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost. 2007;5 Suppl 1:41-50.
206. Ferroni P, Martini F, Portarena I, Massimiani G, Riondino S, La Farina F, et al. Novel high-sensitive D-dimer determination predicts chemotherapy-associated venous thromboembolism in intermediate risk lung cancer patients. Clinical lung cancer. 2012;13(6):482-7.
207. Arpaia G, Carpenedo M, Verga M, Mastrogiacomo O, Fagnani D, Lanfredini M, et al. D-dimer before chemotherapy might predict venous thromboembolism. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2009;20(3):170-5.
208. Stender MT, Frokjaer JB, Larsen TB, Lundbye-Christensen S, Thorlacius-Ussing O. Preoperative plasma D-dimer is a predictor of postoperative deep venous thrombosis in colorectal cancer patients: a clinical, prospective cohort study with one-year follow-up. Diseases of the colon and rectum. 2009;52(3):446-51.
209. Kodama J, Seki N, Masahiro S, Kusumoto T, Nakamura K, Hongo A, et al. D-dimer level as a risk factor for postoperative venous thromboembolism in Japanese women with gynecologic cancer. Ann Oncol. 2010;21(8):1651-6.
210. Ay C, Jungbauer LV, Sailer T, Tengler T, Koder S, Kaider A, et al. High concentrations of soluble P-selectin are associated with risk of venous thromboembolism and the P-selectin Thr715 variant. Clinical chemistry. 2007;53(7):1235-43.

211. Tesselaar ME, Romijn FP, Van Der Linden IK, Prins FA, Bertina RM, Osanto S. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? J Thromb Haemost. 2007;5(3):520-7.
212. Auwerda JJ, Yuana Y, Osanto S, de Maat MP, Sonneveld P, Bertina RM, et al. Microparticle-associated tissue factor activity and venous thrombosis in multiple myeloma. Thromb Haemost. 2011;105(1):14-20.
213. Thaler J, Ay C, Mackman N, Bertina RM, Kaider A, Marosi C, et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. J Thromb Haemost. 2012;10(7):1363-70.
214. Jenkins PV, Rawley O, Smith OP, O'Donnell JS. Elevated factor VIII levels and risk of venous thrombosis. Br J Haematol. 2012;157(6):653-63.
215. O'Donnell J, Tuddenham EG, Manning R, Kemball-Cook G, Johnson D, Laffan M. High prevalence of elevated factor VIII levels in patients referred for thrombophilia screening: role of increased synthesis and relationship to the acute phase reaction. Thromb Haemost. 1997;77(5):825-8.
216. Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet. 1995;345(8943):152-5.
217. Kraaijenhagen RA, in't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thromb Haemost. 2000;83(1):5-9.
218. Patel RK, Ford E, Thumpston J, Arya R. Risk factors for venous thrombosis in the black population. Thromb Haemost. 2003;90(5):835-8.
219. Oger E, Lacut K, Van Dreden P, Bressollette L, Abgrall JF, Blouch MT, et al. High plasma concentration of factor VIII coagulant is also a risk factor for venous thromboembolism in the elderly. Haematologica. 2003;88(4):465-9.
220. Ota S, Yamada N, Ogihara Y, Tsuji A, Ishikura K, Nakamura M, et al. High plasma level of factor VIII: an important risk factor for venous thromboembolism. Circ J. 2011;75(6):1472-5.
221. Yigit E, Gonullu G, Yucel I, Turgut M, Erdem D, Cakar B. Relation between hemostatic parameters and prognostic/predictive factors in breast cancer. European journal of internal medicine. 2008;19(8):602-7.
222. Auwerda JJ, Sonneveld P, de Maat MP, Leebeek FW. Prothrombotic coagulation abnormalities in patients with newly diagnosed multiple myeloma. Haematologica. 2007;92(2):279-80.
223. Battistelli S, Stefanoni M, Lorenzi B, Dell'avanzato R, Varrone F, Pascucci A, et al. Coagulation factor levels in non-metastatic colorectal cancer patients. The International journal of biological markers. 2008;23(1):36-41.
224. Vormittag R, Simanek R, Ay C, Dunkler D, Quehenberger P, Marosi C, et al. High factor VIII levels independently predict venous thromboembolism in cancer patients: the cancer and thrombosis study. Arterioscler Thromb Vasc Biol. 2009;29(12):2176-81.
225. Ferroni P, Guadagni F, Laudisi A, Vergati M, Riondino S, Russo A, et al. Estimated Glomerular Filtration Rate Is an Easy Predictor of Venous Thromboembolism in Cancer Patients Undergoing Platinum-Based Chemotherapy. The oncologist. 2014.
226. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8(11):2450-7.
227. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med. 2012;7(3):291-2.

228. Bikdeli B, Sharif-Kashani B, Shahabi P, Raeissi S, Shahrivari M, Shoraka AR, et al. Comparison of three risk assessment methods for venous thromboembolism prophylaxis. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2013;24(2):157-63.
229. Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med. 2005;352(10):969-77.
230. Carrier M, Khorana AA, Moretto P, Le Gal G, Karp R, Zwicker JI. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. Am J Med. 2014;127(1):82-6 e1.
231. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. International journal of epidemiology. 2012;41(4):961-7.
232. Sundhedsstyrelsen. Det moderniserede Cancerregister – metode og kvalitet 2009. Available from: http://www.ssi.dk/Sundhedsdataogit/Registre/~/media/Indhold/DK%20-%20dansk/Sundhedsdata%20og%20it/NSF/Registre/Cancerregisteret/Det%20moderniserede%20Cancerregister%20%20metode%20og%20kvalitet.ashx.
233. Cancer Registry of Norway. Cancer in Norway 2012 - Cancer incidence, mortality, survival and prevalence in Norway. Cancer Registry of Norway, Oslo, 2014.
234. Morkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trondelag Health Study), Norway. J Am Coll Cardiol. 2014;63(11):1071-8.
235. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjonneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. Circulation. 2009;120(19):1850-7.
236. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society. 1972.
237. Breslow NE. Statistics in epidemiology: the case-control study. J Am Stat Assoc. 1996;91(433):14-28.
238. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. American journal of public health. 1998;88(1):15-9.
239. Rowe AK, Powell KE, Flanders WD. Why population attributable fractions can sum to more than one. American journal of preventive medicine. 2004;26(3):243-9.
240. Normand SL, Sykora K, Li P, Mamdani M, Rochon PA, Anderson GM. Readers guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding. Bmj. 2005;330(7498):1021-3.
241. Greenland S, Morgenstern H. Confounding in health research. Annual review of public health. 2001;22:189-212.
242. Lu CY. Observational studies: a review of study designs, challenges and strategies to reduce confounding. International journal of clinical practice. 2009;63(5):691-7.
243. Rosenbaum BP, Rubin DB. Reducing Bias in Observational Studies Using Subclassification on the Propensity
Score. Journal of the American Statistical Association. 1984;79(387):516-24.
244. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol. 2006;163(12):1149-56.
245. Alison J. Canchola SLS, Leslie Bernstein, Dee W. West, Ronald K. Ross, Dennis Deapen, Richard, Pinder PR, William Wright, Hoda Anton-Culver, David Peel, Al Ziogas, and Pamela L. Horn-Ross. Cox Regression Using Different Time-Scales. Western Users of SAS Software, San Francisco, California. 2003.
246. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Statistics in medicine. 2004;23(24):3803-20.

247. Szklo M, Nieto J. Epidemiology: beyond the basics. Burlington: Jones and Bartlett Learning 2007.
248. Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press; 2002.
249. Rothman KJ. The estimation of synergy or antagonism. Am J Epidemiol. 1976;103(5):506-11.
250. Armstrong BG. The effects of measurement errors on relative risk regressions. Am J Epidemiol. 1990;132(6):1176-84.
251. Fox-Wasylyshyn SM, El-Masri MM. Handling missing data in self-report measures. Research in nursing & health. 2005;28(6):488-95.
252. Buhi ER, Goodson P, Neilands TB. Out of sight, not out of mind: strategies for handling missing data. American journal of health behavior. 2008;32(1):83-92.
253. Campigotto F, Neuberg D, Zwicker JI. Accounting for death as a competing risk in cancer-associated thrombosis studies. Thromb Res. 2012;129 Suppl 1:S85-7.
254. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. International journal of epidemiology. 2012;41(3):861-70.
255. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk Journal of the american statistical association. 1999(94):496-509.
256. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Danish medical bulletin. 1997;44(5):535-9.
257. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer. 2009;45(5):756-64.
258. Crocetti E, Miccinesi G, Paci E, Zappa M. An application of the two-source capture-recapture method to estimate the completeness of the Tuscany Cancer Registry, Italy. Eur J Cancer Prev. 2001;10(5):417-23.
259. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-31.
260. Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scandinavian journal of public health. 2007;35(4):432-41.
261. Engholm G FJ, Christensen N, Johannesen TB, Khan S., Køtlum JE, Milter MC, Ólafsdóttir E, Pukkala E, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 6.1 (25.04.2014). Association of the Nordic Cancer Registries: Danish Cancer Society. Available from: http://www.ancr.nu
262. Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB, Tata LJ. Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2013;8(1):6-11.
263. Walter SD. Effects of interaction, confounding and observational error on attributable risk estimation. Am J Epidemiol. 1983;117(5):598-604.
264. Kenneth J. Rothman SG, Timothy L. Lash. Modern epidemiology. Third edition. Philadelphia, USA: Lippincott Williams and Wilkins; 2008.
265. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.
266. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med. 2005;165(13):1527-32.
267. Whitfield JB, Martin NG. Genetic and environmental influences on the size and number of cells in the blood. Genetic epidemiology. 1985;2(2):133-44.

268. Garner C, Tatu T, Reittie JE, Littlewood T, Darley J, Cervino S, et al. Genetic influences on F cells and other hematologic variables: a twin heritability study. Blood. 2000;95(1):342-6.
269. Jee SH, Park JY, Kim HS, Lee TY, Samet JM. White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans. Am J Epidemiol. 2005;162(11):1062-9.
270. Yarnell JW, Patterson CC, Sweetnam PM, Lowe GD. Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies. Eur Heart J. 2004;25(12):1049-56.
271. Shankar A, Wang JJ, Rochtchina E, Yu MC, Kefford R, Mitchell P. Association between circulating white blood cell count and cancer mortality: a population-based cohort study. Arch Intern Med. 2006;166(2):188-94.
272. Shankar A, Mitchell P, Rochtchina E, Wang JJ. The association between circulating white blood cell count, triglyceride level and cardiovascular and all-cause mortality: population-based cohort study. Atherosclerosis. 2007;192(1):177-83.
273. Connolly GC, Khorana AA, Kuderer NM, Culakova E, Francis CW, Lyman GH. Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy. Thromb Res. 2010.
274. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29(25):3466-73.
275. Quist-Paulsen P, Naess IA, Cannegieter SC, Romundstad PR, Christiansen SC, Rosendaal FR, et al. Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2). Haematologica. 2010;95(1):119-25.
276. Folsom AR, Lutsey PL, Astor BC, Cushman M. C-reactive protein and venous thromboembolism. A prospective investigation in the ARIC cohort. Thromb Haemost. 2009;102(4):615-9.
277. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). Am J Med. 2002;113(8):636-42.
278. Christiansen SC, Naess IA, Cannegieter SC, Hammerstrom J, Rosendaal FR, Reitsma PH. Inflammatory cytokines as risk factors for a first venous thrombosis: a prospective population-based study. PLoS Med. 2006;3(8):e334.
279. Hald EM, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Brox J, et al. High-sensitivity C-reactive protein is not a risk factor for venous thromboembolism: the Tromso study. Haematologica. 2011;96(8):1189-94.
280. Kanz R, Vukovich T, Vormittag R, Dunkler D, Ay C, Thaler J, et al. Thrombosis risk and survival in cancer patients with elevated C-reactive protein. J Thromb Haemost. 2011;9(1):57-63.
281. Zoller B, Li X, Sundquist J, Sundquist K. Autoimmune diseases and venous thromboembolism: a review of the literature. American journal of cardiovascular disease. 2012;2(3):171-83.
282. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost. 2001;85(3):430-4.
283. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med. 2004;164(9):963-8.
284. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet. 2010;375(9715):657-63.

285. von Bruhl ML, Stark K, Steinhart A, Chandraratne S, Konrad I, Lorenz M, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med. 2012;209(4):819-35.
286. Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci U S A. 2012;109(32):13076-81.
287. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet. 2000;355(9212):1295-302.
288. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366(21):1959-67.
289. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. Journal of the neurological sciences. 1996;143(1-2):1-13.
290. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromso Study, Tromso, Norway. J Thromb Haemost. 2010;8(1):157-62.
291. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in solid tumors. International journal of cancer Journal international du cancer. 2012;130(12):2747-60.
292. Edwards RL, Rickles FR, Moritz TE, Henderson WG, Zacharski LR, Forman WB, et al. Abnormalities of blood coagulation tests in patients with cancer. American journal of clinical pathology. 1987;88(5):596-602.
293. van der Bom JG, Heckbert SR, Lumley T, Holmes CE, Cushman M, Folsom AR, et al. Platelet count and the risk for thrombosis and death in the elderly. J Thromb Haemost. 2009;7(3):399-405.
294. Heinmoller E, Schropp T, Kisker O, Simon B, Seitz R, Weinel RJ. Tumor cell-induced platelet aggregation in vitro by human pancreatic cancer cell lines. Scandinavian journal of gastroenterology. 1995;30(10):1008-16.
295. Heinmoller E, Weinel RJ, Heidtmann HH, Salge U, Seitz R, Schmitz I, et al. Studies on tumor-cell-induced platelet aggregation in human lung cancer cell lines. Journal of cancer research and clinical oncology. 1996;122(12):735-44.
296. Jurasz P, Alonso-Escolano D, Radomski MW. Platelet--cancer interactions: mechanisms and pharmacology of tumour cell-induced platelet aggregation. British journal of pharmacology. 2004;143(7):819-26.
297. Karpatkin S, Pearlstein E, Ambrogio C, Coller BS. Role of adhesive proteins in platelet tumor interaction in vitro and metastasis formation in vivo. J Clin Invest. 1988;81(4):1012-9.
298. Garcia J, Callewaert N, Borsig L. P-selectin mediates metastatic progression through binding to sulfatides on tumor cells. Glycobiology. 2007;17(2):185-96.
299. Riedl J, Pabinger I, Ay C. Platelets in cancer and thrombosis. Hamostaseologie. 2013;34(1).
300. Roselli M, Mineo TC, Martini F, Mariotti S, Ambrogi V, Spila A, et al. Soluble selectin levels in patients with lung cancer. The International journal of biological markers. 2002;17(1):56-62.
301. Blann AD, Gurney D, Wadley M, Bareford D, Stonelake P, Lip GY. Increased soluble P-selectin in patients with haematological and breast cancer: a comparison with fibrinogen, plasminogen activator inhibitor and von Willebrand factor. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2001;12(1):43-50.

302. Caine GJ, Lip GY, Stonelake PS, Ryan P, Blann AD. Platelet activation, coagulation and angiogenesis in breast and prostate carcinoma. Thromb Haemost. 2004;92(1):185-90.
303. Woller SC, Stevens SM, Jones JP, Lloyd JF, Evans RS, Aston VT, et al. Derivation and validation of a simple model to identify venous thromboembolism risk in medical patients. Am J Med. 2011;124(10):947-54 e2.
304. Salim A, Hadjizacharia P, DuBose J, Kobayashi L, Inaba K, Chan LS, et al. What is the significance of thrombocytosis in patients with trauma? The Journal of trauma. 2009;66(5):1349-54.
305. Kashuk JL, Moore EE, Johnson JL, Biffl WL, Burlew CC, Barnett C, et al. Progressive postinjury thrombocytosis is associated with thromboembolic complications. Surgery. 2010;148(4):667-74; discussion 74-5.
306. Ho KM, Yip CB, Duff O. Reactive thrombocytosis and risk of subsequent venous thromboembolism: a cohort study. J Thromb Haemost. 2012;10(9):1768-74.
307. Hovens MM, Snoep JD, Tamsma JT, Huisman MV. Aspirin in the prevention and treatment of venous thromboembolism. J Thromb Haemost. 2006;4(7):1470-5.
308. Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. Bmj. 1994;308(6923):235-46.
309. Glynn RJ, Ridker PM, Goldhaber SZ, Buring JE. Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial. Ann Intern Med. 2007;147(8):525-33.
310. Gunsilius E, Petzer A, Stockhammer G, Nussbaumer W, Schumacher P, Clausen J, et al. Thrombocytes are the major source for soluble vascular endothelial growth factor in peripheral blood. Oncology. 2000;58(2):169-74.
311. Ribatti D. The crucial role of vascular permeability factor/vascular endothelial growth factor in angiogenesis: a historical review. Br J Haematol. 2005;128(3):303-9.
312. Nash GF, Walsh DC, Kakkar AK. The role of the coagulation system in tumour angiogenesis. Lancet Oncol. 2001;2(10):608-13.
313. Nash GF, Turner LF, Scully MF, Kakkar AK. Platelets and cancer. Lancet Oncol. 2002;3(7):425-30.
314. Wolrd Health Orgniazation IAfRoC. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
315. Kahn SR, Panju A, Geerts W, Pineo GF, Desjardins L, Turpie AG, et al. Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. Thromb Res. 2007;119(2):145-55.
316. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. 2008;371(9610):387-94.
317. Braekkan S, Grimsgaard S, Hansen JB. [Thromboembolic prophylaxis in hospitalized medical patients]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 2007;127(9):1177-80.

Paper I

Paper II

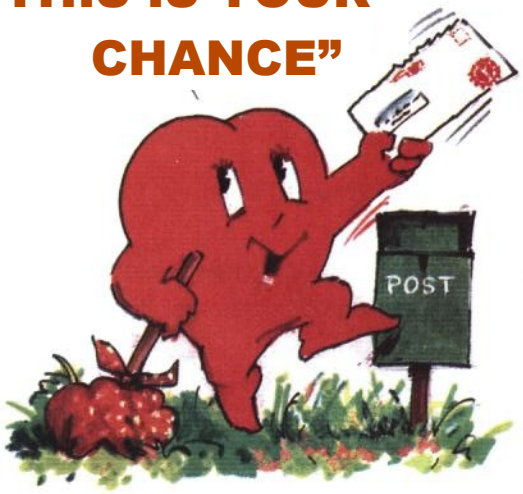
Paper III

Paper IV

Appendix

HEALTH SURVEY
Invitation

"THIS IS YOUR CHANCE"



Date of birth **Social security No.** **Municipality** **Electoral ward No.**

Welcome to the Tromsø Health Survey!

The Health Survey is coming to Tromsø. This leaflet will tell you when and where. You will also find information about the survey in the enclosed brochure.

We would like you to fill in the form overleaf and take it with you to the examination.

The more people take part in the survey, the more valuable its results will be. We hope, therefore, that you will be able to come. Attend even if you feel healthy, if you are currently receiving medical treatment, or if you have had your cholesterol and blood pressure measured recently.

Yours sincerely,
Municipal Health Authorities
Faculty of Medicine - University of Tromsø
National Health Screening Service

"THIS IS A REAL OPPORTUNITY- TAKE IT!"

YOUR OWN HEALTH

What is your current state of health? *Tick one box only.*

Poor	12	1
Not so good		2
Good		3
Very good		4

Do you have, or have you had:

		Yes	No	Age first time
A heart attack	13			years
Angina pectoris (heart cramp)	16			years
A cerebral stroke/ brain haemorrhage	19			years
Asthma	22			years
Diabetes	25			years

Do you use blood pressure lowering drugs?

Currently	28	1
Previously, but not now		2
Never used		3

Have you during the last year suffered from pains and/or stiffness in muscles and joints that have lasted continuously for at least 3 months? 29 Yes / No

Have you in the last two weeks felt:

		No	A little	A lot	Very much
Nervous or worried?	30				
Anxious?	31				
Confident and calm?	32				
Irritable?	33				
Happy and optimistic?	34				
Down/depressed?	35				
Lonely?	36				
		1	2	3	4

SMOKING

Did any of the adults at home smoke while you were growing up? 37 Yes / No

Do you currently, or did you previously, live together with daily smokers after your 20th birthday? 38 Yes / No

If "YES", for how many years in all? 39 ____ Years

How many hours a day do you normally spend in smoke-filled rooms? 41 ____ Hours

Put 0 if you do not spend time in smoke-filled rooms.

Do you yourself smoke:

		Yes	No
Cigarettes daily?	43		
Cigars/ cigarillos daily?	44		
A pipe daily?	45		

If you previously smoked daily, how long is it since you quit? 46 ____ Years

If you currently smoke, or have smoked previously:

How many cigarettes do you or did you usually smoke per day? 48 ____ cigarettes

How old were you when you began daily smoking? 52 ____ Age years

How many years in all have you smoked daily? 54 ____ Years

EXERCISE

How has your physical activity in leisure time been during this last year? *Think of your weekly average for the year.*

Time spent going to work counts as leisure time.

		Hours per week: None	Less than 1	1-2	3 or more
Light activity *(not sweating/out of breath)*	56				
Hard activity *(sweating/ out of breath)*	57				
		1	2	3	4

COFFEE

How many cups of coffee do you drink daily?

Put 0 if you do not drink coffee daily.

Coarsely ground coffee for brewing 58 ____ Cups

Other coffee 60 ____ Cups

ALCOHOL

Are you a teetotaller? 62 Yes / No

How many times a month do you normally drink alcohol? *Do not count low-alcohol beer.*

Put 0 if less than once a month. 63 ____ Times

How many glasses of beer, wine or spirits do you normally drink in a fortnight? 65

Do not count low-alcohol beer.

Put 0 if less than once a month.

Beer	Wine	Spirits
Glasses	Glasses	Glasses

FAT

What type of margarine or butter do you usually use on bread? *Tick one box only.*

Don't use butter/margarine	71	1
Butter		2
Hard margarine		3
Soft margarine		4
Butter/margarine mixtures		5
Light margarine		6

EDUCATION/WORK

What is the highest level of education you have completed?

7-10 years primary/secondary school, modern secondary school	72	1
Technical school, middle school, vocational school, 1-2 years senior high school		2
High school diploma (3-4 years)		3
College/university, less than 4 years		4
College/university, 4 or more years		5

What is your current work situation?

Paid work	73	
Full-time housework	74	
Education, military service	75	
Unemployed, on leave without payment	76	

How many hours of paid work do you have per week? 77 ____ No. of hours

Do you receive any of the following benefits?

Sickness benefit (sick leave)	79	
Rehabilitation benefit	80	
Disability pension	81	
Old-age pension	82	
Social welfare benefit	83	
Unemployment benefit	84	

ILLNESS IN THE FAMILY

Have one or more of your parents or siblings had a heart attack or had angina (heart cramp)? 85

Yes	No	Don't know

The Tromsø Health Survey

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. We would therefore like you to answer some questions about factors that may be relevant for your risk of getting these and other illnesses.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire ..... 17 ☐

Day Month Year

Date for filling in this form:..... 18 ...../...../.....

CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1 year?

..... 24 - 28

If you did not live in Norway, give country of residence instead of municipality.

How was your family's financial situation during your childhood?

- Very good ..... 29 ☐
- Good ..... ☐
- Difficult ..... ☐
- Very difficult ..... ☐

How many of the first three years of your life

- did you live in a town/city? ..... 30 ____years
- did your family have a cat or dog in the home? ..... 31 ____years

How many of the first 15 years of your life

- did you live in a town/city? ..... 32 ____years
- did your family have a cat or dog in the home? ..... 34 ____years

HOME

Who do you live with?

Tick once for each item and give the number .		Yes	No	Number
Spouse/partner	36	☐	☐	
Other people over 18 years	37	☐	☐	_____
People under 18 years	40	☐	☐	_____

How many of the children attend day care/kindergarten? .... 43 _____

What type of house do you live in?

- Villa/detached house ..... 45 ☐ 1
- Farm ..... ☐ 2
- Flat /apartment ..... ☐ 3
- Terraced /semi-detached house ..... ☐ 4
- Other ..... ☐ 5

How big is your house? ..... 46 _____ m^2

Approximately what year was your house built? ..... 49 _____

		Yes	No
Has your house been insulated after 1970?	53	☐	☐
Do you live on the lower ground floor/basement?	54	☐	☐
If "Yes", is the floor laid on concrete?	55	☐	☐

What is the main source of heat in your home?

- Electric heating ..... 56 ☐
- Wood-burning stove ..... ☐
- Central heating system using:
  - Paraffin ..... ☐
  - Electricity ..... ☐

		Yes	No
Do you have fitted carpets in the living room?	60	☐	☐
Is there a cat in your home?	61	☐	☐
Is there a dog in your home?	62	☐	☐

WORK

If you have paid or unpaid work, how would you describe your work?

- Mostly sedentary work? ..... 63 ☐ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ☐ 2
  (e.g. shop assistant, light industrial work, teaching)
- Work that requires a lot of walking and lifting? ..... ☐ 3
  (e.g. postman, nursing, construction)
- Heavy manual work? ..... ☐ 4
  (e.g. forestry, heavy farm-work, heavy construction)

Can you decide yourself how your work should be organised?

- No, not at all ..... 64 ☐ 1
- To a small extent ..... ☐ 2
- Yes, to a large extent ..... ☐ 3
- Yes, I decide myself ..... ☐ 4

		Yes	No
Are you on call, do you work shifts or nights?	65	☐	☐

Do you do any of the following jobs (full- or part-time)?

Tick one box only for each item.		Yes	No
Driver	66	☐	☐
Farmer		☐	☐
Fisherman		☐	☐

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time.
*If you have had the condition several times, how old were you **last** time?*

	Yes	No	Age
Hip fracture 69	❑	❑	_____
Wrist/forearm fracture 72	❑	❑	_____
Whiplash 75	❑	❑	_____
Injury requiring hospital admission 78	❑	❑	_____
Gastric ulcer 81	❑	❑	_____
Duodenal ulcer 84	❑	❑	_____
Gastric/duodenal ulcer surgery 87	❑	❑	_____
Neck surgery 90	❑	❑	_____

Have you you ever had, or do you still have:
Tick one box only for each item.

	Yes	No
Cancer 93	❑	❑
Epilepsy	❑	❑
Migraine	❑	❑
Chronic bronchitis	❑	❑
Psoriasis	❑	❑
Osteoporosis 98	❑	❑
Fibromyalgia/fibrositis/chronic pain syndrome	❑	❑
Psychological problems for which you have sought help	❑	❑
Thyroid disease	❑	❑
Liver disease	❑	❑
Kidney disease 103	❑	❑
Appendectomy	❑	❑
Allergy and hypersensitivity:		
Atopic eczema (e.g. childhood eczema)	❑	❑
Hand eczema	❑	❑
Hay fever	❑	❑
Food allergy 108	❑	❑
Other hypersensitivity (not allergy)	❑	❑

How many times have you had a cold, influenza (flu), vomiting/diarrhoea, or similar in the last six months? ____ times

	Yes	No
Have you had this in the last 14 days? 112	❑	❑

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 113	❑	❑	❑	❑	❑	❑
Heart attack before age 60 119	❑	❑	❑	❑	❑	❑
Cancer 125	❑	❑	❑	❑	❑	❑
Asthma 131	❑	❑	❑	❑	❑	❑
Gastric/duodenal ulcer 137	❑	❑	❑	❑	❑	❑
Osteoporosis 143	❑	❑	❑	❑	❑	❑
Psychological problems 149	❑	❑	❑	❑	❑	❑
Allergy 155	❑	❑	❑	❑	❑	❑
Diabetes 161	❑	❑	❑	❑	❑	❑
– age when they got diabetes 167	___	___	___	___	___	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? ..177	❑	❑
If "Yes":		
Is your cough productive ? 178	❑	❑
Have you had this kind of cough for as long as 3 months in each of the last two years? 179	❑	❑
Have you had episodes of wheezing in your chest? ..180	❑	❑
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 181	❑	❑
In connection with respiratory infections	❑	❑
In connection with physical exertion	❑	❑
In connection with very cold weather	❑	❑
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 185	❑	❑

How often do you suffer from sleeplessness?

Never, or just a few times a year 186	❑ 1
1-2 times a month	❑ 2
Approximately once a week	❑ 3
More than once a week	❑ 4

If you suffer from sleeplessness, what time of the year does it affect you most?

No particular time of year 187	❑ 1
Especially during the polar night	❑ 2
Especially during the midnight sun season	❑ 3
Especially in spring and autumn	❑ 4

	Yes	No
Have you in the last year suffered from sleeplessness to the extent that it has affected your ability to work? ..188	❑	❑

How often do you suffer from headaches?

Rarely or never 189	❑ 1
Once or more a month	❑ 2
Once or more a week	❑ 3
Daily	❑ 4

Does the thought of getting a serious illness ever worry you?

Not at all 190	❑ 1
Only a little	❑ 2
Some	❑ 3
Very much	❑ 4

USE OF HEALTH SERVICES

How many visits have you made during the past year due to your own health or illness:
*Tick **0** if you have **not** had such contact*

	Number of times the past year
To a general practitioner (GP)/Emergency GP 191	_____
To a psychologist or psychiatrist	_____
To an other medical specialist (not at a hospital)	_____
To a hospital out-patient clinic 197	_____
Admitted to a hospital	_____
To a medical officer at work	_____
To a physiotherapist 203	_____
To a chiropractor	_____
To an acupuncturist	_____
To a dentist 209	_____
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	_____
To a healer, faith healer, clairvoyant	_____

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the past year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
*Put **0** for items you have **not** used.*

Medicines

Painkillers	215	_____ months
Sleeping pills		_____ months
Tranquillizers		_____ months
Antidepressants	221	_____ months
Allergy drugs		_____ months
Asthma drugs		_____ months

Dietary supplements

Iron tablets	227	_____ months
Calcium tablets or bonemeal		_____ months
Vitamin D supplements		_____ months
Other vitamin supplements	233	_____ months
Cod liver oil or fish oil capsules		_____ months

Have you in the last 14 days used the following medicines or dietary supplements?
*Tick **one** box only for **each** item.*

		Yes	No
Medicines			
Painkillers	237	❑	❑
Antipyretic drugs (to reduce fever)		❑	❑
Migraine drugs		❑	❑
Eczema cream/ointment		❑	❑
Heart medicines (not blood pressure)		❑	❑
Cholesterol lowering drugs		❑	❑
Sleeping pills		❑	❑
Tranquillizers		❑	❑
Antidepressants		❑	❑
Other drugs for nervous conditions		❑	❑
Antacids	247	❑	❑
Gastric ulcer drugs		❑	❑
Insulin		❑	❑
Diabetes tablets		❑	❑
Drugs for hypothyroidism (Thyroxine)		❑	❑
Cortisone tablets	252	❑	❑
Other medicine(s)		❑	❑
Dietary supplements			
Iron tablets		❑	❑
Calcium tablets or bonemeal		❑	❑
Vitamin D supplements		❑	❑
Other vitamin supplements	257	❑	❑
Cod liver oil or fish oil capsules		❑	❑

FRIENDS

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? 259 _____ good friends
Do not count people you live with, but do include other relatives!

How many of these good friends do you have contact with at least once a month? ..... 261 _____

	Yes	No
Do you feel you have enough good friends? 263	❑	❑

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

Never, or just a few times a year	264	❑ 1
1-2 times a month		❑ 2
Approximately once a week		❑ 3
More than once a week		❑ 4

FOOD HABITS

If you use butter or margarine on your bread, how many slices does a small catering portion normally cover? By this, we mean the portion packs served on planes, in cafés, etc. (10-12g)

A catering portion is enough for about ..... 265 _____ slices

What kind of fat is normally used in **cooking** (not on the bread) in your home?

Butter	266	❑
Hard margarine		❑
Soft margarine		❑
Butter/margarine blend		❑
Oils	270	❑

What kind of bread (bought or home-made) do you usually eat?
Tick one or two boxes!

	White bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread I eat is most similar to:	❑ 271	❑	❑	❑	❑ 275

How much (in **number** of glasses, cups, potatoes or slices) do you usually eat or drink **daily** of the following foodstuffs?
*Tick one box for **each** foodstuff.*

	0	Less than 1	1-2	3-4	5-6	More than 6
Full milk (ordinary or curdled) (glasses) 276	❑	❑	❑	❑	❑	❑
Semi-skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Skimmed milk (ordinary or curdled) (glasses)	❑	❑	❑	❑	❑	❑
Tea (cups)	❑	❑	❑	❑	❑	❑
Orange juice (glasses)	❑	❑	❑	❑	❑	❑
Potatoes 281	❑	❑	❑	❑	❑	❑
Slices of bread in total (incl. crisp-bread)	❑	❑	❑	❑	❑	❑
Slices of bread with						
- fish (e.g. mackerel in tomato sauce)	❑	❑	❑	❑	❑	❑
- lean meat (e.g. ham)	❑	❑	❑	❑	❑	❑
- fat meat (e.g. salami)	❑	❑	❑	❑	❑	❑
- cheese *(e.g. Gouda/ Norvegia)* 286	❑	❑	❑	❑	❑	❑
- brown cheese	❑	❑	❑	❑	❑	❑
- smoked cod caviare	❑	❑	❑	❑	❑	❑
- jam and other sweet spreads	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

How many **times per week** do you normally eat the following foodstuffs?
*Tick a box for **all** foodstuffs listed.*

	Never	Less than 1	1	2-3	4-5	almost daily
Yoghurt 290	❑	❑	❑	❑	❑	❑
Boiled or fried egg	❑	❑	❑	❑	❑	❑
Breakfast cereal/ oat meal, etc.	❑	❑	❑	❑	❑	❑
Dinner with						
- unprocessed meat	❑	❑	❑	❑	❑	❑
- sausage/meatloaf/ meatballs	❑	❑	❑	❑	❑	❑
- fatty fish (e.g. salmon/redfish) 295	❑	❑	❑	❑	❑	❑
- lean fish (e.g. cod)	❑	❑	❑	❑	❑	❑
- fishballs/fishpudding/fishcakes	❑	❑	❑	❑	❑	❑
- vegetables	❑	❑	❑	❑	❑	❑
Mayonnaise, remoulade	❑	❑	❑	❑	❑	❑
Carrots 300	❑	❑	❑	❑	❑	❑
Cauliflower/cabbage/ broccoli	❑	❑	❑	❑	❑	❑
Apples/pears	❑	❑	❑	❑	❑	❑
Oranges, mandarins	❑	❑	❑	❑	❑	❑
Sweetened soft drinks	❑	❑	❑	❑	❑	❑
Sugar-free ("Light") soft drinks	❑	❑	❑	❑	❑	❑
Chocolate	❑	❑	❑	❑	❑	❑
Waffles, cakes, etc. 307	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

ALCOHOL

How often do you usually drink	beer?	wine?	spirits?
Never, or just a few times a year	❑	❑	❑ 1
1-2 times a month	❑	❑	❑ 2
About once a week	❑	❑	❑ 3
2-3 times a week	❑	❑	❑ 4
More or less daily	❑	❑	❑ 5
	308		310

Approximately how often during the last year have you consumed alcohol corresponding to at least 5 small bottles of beer, a bottle of wine, or 1/4 bottle of spirits?

- Not at all the last year ..... ❑ 1
- A few times ..... ❑ 2
- 1-2 times a month ..... ❑ 3
- 1-2 times a week ..... ❑ 4
- 3 or more times a week ..... ❑ 5

For approximately how many years has your alcohol consumption been as you described above? ..... 312 ____years

WEIGHT REDUCTION

About how many times have you deliberately tried to lose weight? Write **0** if you never have.

- before age 20 ..... 314 _____ times
- later ..... 316 _____ times

If you have lost weight deliberately, about how many kilos have you ever lost at the most?

- before age 20 ..... 318 _____ kg
- later ..... 320 _____ kg

What weight would you be satisfied with (your "ideal weight")? ..... 322 _____ kg

URINARY INCONTINENCE

How often do you suffer from urinary incontinence?

- Never ..... 325 ❑ 1
- Not more than once a month ..... ❑ 2
- Two or more times a month ..... ❑ 3
- Once a week or more ..... ❑ 4

Your comments:

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 326 _____years

If you no longer menstruate, how old were you when you stopped menstruating? ..... 328 _____years

Apart from pregnancy and after giving birth, have you ever stopped having menstruation for 6 months or more? ..... 330 Yes ❑ No ❑

If "Yes", how many times? ..... 331 _____ times

If you still menstruate or are pregnant:

What date did your last menstruation period begin? 333 day/month/year ___/___/___

Do you usually use painkillers to relieve period pains? ..... 339 Yes ❑ No ❑

PREGNANCY

How many children have you given birth to? ..... 340 _____ children

Are you pregnant at the moment? ..... 342 Yes ❑ No ❑ Don't know ❑

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 343 Yes ❑ No ❑

If "Yes", during which pregnancy?

	Pregnancy First	Later
High blood pressure 344	❑	❑
Proteinuria 346	❑	❑

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child.

Child	Year of birth:	Number of months breastfed:
1	348 _____	_____
2	_____	_____
3	356 _____	_____
4	_____	_____
5	364 _____	_____
6	_____	_____

CONTRACEPTION AND ESTROGEN

Do you use, or have you ever used:	Now	Before	Never
Oral contraceptive pills (incl. minipill) ... 372	❑	❑	❑
Hormonal intrauterine device	❑	❑	❑
Estrogen (tablets or patches) 374	❑	❑	❑
Estrogen (cream or suppositories)	❑	❑	❑
	1	2	3

If you use oral contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?

376 .....

If you use or have ever used oral contraceptive pills:

Age when you started to take the pill? ..... 380 _____years

How many years in total have you taken the pill? ..... 382 _____years

If you have given birth, how many years did you take the pill before your first delivery? ..... 384 _____years

If you have stopped taking the pill:

Age when you stopped? ..... 386 _____years

Thank you for the help! Remember to mail the form today!

The Tromsø Health Survey

Tromsø Health Survey
for the over 70s

The main aim of the Tromsø Study is to improve our knowledge about cardiovascular diseases in order to aid prevention. The survey is also intended to improve our knowledge of cancer and other general conditions, such as allergies, muscle pains and mental conditions. Finally, the survey should give knowledge about the older part of the population. We would therefore like you to answer the questions below.

This form is a part of the Health Survey, which has been approved by the Norwegian Data Inspectorate and the Regional Board of Research Ethics. The answers will only be used for research purposes and will be treated in strict confidence. The information you give us may later be stored along with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

If you are in doubt about what to answer, tick the box that you feel fits best.

The completed form should be sent to us in the enclosed pre-paid envelope.

Thank you in advance for helping us.

Yours sincerely,

Faculty of Medicine
University of Tromsø

National Health
Screening Service

If you do not wish to answer the questionnaire, tick the box below and return the form. Then you will not receive reminders.

I do not wish to answer the questionnaire .....17 ❑

Day Month Year

Date for filling in this form: .....18 ...../...../.....

CHILDHOOD/YOUTH

In which Norwegian municipality did you live at the age of 1year?

.....24 -28

If you did not live in Norway, give country instead of municipality

How was your family's financial situation during your childhood?

- Very good .....29 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

How old were your parents when they died?

- Mother .....30 _____Years
- Father .....32 _____Years

HOME

Who do you live with?
Tick once for each item and give the number.

	Yes	No	Number
Spouse/partner 34	❑	❑	
Other people over 18 years 35	❑	❑	_____
People under 18 years 38	❑	❑	_____

What type of house do you live in?

- Villa/ detached house .....41 ❑ 1
- Farm ..... ❑ 2
- Flat/apartment ..... ❑ 3
- Terraced /semi-detached house ..... ❑ 4
- Other ..... ❑ 5

How long have you lived in your present home? .....42 _____years

	Yes	No
Is your home adapted to your needs? 44	❑	❑
If "No", do you have problems with:		
Living space 45	❑	❑
Variable temperature, too cold/too warm 46	❑	❑
Stairs 47	❑	❑
Toilet 48	❑	❑
Bath/shower 49	❑	❑
Maintenance 50	❑	❑
Other (please specify) 51	❑	❑

Would you like to move into a retirement home? ...52 ❑ ❑

PREVIOUS WORK AND FINANCIAL SITUATION

How will you describe the type of work you had for the last 5-10 years before you retired?

- Mostly sedentary work? .....53 ❑ 1
  (e.g. office work, mounting)
- Work that requires a lot of walking? ..... ❑ 2
  (e.g. shop assistant, housewife, teaching)
- Work that requires a lot of walking and lifting? ..... ❑ 3
  (e.g. postman, nurse, construction)
- Heavy manual work ..... ❑ 4
  (e.g. forestry, heavy farm-work, heavy construction)

Did you do any of the following jobs (full-time or part-time)?
Tick one box only for each item.

	Yes	No
Driver 54	❑	❑
Farmer 55	❑	❑
Fisherman 56	❑	❑

How old were you when you retired? .....57 _____Years

What kind of pension do you have?

- Basic state pension .....59 ❑
- An additional pension .....60 ❑

How is your current financial situation?

- Very good .....61 ❑ 1
- Good ..... ❑ 2
- Difficult ..... ❑ 3
- Very difficult ..... ❑ 4

HEALTH AND ILLNESS

Has your state of health changed in the last year?

- Yes, it has got worse .....62 ❑ 1
- No, unchanged ..... ❑ 2
- Yes, it has got better ..... ❑ 3

How do you feel your health is now compared to others of your age?

- Much worse .....63 ❑ 1
- A little worse ..... ❑ 2
- About the same ..... ❑ 3
- A little better ..... ❑ 4
- Much better ..... ❑ 5

YOUR OWN ILLNESSES

Have you ever had:
Tick one box only for each item. Give your age at the time. If you have had the condition several times, how old were you last time?

	Yes	No	Age
Hip fracture 64	❑	❑	_____
Wrist /forearm fracture 67	❑	❑	_____
Whiplash 70	❑	❑	_____
Injury requiring hospital admission 73	❑	❑	_____
Gastric ulcer 76	❑	❑	_____
Duodenal ulcer 79	❑	❑	_____
Gastric/duodenal ulcer surgery 82	❑	❑	_____
Neck surgery 85	❑	❑	_____

Have you ever had, or do you have:
Tick one box only for each item.

	Yes	No
Cancer 88	❑	❑
Epilepsy	❑	❑
Migraine	❑	❑
Parkinson's disease	❑	❑
Chronic bronchitis	❑	❑
Psoriasis 93	❑	❑
Osteoporosis	❑	❑
Fibromyalgia/fibrositis/chronic pain syndrome	❑	❑
Psychological problems for which you have sought help	❑	❑
Thyroid disease	❑	❑
Liver disease 98	❑	❑
Recurrent urinary incontinence	❑	❑
Glaucoma	❑	❑
Cataract	❑	❑
Arthrosis (osteoarthritis)	❑	❑
Rheumatoid arthritis 103	❑	❑
Kidney stones	❑	❑
Appendectomy	❑	❑
Allergy and hypersensitivity		
Atopic eczema (e.g. childhood eczema)	❑	❑
Hand eczema	❑	❑
Hey fever 108	❑	❑
Food allergy	❑	❑
Other hypersensitivity (not allergy)	❑	❑

How many times have you had a common cold, influenza (flu), diarrhoea/vomiting or similar in the last 6 months? 111 _____ times

	Yes	No
Have you had this in the last 14 days? 113	❑	❑

ILLNESS IN THE FAMILY

Tick for the relatives who have or have ever had any of the following diseases:
Tick "None" if none of your relatives have had the disease.

	Mother	Father	Brother	Sister	Child	None
Cerebral stroke or brain haemorrhage 114	❑	❑	❑	❑	❑	❑
Heart attack before age 60 120	❑	❑	❑	❑	❑	❑
Cancer 126	❑	❑	❑	❑	❑	❑
Hypertension 132	❑	❑	❑	❑	❑	❑
Asthma 138	❑	❑	❑	❑	❑	❑
Osteoporosis 144	❑	❑	❑	❑	❑	❑
Arthrosis (osteoarthritis) 150	❑	❑	❑	❑	❑	❑
Psychological problems 156	❑	❑	❑	❑	❑	❑
Dementia 162	❑	❑	❑	❑	❑	❑
Diabetes 168	❑	❑	❑	❑	❑	❑
- age when they got diabetes 174	__	__	__	__	__	

SYMPTOMS

	Yes	No
Do you cough about daily for some periods of the year? 184	❑	❑
If "Yes":		
Is your cough productive? 185	❑	❑
Have you had this kind of cough for as long as 3 months in each of the last two years? 186	❑	❑
Have you had episodes with wheezing in your chest?187	❑	❑
If "Yes", has this occurred:		
Tick one box only for each item.		
At night 188	❑	❑
In connection with respiratory infections	❑	❑
In connection with physical exertion	❑	❑
In connection with very cold weather 191	❑	❑
Have you noticed sudden changes in your pulse or heart rhythm in the last year? 192	❑	❑
Have you lost weight in the last year? 193	❑	❑
If "Yes":		
How many kilograms? 194	_____ kg	

How often do you suffer from sleeplessness?

- Never, or just a few times a year .....196 ❑ 1
- 1-2 times a month ..... ❑ 2
- Approximately once a week ..... ❑ 3
- More than once a week ..... ❑ 4

If you suffer from sleeplessness, what time of the year does it affect you most?

- No particular time of year .....197 ❑ 1
- Especially during the polar night ..... ❑ 2
- Especially during the midnight sun season ..... ❑ 3
- Especially in spring and autumn ..... ❑ 4

	Yes	No
Do you usually take a nap during the day? 198	❑	❑
Do you feel that you usually get enough sleep?	❑	❑

Do you suffer from:	No	A little	A lot
Dizziness 200	❑	❑	❑
Poor memory	❑	❑	❑
Lack of energy	❑	❑	❑
Constipation 203	❑	❑	❑

Does the thought of getting a serious illness ever worry you?

- Not at all ..... 204 ☐
- Only a little ..... ☐
- Some ..... ☐
- Very much ..... ☐

BODILY FUNCTIONS

Can you manage the following everyday activities on your own without help from others?	Yes	With some help	No
Walking indoors on one level 205	☐	☐	☐
Walking up/down stairs	☐	☐	☐
Walking outdoors	☐	☐	☐
Walking approx. 500 metres	☐	☐	☐
Going to the toilet	☐	☐	☐
Washing yourself 210	☐	☐	☐
Taking a bath/shower	☐	☐	☐
Dressing and undressing	☐	☐	☐
Getting in and out of bed	☐	☐	☐
Eating	☐	☐	☐
Cooking 215	☐	☐	☐
Doing light housework *(e.g. washing up)*	☐	☐	☐
Doing heavier housework *(e.g. cleaning floor)* ..	☐	☐	☐
Go shopping	☐	☐	☐
Take the bus	☐	☐	☐

	Yes	With difficulty	No
Can you hear normal speech (if necessary with hearing aid)? 220	☐	☐	☐
Can you read (if necessary with glasses)? 221	☐	☐	☐

Are you dependent on any of the following aids? ?

	Yes	No
Walking stick 222	☐	☐
Crutches	☐	☐
Walking frame/zimmer frame	☐	☐
Wheelchair	☐	☐
Hearing aid	☐	☐
Safety alarm device..... 227	☐	☐

USE OF HEALTH SERVICES

How many visits have you made during the past year due to vour own health or illness:
Put 0 if you have not had such contact

	Number of times the past year
To a general practitioner (GP)/emergency GP 228	
To a psychologist or psychiatrist	
To an other medical specialist (not at a hospital)	
To a hospital out-patient clinic 234	
Admitted to a hospital	
To a physiotherapist	
To a chiropractor 240	
To a acupuncturist	
To a dentist	
To a chiropodist 246	
To an alternative practitioner (homoeopath, foot zone therapist, etc.)	
To a healer, faith healer, clairvoyant	

Do you have home aid?	Yes	No
Private 252	☐	☐
Municipal	☐	☐

Do you receive home nursing care? ..... ☐ ☐

Are you pleased with the health care and home assistance services in the municipality?

	Yes	No	Don't know
Assigned family GP 255	☐	☐	☐
Home nursing care	☐	☐	☐
Home assistance services	☐	☐	☐

Do you feel confident that you will receive health care and home assistance services if you need it?

- Confident ..... 258 ☐ 1
- Not confident ..... ☐ 2
- Very unsure ..... ☐ 3
- Don't know ..... ☐ 4

MEDICATION AND DIETARY SUPPLEMENTS

Have you for any length of time in the last year used any of the following medicines or dietary supplements daily or almost daily? Indicate how many months you have used them.
Put 0 for items you have not used.

Medicines:

- Painkillers ..... 259 _____months
- Sleeping pills ..... _____months
- Tranquillizers ..... _____months
- Antidepressants ..... 265 _____months
- Allergy drugs ..... _____months
- Asthma drugs ..... _____months
- Heart medicines (not blood pressure) ..... 271 _____months
- Insulin ..... _____months
- Diabetes tablets ..... _____months
- Drugs for hypothyroidism (Thyroxine) ..... 277 _____months
- Cortisone tablets ..... _____months
- Remedies for constipation ..... _____months

Dietary supplements:

- Iron tablets ..... 283 _____months
- Vitamin D supplements ..... _____months
- Other vitamin supplements ..... _____months
- Calcium tablets or bone meal ..... 289 _____months
- Cod liver oil or fish oil capsules ..... _____months

FAMILY AND FRIENDS

Do you have close relatives who can give you help and support when you need it? 293	Yes	No
	☐	☐
If "Yes", who can give you help?		
Spouse/partner 294	☐	
Children	☐	
Others	☐	

How many good friends do you have whom you can talk confidentially with and who give you help when you need it? ..... 297 ____ good friends

Do not count people you live with, but do include other relatives!

	Yes	No
Do you feel you have enough good friends?..... 299	☐	☐

Do you feel that you belong to a community (group of people) who can depend on each other and who feel committed to each other (e.g. a political party, religious group, relatives, neighbours, work place, or organisation)?

- Strong sense of belonging ..... 300 ☐ 1
- Some sense of belonging ..... ☐ 2
- Not sure ..... ☐ 3
- Little or no sense of belonging ..... ☐ 4

How often do you normally take part in organised gatherings, e.g. sewing circles, sports clubs, political meetings, religious or other associations?

- Never, or just a few times a year ..... 301 ☐ 1
- 1-2 times a month ..... ☐ 2
- Approximately once a week ..... ☐ 3
- More than once a week ..... ☐ 4

FOOD HABITS

Number

How many meals a day do you normally eat (dinner and bread meals)? ..... 302 _____

How many times a week do you eat warm dinner? ..... 304 _____

What kind of bread (bought or home-made) do you usually eat?

Tick one or two boxes.

	White Bread	Light textured	Ordinary brown	Coarse brown	Crisp bread
The bread type is most similar to:	☐ 306	☐	☐	☐	☐ 310

What kind of fat is normally used in *cooking* (not on the bread) in your home?

- Butter ..... 311 ☐
- Hard margarine ..... ☐
- Soft margarine ..... ☐
- Butter/margarine blend ..... ☐
- Oils ..... 315 ☐

How much (in number of glasses, cups, potatoes or slices) do you usually eat/drink daily the following foodstuffs?

Tick one box for each foodstuff.

	None	Less than 1	1-2	3 or more
Milk of all types (glasses) 316	☐	☐	☐	☐
Orange juice (glasses)	☐	☐	☐	☐
Potatoes	☐	☐	☐	☐
Slices of bread in total (incl. crispbread)	☐	☐	☐	☐
Slices of bread with				
– fish (e.g. mackerel in tomato sauce)	☐	☐	☐	☐
– cheese *(e.g. Gouda/Norvegia)*	☐	☐	☐	☐
– smoked cod caviare 322	☐ 1	☐ 2	☐ 3	☐ 4

How many times per week do you normally eat the following foodstuffs?

Tick for all foodstuffs listed.

	Never	Less than 1	1	2 or more
Yoghurt 323	☐	☐	☐	☐
Boiled or fried egg	☐	☐	☐	☐
Breakfast cereal/oatmeal, etc.	☐	☐	☐	☐
Dinner with				
– unprocessed meat	☐	☐	☐	☐
– fatty fish (e.g. salmon/red-fish)	☐	☐	☐	☐
– lean fish (e.g. cod) 328	☐	☐	☐	☐
– vegetables (fresh or cooked)	☐	☐	☐	☐
Carrots (fresh or cooked)	☐	☐	☐	☐
Cauliflower/cabbage/broccoli	☐	☐	☐	☐
Apples/pears	☐	☐	☐	☐
Oranges, mandarins, etc. 333	☐ 1	☐ 2	☐ 3	☐ 4

WELL BEING

How content do you generally feel with growing old?

- Good ..... 334 ☐ 1
- Quite good ..... ☐ 2
- Up and down ..... ☐ 3
- Bad ..... ☐ 4

What is your view of the future?

- Bright ..... 335 ☐ 1
- Not too bad ..... ☐ 2
- Quite worried ..... ☐ 3
- Dark ..... ☐ 4

TO BE ANSWERED BY WOMEN ONLY

MENSTRUATION

How old were you when you started menstruating? ..... 336 _____ years

How old were you when you stopped menstruating? ..... 338 _____ years

PREGNANCY

How many children have you given birth to? ..... 340 _____ Children

If you have given birth, fill in for each child the year of birth and approximately how many months you breastfed the child. If you have given birth to more than 6 children, note their birth year and number of months you breastfed at the space provided below for comments.

Child	Year of birth:	Number of months breastfed:
1	342 _____	_____
2	346 _____	_____
3	_____	_____
4	_____	_____
5	358 _____	_____
6	_____	_____

Have you during pregnancy had high blood pressure and/or proteinuria? ..... 366 Yes ☐ No ☐

If "Yes", during which pregnancy?	Pregnancy First	Later
High blood pressure 367	☐	☐
Proteinuria 369	☐	☐

ESTROGEN

Do you use, or have you ever used estrogen:

	Now	Previously	Never
Tablets or patches 371	☐	☐	☐
Cream or suppositories 372	☐	☐	☐

If you use estrogen, what brand do you currently use?

..... 373

Your comments:

Thank you for the help! Remember to mail the form today!

Tromsø Health Survey