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Cancer and venous thromboembolism

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SUMMARY

Venous thromboembolism (VTE) is a collective term for pulmonary embolism and deep venous thrombosis. VTE is a common finding and a leading cause of death in cancer patients. This underlines the need for exploring risk factors for cancer-related VTE to enable prophylactic treatment in high-risk patients. It is also known that VTE may represent the first sign of an undetected cancer. The first aim of this thesis was to investigate whether leukocyte- and platelet counts measured prior to cancer diagnosis were associated with risk of VTE in cancer patients and in subjects who remained cancer-free during follow-up. Secondly, we aimed to study the risk of cancer in patients with and without VTE and explore whether different VTE characteristics were associated with an increased risk of subsequent cancer.

In paper I and II, our study population was recruited from the fourth survey of the Tromsø Study (Tromsø 4) conducted in 1994-1995, which included more than 27000 participants. Paper III and IV are based on the Scandinavian Thrombosis and Cancer (STAC) Cohort, which comprises individual data from the Tromsø 4 Study, the second Nord-Trøndelag Health Study (HUNT 2), and the Danish Diet, Cancer and Health Study and includes almost 145000 participants. Validated VTE events and cancer diagnoses in all papers have been registered from inclusion (1993-1997) to the end of follow-up (2007-2012).

The incidence rates of VTE in the Tromsø 4 Study (1994-2009) was 13.5 per 1000 person-years in cancer patients and 1.2 per 1000 person-years in cancer-free patients. In cancer patients, both pre-cancer leukocyte- and platelet counts above the 80^{th} percentile were associated with a two-fold increased risk of VTE compared to the 40^{th} percentile, and high levels of both parameters had a synergistic effect on risk of VTE. Conversely, no associations between these parameters and VTE were found in cancer-free subjects. Our findings suggest that leukocyte- and platelet counts may play a role in the pathogenesis of cancer-related VTE.

In the STAC Cohort, we assessed the risk of cancer after VTE. The incidence rates of cancer were 60.6 per 1000 person-years the first year after VTE and 9.5 per 1000 person-years in VTE-free subjects. Subjects with VTE had a 4-fold higher multivariable-adjusted cancer risk than subjects without VTE the first year after VTE and a 1.3-fold higher risk during subsequent years. The anatomical location of VTE was not predictive of cancer risk, and only minor differences in cancer risk were found in subjects with unprovoked and provoked VTE. These results suggest that future studies investigating the benefits of examination for an undetected cancer after VTE should not be restricted by these factors.

SAMMENDRAG

Venøs tromboembolisme (VTE) er et samlebegrep for lungeemboli og dyp venetrombose. VTE rammer ofte kreftpasienter og representerer en ledende dødsårsak i denne pasient gruppen. Dette understreker viktigheten av å kartlegge risikofaktorer for kreft-relatert VTE for å muliggjøre forebyggende behandling hos pasienter med høy risiko. En VTE hendelse kan også være det første symptomet på en bakenforliggende kreft som ennå ikke er påvist. Målet med denne avhandlingen var å undersøke om nivået av hvite blodceller og blodplater, målt før kreftutvikling, påvirket VTE risiko hos de med og uten kreft gjennom studieperioden. Videre ville vi undersøke risikoen for påfølgende kreft hos de med og uten VTE og kartlegge om forskjellige VTE kjennetegn hadde innvirkning på kreft risiko.

I artikkel I og II er vår studiepopulasjon hentet fra den fjerde Tromsøundersøkelsen (Tromsø 4) gjennomført i 1994-1995, som inkluderte mer enn 27000 deltagere. Artikkel III og IV er basert på «the Scandiavian Thrombosis and Cancer (STAC) Cohort», som er en stor studie hvor Tromsø 4 studien, helseundersøkelsen i Nord-Trøndelag (HUNT 2) og den danske «Diet, Cancer and Health» studien er slått sammen, og inkluderer nesten 145000 deltagere. I alle fire artiklene er validerte VTE hendelser og kreft diagnoser registrert fra inklusjon (1993-1997) til studieslutt (2007-2012).

Insidensraten av VTE i Tromsø 4 (1994-2009) var 13.5 per 1000 person-år blant kreftpasienter og 1.2 per 1000 person-år blant de uten kreft. Hos kreftpasientene var både nivået av hvite blodceller og blodplater over 80-persentilen målt før kreftutvikling forbundet med dobling i VTE risiko sammenlignet med 40-persentilen. Kombinasjonen av høye nivåer av begge parameterne ga en synergistisk effekt på VTE risikoen. Hos kreftfrie deltagere derimot, ble det ikke påvist en sammenheng mellom disse parameterne og VTE. Resultatene våre tyder på at nivået av hvite blodceller og blodplater bidrar til VTE hos kreftpasienter.

I STAC kohorten studerte vi risikoen for kreft etter VTE. Insidensraten av kreft var 60.6 per 1000 person-år det første året etter VTE sammenlignet med 9.5 per 1000 person-år hos deltagere uten VTE. Pasienter med VTE hadde en firedoblet risiko for kreft sammenlignet med VTE-frie det første året etter VTE, og en 1.3 ganger høyere risiko de påfølgende år. Den anatomiske lokalisasjonen av blodproppen påvirket i liten grad kreftrisikoen, og det var også små forskjeller i kreftrisiko mellom pasienter med uprovosert og provosert VTE. Resultatene indikerer at fremtidige studier som kartlegger nytten av systematisk kreftutredning etter VTE ikke bør begrenses av disse faktorene.

LIST OF PAPERS

The thesis is based on the following papers:

I. 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 SK, Hansen JB.
PLoS ONE. 2013 September; 8(9): e73447

II. Platelet count measured prior to cancer development is a risk factor for future symptomatic venous thromboembolism: The Tromsø Study.
Jensvoll H, Blix K, Brækkan SK, Hansen JB.
PLoS ONE. 2014 March; 9(3): e92011

III. Existing data sources in clinical epidemiology: The Scandinavian Thrombosis and Cancer (STAC) Cohort.
Jensvoll H, Severinsen MT, Hammerstrøm J, Brækkan SK, Kristensen SR, Cannegieter SC, Blix K, Tjønneland A, Rosendaal FR, Dziewiecka O, Overvad K, Næss IA, Hansen JB.
Clinical Epidemiology. In press.

IV. Risk of cancer after venous thromboembolism - the Scandinavian Thrombosis and Cancer (STAC) Cohort.
Jensvoll H, Severinsen MT, Hammerstrøm J, Brækkan SK, Kristensen SR, Cannegieter SC, Blix K, Tjønneland A, Rosendaal FR, Dziewiecka O, Overvad K, Næss IA, Hansen JB.
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ABBREVIATIONS

ACCP	American College of Chest Physicians
ASCO	American Society of Clinical Oncology
BMI	body mass index
CATS	Vienna Cancer and Thrombosis Study
CI	confidence interval
CLOT	The randomized Comparison of Low-molecular-weight heparin versus Oral anticoagulant therapy for the prevention of recurrent venous Thromboembolism in patients with cancer
CRN	Cancer Registry of Norway
CRT	catheter-related thrombosis
CT	computed tomography
DCH	Diet, Cancer and Health
DVT	deep venous thrombosis
EDTA	ethylenediaminetetraacetic acid
FVL	factor V Leiden
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
HUNT	Health Survey in Nord Trøndelag (Helseundersøkelsen i Nord-Trøndelag)
ICD	International Classification of Diseases
IR	incidence rate
LITE	Longitudinal Investigation of Thromboembolism Etiology
LMWH	Low Molecular Weight Heparin
MEGA	Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis
MP	microparticle
NETs	neutrophil extracellular traps

NOAC	new oral anticoagulant
OR	odds ratio
PE	pulmonary embolism
RCT	randomized controlled trial
RIETE	Registro Informatizado de la Enfermedad Trombo Embolica
RR	relative risk
SIR	Standardized incidence ratio
SOMIT	Extensive Screening for Occult Malignancy in Idiopathic Thromboembolism
STAC	Scandinavian Thrombosis and Cancer
SVT	superficial venous thrombosis
TF	tissue factor
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism
vWF	von Willebrand factor
WBC	white blood cell

1. INTRODUCTION

"I am lost. The phlebitis that appeared tonight leaves me no doubt about the nature of my illness"
(The French physician Armand Trousseau, 1865)

Venous thromboembolism (VTE), including deep venous thromboembolism (DVT) and pulmonary embolism (PE), is a common multifactorial disease with a potentially fatal outcome.[1] DVT is the formation of a blood clot in the deep veins that may obstruct venous flow. The large veins of the lower extremities are most frequently affected. Classical DVT symptoms are pain, swelling, redness and warmness of the affected extremity. PE primarily occurs when fragments of a blood clot dislodge from the original DVT site and are transported by the blood stream to the arteries of the lungs. PE is characterized by pleuritic chest pain, tachypnea, dyspnea, coughing, and eventually, circulatory collapse and death.

In the 1860s the French physician Armand Trousseau described the association between cancer and VTE. He even diagnosed himself with VTE secondary to gastric cancer, which was detected shortly after the VTE event, and he died two months later.[2] Today, cancer is established as an important risk factor for VTE and is associated with as much as 20-30% of the incident VTE events and yields a 4-7-fold increased risk of VTE compared with no cancer.[3] VTE is a preventable disease with the prophylactic use of low molecular heparin, but current guidelines do not recommend thromboprophylaxis to all cancer patients due to the heterogeneity of this patient group.[4] Despite increasing awareness of VTE in cancer patients, VTE represents a leading cause of death in these patients.[5] This underlines the importance of exploring risk factors for cancer-related VTE and identifying high-risk patients who may benefit from thromboprophylaxis.

Trousseau´s syndrome refers to an unexplained VTE event that precedes the diagnosis of cancer.[2] Several studies have shown a substantially increased risk of cancer after VTE, especially the first 6-12 months after the VTE event,[6-8] and this association has been explained by the presence of an occult (undetected) cancer at the time of VTE diagnosis. Consequently, an important and debated clinical issue is to what extent subjects with VTE should be screened for cancer. Furthermore, some studies have also demonstrated an increased risk of cancer several years after the VTE event,[6,9] which raises the question whether VTE may influence cancer development. The epidemiology and risk factors of the two-way association between cancer and VTE is the topic of my thesis.

1.1 Epidemiology

1.1.1 Venous thromboembolism in the general population

VTE is the third most common cardiovascular disease after ischemic heart disease and stroke.[10] A recent review reported that the annual incidence of VTE in adults in Western countries ranges from 0.75 to 2.69 per 1000 person-years, and the incidence increases markedly with age.[11] Even though VTE is a potentially preventable disease,[12] it represents a leading cause of lost healthy life years worldwide due to premature deaths,[11] and the incidence is increasing.[13]

About 2/3 of the VTE events present as DVT and 1/3 as PE,[14] but the two conditions are often present at the same time. VTE can further be classified into provoked and unprovoked (idiopathic) events, depending on the presence of acquired transient risk factors at the time of the VTE event.[15] Provoked VTE events occur in the presence of an acquired risk factor, while such risk factors cannot be found in unprovoked VTE events. This classification has implications for the duration of anticoagulation treatment, risk of VTE recurrence and screening approach for a potentially occult cancer.

VTE is associated with significant mortality and morbidity. One-month case-fatality rates vary considerably between studies and have been reported to be 5-10% after DVT and 10-30% after PE.[16-19] As case fatality rate reports the number of deaths due to any cause divided by the total number of VTE events, these deaths are not only attributable to PE, but also to underlying medical conditions like cancer. The variations in mortality data may reflect different study populations with various comorbidities and whether or not autopsy-confirmed VTE deaths are included in the study. In a Norwegian study of 740 first-time VTE events that did not include any autopsy cases, the proportions of deaths among cancer-free patients with VTE were 3.6% after 30 days and 12.6% after a year.[16] The proportion attributed to PE after 30 days was 45%.[16] Identification of VTE deaths is challenging since PE often presents as sudden death,[18] and it has been demonstrated that unrecognized PE deaths are frequently attributed to cardiac causes in the death certificates.[20] Some studies have reported that less than half of autopsy-detected PE cases are diagnosed prior to death,[21,22] and autopsy rates are low in many Western countries.[23] Altogether these factors may underestimate the death burden due to PE.

Post-thrombotic syndrome is a common long-term complication that affects 20-50% of patients with DVT in the lower limbs.[24,25] The syndrome is characterized by swelling, chronic

pain, pruritus, skin changes, varicose veins and, in severe cases, leg ulcers.[26] Chronic thromboembolic pulmonary hypertension is a life-threatening long-term complication that may affect subjects with PE and is defined as mean pulmonary artery pressure above 25 mm Hg which persists six months after a PE diagnosis.[27] Up to 4-5% of patients with PE develop this condition within 1-2 years after the PE event,[28,29] and their symptoms include increasing dyspnea, hypoxemia and right ventricular failure.

The overall risk of recurrence of VTE is high, especially during the first 6-12 months after a VTE event,[30] and about 30% of VTE patients experience a recurrent episode within 10 years.[31,32] Subjects with unprovoked VTE are at higher risk of recurrence than those with provoked VTE.[33]

1.1.2 Venous thromboembolism in cancer patients

Cancer is established as a major cause of VTE, and several studies have confirmed that 20-30% of all first VTE events are associated with cancer.[16,34,35] Cancer patients have an overall 4 to 7-fold higher risk of developing VTE than cancer-free subjects in the general population.[36-39] The reported absolute risk of cancer-related VTE in terms of cumulative incidence varies widely between 1 and 12%.[40-43] The differences in cumulative incidence in previous studies can be partly explained by methodological issues such as selection of study population, duration of follow-up time, and validation of cancer and VTE events. Furthermore, the general cancer population is heterogeneous, and risk estimates are highly dependent on cancer-related, patient-related, and treatment-related risk factors. For instance, in a recent meta-analysis, the pooled incidence of VTE was 12.6 per 1000 person-years in average risk patients with cancer, while high risk patients (high grade disease, metastatic disease or high-risk treatment) had a pooled incidence rate of 68 per 1000 person-years.[44]

VTE in cancer patients is associated with poor survival. In a Norwegian study, cancer patients with VTE had 30-days and one-year case fatality rates of 19.1% and 63.4%, respectively, and the risk of death was 5-fold higher than for non-cancer patients with VTE (3.6% and 12.6%, respectively). In this study, the two leading causes of death in cancer patients with VTE within 30 days were cancer (43%) and PE (28%).[16] In a registry-based study from California, VTE was a significant predictor of death within 1 year for all the 12 cancer sites analyzed and yielded hazard ratios between 1.6 and 4.2 after adjustment for age, race, and stage.[40] VTE was associated with an increased risk of death for all stages (local,

regional, metastatic), but the relative impact of VTE on survival was greatest among patients with localized disease, as metastatic disease at the time of cancer diagnosis was the strongest predictor of death in this study.[40] In a much cited prospective study of 4466 ambulatory cancer patients initiating chemotherapy in the United States, 3.1% (n=141) died during a mean follow-up of 75 days[45]. The majority of these patients (70.9%) died due to cancer progression, while thrombosis (arterial and venous) was rated as the second leading cause of death along with infections (9.2% for both). As discussed by the authors in this study, the proportion of death attributed to VTE was probably underestimated as autopsies were not performed in these patients, and autopsy studies have shown higher rates of PE in cancer patients than clinical rates of symptomatic VTE.[45]

Cancer patients with VTE are at higher risk of recurrent VTEs and bleeding complications than cancer-free VTE patients. In a prospective study by Prandoni et al., the one-year cumulative incidence of recurrent VTEs and major bleeding in cancer patients were 20.7% and 12.4%, respectively.[46] Although cancer patients had a longer duration of anticoagulation (heparin followed by warfarin) than cancer-free patients (median 224 versus 90 days), cancer patients had a 3.2-fold increased risk of recurrent VTE. The risk of major bleeding was increased 2.2-fold among cancer patients. Both recurrences and bleeding were most prevalent the first month of anticoagulation and could not be explained by INR values below or above the therapeutic range. The study also confirmed that patients with extensive cancer (stage III and IV according to TNM classification) were at higher risk of recurrence and bleeding than localized disease (stage I and II). Sparse knowledge exists on the association between cancer-related VTE and long-term risk of post-thrombotic syndrome. Recurrent VTE is a well-established risk factor for the post-thrombotic syndrome,[24] and accordingly, the prevalence of this syndrome is probably high in cancer patients with VTE due to their high recurrence rate.

The incidence of cancer-related VTE is increasing.[38,47,48] In a recent retrospective study by Walker et al. with linkage of 4 United Kingdom databases, the overall incidence of VTE in cancer patients increased from 10.3 per 1000 person-years in 1997 to 19 per 1000 person-years in 2006, while no such increase was observed in cancer-free controls.[38] This rising incidence over time was attributed to increased awareness of cancer-related VTE, more aggressive cancer treatments in patients, and the implementation of novel therapies, such as anti-angiogenic drugs. Khorana and coworkers investigated time trends for cancer-related VTE in a large retrospective registry-based study including more than a million hospitalized

cancer patients between 1995 and 2003 in the United States.[47] The proportion of hospitalized cancer patients with VTE increased from 3.6% in 1995-1996 to 4.6% in 2002-2003. This increased VTE risk over time was most pronounced for patients receiving chemotherapy, while a similar trend was not observed for cancer patients undergoing major surgery. This could be due to higher rates of appropriate thromboprophylaxis in surgical than medical patients, which has been reported in a previous study.[49] Another possibility is that newer chemotherapy agents and regimens are influencing time trends of cancer-related VTE.[47] Moreover, extended use of computed tomography (CT) scan to evaluate cancer treatment may have increased the incidence of VTE over time, especially incidental VTEs, which are asymptomatic or unexpected cases. However, an increased use of diagnostic procedures over time was not found in the study by Khorana et al., but improved CT scan technology may have enhanced the sensitivity of the CT procedures.[47]

Incidental VTEs are a relatively common finding in cancer patients.[50] In a retrospective study by Di Nisio et al., of 1921 cancer patients initiating chemotherapy between 2003 and 2009, 3.2% had incidental VTE while 2% had symptomatic VTE.[51] In cancer patients with incidental PE, the rates of mortality, recurrence, and bleeding are comparable to cancer patients with symptomatic PE.[52,53]

1.1.3 Risk of cancer after venous thromboembolism

As described by Armand Trousseau in the 1860s, a VTE event may represent the first sign of an occult cancer. Several studies have confirmed that patients with VTE are at increased risk of subsequent cancer compared to the general population, especially within the first 6-12 months after VTE diagnosis. Table 1 shows selected large population-based studies reporting the absolute and/or relative risk of cancer after a VTE event. In most of these studies the relative risk of cancer was calculated by standardized incidence ratios (SIRs), which is the ratio of observed numbers of incident cancers compared to those expected. In a large Swedish inpatient register, Baron et al. reported the SIR for cancer as 4.4 during the first year after VTE diagnosis. The SIR declined to 1.4 the second year, while a 1.3-fold significantly increased risk was found more than 10 years after the VTE event.[6] A similar declining risk of cancer was also found the first two years after VTE in a nationwide Scottish study by Murchison et al., but this study did not confirm any increased risk after two years.[7] A meta-analysis based on 40 studies reported a pooled relative risk of cancer of 3.2 in patients with

VTE compared to patients without during a mean follow-up of five months.[54] Another meta-analysis based on 36 studies reported absolute risk of cancer after VTE in terms of period prevalence, and 4.1% of the VTE patients were diagnosed with cancer within one month after the VTE event and 6.3% within the first year.[55] In the same study, 10% of those with unprovoked VTE were diagnosed with cancer during the first year, while the corresponding proportion was 2.6% among those with provoked VTE.[55]

The cancer sites found after VTE constitute a large and heterogeneous group.[6-8,56] A meta-analysis based on four large registry-based cohort studies reported the highest pooled relative risk for ovarian, pancreatic, liver, blood, brain, kidney and lung cancer, while bladder and breast cancer had the lowest risk.[54] Subjects with cancer subsequent to VTE have more advanced malignancies[56-58] and a poorer prognosis[57,58] than comparable cancer patients. In a large Danish study,[57] the one-year survival rate in those diagnosed with cancer at the same time as VTE was only 12% compared to 36% in cancer patients without VTE, matched in terms of cancer type, age, sex, and year of diagnosis. Patients diagnosed with cancer within one year after VTE diagnosis also had a poor prognosis as only 38% were alive after one year compared with 47% of the cancer controls. Among those with cancer at the same time as VTE, 44% had distant metastasis, compared to 35% among comparable cancer patients. In the RIETE Registry, as much as 51% of those diagnosed with cancer had disseminated disease within three months after VTE.[58]

Table 1. Overview of studies assessing the risk of cancer after VTE

Authors, year	Study design	Number of patients	Follow-up time	Absolute risk	Relative risk (95 % CI) at different follow-up times	
Nordstrom et al, 1994[59]	Cohort study of patients referred to venography	1383 DVT	3-7 years	4.8% the first 6 months	0-6 months: > 6 months:	SIR 5.3 (4.1-6.7) SIR 1.0 (0.8-1.3)
Baron et al, 1998[6]	Registry-based cohort study	61998 VTE	7.7 years (mean)	4% the first year	0-12 months: > 12 months:	SIR 4.4 (4.2-4.6) SIR 1.3 (1.3-1.3)
Sørensen et al, 1998[8]	Registry-based cohort study	15348 DVT 11305 LE (Unprovoked)	DVT: 6.1 years (mean) LE: 3.6 years (mean)	2.1% the first year	0-12 months: > 12 months:	SIR DVT 2.1 (1.9-2.4) SIR LE 2.3 (2.0-2.7) SIR DVT 1.1 (1.1-1.2) SIR LE 1.2 (1.1-1.3)
Murchison et al, 2004[7]	Registry-based cohort study	59534 VTE (Unprovoked)	Up to 19 years (excluding first month)	2.3% the first year	1-6 months: 12-24 months: 24 -30 months:	SIR 4.2 (3.9-4.5) SIR 1.2 (1.1-1.4) SIR 1.0 (0.9-1.2)
White et al, 2005[56*]	Registry-based cohort study	528693 cancer cases	1 year before cancer diagnosis	0.11% unprovoked VTE within 1 year before cancer diagnosis	Within 1 year before cancer	SIR VTE: 1.3 (1.2-1.5)
Trujillo Santos et al, 2008[58]	Population-based cohort study	14623 VTE	3 months (excluding first 14 days)	1.2% the first 3 months		
Carrier et al, 2008[55]	Meta-analysis of 34 studies	9516 VTE	1 year	6.3% overall VTE, 10.0 % unprovoked and 2.6% provoked		
Iodice et al, 2008[54]	Meta-analysis of 40 studies	8191 VTE	0-25 years 5 months (mean)	-	Pooled RR:	VTE/no VTE: 3.2 (2.4-4.5) Unprovoked/provoked 3.8 (2.6-5.4)
Douketis et al, 2009[9]	Population-based cohort (Inception cohort?)	1852 VTE	4.2 years (mean) (excluding first 3 months)	-Annual incidence rate per 100 person-years: 1.32 (1.09-1.60) -5.7 % during follow-up		
Sorensen et al, 2012[60]	Registry-based cohort study	45252 DVT 24332 PE 7663 SVT	5 years (mean)	2.7% the first year	0-12 months: > 12 months:	SIR 2.9 (2.8-3.0) SIR 1.1 (1.1-1.2)

*Study assessing the risk of VTE prior to cancer diagnosis instead of risk of cancer after VTE.

1.2 Pathophysiology

1.2.1 General pathophysiology of venous thromboembolism

The brilliant pathologist Rudolph Virchow is regarded as the father of research on VTE.[61] In 1856, he postulated his famous triad (figure 1) of contributors to the pathophysiology of thrombosis: alterations of the vessel walls (endothelial damage or activation), changes in blood flow (stasis), and changes in blood composition (hypercoagulability).[62] Today, our knowledge has greatly expanded, but this triad still represents a cornerstone in our understanding of the pathophysiological mechanisms of thrombosis.

The blood coagulation system is essential for hemostasis and wound repair, but activation of this system may also lead to arterial and venous thrombosis. The coagulation system consists of a series of proteins that are activated in a complex cascade reaction.[63] ***Endothelial damage*** in the vessel walls leads to exposure of subendothelial tissue factor (TF), which is a main trigger of the coagulation cascade.[64] In this process, activated platelets aggregate and adhere to subendothelial tissue via von Willebrand factor (vWF) and form a primary platelet plug at the site of injury.[64] TF also binds to activated factor VII which triggers the extrinsic pathway of the coagulation system by activation of factor IX and factor X. Thereafter factor X and activated co-factor V convert prothrombin to thrombin, which finally leads to fibrin deposition and clot formation. The platelets amplify the coagulation process by providing a surface for large scale thrombin generation.[63] Endothelial damage is central in arterial thrombosis, where atherosclerotic plaques rupture and expose subendothelial TF, collagen and vWF.[65] In contrast, the role of endothelial damage in VTE is less certain. Risk factors like surgery, trauma, and central venous catheters may injure the venous vessel wall. However, the endothelium in most VTE events is not injured,[66] indicating that the pathogenesis of arterial and venous thrombosis are quite different from one another. This is supported by the notion that arterial clots are platelet-rich and generally treated with antiplatelet drugs, while venous clots are rich in fibrin and red blood cells and treated with anticoagulation drugs.[67]

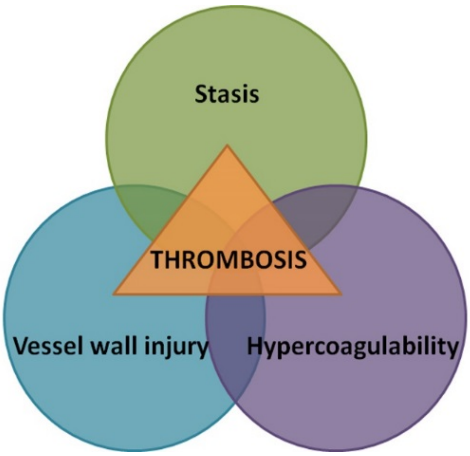

Figure 1. Virchow`s triad

The venous valves in the large veins prevent the reflux of blood, and it is generally accepted that the sinuses of the venous valves are predilection sites for DVT.[68] Experimental studies have shown that blood is trapped in the deepest recess of the valvular sinus, which leaves hemoglobin vulnerable to desaturation, and localized hypoxia may develop.[68] Hypoxia is further enhanced by clinical situations leading to prolonged ***stasis*** like immobilization, which increase the residence time in the large vessels.[68] The endothelium contain several anticoagulant components,[69] but hypoxia and stasis activate the endothelial cells and induce a prothrombotic state.[67] Activated endothelium downregulates anticoagulant proteins like thrombomodulin, while procoagulant TF is upregulated.[70] Furthermore, the endothelial cells mobilize P-selectin and vWF on their surface, which recruit leukocytes and platelets.[65,71] Activated platelets and leukocytes, especially monocytes, express procoagulant TF which activates the coagulation cascade; additionally they bud off microparticles, which are small membrane vesicles (0.1-1.0 µm)[72] (figure 2). These microparticles are also procoagulant due to the presence of TF and negatively charged phospholipids on their surface, and it has been suggested that they are important triggers of VTE.[67]

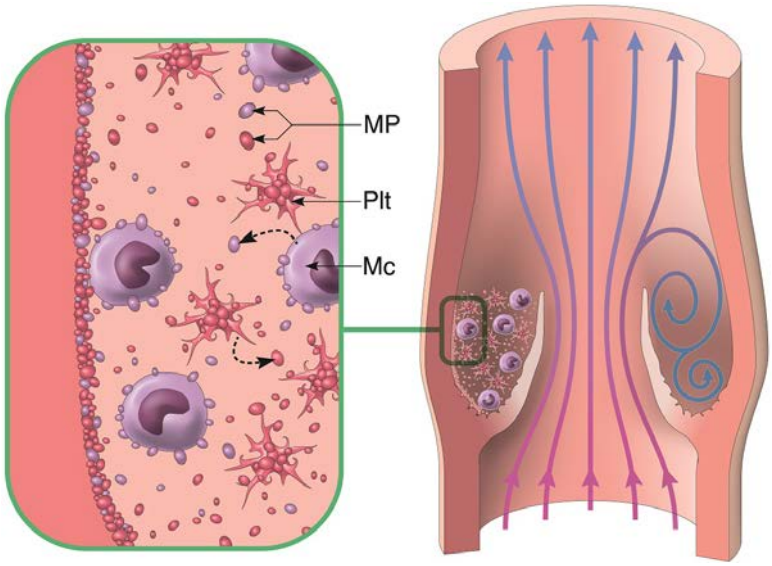

Figure 2. The pathophysiology of DVT in the venous valves: The vertical flow in venous valvular sinuses leads to localized hypoxia. This activates the endothelium, which recruits leukocytes and platelets (Plt). Activated platelets and leukocytes, especially the monocytes (Mc), express tissue factor and bud of tissue factor positive microparticles (MP), which may activate the coagulation cascade and initiate formation of thrombosis.

Neutrophils are also involved in the formation of VTE. In a recent mouse model of stasis-induced VTE, the initiating stimulus for DVT development was the crawling and adhering of neutrophils and monocytes to the venous endothelium.[71] As part of the antimicrobial defense, activated neutrophils release neutrophil extracellular traps (NETs), which are extracellular DNA fibers covered with proteases that entrap and kill microbes.[71,73]

The NETs promote VTE by providing a scaffold for the adhesion and activation of platelets and red blood cells in mice.[73] NETs have also been found in venous thrombus in humans[74] and in plasma of patients with DVT.[75]

Changes in blood composition are also essential in the pathogenesis of VTE. The term thrombophilia refers to a tendency to develop VTE due to a hypercoagulable state explained by inherited or acquired disorders of blood coagulation or fibrinolysis.[76] Inherited thrombophilia may induce hypercoagulability by decreasing the levels of anticoagulant factors or by increasing the levels of procoagulant factors.[76] Several known risk factors of VTE lead to acquired thrombophilia, and cancer is one example.

1.2.2 Pathophysiology of cancer-related venous thromboembolism

Cancer represents a ***hypercoagulable*** state, and it is demonstrated that cancer patients have elevated levels of several coagulation factors, antithrombin-thrombin complex, D-dimer, and prothrombin fragments compared to cancer-free controls.[77,78] Cancer can activate the coagulation system through several mechanisms.[79] Tumor cells express TF, which strongly initiates the extrinsic pathway of the coagulation cascade, and they also release procoagulant TF-bearing microparticles (MPs).[80] MP-TF activity levels are higher in cancer patients with VTE than in cancer patients without VTE.[81] Some prospective studies have indicated that MP-TF activity is predictive of VTE in cancer patients,[82,83] while other studies have not confirmed this.[84,85] These discrepancies may partly be due to methodological issues in the measurements of MP-TF activity. Cancer cells are also able to release proinflammatory cytokines like tumor necrosis factor alpha, which activates the endothelium.[79] Furthermore, cancer-induced deficiency of the vWF cleavage protein ADAMTS-13 has been described, leading to unusually large vWF multimers.[86]

Platelets are of particular interest in cancer-related VTE as they are essential in tumor-growth, angiogenesis, and metastasis.[87,88] Tumor cells can activate platelets directly and induce platelet aggregation,[89,90] and this ability correlates with their metastatic potential.[89] It has also been suggested that cisplatin-based chemotherapy can activate the platelets directly.[91] Activated platelets express the adhesion molecule P-selectin, which interacts with cancer cells, endothelium and leukocytes.[92] P-selectin has also been found predictive of cancer-related VTE.[93] A complex interplay between cancer cells, leukocytes, platelets, and the coagulation system has also been confirmed for microthrombi induced by carcinoma mucins,

which are secreted from several adenocarcinomas, in particular those of gastric and pancreatic origin.[94] In a murine model, bidirectional platelet-leukocyte interactions mediated by P-selectin on platelets and L-selectin- and P-selectin glycoprotein ligands on leukocytes were necessary to establish mucin-induced thrombosis.[95]

There is increasing interest in the role of NETs in cancer-related VTE.[96] It has been demonstrated in a recent mouse model that cancer predisposes neutrophils to release NETs and thereby activate the coagulation cascade, and this ability increased as the tumor progressed.[97]

As in non-cancer related VTE, ***disturbed blood flow*** is a central pathophysiologic mechanism of cancer-related VTE as solid tumors can compress veins, leading to venous stasis.[94] Moreover, surgery and in-dwelling central venous catheters can impede blood flow, and venous stasis due to immobilization is a frequent risk factor of VTE in this patient group due to advanced cancer or treatment complications.[94]

Solid tumors may also invade and ***injure the vessel wall*** and subsequently activate the endothelium, and cancer-related surgery and the insertion of central venous catheters may increase the risk of VTE in the same way.[94] It has also been demonstrated that cisplatin-based chemotherapy, which is a well-known risk factor for VTE, causes endothelial cell injury and apoptosis in vitro, which results in a more than 5-fold increased release of highly procoagulant MPs.[98] The chemotherapies doxorubicin and epirubicin have been shown to induce DNA-release from neutrophils which resulted in thrombin generation in vitro,[99] suggesting a link between chemotherapy and the release of procoagulant NETs.[96]

1.3 Risk factors

A risk factor is a characteristic which increases the likelihood of developing a disease,[100] but does not necessary imply causality. VTE is a multifactorial disease, where genetic and environmental risk factors interact, and often several factors are needed at the same time to induce thrombosis. The impact of a risk factor is dependent on both its prevalence and relative risk.[101] Several risk factors of VTE are known, and they are often divided into hereditary and acquired risk factors.

1.3.1. Hereditary risk factors for venous thromboembolism

A family history of VTE is associated with a 2-3 fold increased risk of VTE,[102-104] and family- and twin studies have shown that genetic factors account for about 60% of the variation in susceptibility to VTE.[105,106] Inherited thrombophilia can be categorized into two main groups according to the underlying pathophysiological mechanism: loss-of-function of anticoagulant factors and gain-of-function of procoagulant factors.[76]

The ***loss-of-function group*** includes deficiencies or dysfunctions of antithrombin, protein C and protein S, which are rare genetic defects that are associated with a high risk of VTE.[76]***Antithrombin deficiency*** was first described by the Norwegian physician Olav Egeberg in 1965.[76] Antithrombin is a strong inhibitor of thrombin and other factors in the coagulation cascade,[107] and these interactions are strongly enhanced by heparin.[108] Antithrombin deficiencies are very rare and found in about 0.2% of the general population,[107] and they yield a 10-20 fold increased risk of VTE.[109-111] Protein C is another natural anticoagulant which inactivates activated factor V and VIII, and protein S is a cofactor in this process.[107] The prevalence of protein C deficiency and S deficiency are lower than 1% in the general population, and heterozygous carriers have a 10-fold increased risk of VTE compared to non-carriers.[109]

The ***gain-of-function group*** is characterized by more prevalent genetic risk factors that are associated with a lower risk of VTE than the previously described loss-of-function deficiencies. This group includes factor V Leiden (FVL) mutation and prothrombin G20210A mutation, as well as non-O blood types.[76] The FVL mutation is present in approximately 5% of the European population and in 10% of patients with VTE.[107] This mutation makes factor V resistant to inactivation by activated protein C, which leads to decreased anticoagulant effects.[107] Heterozygous carriers have a 2-5 fold increased risk of VTE compared to non-carriers,[109,112-114] while homozygous carriers, who are very rare (1/5000), have a 10-80 fold increased risk.[115] The prothrombin mutation causes increased levels of normal prothrombin.[107] It is a quite common mutation with a prevalence of 2-3% in the general population[114,116,117] and is associated with a 1.5-2.5 fold increased risk of VTE.[109,114] The presence of both the FVL and the prothrombin mutation have synergistic effects on the risk of VTE, and one study reported a 20-fold increased risk of VTE in double heterozygotes compared to non-carriers.[112] The ABO blood types also influence the risk of VTE. The non-O blood types are present in approximately 60-70% of the general population and associated with a 1.5-2.0 fold increased risk of VTE.[109,114,118] This association is partly explained by higher vWF and factor VIII

levels in non-O blood types, but other mechanisms are probably also involved.[109] Even though the risk estimates for VTE by non-O blood types are quite moderate, the attributable risk for VTE is substantial due to their high prevalence in the population.[114] Thus, it has been recently suggested that ABO blood type should be included in genetic screening for thrombophilia.[114]

Limited and conflicting knowledge exists for the association between genetic risk factors and cancer-related VTE. Several studies have not found an association, indicating that cancer outweighs the effect of inherited thrombophilia.[119-122] However, these studies are small and may be underpowered. In the prospective Vienna Cancer and Thrombosis Study (CATS), 7.3% out of 982 cancer patients had the FVL mutation, and a 2-fold multivariable adjusted increased risk of VTE were found in these cancer patients compared to non-carriers with cancer.[123] The same risk estimate was reported in a case-control study from Leiden.[39]

As mentioned, family- and twin studies have indicated that genetic factors account for 60% of the VTE risk. However, established gene variants account for only 10-20% of the VTE events,[105,106] which emphasizes the importance of unraveling novel genetic variants. In recent years, genome-wide association studies have investigated the presence of single nucleotide polymorphisms associated with VTE in case-control studies, and several common, but weak, genetic mutations have been detected.[109] Hopefully, ongoing and future genomic studies will improve our understanding of genetic factors in both cancer and non-cancer patients.

1.3.2 Acquired risk factors for venous thromboembolism in the general population

Cancer is a major acquired risk factor for VTE, and will be discussed in the next section. Other well-established factors are age, previous VTE, obesity, hospitalization, trauma, surgery, acute medical conditions, immobility, pregnancy and estrogen treatment. **Advancing age** is a strong and consistent risk factor for VTE, and several studies have shown that the risk increases exponentially with age.[10,16,124] The incidence of VTE varies from 1/100000 per year in childhood[125] to nearly 1/100 in the elderly.[34,124,126] In a previous paper from the Tromsø Study it has been reported that subjects above the age of 70 years have 11-fold higher risk of VTE than subjects below 50.[34] It is not clear why age increases the risk, but age-related vascular changes such as increased levels of procoagulant proteins[127] and degeneration of venous walls and valves[68] may contribute. It has also been suggested that the accumulation of comorbidities like cancer and immobility are of importance.[128] However, a recent publication

from the Tromsø Study indicated that the increased risk of VTE by advancing age could not be explained by the higher incidence of cancer in the elderly.[129]

Previous VTE is a strong predictor of a new VTE event, and a 4-5-fold increased risk has been reported.[130,131] An initial VTE precipitated by a transient risk factor like surgery is less likely to recur, while the recurrence risk is high when the initial VTE was unprovoked or triggered by persistent risk factors like cancer.[25,132] **Obesity** is another important risk factor for VTE. Several observational studies have found a 2-3 fold increased risk of VTE in obese subjects with body mass index (BMI) > 30 kg/m^2 compared with normal weight subjects (BMI < 25 kg/m^2).[133] Anthropometric measures of obesity other than BMI have also been found predictive of VTE,[134,135] and in the Tromsø Study waist circumference identified the subjects most at risk and yielded the highest risk estimates in both genders.[136]

Hospitalization is a major risk factor for VTE as hospitalized patients have more than 100-fold increased risk of VTE than community residents.[137] Approximately 60% of all VTE events have been attributed to institutionalization, and surgical and medical patients accounted for similar proportions of the cases (22% and 24%, respectively),[138] which underlines the importance of thromboprophylaxis in these patients. Hospitalized patients are at risk of VTE both during and following the hospital stay, and a study of residents from the Worcester metropolitan area reported that more VTE events were diagnosed in the three months following hospitalization than during hospitalization.[35] Both **trauma** and **surgery** are established as important risk factors for VTE. Hospitalized trauma patients without thromboprophylaxis have a risk of DVT exceeding 50%,[139] and one study showed that even with the use of thromboprophylaxis, 28% of major trauma patients developed DVT.[140] A review has reported that surgery within the last 45-90 days was associated with a 4-22 fold increased risk of VTE.[141] A large study assessing the VTE risk after 76 selected procedures identified invasive neurosurgery, total hip arthroplasty, and major vascular surgery as high risk procedures with an incidence of 2-3% within 3 months, and 56% of all the VTE events were diagnosed after hospital discharge.[142]

Several **acute medical conditions** leading to hospitalization are recognized by ACCP guidelines as independent risk factors for VTE; these include congestive heart failure, respiratory disease, myocardial infarction, ischemic stroke, infections, and rheumatologic disorders.[12]

Immobility is another important risk factor which has been associated with VTE occurrence in various situations like neurologic paralysis or paresis,[143] use of plaster casts or

external fixation[143], and prolonged air travel exceeding four hours.[144] In immobilized medical patients, a meta-analysis has reported a 2-fold increased risk of VTE compared to mobilized medical patients.[145]

The overall incidence of first VTE is approximately similar for women and men, but **sex differences** are found across age groups.[16,126,146] Middle-aged and elderly men have a higher risk of VTE than women of the same age,[126,146,147] and at least part of this sex difference can be attributed to body height.[146,147] Increasing body height is recognized as risk factor for VTE,[147-149] and in men a 30% higher risk of VTE per 10 cm increase has been noted.[148] Women of childbearing age have a higher risk of VTE than men of the same age,[16,126,146] which has been attributed to **pregnancy** and **use of combined oral contraceptives**.[150] Already in 1750, it was described that some women had a swollen leg post-partum which was explained by retention of milk in the leg.[146] Today, VTE is still a leading cause of maternal death in the developed world.[151] Pregnant women have a 4-5 fold increased risk compared to non-pregnant women, and an even higher risk is reported post-partum, especially in the first 6 weeks after delivery.[152,153] A combined oral contraceptive pill contains estrogen and a progestogen, and both compounds influence the risk of VTE. A recent Cochrane review reported an overall 3.5-fold increased risk of VTE in users of combined oral contraceptives compared with non-users.[154] Postmenopausal **hormone replacement therapy** is also associated with increased risk of VTE. A meta-analysis reported a 2-fold increased risk of VTE in users of this therapy and the risk was highest during the first year of use.[155]

Despite current knowledge about inherited and acquired risk factors, 30-50% of all incident VTE events are unprovoked (i.e. without predisposing factors).[14,19,34]

1.3.3 Acquired risk factors for venous thromboembolism in cancer patients

In cancer patients, risk factors can be divided into patient-related, cancer-related, and treatment-related risk factors.

1.3.3.1 Patient-related risk factors

Several of the acquired risk factors for VTE described for non-cancer patients in the previous section also apply to cancer patients. A **previous history of VTE** is an even stronger risk factor for future VTE in cancer patients than in the general population as the recurrence rate is

significantly higher in cancer patients than in cancer-free patients.[25] Cancer patients with a prior history of VTE have a 6-8 fold increased risk of developing VTE compared to cancer patients without previous VTE.[156,157]

While **increasing age** is a clear risk factor for VTE in the general population, conflicting results have been found in cancer patients. In a prospective observational study of 2373 patients undergoing cancer surgery, age above 60 years was associated with a 2.6-fold higher risk of VTE than age below 60 years.[156] In a large registry-based study of 1 million hospitalized cancer patients, age $\geq$ 65 years was associated with a slightly higher risk of VTE (Odds ratio (OR) =1.08, 95 % CI 1.05-1.10).[47] However, most studies did not find increasing age to be associated with increased VTE risk in cancer patients.[37,39,40,128,129] In a Danish registry-study of 57 791 cancer patients, the crude incidence rate of VTE increased with age, but the adjusted relative risk declined with increasing age.[37] A higher relative risk VTE due to cancer in the younger compared with the elderly was also found in the Tromsø Study.[129] Lastly, high age has not been included in the Khorana risk score model, which is a validated score for assessing the risk of VTE in ambulatory cancer patients.[158]

Obesity (BMI > 35kg/m^2) has been identified as one out of five variables included in the Khorana risk model and has been found associated with a 2.5-fold increased risk of VTE.[158] However, in CATS, BMI > 35kg/m^2 was a rare observation and not associated with risk of VTE.[159] The association between anthropometric measures and cancer-related VTE is actually not well described, which may be explained by the fact that the majority of studies within this field are registry-based linkage studies which lack such information.

The presence and number of **medical comorbidities** in cancer patients can be obtained from registry-based linkage studies and has been described to influence the risk of VTE. Significant multivariate adjusted ORs were found for acute infection, renal disease, pulmonary disease, arterial thromboembolism, and anemia (ORs 1.8, 1.5, 1.5, 1.4 and 1.4, respectively) in the study of hospitalized cancer patients by Khorana et al.[47] In a retrospective study of 92 000 lung cancer patients registered in the California Cancer Registry between 1993 and 1999, a 2.8-fold increased risk was reported for the presence of 3 or more comorbid medical conditions compared to no comorbidities.[160] An enhanced VTE risk with increasing number of comorbidities has also been reported for several other cancer types in the California Cancer Registry.[161-165]

Immobility is another important risk factor of VTE in cancer patients, and in a recent paper on cancer-related VTE in the Tromsø Study, immobility was the most frequent

provoking factor and present in 23% of the cancer-related VTE events.[129] In cancer patients undergoing surgery, bed rest for four days or more has been shown to increase the risk of VTE 4-fold.[156] Performance status is a widely used clinical tool to assess mobility in cancer patients and describes to what extent the patients are bedridden. Among 3003 ambulatory cancer patients initiating chemotherapy, there was a non-significant trend towards higher rates of VTE in patients with poor performance status, but this patient group represented only 9% of the study population.[166] The impact of performance status or immobility itself on cancer-related risk of VTE may be hard to estimate as immobility may be a consequence of other risk factors such as more advanced cancer or extensive treatment. However, in a retrospective study of 932 cancer patients treated with cisplatin-based chemotherapy, a poor performance status was associated with an increased risk of VTE after adjusting for stage.[167]

1.3.3.2 Cancer-related risk factors

Several cancer-related risk factors for VTE such as cancer type, stage, tumor grade, histologic subtype, and time since cancer diagnosis have been identified. Numerous studies have described that the risk of VTE varies widely among different **cancer types**. However, cancer-specific absolute and relative risk estimates also vary between studies and are difficult to compare due to differences in study populations, study design, and follow-up times. Patients with cancers of the pancreas, brain, lung and ovary are generally reported to be at high risk of VTE.[37,38,40,47,168] Moderate to high risks have also been reported for lymphoma, multiple myeloma, stomach, and kidney cancer.[39,40,47,168] In the meta-analysis by Horsted, pooled incidence rates were reported for eight cancer types, and pancreatic, brain and lung cancer were at highest risk, while breast and prostate cancer were at lowest risk.[44] However, it should be noted that even though cancers like breast, prostate, and colorectal have low rates of VTE, they may still contribute greatly to the overall burden of VTE in a the general population due to their high prevalence.

Cancer stage has a substantial impact on risk of VTE, and metastatic disease has been reported among the strongest risk factors of VTE in cancer patients in several studies.[37,39,40] In a large Danish registry-based study by Cronin-Fenton et al., 57591 cancer patients were compared with cancer-free controls from the general population from 1997 to 2006, and the risk of cancer-related VTE increased strongly with advancing stage. The adjusted relative risks were 2.9, 2.9, 7.5, and 17.1 for stage, I, II, III, and IV disease, respectively.[37] The same trend was reported across stages (local, regional and distant) for 12 selected cancer sites in the

California Cancer Registry.[40] The prospective CATS reported that regional and distant disease were associated with a 3.7-fold and 5.4- fold increased risk of VTE compared to localized disease, after adjusting for age, newly diagnosed disease (versus progression of disease), and cancer treatment.[169] Interestingly, advanced stage has not been recognized as a risk factor for VTE in the Khorana risk prediction model.[158] The authors claimed that the excellent performance status among their study participants may explain their finding since low performance status could represent a confounder in the association between advanced stage and risk of VTE.[158,170] This is supported by the study of cisplatin-treated cancer patients, where distant metastasis was a risk factor for VTE in univariate analyses, but significance was lost in multivariate analyses, including Karnofsky's performance status.[167] However, little is known with regard to performance status and risk of VTE, and high quality prospective studies are warranted to explore the true impact of performance status on risk of VTE at different cancer stages.

Histological subtype has been associated with VTE risk for some cancer types.[171] For instance, in the California Cancer Registry, patients with adenocarcinoma of the lung had a 2-fold increased risk of VTE compared to patients with squamous cell cancer of the lung.[160] **Tumor grade** has also been confirmed as a risk factor for VTE in CATS, and a 2-fold increased risk has been found for high grade tumors (G3 and G4) versus low grade tumors (G1 and G2) after adjusting for age, sex, cancer type, stage and histology.[172]

Time since cancer diagnosis influences the risk of VTE, and the highest risk has been reported for the initial 3-12 months after cancer diagnosis.[37-40] In the MEGA Study, cancer patients were at highest risk in the first 3 months after cancer diagnosis (adjusted OR 53.5, compared to cancer-free patients). Thereafter the risk declined to 13.4 between 3 and 12 months, and even up to 10 years after cancer diagnosis a significantly increased 2.4-fold risk was still found.[39] The higher risk of VTE in the initial period after cancer diagnosis has been attributed to high tumor burden, therapeutic interventions, and hospitalizations.

1.3.3.4 Treatment-related factors

Chemotherapy is established as a strong risk factor for VTE, and a review has reported an annual incidence between 11 and 20% for cancer patients receiving this treatment modality.[173] Compared with the general population, cancer patients undergoing chemotherapy have a 2-6 fold increased risk.[36,174,175] In the much cited case control study from Olmsted County, cancer

was associated with a 4.1-fold risk of VTE, while adding chemotherapy resulted in a 6.5-fold increased risk.[36] In a randomized trial of adjuvant therapy in women with breast cancer, the risk of VTE was assessed in women with a combination of tamoxifen for two years plus six months of chemotherapy versus tamoxifen alone. The cumulative incidence of VTE in the combined treatment group was 13.6% compared to 2.6% in the tamoxifen only group.[176] Several specific chemotherapeutic agents have been identified that are associated with particularly high risk. In a retrospective study of 932 cancer patients treated with cisplatin-based chemotherapy, 16.6% (n=155) developed VTE during treatment or within 4 weeks of the last dose.[167] Multiple myeloma patients are at high risk of VTE, and treatment with the immunomodulatory drugs thalidomide and lenalidomid highly contributes to this elevated risk.[177] When these drugs are combined with steroids or chemotherapy in newly diagnosed patients with multiple myeloma, VTE rates between 10 and 75% have been reported.[177] Bevacizumab, an anti-angiogenic agent used in the treatment of several cancer types, has been reported to increase VTE risk by about 30% in a recent meta-analysis of 15 randomized trials.[178]

Cancer patients undergoing **surgery** have about a 2-fold increased risk of perioperative DVT[179] and a more than 3-fold risk of fatal PE compared to cancer-free patients going through similar procedures.[180] Cancer patients undergoing abdominal or pelvic surgery are at particularly high risk.[181] It has also been reported that 1/3 of the VTE patients in surgical cancer patients occur post discharge.[182,183] Few studies have investigated the risk of VTE in patients undergoing **radiation therapy**. Two retrospective studies reported no association between radiation therapy and VTE,[174,184] while the prospective CATS found a 2.3-fold increased risk for this treatment modality,[185] but this risk estimate was not adjusted for cancer site or stage. Other treatment-related factors like use of erythropoiesis-stimulating agents[186] and transfusions[187] have been associated with 1.7-fold and 1.5-fold increased risk of VTE, respectively.

In-dwelling central venous catheters are often used for administration of chemotherapy, parenteral nutrition, and blood products in cancer patients, and they represent a common risk factor for upper-extremity DVT. A review from 2003 reported that the incidence of symptomatic catheter-related thrombosis (CRT) varied between 0.3% and 28.3% in adult cancer patients, while the corresponding rate detected incidentally by venography ranged from 27% to 66%.[188] A lower rate of symptomatic CRT of 4.3% has been reported in a more recent prospective study of 444 cancer patients, and the same study reported that long-term

complications were uncommon in the affected patients.[189] Several device-related risk factors of CRT have been identified as multiple insertion attempts, central venous catheters infection, catheter tip position, catheter type, catheter site, catheter side, lumen diameter, and number of lumens.[190]

The complex interplay between inherited and acquired risk factors in cancer and non-cancer patients may be explained by the thrombosis potential model.[101] As illustrated in figure 3, the combination of individual risk factors like high age and FVL may not be sufficient to trigger VTE. The development of cancer may bring the risk close to the threshold, and further addition of a high-risk situation like chemotherapy and infection may then exceed the thrombosis threshold and result in symptomatic VTE.

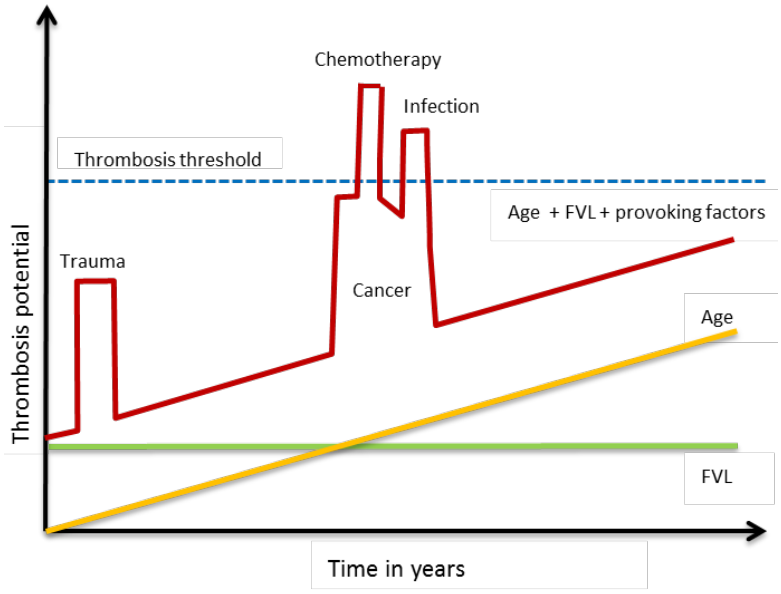

Figure 3. The thrombosis potential model. The green line represents an intrinsic risk factor such as Factor V Leiden (FVL), and the orange line represents advancing age. The red line demonstrates the joint effect of age, FVL and provoking factors. A trauma combined with FVL at young age is not enough to reach the thrombosis threshold, but development of cancer later in life brings the person close to the threshold. The addition of chemotherapy then exceeds the threshold and results in VTE, and the development of an acute infection shortly after chemotherapy exceeds the threshold again and results in recurrent VTE, despite of anticoagulation treatment.

1.3.4 White blood cell count and risk of venous thromboembolism

The white blood cell (WBC) count is normally defined within the reference range of 4-11 x 10^9/L, and neutrophils are the dominating cells. The WBC count is determined by both environmental[191,192] and genetic factors.[193,194] Leukocytosis, defined as WBC count above 11 x 10^9/L, is a common laboratory finding which reflects the normal response of the bone marrow to infections or inflammatory processes, but may also be secondary to medications, physical and emotional stress.[195] Furthermore, leukocytosis may be due to primary bone marrow disorders like leukemia or myeloproliferative diseases.[195]

Prospective general population-based studies have confirmed that a high WBC count is associated with increased risk of arterial thrombosis,[196] cancer[197] and overall mortality.[198-201] In myeloproliferative diseases, leukocytosis above 15 x 10^9/L is associated with both arterial and venous thrombosis,[202-205] and there is an ongoing debate whether there is a causative relationship.[206] However, little information exists on the association between WBC count and VTE in the general population. The LITE Study has investigated the risk of VTE in 19237 cancer-free adults and reported that WBC count was not related to future risk of VTE.[207] Monocyte count has been explored in the Tromsø Study, and subjects with monocyte count in the upper tertile had a borderline significant 2.5-fold increased risk of VTE compared with those in the lower tertile during the first year of follow-up.[208]

In cancer patients, leukocytosis is a common finding and associated with increased mortality.[209-211] Several studies have confirmed an association between leukocytosis and risk of cancer-related VTE.[51,158,167,212,213] In a retrospective study of 1921 cancer patients by Di Nisio et al., a leukocyte count $\geq$ 10 x 10^9/L was associated with both incidental VTE (RR 2.9, 95% CI 1.1-7.3) and symptomatic VTE (RR 3.4, 95% CI 1.5-7.7).[51] In a prospective study of 4291 ambulatory cancer patients initiating chemotherapy, an elevated pre-chemotherapy leukocyte count $\geq$ 11 x 10^9/L was associated with a 2.2-fold increased risk of VTE compared to a lower leukocyte count and has been included in the Khorana risk model as predictive biomarker.[158] Subgroups of leukocytes have been investigated in the same population, and it is confirmed that both elevated neutrophil count and monocyte count are predictive of VTE risk, while lymphocytosis is not.[214] The RIETE Registry has found that cancer patients with VTE and leukocytosis have a higher risk of recurrence, bleeding, and death than cancer patients with VTE and lower WBC count.[215]

1.3.5 Platelet count and risk of venous thromboembolism

The normal platelet count is generally defined within the range of 150 - 400 x 10^9/L. Like the WBC count, the platelet count is influenced by environmental and genetic factors,[193,194,216] and it has also been shown that the WBC count and the platelet count are positively associated.[216] Platelets are our smallest circulating blood cells. They have no nucleus, but contain numerous molecules and cytokines used in various physiological processes. They are essential in hemostasis and thrombosis, and are also involved in inflammation and cancer development.[217] Traditionally, the platelets have been regarded much more important in the

pathogenesis of arterial thrombosis than in venous thrombosis, and accordingly, antiplatelet treatment is well established in arterial thrombosis, while it does not have a place in the treatment of VTE. However this view is being challenged as a recent meta-analysis of two large randomized trials has demonstrated that the antiplatelet drug aspirin reduces the risk of recurrent VTE by 30%.[218] Furthermore, increasing mean platelet volume, a marker of platelet activity, has been associated with VTE in the Tromsø Study.[219] Platelet count has not been associated with future VTE in several large population-based studies.[124,219,220] Conversely, reactive thrombosis during hospitalization has been demonstrated as a risk factor for VTE in medical patients,[221] intensive care unit patients[222] and trauma patients.[223,224] In a study of 1446 critically ill patients admitted to the intensive care unit, 10% had reactive thrombocytosis above 500 x 10^9/L at discharge, and the presence of thrombocytosis increased the risk of VTE 5-fold after adjusting for other covariates.[222]

Cancer represents a hypercoagulable state, and activated platelets are involved in angiogenesis, tumor progression and metastasis.[87,88] Thrombocytosis was noted as a common finding among cancer patients already in 1872.[89] In a prospective study of 3003 ambulatory cancer patients, thrombocytosis, defined as a platelet count ≥ 350 x 10^9/L was found in 23% of the patients[166] and associated with a 2.8-fold increased risk of VTE compared to a platelet count < 200 x 10^9/L. Thrombocytosis is also a predictor of poor survival.[87,225] An association between thrombocytosis and VTE has been confirmed for cancer patients undergoing surgery[182] and initiating chemotherapy.[157,166,226] In CATS, patients with platelet counts above 443 x 10^9/L, representing the 95th percentile, had a 3.5-fold increased multivariable adjusted risk compared to those below this level[226]. When a cut-off of 350 x 10^9/L was chosen, a significant 2.4-fold increased risk was found in univariate analyses, but significance was lost in multivariable analyses (HR 1.63, 95% CI 0.79-3.37). The lack of a statistically significant association for this level could be due to that there were only 44 VTE events in this study. In a study of cisplatin-treated patients, thrombocytosis was not a risk factor for VTE.[167] As discussed by the authors of this article, a possible explanation for the lack of association could be that cisplatin is such a strong risk factor that it outweighs the impact of platelet count. Platelet counts ≥ 350 x 10^9/L has been included among the 5 predictive variables in the Khorana risk score model.[158]

1.3.6 Risk factors for subsequent cancer in patients with venous thromboembolism

Diverging results have been reported regarding the association between age and risk of cancer after VTE. Some studies have reported advancing age at VTE diagnosis as a risk factor for cancer.[9,227] Other studies have found higher relative risk in VTE patients below 60-65 years when cancer patients in general are used as a reference,[6-8] and the prospective RIETE Study reported that subjects with VTE aged 60-75 years were at highest relative risk.[58] As advancing age is a strong risk factor for cancer,[228] providing both absolute and relative risk estimates of cancer after VTE will give valuable information. No or minor sex differences have been found in cancer risk after VTE.[6,9,58,60,227]

Different VTE characteristics have been investigated as predictors of subsequent cancer, and several studies have demonstrated a higher risk of subsequent cancer among patients with unprovoked VTE than in patients with provoked VTE.[9,54,58,229] In a population-based cohort of 1852 patients with VTE, a HR of cancer of 1.9 was found for unprovoked versus provoked VTE during a mean follow-up of 4.2 years.[9] In the RIETE Registry, the presence of an unprovoked VTE was associated with a 3-fold increased risk of subsequent cancer up to three months after the VTE event.[58] A meta-analysis reported a pooled relative risk of cancer of 3.8 for unprovoked versus provoked VTE, but there was large between-study heterogeneity.[54] Conversely, in a registry-based Danish study from 2012, approximately equal risk estimates for cancer were found for both provoked and unprovoked DVT/PE during the first year of follow-up and subsequent years when compared with the general population.[60] In another recent Danish registry-based study, 3-4-fold higher SIRs of cancer during 1-year of follow-up were found for VTE secondary to stroke and myocardial infarction,[230] which was similar to the risk estimate found after unprovoked VTE in another Danish study.[8]

Subtypes of VTE in terms of DVT or PE have not been associated with differences in subsequent cancer risk when investigated in several studies.[6,8,58,231] Only a few studies have assessed the risk of cancer in patients with proximal versus distal VTE, and no difference has been reported.[58,232] In the RIETE Registry, the presence of bilateral DVT was associated with a 2.3-fold increased risk of subsequent cancer during 3 months of follow-up, while no association was found for recurrent VTE.[58] However, recurrence has been associated with occult cancer in other studies.[8,229] Whether superficial venous thrombosis (SVT) should be considered predictive of subsequent cancer is controversial. A lack of association between SVT and cancer has been reported in two retrospective studies.[233,234] On the contrary, a recent Danish registry-based study reported that patients with SVT had an increased risk of cancer of

the same magnitude as those with PE and DVT when the general population was used as the reference group.[60] This finding was supported by a recent small French prospective study with standardized ultrasonography, where the presence of SVT had the same association with subsequent cancer as proximal and distal DVT.[232]

The RIETE Registry has investigated some biomarkers as predictors of a cancer diagnosis within 3 months after VTE, and anemia (defined as hemoglobin < 13 g/dL for men and < 12 g/dL for women) at the time of VTE diagnosis was associated with a 1.9-fold increased risk. Platelet count and D-dimer were not predictive of subsequent cancer.[58] Conversely, two small retrospective studies have found associations between D-dimer levels in VTE patients and subsequent cancer risk.[235,236] Altogether, large prospective studies investigating clinical and laboratory variables as predictors for subsequent cancer are warranted.

1.4 Clinical practice in cancer patients

1.4.1. Risk assessment of venous thromboembolism and thromboprophylaxis

Cancer patients constitute a heterogeneous group in terms of risk of VTE, and risk assessment and thromboprophylaxis are particularly important in the following populations: hospitalized cancer patients with acute medical illness, ambulatory cancer patients initiating chemotherapy, and surgical cancer patients. In hospitalized medical patients, the ACCP guidelines suggest risk assessment by the Padua prediction score (table 2a), which assigns points to 11 common risk factors for VTE, including cancer.[12] The presence of active cancer results in 3 points, and patients with a risk score ≥ 4 are considered high risk patients qualified for thromboprophylaxis.[237] No cancer-specific randomized trials (RCTs) have been carried out in ***hospitalized non-surgical medical cancer patients***. However, several large RCTs have confirmed significantly decreased risk of VTE in hospitalized medical patients treated prophylactically with low-molecular-weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux, and the percentage of cancer patients in these studies varied between 5 and 15%.[238] In a post-hoc analysis of a randomized trial, a 50% risk reduction was found among cancer patients with 40 mg enoxaparin versus placebo, but the finding was not statistically significant due to insufficient power in this subgroup.[239] However, both ASCO and ACCP guidelines agree that hospitalized medical cancer patients with reduced mobility or acute

Table 2.

a) Padua Prediction Score[237]

Patient characteristics at admission to hospital	Score
Active cancer	3
Previous VTE	3
Reduced mobility	3
Known inherited thrombophilia	3
Recent trauma or surgery (≤ 1 month)	2
Elderly age (≥70 years)	1
Heart or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection or rheumatologic disorder	1
BMI ≥30 kg/m^2	1
Ongoing hormonal treatment	1

High-risk score ≥ 4

b) Khorana Risk Score[158]

Patient characteristics prior to chemotherapy	Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Platelet count ≥ 350 x 10^9/L	1
Hemoglobin ≤ 10 g/dl or use of ESAs	1
Leukocyte count ≥ 11 x 10^9/L	1
BMI ≥ 35 kg/m^2	1

ESA=erythropoietin-stimulating agents
High-risk score ≥ 3

medical illness should be recommended thromboprophylaxis with LMWH, UFH or fondaparinux.[4,240]

A recent Cochrane review has identified 21 RCTs with a total of 9861 patients, evaluating pharmacological interventions in ***ambulatory cancer patients receiving chemotherapy.***[241] The use of LMWH was associated with 47% significantly lower incidence of symptomatic VTE compared with no prophylaxis (RR 0.53, 95% CI 0.38-0.75) and with approximately similar rates of major bleeding (RR 1.30, 95% 0.75-2.23). Due to the wide confidence interval around the estimate for major bleeding, the authors concluded that routine prophylaxis in all ambulatory cancer patients cannot be recommended before safety issues are adequately addressed.

Routine thromboprophylaxis is only established for multiple myeloma patients initiating combination therapy, which includes thalidomide or lenalidomide. Other ambulatory cancer patients should be assessed individually for thromboprophylaxis according to risk factors.[4,238] The Khorana Risk Score (Table 2b) has been suggested for risk assessment of ambulatory cancer patients in international guidelines.[4,242,243] This risk score was originally derived from a development cohort of 2701 cancer patients and further validated in an independent cohort of 1365 cancer patients.[158] Overall, 2.1% developed VTE during a median follow-up of 2.5 months. Five predictive variables were identified in a stage-adjusted multivariable model: cancer site, BMI ≥ 35 kg/m^2, platelet count ≥ 350 x 10^9/L, leukocyte count ≥ 11 x 10^9/L and hemoglobin < 10 g/dL or use of erythropoietin-stimulating agents. The model assigned 2 points to very high risk cancer sites (stomach, pancreas), 1 point to high risk sites (lung, lymphoma, gynecologic, bladder, testicular) and 1 point for the presence of each of the other 4 variables. The rates of VTE in the development cohort were 0.8% in the low-

risk category (score = 0), 1.8% in the intermediate-risk category (score 1-2) and 7.1% in the high-risk category (score ≥ 3), respectively. The high-risk patients represented 12% of the whole study population. A limitation of the study was insufficient numbers of patients included with multiple myeloma, brain, and renal cancers, which are known to be strongly associated with VTE. The Khorana Risk Score has been validated in independent cohorts.[167,244,245] The prospective CATS, which includes cancer patients undergoing chemotherapy, surgery, and radiotherapy, and even untreated patients, has expanded the model and improved prediction by including the biomarkers D-dimer (≥ 1.44 µg/mL) and soluble P-selectin (≥ 53.1 ng/mL).[244] In their model, the cumulative probabilities of developing VTE after six months were 35% in patients with score ≥ 5, 10.3% in patients with score 3 and only 1.0% in patients with score 0. However, the proportion of patients in the high-risk group was low (3.7%), and a disadvantage with this model is that P-selectin is not an established biomarker in daily clinical practice.

Cancer patients undergoing major surgery are at high risk of postoperative VTE, and international guidelines agree that thromboprophylaxis with UFH or LMWH should be started preoperatively and be continued 7-10 days postoperatively unless contraindicated due to active bleeding or high bleeding risk.[4,181,238,243] Patients undergoing curative surgery for abdominal or pelvic cancer are at particularly high risk of VTE, and international guidelines recommend extended thromboprophylaxis with LMWH for 4 weeks in these patients.[4,181,238,243]

1.4.2 Anticoagulation treatment of venous thromboembolism

The conventional treatment of VTE in non-cancer patients has for several years been initial parental anticoagulation with LMWH (low molecular weight heparin), UFH (unfractionated heparin), or fondaparinux for up to seven days combined with long term treatment with a Vitamin K antagonist (VKA) for at least three months.[240] In recent years, new oral anticoagulants (NOACs) have also become an attractive treatment option due to their oral administration, fixed dose, and no need for regular laboratory monitoring. However, cancer patients are treated differently from other VTE patients. In 2003, the ground-breaking randomized CLOT trial showed that in cancer patients with VTE, administering a full dose of LMWH dalteparin for one month, followed by 75% dose for five months was significantly more effective than VKA in reducing the risk of recurrent VTE without increased risk of

bleeding.[246] A recent Cochrane review based on 10 RCTs confirmed a significantly reduced risk of 53% of recurrent VTE in cancer patients treated with LMWH compared to VKA, but no differences between the two groups were found for bleeding or mortality.[247] In international guidelines, six months of treatment with LMWH is preferred over VKA.[4,240,243] Not much is known about NOACs in the management of cancer-related VTE, since all trials to date have included few cancer patients.[248,249] Thus, dedicated RCTs of cancer patients are needed to investigate the efficacy and safety of NOACs compared to LMWH before these drugs can be implemented in cancer patients.

1.4.3 Screening for cancer in patients with venous thromboembolism

If and to what extent patients with VTE should be further examined for an occult cancer is a debated clinical issue. Considering the diversity in cancer sites found after VTE,[54] an extended diagnostic work-up would be needed to improve cancer detection. To date, the SOMIT trial is the only randomized trial that has compared extensive and limited screening procedures.[250] In this study, 201 patients with unprovoked VTE were included and followed for two years, and more cancers were detected in the extensive screening group, which included abdominal and pelvic CT scans, tumor markers and several other invasive and noninvasive examination procedures. CT scans of the pelvis and abdomen had the highest yield,[250] which is in accordance with a meta-analysis by Carrier et al.[55] However, there is no clear evidence that diagnosing these cancers earlier improves survival,[250,251] and an extensive screening procedure has not been found cost-effective.[252] In general, it is suggested that a limited cancer examination, including medical history, physical examination, chest X-ray, and some basic blood tests should be confined to subjects with unprovoked VTE, while extended radiological or invasive procedures should only be carried out if alarming symptoms or signs are present.[251,253,254]

2. AIMS OF THE THESIS

The aims of the thesis were:

- To investigate the association between pre-cancer white blood cell count and neutrophil count and risk of venous thromboembolism in subjects who developed cancer and in subjects who remained cancer-free during follow-up in a population-based cohort study.

- To investigate the association between pre-cancer platelet count alone and together with white blood cell count and the risk of venous thromboembolism in subjects who developed cancer and in subjects who remained cancer-free during follow-up in a population-based cohort study.

- To describe the profile of the Scandinavian Thrombosis and Cancer Cohort, a large prospective collaborative population-based cohort, established to investigate the epidemiology and risk factors for cancer-related venous thromboembolism.

- To investigate the risk of subsequent cancer in subjects with venous thromboembolism compared with subjects without venous thromboembolism in the general population.

3. STUDY POPULATIONS AND METHODS

3.1 The Tromsø Study

The Tromsø Study is a single center population-based cohort study with repeated surveys of the inhabitants of the municipality of Tromsø, Norway. The study was initiated in the 1970s to explore the reasons for the high cardiovascular mortality in Northern Norway, but has gradually been expanded to include a broad spectrum of other chronic diseases. In total, six surveys have been conducted between 1974 and 2008, and a seventh survey is currently ongoing. In paper I and II, all participants have been included from the fourth survey of the Tromsø Study, while in paper III and IV, the participants are from the merged Scandinavian Cancer and Thrombosis (STAC) Cohort, which also includes the fourth Tromsø Study. The Tromsø 4 Study was carried out in 1994-1995 and is the largest of the sixth surveys. This study consisted of two screening visits 4-12 weeks apart, and all inhabitants aged 25 years or older in the municipality of Tromsø were invited to the first visit; 27158 attended (77% of the eligible population). All subjects aged 55-74 years and 5-10% random samples of subjects 25-54 years and above 75 years were invited to a more extended second visit, and 7965 participated (78%). In paper I and II the participants were followed from the day of enrollment in 1994-1995 through September 1, 2007 and December 31, 2009, respectively. The follow-up time for the two papers differed due to an update of the VTE outcome registry.

3.2 The Scandinavian Thrombosis and Cancer Cohort

In paper III and IV the participants were included from the STAC Cohort, which is a large population-based cohort, comprising data from the already described Tromsø 4 Study, the second Nord-Trøndelag Health (HUNT 2) Study and the Danish Diet, Cancer and Health (DCH) Study. The HUNT 2 Study in 1995-1997 is the second out of three health surveys conducted in the Nord-Trøndelag County, Norway. The HUNT 2 was designed to investigate cardiovascular disease and other chronic diseases in accordance with national health priorities. All residents of Nord-Trøndelag County ≥ 20 years were invited, and 65237 participated (69% of the eligible population). The DCH Study was aimed to investigate the associations between diet, lifestyle factors, and the development of cancer and other chronic diseases. It was carried out in 1993-1997, and the invited inhabitants were aged 50-64 years, born in Denmark, living in the urban areas of Copenhagen and Aarhus and without previous cancer; 57054 attended (35% of those invited).

The STAC Cohort was established to investigate epidemiology and risk factors for VTE in cancer patients recruited from the general population. In total, 144952 subjects without previous cancer or VTE were included in the STAC Cohort and followed from the date of inclusion (1993-1997) to the end date of follow-up (2007-2012).

3.3 Baseline measurements

Baseline information in the Tromsø 4 Study was collected from physical examination, non-fasting blood-samples and self-administered questionnaires. Height and weight were measured in subjects wearing light clothing and no shoes, and BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m^2). Blood pressure was recorded using an automatic device (Dinamap Vital Signs Monitor), and three measurements were performed on the right arm after two minutes at rest in a sitting position, and the average of the two last readings was used in the analyses. Blood samples were collected from an antecubital vein and analyzed at the Department of Clinical Biochemistry, University hospital of North Norway. For measurement of mean platelet volume, WBC-, neutrophil- and platelet count, 5 ml of blood were collected into Vacutainer tubes containing EDTA as anticoagulant (K_3- EDTA 40 µL, 0.37 mol/L per tube), and analyzed within 12 hours by an automated blood cell counter (Coulter Counter®, Coulter Electronics, Luton, UK). The self-administered questionnaires provided information about education level, leisure time physical activity, weekly alcohol consumption and smoking habits (never/former/current, number of daily cigarettes and duration in years). Information about diabetes, previous history of cardiovascular disease (myocardial infarction, angina, and stroke) and use of antihypertensives was also obtained from the questionnaires. Baseline information in the HUNT 2 Study and the DCH Study was collected in similar ways, but hematological variables were not available at baseline.

3.4 Identification and validation of cancer diagnoses

Incident cancer diagnoses during follow-up were identified by linkage to the Cancer Registry of Norway (CRN) (paper I-IV) and the Danish Cancer Registry (paper III-IV) through the unique national civil registration number which is assigned to all newborns and people residing in the Nordic countries. Notification of cancer cases has been mandatory by law since 1953 in Norway and 1987 in Denmark, and general practitioners, hospital doctors and

pathological laboratories are obliged to report cases.[255,256] Informed consent of the patients is not required. The cancer registries also have access to the date and cause of death noted on the death certificates. Both cancer registries are linked to discharge diagnosis registries as well, but since the validity of these diagnoses is low, this information is only used for sending out reminders for cancer notifications.[255,256] In Norway, electronic reminders are sent three times a year to physicians who have failed to report the case to CRN within two months of a new cancer discharge diagnosis. Both cancer registries have been evaluated as complete and valid,[255,256] which will be further discussed in the methodological consideration section.

The cancer registries provide information about date of cancer diagnosis, location of the disease (ICD-7 (International Classification of Diseases 7th Revision) codes 140-205 and ICD-10 codes C00-96), cancer stage (localized, regional, distant or unknown), histological grade (IC0-3) and initial treatment.

3.5 Identification and validation of venous thromboembolic events

Only first life time symptomatic, objectively confirmed VTE events during follow-up have been included in the Tromsø 4 Study and the STAC Cohort. Each VTE event has been identified and validated by trained personnel who have reviewed medical records for all potential cases. Both inpatients and outpatients have been included. In the Tromsø 4 Study, the VTE events were identified by searching the hospital discharge registry, the radiology procedure registry and the autopsy registry at the University Hospital of North Norway. This is the only hospital serving the municipality of Tromsø, and all hospital care and relevant radiological procedures are provided here. The relevant discharge codes were the ICD-9 codes 325,415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994-1998 and the ICD-10 codes I26,180,I81, I82, 167.6,O22.5, O87.1 and O87.3 for the period 1999-2010.[34] A VTE event identified from the hospital discharge registry or the radiology procedure registry was recorded when all four of the following criteria were met: (1) signs and symptoms consistent with DVT or PE were present, (2) the medical record indicated that a diagnosis of VTE was made by a physician, (3) objective confirmation by diagnostic procedures (compression ultrasonography, venography, perfusion-ventilation scan, computed tomography (CT), pulmonary angiography or autopsy) and (4) the patients underwent anticoagulant treatment (heparin, warfarin, or similar agents), thrombolytics, or vascular surgery.[34] The

VTE events identified from the autopsy registry required that the autopsy record had registered VTE as the cause of death or as a significant contributor.

In the HUNT 2 Study, VTE events were identified by searching the hospital discharge diagnosis registry and the radiology procedure registry at the two local hospitals and at the regional hospital. The validation criteria included symptomatic VTE events that required treatment and were confirmed by objective diagnostic tests (ultrasonography, venography, perfusion-ventilation scan or CT scan).[16] In the DCH Study, the VTE events were identified by linkage to the Danish National Patient Registry and the Danish National Death Registry by use of the personal civil registration numbers. A VTE event was verified when typical clinical symptoms were combined with a confirmatory diagnostic test (ultrasonography, venography, perfusion-ventilation scan, CT scan, echocardiography or autopsy).[257] VTE deaths identified from the Danish National Death Registry required that an autopsy verified the VTE event.

The VTE events in the Tromsø 4 Study and the STAC Cohort were classified as DVT or PE, and concurrent DVT and PE was recorded as PE. The VTE events were further classified as provoked and unprovoked VTE. The definitions of provoking factors were slightly different between the three cohorts included in the STAC Cohort. However, all of the studies included the following provoking factors: active cancer, recent trauma or surgery, marked immobilization, travel or other risk factors described by the physician, like central vein catheters. The Tromsø 4 Study and the DCH Study included acute medical conditions as provoking factors, while the HUNT 2 Study registered prolonged bed rest (immobility) due to acute medical conditions. Use of oral contraceptives and pregnancy/puerperium were only included as provoking factors in the HUNT 2 Study.

4. MAIN RESULTS

4.1 Paper I

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

Elevated white blood cell (WBC) count is associated with risk of VTE in cancer patients initiating chemotherapy. It is not known whether elevated WBC count plays a causal role in cancer-related VTE or merely reflects the underlying malignant disease or concomitant inflammatory conditions. To address this question, we investigated whether WBC count measured prior to cancer development was associated with risk of VTE in subjects who did and did not develop cancer during follow-up in a prospective population-based study. WBC count and other baseline characteristics were measured in 24304 initially cancer-free subjects, who participated in the Tromsø 4 Study in 1994-1995. In total, 1720 were diagnosed with cancer and 388 with VTE during follow-up until September 1st, 2007. The incidence rates of VTE were 6.9 per 1000 person-years in subjects who developed cancer and 1.1 per 1000 person-years in cancer-free subjects. In those who developed cancer, pre-cancer WBC count above the 80th percentile ($\geq$ 8.6 x 10^9/L) was associated with a 2.4-fold higher risk (HR 2.36, 95% CI: 1.44-3.87) of VTE compared to WBC count below the 40th percentile (<6.4 x 10^9/L). WBC count as continuous variable was also predictive of cancer-related VTE. In cancer-free subjects, no association was found (HR 0.94, 95% CI 0.65-1.36). Similar findings were observed for neutrophil count. In conclusion, pre-cancer WBC count was associated with increased risk of VTE in cancer patients, but not in cancer-free subjects. Our findings suggest that WBC count may play a casual role in the pathogenesis of cancer-related VTE.

4.2 Paper II

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

Platelets are essential in hemostasis, thrombosis, and cancer progression. Elevated platelet count is associated with risk of venous thromboembolism (VTE) in cancer patients initiating chemotherapy. It is not known whether this risk by platelet count is causal or merely reflects the malignant disease or comorbid conditions. Recently it was shown in the Tromsø Study that leukocyte count measured prior to cancer development is predictive of cancer-related VTE. Consequently, we addressed the question whether pre-cancer platelet count alone and together with leukocyte count is associated with risk of VTE in subjects who did and did not develop cancer during follow-up in the prospective Tromsø Study. Baseline characteristics, including platelet count and leukocyte count, were measured in 25160 cancer-free subjects who participated in the Tromsø 4 Study in 1994-95. During follow-up until December 31st 2009, 2082 subjects developed cancer. There were 129 VTE events in the cancer cohort (13.5 per 1000 person-years) and 377 in the cancer-free cohort (1.2 per 1000 person-years). In cancer patients, pre-cancer platelet count above the 80th percentile ($\geq$ 295x 10^9/L) was associated with a 2-fold higher risk of VTE (HR: 1.98, 95% CI 1.21-3.23) compared to platelet count below the 40th percentile (< 235x 10^9/L). Concomitant high platelet and leukocyte counts had a synergistic effect on the risk of cancer-related VTE and yielded a 3-fold higher increased risk (HR 2.96, 95 % CI 1.72-5.08). No association was found in those who remained cancer-free. In conclusion, high pre-cancer platelet count alone and together with high leukocyte count was associated with risk of VTE in cancer patients. Our findings suggest that platelet count and platelet-leukocyte interactions may play a role in the pathogenesis of cancer-related VTE.

4.3 Paper III

EXISTING DATA SOURCES IN CLINICAL EPIDEMIOLOGY: THE SCANDINAVIAN THROMBOSIS AND CANCER (STAC) COHORT

Even though venous thromboembolism (VTE) is a known common complication in cancer patients, only limited knowledge exists on patient-related and cancer-specific risk factors in the general population. The Scandinavian Thrombosis and Cancer (STAC) Cohort was established by merging individual data from three large Scandinavian cohorts (The Tromsø Study, the Nord-Trøndelag Health (HUNT) Study and the Danish Diet, Cancer and Health (DCH) Study). This paper describes the design and methods of the STAC Cohort and provides age-specific incidence rates of VTE and cancer. The STAC Cohort includes 144952 subjects aged 19-101 years without previous VTE or cancer. Baseline information in 1993-1997 included physical examination, self-administered questionnaires, and blood samples. Validated VTE and cancer events were registered up to 2007-2012. There were 2444 VTE events (1.4 per 1000 person-years) during follow-up, and the incidence increased exponentially from 0.3 per 1000 person-years in subjects aged 20-29 years to 6.4 per 1000 person-years in subjects aged 80+. Overall, 51% of the VTE events were provoked, and cancer was the most common provoking factor (19%), followed by immobilization and surgery (both 15%). In total, 19757 subjects developed cancer during follow-up (9.8 per 1000 person-years), and the 5-year age-specific incidence rates of cancer were concordant with corresponding rates from the Norwegian Cancer Registry. In conclusion, the STAC Cohort will provide a unique opportunity to explore the epidemiology and impact of genetic and environmental patient-related and cancer-specific risk factors of VTE in the general population.

4.4 Paper IV

RISK OF CANCER AFTER VENOUS THROMBOEMBOLISM – THE SCANDINAVIAN THROMBOSIS AND CANCER (STAC) COHORT

Patients with venous thromboembolism (VTE) have an increased risk of cancer the first 6-12 months after a VTE event. Subjects with unprovoked VTE are considered at highest risk, but the benefits of examination for occult cancer are debated. The aim of the study was to investigate the association between VTE and subsequent cancer in the Scandinavian Thrombosis and Cancer (STAC) Cohort, which comprises individual data from three population-based cohorts in Norway and Denmark. Overall, 144912 subjects aged 19-101 years, without previous VTE or cancer, were included. Baseline information (1993-1997) included physical examination, self-administered questionnaires, and blood samples. Validated VTE events and cancer diagnoses were registered up to 2007-2012. Multivariable adjusted hazard ratios (HRs) of cancer with 95% confidence intervals (CIs) were calculated in subjects with VTE and compared with subjects without VTE. There were 1884 subjects with VTE and 17651 with cancer during a median follow-up of 13.6 years. The crude incidence rate (IR) of cancer in subjects without VTE was 9.5 per 1000 person-years (PY), whereas the IR of cancer during the first year after VTE was 60.6 per 1000 PY and 19.1 per 1000 PY during subsequent years. A VTE event was associated with a 4.0-fold (95% CI 3.25-5.02) higher risk of cancer during the first year after VTE, and a 1.3-fold (95% CI 1.12-1.53) higher risk during subsequent years. The relative risk was most pronounced for kidney, ovarian, lymphatic, pancreatic, stomach and lung cancer. The risk of cancer did not differ between different anatomical locations of the thrombus. Only minor differences in cancer risk were found between subjects with unprovoked (HR 4.47, 95% 3.43-5.83) and provoked VTE (HR 3.51, 95% CI 2.39-5.17) during the first year of follow-up. In conclusion, subjects with VTE had an increased risk of cancer several years after the VTE event. The cancer risk did not differ according to the anatomical location of the venous thrombus nor the provoking nature of the VTE. Our findings suggest that future studies investigating the benefits of examination for occult cancer should not be restricted by these factors.

5. GENERAL DISCUSSION

5.1 Methodological considerations

5.1.1 Study design

The four papers in this thesis are based on data from prospective population-based cohort studies. In a prospective cohort, a defined population is followed from inclusion until the outcome of interest or other defined censoring events like death, migration, or end of study period. The subjects are classified according to a defined exposure status, and differences in outcome are investigated in exposed and non-exposed individuals. Cohort studies have several advantages. The design makes it possible to investigate the natural history and risk factors of a disease, and both absolute and relative risks may be provided.[100] The temporal sequence of exposure and outcome allows some indication of causality, as opposed to case-control studies, where information about prior exposure is collected after the occurrence of outcome. Additionally, a large number of participants are normally included in cohort studies, which enhances the generalizability of study results to other populations. However, the high number of required participants combined with long follow-up time, make these studies both time- and resource consuming and not appropriate when studying rare diseases.[100] For instance, the occurrence of cancer after VTE is quite rare as the annual incidence of VTE is 1-2 per 1000 person-years,[1,16,19] and only 6% are diagnosed with subsequent cancer the first year after a VTE event.[55] As a consequence, statistically meaningful results could not be obtained when investigating the risk of cancer after a VTE event (paper IV) by only including the Tromsø 4 Study, but the establishment of the large STAC Cohort improved this problem. Lastly, the non-randomized design of cohort studies make them prone to bias and confounding, which will be further discussed.

5.1.2 Causality

Epidemiological studies investigate diseases and their cause and effect relations. Sir Bradford Hill has defined nine criteria to assess when discussing whether or not an observed association is causal. However, failure to satisfy most of these criteria does not disprove a causal association, and Hill emphasized that causal inferences cannot only be based on these rules. Szklo and Niete have defined the following six as the most useful criteria: *temporality, strength, consistency, biological gradient, plausibility and experimental evidence*.[258] In the

following section these criteria will be discussed for platelet count as a risk factor for cancer-related VTE (paper II), and the same discussion also applies to WBC count as risk factor (paper I).

Temporality means that the exposure should precede the outcome, and this is the only absolute criterion. The design of cohort studies facilitates temporality, but when assessing the risk of cancer, it can be difficult to establish the onset of the disease due to a long subclinical phase. In paper II, subjects with previous cancer at inclusion or a cancer diagnosis the following year after baseline were excluded in order to restrict the impact of overt and occult cancer on platelet count. Furthermore, platelet count was measured on average eight years before cancer diagnosis and the cancer-related VTE event, which can be regarded as a convincing temporal sequence.

Strength of association implies that a strong association is more difficult to attribute to bias or confounding than a weak association. Szklo and Nieto suggest that a weak association is characterized by a relative risk below 2.0.[258] Accordingly, our finding of a 2-fold increased risk of cancer-related VTE in subjects with platelet count in the upper versus lower level would represent a borderline value.

Consistency means that the same association is observed in studies with other study populations and designs. As previously described, an elevated platelet count at the time of cancer diagnosis has been found predictive of VTE in several studies, but our study is the first to identify pre-cancer platelet count as a predictor of cancer-related VTE. Accordingly, further studies are warranted.

Biological gradient implies the presence of a dose-response relationship. A significantly graded risk of VTE was not found across the three platelet categories, but this does not reject causality since it could be that the excessive risk of VTE only appears above a certain threshold value of platelet count.

Biological plausibility means that the association is plausible with biological knowledge. The underlying biological mechanism by which platelet count may contribute to cancer-related VTE is not clear, but platelets are essential for tumor progression and are involved in interactions with tumor cells, endothelium, leukocytes and the coagulation system.[89,90]

Experimental evidence refers to the use of randomized controlled trials (RCTs), which are considered the gold standard when investigating cause-and effect relationships. RCTs compare outcomes in subjects with and without an intervention, and the subjects are randomly

allocated to these groups, which reduces the risk of confounding, a major challenge in cohort studies. With regard to platelet count and risk of VTE, the use of RCTs would imply the manipulation of platelet count, which is practically and ethically difficult to implement, especially for a long follow-up time.

To summarize, several of Hill`s criteria are fulfilled with regard to platelet count as a potential causal factor of cancer-related VTE, but since a RCT is not a feasible option within this field, it is hard to fully establish causality. Furthermore, more studies investigating pre-cancer platelet count and risk of VTE are needed.

5.1.3 Identification and validation of outcomes

5.1.3.1 Cancer

Cancer is the main exposure variable in paper I-II and the outcome of interest in paper III-IV, and the cancer information is obtained from national cancer registries in Norway and Denmark. To ensure that the incidence and survival rates are close to their true values, completeness is an important attribute of a cancer registry and can be defined as "the extent to which all of the incident cancers occurring in the population are included in the registry database".[259] The Cancer Registry of Norway (CRN) receives cancer notifications from several medical sources (general physicians, hospitals, pathological laboratories and death certificates) which reduces the possibility of missing cases. In a recent evaluation of the CRN for the period 2001-2005, the average number of notifications per case for all cancer sites combined was 3.2. The estimated overall completeness in the same period was 98.8%, which makes the CRN among the most complete cancer registries in Europe.[255]

Validity is another important feature of a cancer registry and can be defined as: "the proportion of cases in a dataset with a given characteristic that truly have the attribute".[260] A cancer diagnosis is regarded more accurate if it is based on morphological verification, and the validity of the cancer cases in CRN in 2001-2005 was high with 93.8% of the cases being morphologically verified.[255] In the Danish Cancer Registry, 95-98% completeness has been reported with 93% microscopically confirmed diagnoses.[256] Delayed notification of cancer cases may reduce data quality, and the median time from the date of diagnosis to a registered new case in CRN in 2005 was 261 days.[260] However, the delayed reporting has probably a minor influence on the incidence rates of cancer in the papers of this thesis since only cancer diagnoses up to 2012 have been included.

5.1.3.2 Venous thromboembolism

VTE is the main exposure variable in paper IV and the outcome of interest in paper I, II, and III. The VTE events in all papers were symptomatic and objectively confirmed by radiological procedures. In the Tromsø 4 Study, incident VTE events were identified retrospectively by searching the hospital discharge registry, the radiology procedure registry, and the autopsy registry. The University Hospital of North Norway is the only hospital in the region to provide diagnostic procedures and hospital care to the inhabitants of the municipality of Tromsø, which enhances the probability of a complete VTE register. The strict validation criteria limited the possibility of false positive VTE events. However, some cases have probably been missed due to diagnosis and treatment outside the region.

In paper III, it is shown that the overall and 10-year age-specific incidence rates of VTE were highest in the Tromsø 4 Study, followed by the HUNT 2 Study, and lastly the DCH Study. This is probably explained by the 5 year longer follow-up time of VTE in the Tromsø Study, along with the most comprehensive VTE identification process by searching the three above-mentioned registries. In comparison, the DCH Study did not explore the radiology procedure registry and the HUNT 2 study did not search the autopsy registry. The VTE events in all three cohorts were identified and validated by trained personnel reading the medical records. These personnel were blinded to baseline information, but they would have access to information about cancer development in the medical journals. Since cancer is a well-known provoking factor of VTE, it cannot be excluded that reading this information could influence the validation of the VTE event leading to some degree of differential classification. However, because of strict validation criteria for all the three included cohorts in the STAC Cohort, this misclassification would probably have only a minor influence on the risk estimates.

5.1.4 Bias

Bias can be defined as “the result of a systematic error in the design and conduct of a study” and represent a major challenge when interpreting the results from cohort studies.[258] Bias may influence both internal and external validity. Internal validity refers to whether the finding is true for the population studied, while external validity refers to whether the findings can be

generalized to other populations. Bias can be divided into selection bias and information bias.[258]

5.1.4.1 Selection bias

Selection bias occurs when there are systematic errors in the recruitment or retention of study participants which in turn influences the association between exposure and outcome.[258] The Tromsø 4 Study invited all inhabitants of the municipality of Tromsø ≥ 25 years, and the attendance rate was high (77%), which reduces the risk of selection bias and enhances the probability that the study population is representative of the general population. This is supported by a distribution of baseline characteristics which is reasonable in accordance with other large Western study populations like the HUNT 2 Study.[16] However, *self-selection* is still an important issue that may threaten external validity. The attenders in health surveys tend to be more educated and have a healthier lifestyle than non-attenders.[261] In the Tromsø 4 Study, the attendance rates were lower in subjects < 40 years and ≥ 80 years,[262] which might weaken the generalizability for these age groups. Furthermore, the vast majority of the participants were Caucasians, which limits applicability to other ethnicities.[262]

In the large DCH Study, 57053 subjects were included, but the participation rate was low (35%). The participants, especially the women, had a higher education, income and occupational status than the non-participants.[263] An underrepresentation of participants with low socioeconomic status might have decreased the incidence of cancer. However, the age-standardized incidence rates of cancer were not different form the general Danish population, indicating that the low attendance rate did not have a substantial impact on the external validity of the DCH Study with regard to cancer risk.[263]

Another selection bias is *differential losses to follow*, which means that participants lost to follow-up during the study period are different from those who remain in the study. This bias can be an issue in cohort studies if censoring of events like death affects exposed and unexposed subjects differently.[258] The absolute risk of VTE is both a function of the rate of VTE and the rate of death,[264] and in studies investigating cancer exposure and risk of VTE, the mortality rates are higher in cancer patients than in non-cancer patients. It has been shown that this may lead to overestimation of cumulative incidences and hazards ratios in cancer patients.[264,265] To overcome this problem, a statistical model by Fine and Grey can be used, where death is considered a competing event instead of censoring event.[266] In a recent

publication by the CATS-investigators, it was shown that that this bias was negligible in cancer types with low mortality like lymphoma.[264] However, for pancreatic cancer, which has high early mortality, considerable difference between the cumulative incidence and the competing risk estimate was found.[264] The authors recommended that the competing risk approach should be used for prognostic research (risk score models), while etiologic studies may choose ordinary Cox models.[264]

5.1.4.2 Information bias

Information bias is systematic error due to "imperfect definitions of study variables or flawed data collections procedures" which result in misclassifications of exposure or outcome.[258] All the papers of this thesis have obtained several baseline variables from self-administered questionnaires, which is a valuable and cheap source of information, but where inaccurate recall of medical history or lifestyle factors may lead to misclassifications of the exposure variables. *Recall bias* is first of all a methodical challenge in case-control studies, where the retrospective design may influence the cases to report previous lifestyle factors differently than the controls. This misclassification is *differential* since exposed and unexposed individuals are affected unequally. Differential misclassifications may lead to under- or overestimation of the association between exposure and outcome, and the direction of the bias is difficult to predict.[258] In prospective cohorts, the exposure variables are not related to outcome of interest since baseline information is collected prior to the outcome. This misclassification will generally be *non-differential*, which tends to weaken true associations.[258]

None of the main exposure variables in the four papers are based on self-administered questionnaires, which limits the degree of misclassification in these variables. WBC count and platelet count may be exposed to technical measurements errors, but these errors represent random errors, not systematic errors. Random errors decrease with increasing study population size,[267] and these errors are expected to have a minor non-differential influence on a large cohort like the Tromsø 4 Study.

Several self-reported lifestyle factors are included as covariates in the Cox regression models in all four papers. High validity has been found for self-reported questionnaires regarding smoking habits,[268] previous stroke,[269] and previous myocardial infarction.[270] However, a likely non-differential misclassification is present for the diabetes variable in the

Tromsø 4 Study since the self-reported prevalence is 1.7%, which is markedly lower than the reported prevalence of approximately 5% in developing countries in the same period.[271,272] The self-reported level of leisure time physical activity is also prone to misclassifications. It is shown that moderate activity is often overestimated in self-administered questionnaires,[273] which may result in non-differential misclassifications and incomplete adjustment for this variable as confounder. Questions regarding both hard and moderate leisure time physical activity are used in Tromsø 4 and HUNT 2, but only the question regarding hard physical activity has shown acceptable repeatability and correlation with objective measures of physical activity.[274] Thus, hard physical activity was used as an exposure variable in paper I and II. However, for the STAC Cohort, we had to generate a combined variable of moderate and hard physical activity because there were 20000 participants with missing values for hard physical activity in the HUNT 2 Study.

Modifiable exposure variables like smoking habits or laboratory measurements may change over time and lead to *regression dilution bias*, which is a potential limitation of cohort studies, especially when a long period of time elapses between baseline assessment and outcome. It has been shown that when exposure variables are measured at baseline, the strength of an association is reduced by one-third during a decade.[275] WBC count has a reported within-subject biological variation of 10.9%, while platelet count has 9.1%,[276] but during the long observational times (11.0 and 12.5 years), a higher variation can be expected. Repeated measurements of WBC and platelet count could have limited the dilution effect, but were unfortunately only available for a small part of our study population. Nevertheless, this bias would represent a non-differential misclassification since exposed and non-exposed individuals are affected equally and therefore only weaken true associations.[258]

Missing variables are another challenge in large cohort studies and may be due to many causes. For instance, laboratory samples can be lost or technically unsatisfactory or participants, intentionally or unintentionally, may not have completed the whole questionnaire.[277] Missing answers in a questionnaire may be replaced if the participants are asked to fill out the questionnaire again, but this approach is time- and resource consuming for large cohorts. Other possible options are to omit variables with a lot of missing, to omit subjects with missing variables, or to complete the dataset by imputation.[277] Imputation refers to a replacement of missing variables with another value, calculated from other values in the data set. Which one of these approaches that are selected, depends on the missing data mechanism and the volume of missing data. In paper I and II, subjects with missing values for

the main exposure variables WBC count (6%) and platelet count (3%) were omitted. This is regarded a valid approach when the missing variables are "missing completely at random",[277] which means that the missing variables are without relation to the value itself or other variables. When the missing status is independent of the value itself, but related to other variables in the dataset, like sex and age, the mechanism is termed "missing at random".[278] The greatest concern is when data are "not missing at random", meaning that the non-response is related to the true response.[278] For instance, one reason for people not answering questions about physical activity could be that they are physically inactive. In the STAC Cohort, those with missing information on physical activity were elderly and therefore probably less active, so deleting these subjects could introduce bias in the dataset. Furthermore, only 4.5% of the STAC population had missing variables for physical activity, and below 5% is regarded acceptable.[278] As a consequence, subjects with missing values for physical activity were not deleted from the dataset, only excluded from the relevant multivariable Cox regression models in paper IV. A disadvantage of deletion of study participants or variables is loss of statistical power, which increases the risk of a type II error, i.e. failing to detect an association that is present.[278]

5.1.4 Confounding

Confounding represents a formidable threat to the evaluation of causal relationships in cohort studies and refers to a situation where the association between an exposure variable and outcome can be attributed to the influence of a third variable.[258] The confounding variable is related to both exposure and outcome and should not be an intermediate variable in the causal pathway. Confounding may strengthen, weaken or even change the direction of the observed association.[258]

There are several strategies to deal with confounding. Ideally, the exposed and non-exposed group should be identical except from the variable of interest, but this is not possible in cohort studies due to their non-randomized design. Instead, stratification and multivariable analysis are strategies to control or minimize confounding.[258] Multivariable analysis is a statistical technique where potential confounders are included as covariates in multivariable regression models.[258] In paper I, II, and IV, the hazard ratios of outcome (VTE or cancer) are presented in age- and sex-adjusted Cox regression models, as well as more complex multivariable models including age, sex, and several potential confounders. In paper II, the

observed association between higher platelet count and risk of VTE in subjects with cancer could potentially be confounded by the presence of a more advanced cancer in these subjects. A higher cancer stage is a well-known risk factor for VTE,[3] and the proportion of subjects with localized disease was lower in the upper platelet category than in the lower platelet category. However, the inclusion of the variable stage (regional/disseminated versus localized disease) in our multivariable regression model did not change the risk estimate, and accordingly stage was not a confounder.

Another example on how to handle confounding by age in multivariable analysis is found in paper IV. A common approach when using Cox regression models in cohort studies is to use follow-up time as time-scale and adjust for baseline age.[279] However, in paper IV we have used *age as time scale*, with the baseline age as entry-time and age at outcome/censoring event as exit-time. This means that the risk of cancer is compared in subjects at the same age instead of at the same follow-up time. The main argument is that the risk of cancer changes more as a function of age than as a function of follow-up time.[279] Using age as time scale is considered a good strategy for large-scale longitudinal surveys where there are enough people at risk at all ages. In addition, this method improves risk assessment of cancer at different age groups during follow-up as subjects may switch age groups while aging. Since the follow-up time between VTE and subsequent cancer is also of great importance, the risk of cancer at different time intervals after VTE was also calculated in paper IV.

Even though several statistical techniques have been used in all papers to handle confounding, *residual confounding* cannot be ruled out. Possible sources of residual confounding are misclassifications of confounding variables, lack of information about potential confounders, and imprecise definitions of included confounders.[258] For instance, information about hereditary thrombophilia was not available at baseline. However, to the best of my knowledge, an association between thrombophilia and WBC count, platelet count, or cancer is not described. In paper IV, where we investigate the risk of cancer after VTE, smoking was included as a potential confounder in our Cox regression model, but did not change the risk estimate. Residual confounding by other smoking characteristics such as smoking duration (years) and daily heavy smoking (> 25 cigarettes per day) was also investigated by replacing current smoking with each of these variables in two additional Cox models, but this did not change the results either.

5.1.5 Interaction

The term interaction can be defined as a situation where the effect of an exposure variable on outcome differs across strata of a third variable, and this variable is called an *effect modifier*.[258] When an interaction is present, it can be dealt with by stratifying the sample on the basis of the effect modifier. In paper I and II, we investigated the impact of WBC and platelet count on the risk of VTE, and statistical interactions between these two variables and cancer were confirmed in our Cox regression model. As a consequence, we conducted separate analyses for subjects with and without cancer, and both WBC and platelet count were risk factors for VTE in subjects who developed cancer, while no association was found in cancer-free subjects.

Another definition of interaction is based on the comparison between observed and expected joint effect of two variables on a given outcome. In this situation, the observed joint effect of the two variables on outcome differs from what is expected on the basis of their independent effects.[258] In paper II, we investigated the joint effect of high WBC and platelet count on future risk of VTE by means of the Rothman synergy index.[280] A value above 1 suggests that the joint effect exceeds the sum of the separate effects, and we found a synergy index of 2.25 in subjects with cancer, which confirmed that high WBC count and platelet count had a synergistic effect on risk of cancer-related VTE. As discussed in paper II, there may be biological mechanisms underlying a causal relationship for platelet-leukocyte interactions in cancer-related VTE. However, as opposed to statistical interactions, there is no formal test for biological interactions, and epidemiologic studies have limited ability to identify intermediate variables. Accordingly, interpreting interactions should be done with caution.

5.2 Discussion of main results

5.2.1 White blood cell count and risk of venous thromboembolism (Paper I)

In paper I, we reported that high pre-cancer WBC count was associated with a 2.4-fold increased risk of VTE compared to low WBC count in patients who developed cancer during follow-up. Conversely, no association was found in cancer-free subjects, which is in accordance with the LITE Study.[207] Similar results were shown for neutrophil count. Our study is the first to investigate pre-cancer WBC and neutrophil counts as risk factors for cancer-related VTE. Leukocytosis is a common finding in cancer patients,[167,214] and several

studies have demonstrated that leukocytosis is predictive of VTE in cancer patients initiating chemotherapy.[51,158,167,212,213] Leukocytosis is included as one out of five predictive variables for VTE in the validated Khorana risk score model.[158] In these previous studies, leukocytosis could be a marker of the inflammatory state associated with cancer or secondary to previous surgery or other comorbid conditions like infections. Thus, it is not known from these studies if leukocytosis *per se* is a risk factor for VTE. In our study, the WBC count was measured at least one year prior to cancer diagnosis, and mean time from baseline measurement and cancer diagnosis was seven years, which eliminates the impact of cancer treatment on WBC count and reduces the influence of occult cancer to a minimum. WBC count could represent a common risk factor for cancer and VTE, as it is previously shown that WBC count is associated with cancer development,[197] but an association between WBC count and cancer was not found in our study.

Leukocytosis is a marker of inflammation,[195] and the association between inflammation and development of cancer is well documented.[281] Furthermore, acute inflammation, both due to infectious[282-284]and non-infectious causes[285-287], predisposes to VTE. However, conflicting results have been found for low-grade inflammation measured as hs-CRP and risk of VTE.[207,288-291] A previous investigation of a subpopulation of the Tromsø 4 Study found no associations between hs-CRP and provoked/unprovoked VTE, and exclusion of subjects with cancer prior to inclusion or during follow-up did not change the results.[288] Unfortunately, we did not have hs-CRP for the whole study population at baseline or information about inflammatory diseases. Nevertheless, if the risk of VTE by leukocyte count was mediated through low-grade inflammation, an association between WBC count and VTE would have been expected in cancer-free subjects, too. Since our finding is restricted to cancer patients with VTE only, it may indicate that leukocytes interact with cancer cells in the formation of cancer-related VTE.

Leukocytes are recognized as cellular components of venous thrombi. In a stasis-based DVT model in mice by von Bruhl and coworkers, it was demonstrated that the adherence of neutrophils and monocytes to the endothelium was the initiating stimulus for DVT formation.[71] The monocytes were the main contributors of TF-driven coagulation, while the neutrophils propagated DVT through the release of NETs. Interestingly, neutropenic mice developed smaller thrombi.[71] There is an increasing interest in the leukocyte's role in the development of cancer and cancer-related VTE. It is shown that tumor-associated neutrophils exhibit protumoral properties and are part of the tumor's inflammatory microenvironment.[292]

However their role in tumor progression is still debated, as the neutrophils also have antitumoral properties.[292,293] Recently, it has been suggested that NETs generated from neutrophils promote tumor progression, and there is also increasing knowledge of the role of NETs in cancer-related VTE.[96] In a recent study, it was demonstrated that neutrophils in mice with cancer released prothrombotic NETs more easily than neutrophils in cancer-free mice,[97] and chemotherapy has also been shown to promote the release of NETs from neutrophils.[96] More studies are warranted, and experimental studies investigating the association between different leukocyte count levels and cancer-related VTE would contribute important knowledge within this field.

5.2.2 Platelet count and risk of venous thromboembolism (Paper II)

In paper II, a positive association was found for pre-cancer platelet count and risk of cancer-related VTE. Platelet count was measured on average eight years prior to cancer development, and platelet count above the 80th percentile was associated with a 2-fold higher risk of cancer-related VTE than platelet count below the 40th percentile. Platelet count has not been found predictive of VTE in the general population,[124,219,220] which is in accordance with our negative findings for cancer-free subjects. However, previous studies have shown that thrombocytosis secondary to hospitalizations,[294] traumas,[223,224] and intensive care treatment[222] is associated with VTE.

Several studies have also confirmed that thrombocytosis is a predictive biomarker for VTE in cancer patients initiating chemotherapy.[157,166,226] In a prospective study by Khorana et al., of 3000 ambulatory cancer patients, a 2.8-fold higher risk of VTE was found for platelet counts $\geq 350 \times 10^9$ compared with platelet counts $< 200 \times 10^9$,[166] and thrombocytosis is included in the Khorana risk score model. Thrombocytosis is a common finding in cancer patients[166,167] and is associated with poor survival.[87,225] As discussed for leukocytosis, it is neither known if thrombocytosis is a risk factor *per se* or just a biomarker of the inflammatory state associated with cancer, previous surgery, or comorbid conditions. However, our findings reveal that the risk of cancer-related VTE by platelet count is also dependent on pre-cancer values and may indicate that platelet count is a causal factor for cancer-related VTE, as previous discussed under the causality section in this thesis.

Platelets stimulate metastasis formation,[87,88], and an advanced cancer stage is a well-known risk factor for VTE.[3] Accordingly, our findings could be due to more advanced

cancers among patients with higher platelet count. Interestingly, a significantly lower proportion of localized disease was seen in the upper compared to the two lower platelet categories. However, adjustment for cancer stage (localized versus regional/distant metastasis) in our multivariable Cox regression model did not change the result. Cancer sites may also influence the risk of VTE, but with the exception of lung cancer, there was no overrepresentation of high-risk cancer sites in the upper category. Overall, a wide range of potential confounders at baseline and at cancer diagnosis have been explored for the association between platelet count and VTE with negative results.

There is increasing evidence for the role of platelets in the development of both cancer and cancer-related VTE.[89,90] In vitro studies have demonstrated that tumor cells activate platelets and induce platelet aggregation, and in vivo studies have shown that cancer patients have higher levels of different markers of platelet activation than healthy controls.[89] Several studies have also shown that activated platelets promote tumor growth, angiogenesis and tumor spread.[87,88] Activated platelets and platelet-derived microparticles represent a link with the coagulation system as they express negatively charged phospholipids and thereby expose a procoagulant surface for the activation of thrombin, a key enzyme in the coagulation cascade.[295] Interestingly, thrombin may also induce tumor progression,[296] which highlights the complex interplay between platelets, cancer and the coagulation system. Our current understanding of the platelet marker P-selectin represents another example of this interplay. P-selectin is elevated in cancer patients compared to controls and facilitates interaction with cancer cells, leukocytes and endothelial cells[89,92] and P-selectin is identified as a risk factor for VTE in cancer patients.[93] In our study, we also confirmed a synergistic effect of high leukocyte and platelet counts on cancer-related risk of VTE, which is supported by the recognition of platelet-leukocyte interactions as essential in the development of cancer-related VTE in in vitro studies.[95,297]

Altogether, our and previous studies have shown that platelet count in a general population is not associated with VTE, but along with strong provoking factors like trauma or cancer, high platelet count is converted into a risk factor. This is probably due to altered platelet function in combination with the quantitative effect of high platelet count which increases the amount of interactions between activated platelets, leukocytes, cancer cells, and the coagulation system.

5.2.3 The STAC Cohort (Paper III)

Discharge registries represent large and valuable databases when exploring the risk of VTE in cancer patients, especially when comparing risk by cancer sites, which requires a large study population. However, discharge registry-based studies often lack baseline information regarding lifestyle factors, which may represent important confounders. Furthermore, the validation of VTE events in these studies is a methodological issue as they often are solely based on discharge diagnosis. For instance, a French study has reported that 40% of the DVT events are lost when using ICD-10 discharge codes.[298] Furthermore, a Danish study has found that the positive predictive value of VTE cases based on discharge coding is 75% for a primary VTE diagnosis and 67% for a secondary VTE diagnosis, indicating that without any further VTE validation, these data should be used with caution in medical research.[299]

Paper III describes the cohort profile of the STAC Cohort, a large Scandinavian collaboration study including three cohorts, which is established to investigate the risk of symptomatic, objectively confirmed cancer-related VTE events in the general population. The STAC Cohort has thorough validation of each VTE event, detailed information on cancer diagnoses from complete cancer registries, and baseline data including several lifestyle factors. The STAC Cohort is also characterized by wide age-distribution (19-101 years) and a long follow-up time.

The overall incidence rate (IR) of VTE in the STAC Cohort was 1.4 per 1000 person-years during 11.7 years of follow-up, which is in accordance with previous studies in Western populations.[1,19,101] The risk of VTE increases exponentially with age,[124,126] which was also confirmed in the STAC Cohort and in the three cohorts included. The overall and 10-year age-specific IRs of VTE were highest in the Tromsø 4 Study, followed by the HUNT 2 Study and the DCH Study. This is probably explained by 5-years longer follow-up time and the most comprehensive VTE identification procedure in the Tromsø 4 Study by searching the hospital discharge diagnosis registry, the radiology procedure registry, and the autopsy registry. In comparison, the DCH Study did not explore the radiology procedure registry and the HUNT 2 Study did not search the autopsy registry. Another explanation for the low IR in the DCH Study could be that the underrepresentation of participants with lower socioeconomic status has lowered the IR. Lastly, VTE may theoretically be more common in Norway, and especially in Northern Norway.

As mentioned, the DCH Study had a low attendance rate and an underrepresentation of participants with low socioeconomic status. Nevertheless, age-adjusted IRs of cancer in the

DCH Study did not differ from that of the general population.[263] In paper III, we compared 5-year age-specific IRs of cancer in the STAC Cohort with national figures from the Norwegian Cancer Registry, and they were concordant. The low attendance rate in the DCH Study may have influenced the distribution of specific cancer sites among their participants. However, the distribution of cancer types in the DCH study was not different from the two Norwegian studies. Overall, the STAC Cohort will provide a unique opportunity to explore genetic and environmental risk factors for cancer–related VTE.

5.2.4 Risk of cancer after venous thromboembolism (Paper IV)

In paper IV, we confirmed a high short-term risk of cancer after VTE and a much weaker constant long-term risk, which is in agreement with previous studies.[6,8,60] Overall, 5.3% of the patients with VTE were diagnosed with cancer during the first year of follow-up. The risk of cancer was increased 4-fold compared with the general population in the same period, while a 1.3-fold increased risk of cancer was found during subsequent years. This rapidly declining risk of cancer during the first year after the VTE event has also been found in other studies[6-8,59,60] and indicates that the hypercoagulable state associated with cancer[77-79] may also result in VTE for occult cancers. However, it is harder to explain an association between VTE and subsequent cancer several years after the VTE event by the presence of an occult cancer at the time of VTE diagnosis. Another explanation for this long-term risk could be the presence of shared risk factors for VTE and cancer. Our study adds to current knowledge by adjusting statistically for variables like BMI, height, and heavy smoking, which are all recognized risk factors for both conditions.[127,148,257,300-303] However, the adjustment for these and several other variables did not change our results. Nevertheless, others factors not available in our study like the presence of inflammatory diseases may represent confounders in the association between VTE and the long-term risk of cancer. Another more speculative explanation could be that VTE promotes cancer development through generation of thrombin, which is shown to enhance tumor growth or through sustained inflammatory responses after VTE.[296]

In our study we explored whether the risk of VTE differed according to the anatomical location of VTE, but as previously described,[6,8,58,232] no differences were found. As opposed to several previous studies,[9,54,55,58,229] only minor differences were found in cancer risk between subjects with unprovoked and provoked VTE. A meta-analysis with large between-study heterogeneity reported a 3.8-fold higher pooled relative risk of cancer for provoked

versus unprovoked VTE,[54] while a prospective study of 1852 patients with VTE found a more modestly increased risk of 1.9 in subjects with unprovoked versus provoked VTE.[9] Conversely, unprovoked and provoked VTE had similar short-and long-term risk of cancer in a large Danish registry-based study.[60] In another recent Danish study, VTE secondary to myocardial infarction and stroke had a 3-4 fold increased risk of cancer the first year after VTE,[230] and these risk estimates were similar to the reported risk of cancer in subjects with unprovoked VTE in another Danish study.[8] Interestingly, these risk estimates are of similar magnitude as the hazard ratios of cancer found in our study in subjects with unprovoked and provoked VTE. Our study includes several provoking factors other than medical conditions and may therefore indicate that VTE is a marker of occult cancer regardless of provoking factor.

Whether subjects with VTE should be further examined for an occult cancer is a debated clinical issue. It is generally recommended that only subjects with unprovoked VTE should undergo a limited examination for cancer, including thorough medical history, physical examination, and some basic blood tests.[251,253,254] However, our findings of a high risk of cancer also in patients with provoked VTE, suggest that clinicians should not only be suspicious of occult cancer in patients with unprovoked VTE. Future studies investigating the benefits of examination for occult cancer should not be restricted by the anatomical location of the venous thrombus nor by the provoking nature of the VTE.

6. CONCLUSIONS

- High pre-cancer WBC count was associated with a 2.4-fold higher risk of VTE than low WBC count in subjects who developed cancer during follow-up. In agreement with previous studies, no association was found for subjects who remained cancer-free. Similar findings were observed for neutrophil count. Increased WBC count measured prior to chemotherapy is identified as a biomarker of cancer-related VTE. Since our pre-cancer WBC measurement cannot be attributed to the malignant disease or associated comorbidities, our findings contribute to current knowledge by suggesting that WBC count may play a causal role in VTE development in cancer patients.

- High pre-cancer platelet count was associated with a 2-fold higher risk of VTE than low platelet count in those who developed cancer during follow-up, while no association was found for cancer-free subjects. Concomitant high platelet and leukocyte count had a synergistic effect on risk of VTE in cancer patients. Increased pre-chemotherapy platelet count is associated with risk of VTE in cancer patients, but these measurements are influenced by the presence of the malignant disease and other comorbidities. Our findings suggest that platelet count and platelet-leukocyte interactions may play a causal role in the pathogenesis of cancer-related VTE.

- The STAC Cohort is a large population-based cohort with a wide age-distribution, long follow-up time, and thorough validation of VTE events and cancer diagnoses. The incidence rates of VTE are representative of adult populations in Western countries, and the incidence rates of cancer are in accordance with national figures from the Norwegian Cancer Registry. Thus, the STAC Cohort is well suited to explore the epidemiology and risk factors of cancer-related VTE.

- In agreement with previous studies, we have confirmed an increased risk of cancer after a VTE event. We found a 4-fold higher risk the first year of follow-up while a 1.3- fold higher risk was found for subsequent years. Only minor differences in cancer risk were found in subjects with unprovoked and provoked VTE and in subjects with different anatomical locations of the thrombus.

7. FINAL REMARKS AND FUTURE PERSPECTIVES

We have confirmed that cancer is a major risk factor for VTE. In the Tromsø 4 Study, the incidence of VTE between 1994 and 2009 was 13.5 per 1000 person-years in cancer patients and 1.2 per 1000 person-years in cancer-free subjects. Elevated WBC and platelet counts are established as predictive biomarkers of VTE in ambulatory cancer patients and are included in the Khorana risk score model. Our studies are the first to demonstrate the same associations between pre-cancer WBC and platelet counts and risk of cancer-related VTE. Further studies are needed to explore how pre-cancer values are related to pre-chemotherapy values, and experimental studies are required to investigate how different WBC and platelet counts levels influence development of cancer-related VTE. Future studies should also continue to assess risk prediction models of VTE in both cancer outpatients and inpatients. Despite increasing knowledge of VTE in cancer patients, the administration of thromboprophylaxis to hospitalized cancer patients is poor.[49,304,305] The Padua score can be used for risk assessment in hospitalized cancer patients, but does not take different cancer sites or stage into account, and the impact of leukocytosis and thrombocytosis in these patients is not known. The cut-off level of 70 years as high-risk age in Padua score is also questionable in cancer patients, as both the absolute and relative risk of VTE in younger cancer patients is high.[129] The Khorana risk score model for ambulatory cancer patients initiating chemotherapy is promising, but BMI > 35 kg/m^2 was a rare finding and not associated with VTE in the Austrian CATS,[159] which underlines that a validation of the model in Scandinavian countries is required. The newly established STAC Cohort represents a unique opportunity to identify risk factors for cancer-related VTE and to explore predictive risk assessment models.

In accordance with previous studies, we have confirmed that the presence of VTE is associated with short- and long-term risk of cancer. In the clinical setting, it is important to know if different VTE characteristics can indicate which subjects with VTE that should be further examined for an occult cancer. We found only minor differences in cancer risk between different anatomical locations of VTE and between provoked and unprovoked VTE, suggesting that future studies assessing the benefits of screening for occult cancer should not be restricted by these factors. Furthermore, more studies are warranted that explore whether different biomarkers alone or in combinations (D-dimer, CRP, platelet count, leukocyte count etc.) at VTE diagnosis are predictive of occult cancer.

8. REFERENCES

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Appendix

You are invited to the large health survey in the municipality of Tromsø 1994 - 95

We will reach everyone

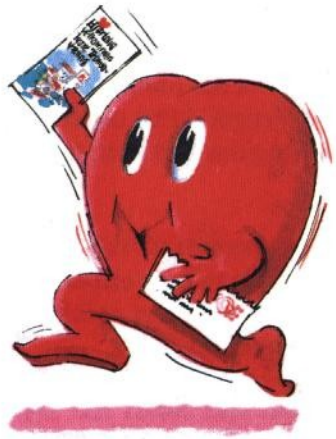
We will start in the outskirts of the municipality. Here, the examination will take place in schools and other premises – see the information in the invitation accompanying this letter.
From late October 1994 until summer 1995, the examination will take place in Mellomveien 50 (the Elisabeth centre; the old maternity hospital). We prefer that you attend at the location specified in the invitation letter.

Why did you receive this offer?

Because we offer this examination to everyone born 1969 or earlier.

What is the purpose?

The survey is first and foremost aimed at cardiovascular diseases, but is also important to gather new knowledge about other serious chronic diseases (amongst them cancer).
This time we will also study musculo-skeletal pain conditions, for instance fibromyalgia. Therefore, some people will be invited to a separate examination in the fall of 1995.
Large cardiovascular surveys were carried out in Tromsø in 1974, 1979-80, and 1986-87. The attendance rate was high, and several cases of cardiovascular disease were detected – who are now being treated.
The surveys have also contributed with important knowledge to combat these diseases. The knowledge we gained through the previous surveys, made the University of Tromsø to one of the renowned research centres in the world with regard to cardiovascular diseases. Again, we aim to detect hitherto undiscovered cardiovascular disease. We also hope to reach those at particular high risk, so that they may get the possibility of prevention and other measures to stop the development of disease. Cardiovascular diseases are still one of our largest health problems.



Not only for your own sake ...

The examination not only is important for you personally. It is also important that the results may be used in medical research, for instance by using them together with information about disease that occur in the future. Thereby we will learn more about how cardiovascular diseases, cancer, and other population diseases develop, and how they may be prevented. By attending the survey, you are helping to fight these diseases.

The examination includes

- **Measurement of height and weight**
- **Measurement of blood pressure**
- **Blood sample.** In this sample, we will measure the content of lipids (e.g. cholesterol), calcium and a liver enzyme. The result of these measurements will be forwarded to your doctor if you consent. The result of other analyses will be used for medical research only. The blood sample will be frozen to make it possible to perform other blood analyses in order to study disease development. Before such analyses are performed, the study will be presented to the Regional Ethical Committee of North Norway.

ECG is a test that registers the heart activity. We will use a simplified version, and the results will be used for research purposes only.

- **Questionnaire**
- **Special examination.** Everybody born between 1920–1939 and a sample of the others, will be offered a more extensive examination for free. The content of the examination varies somewhat, but will provide a better examination of the heart, the aortic artery, atherosclerosis, and the tendency to osteoporosis. You will get an appointment for the examination when you attend.

Questionnaire

This you will find on the reverse side of the invitation letter. Please fill in the questionnaire beforehand and bring it to the examination site. If some questions are difficult to answer, you may get some help when you attend.

About consent

The information about you will be treated confidentially. The information will be stored and used according to the rules set by the Data Inspectorate and the Regional Ethical Committee of North Norway. For the information to be used in medical research, you have to consent. Your consent is also necessary if your doctor shall have the results of the analyses (and which you will be mailed the results of) and of your answers to the questionnaire enclosed with this letter. When attending, we therefore ask you to give your consent that:

- a letter with your results is sent to your family doctor, and will be stored in your medical record
- that your blood sample may be used for medical research. The purpose of such research is to learn about causes of diseases.
- that your results may be used for medical research, by linking that information with other health- and disease registries (for instance cancer registry and causes of death registry) and with information form the previous health surveys in Tromso. Before the information is used for analyses, your name and personal identification number will be removed. Even if you give your consent now, you may withdraw your consent later.

Follow-up examination

Some of those who are examined may later be referred to their own doctor for a more thorough control. If you are in need of treatment, you will be offered such treatment.

What does it cost?

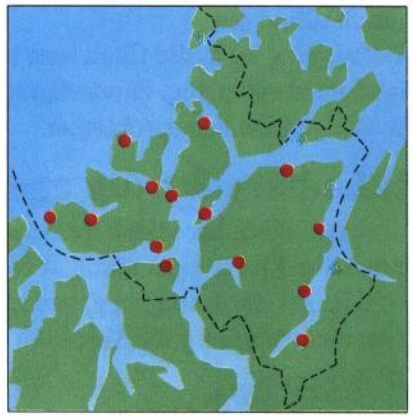
A small fee is necessary for this examination. It is very modest compared to the actual cost. You will find the amount in the letter you have received now. The special examination is free of charge. If you will need an examination by your own doctor or at the Regional hospital, you will have to pay the ordinary fee.

Clothing

Because of the blood pressure measuring, we ask you to wear clothes that are sleeveless or with short sleeves that are not tight. It is not necessary to take the clothes off.

Places that will be visited by the health survey

- Kaldfjord
- Tromvik
- Lakselvbukt
- Sjursnes
- Breivikeidet
- Fagernes
- Skittenelv
- Ersfjordbotn
- Straumsbukta
- Brensholmen
- Vikran
- Trondjord
- Sjøtun
- Tromsø sentrum



Welcome!

Sincerely

- The municipality health service
- The Faculty of medicine, University of Tromsø

Statens helseundersøkelser

(The National Health Screening Service)

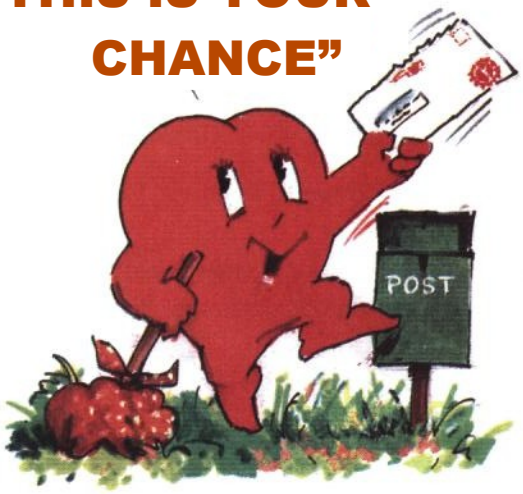
Repro & Grise A/S 360 95 955

(Heartily welcome, dear Tromsø inhabitant)

Hjertelig velkommen, kjære Tromsø-væring

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