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ENGLISH SUMMARY

Venous thromboembolism (VTE) constitutes deep vein thrombosis and pulmonary embolisms, obstructing central or peripheral lung arteries. VTE can occur unprovoked or provoked by known risk factors. The association between surgery and VTE is well recognized in previous investigations that found these complications preventable with pharmacologic and mechanical prophylaxis. Since, surgical techniques have improved and it has been proposed that e.g. minimally invasive surgery is associated with a lower risk of VTE.

Recently, cancer-associated VTE has gained increased attention and numerous studies have examined suggested risk factors and biomarkers for predicting the risk in cancer patients. Some cancer types are associated with higher VTE risk than others, ovarian cancer being one of them.

This thesis examines the incidence of VTE in different risk groups within the gynecology specialty. Study I showed a low incidence of VTE following hysterectomy, especially if performed with a minimally invasive technique and if postoperative prophylactic low molecular weight heparin was administered. With the available study population in study II we were not able to show a difference in postoperative VTE risk when comparing hysterectomy for benign conditions to patients with endometrial cancer as the primary indication for hysterectomy. Study III examined the incidence of VTE in all patients diagnosed with ovarian cancer during a 10-year period in Denmark. The result showed a high incidence of VTE, especially within the first year after cancer diagnosis. We identified several risk factors, e.g. that VTE risk was increased following surgery and chemotherapy. In study IV, women with suspected ovarian cancer, referred to Aalborg University Hospital, were followed with objective examinations for VTE one year after first referral. The incidence of VTE at the time of first referral was lower than expected, although the cumulative one-year VTE incidence was high in women with confirmed ovarian cancer. A notable proportion of women were diagnosed with VTE in relation to non-surgical treatment for ovarian cancer.

These results contribute with new insights into the risk of VTE after gynecologic surgery and VTE risk factors in relation to ovarian cancer. Clinical trials are warranted before modification of current guidelines on postoperative VTE prophylaxis. Molecular biology research will potentially contribute to a better understanding of the mechanisms behind the proposed disturbance in the homeostasis of the coagulation system in ovarian cancer.

DANSK RESUME

Venøs tromboemboli (VTE) er en samlet betegnelse for blodpropper, der opstår i kroppens dybe vener eller lungeemboli, som obstruerer centrale eller perifere arterier i lungerne. VTE kan opstå uden kendt årsag eller være provokeret af kendte risikofaktorer. Sammenhængen mellem VTE og operation er velkendt og undersøgt i mange tidligere studier, som også viste, at disse komplikationer kunne forebygges medicinsk og mekanisk. Der er sket store forbedringer inden for operationsteknikker, siden mange af disse studier er udført, og meget tyder på, at blandt andet minimalt invasiv kirurgi er forbundet med en lavere VTE risiko.

Der har i de senere år været øget fokus på cancer-associeret VTE, og mange studier har undersøgt mulige risikofaktorer og biomarkører til forudsigelse af, om en patient er i særlig høj risiko. Nogle kræfttyper er forbundet med højere VTE risiko end andre, herunder æggestokkræft.

Denne afhandling undersøger forekomsten af VTE i forskellige risikogrupper indenfor det gynækologiske speciale. Studie I viste en lav VTE forekomst efter operativ fjernelse af livmoderen, specielt efter minimalt invasiv kirurgi og hvis der blev givet forebyggende lavmolekylært heparin efter operation. I studie II kunne vi i den tilgængelige studiepopulation ikke påvise en forskel i VTE risiko efter operation ved sammenligning af kvinder, som fik fjernet livmoderen på grund af godartet sygdom, med kvinder, som havde livmoderkræft som årsag til fjernelse af livmoderen. Studie III undersøgte forekomsten af VTE hos alle patienter med æggestokkræft i Danmark diagnosticeret inden for en 10-årig periode. Resultatet viste en høj forekomst af VTE især det første år efter cancerdiagnosen. Vi identificerede flere risikofaktorer og fandt blandt andet, at risiko for VTE var øget i perioder efter operation og kemoterapi. Studie IV fulgte kvinder henvist til Aalborg Universitetshospital på mistanke om æggestokkræft med objektive undersøgelser for VTE det første år efter henvisning. Forekomsten af VTE på henvisningstidspunktet var lavere end forventet, men den sammenlagte et-årige forekomst var høj hos kvinder med bekræftet æggestokkræft. Kvinderne blev især diagnosticeret med VTE i forbindelse med ikke-kirurgisk behandling for æggestokkræft.

Disse resultater bidrager med ny viden om risiko for VTE efter gynækologisk operation og VTE risikofaktorer ved æggestokkræft. Der er behov for flere kliniske studier, før der kan laves nye anbefalinger for forebyggelse af VTE efter operation. Indenfor æggestokkræft kan molekylær biologisk forskning potentielt hjælpe til at forstå mekanismerne bag den formodede ubalance i blodstørkningssystemet.

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LIST OF PAPERS IN THE THESIS

I.

Venous Thromboembolic Complications to Hysterectomy for Benign Disease: A Nationwide Cohort Study

Kahr HS, Thorlacius-Ussing O, Christiansen OB, Skals RK, Torp-Pedersen C, Knudsen A

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II.

Endometrial Cancer does not increase the 30-day risk of Venous Thromboembolism following hysterectomy compared to benign disease. A Danish National Cohort Study

Kahr HS, Christiansen OB, Høgdall C, Grove A, Mortensen RN, Torp-Pedersen C, Knudsen A, Thorlacius-Ussing O

Gynecologic Oncology. 2019;
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III.

Timing and Risk Factors of Venous Thromboembolic Complications in Epithelial Ovarian Cancer. A Nationwide Cohort Study

Kahr HS, Riddersholm SJ, Gade IL, Christiansen OB, Torp-Pedersen C, Knudsen A, Thorlacius-Ussing O

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IV.

Venous Thromboembolism in Epithelial Ovarian Cancer. A prospective cohort study

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ABBREVIATIONS

ACCP: American College of Chest Physicians

ASA: American Society of Anesthesiologists (physical classification system)

ATC: Anatomical therapeutic chemical classification

BMI: Body mass index

CDR: Clinical decision rule

CI: Confidence interval

CTPA: Computed tomography pulmonary angiography

CUS: Compression ultrasound scan

DAG: Directed Acyclic Graph

DCB: Danish Cancer Biobank

DGCD: Danish Gynecologic Cancer Database

DNPR: Danish National Patient Register

DVT: Deep vein thrombosis

ECAT: European Concerted Action on Thrombosis procedures

EOC: Epithelial ovarian cancer

^{18}F-FDG PET-CT: ^{18}F-labeled fluoro-2deoxyglucose positron emission and computed tomography

FIGO: International Federation of Gynecology and Obstetrics

HR: Hazard Ratio

ICD: International coding of diseases

LMWH: Low molecular weight heparin

LND: Lymph node dissection

LOS: Length of stay

MIS: Minimally invasive surgery

MRI: Magnetic resonance imaging

NACT: Neoadjuvant chemotherapy

NOAC: Non vitamin K oral anticoagulants

NOMESCO: Nordic Medico Statistical committee's classification of surgical procedures

OR: Odds ratio

PARP: Poly ADP Ribose Polymerase

PE: Pulmonary Embolism

RMI: Risk of Malignancy Index

STROBE: Strengthening the reporting of observational studies in epidemiology

TF: Tissue factor

TNM: Classification system used to describe tumor size and spread to nearby tissue, lymph nodes and metastasis

VEGF: Vascular endothelial growth factor

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

WHO-PS: World Health Organization performance status

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PREFACE

"Je suis perdu; une phlegmatia qui vient de se déclarer cette nuit, ne me laisse aucun doute sur nature de mon mal." —Armand Trousseau[1]

"I am lost; a phlebitis which has declared itself this night leaves me no doubt about the nature of my illness."

Armand Trousseau (1801-1867) is recognized for his studies of the association between visceral cancer and migratory thrombophlebitis. Trousseau observed, that a first sign of cancer could be painful oedema of the lower or upper extremities, also known as Trousseau's syndrome. After retiring from the Faculty of Medicine and the hospital Hôtel-Dieu de Paris, he suffered from stomach pain, tiredness, reduced appetite and weight loss, but found no palpable abdominal tumor. After developing the symptoms of deep vein thrombosis, he was certain that a visceral cancer was the cause of his symptoms, and he was right, as gastric cancer caused his death months later. Since Armand Trousseau taught medical students about "*phlegmasia alba dolens"*[2]as an important first sign of cancer, many studies have been conducted to investigate cancer-associated thrombosis.[3]

This thesis investigates the risk of venous thromboembolism in patients undergoing treatment for gynecologic disease, focusing on incidence according to the underlying benign or malignant disease. Furthermore, the thesis focuses on patient- and treatment-related risk factors.

BACKGROUND

1.1. VENOUS THROMBOEMBOLISM (VTE)

Pulmonary embolism (PE) with obstruction of central or peripheral lung arteries and deep vein thrombosis (DVT) most often located in the deep veins of lower extremities constitute venous thromboembolism (VTE).[4] VTE episodes are classified as provoked, in the presence of a well-known risk factor, or unprovoked in the absence of risk factors. Risk factors can be categorized as permanent (e.g. thrombophilia, non-curable cancer, autoimmune disease) or transient (surgical trauma, hormone treatment, pregnancy).[5] Unprovoked VTEs are associated with the highest risk of recurrence. In a study population without cancer, 20 % with unprovoked first-time VTE experienced recurrence, whereas recurrence was 8 % in patients with non-surgical provoked VTE, and no recurrence after VTEs provoked by surgery.[6]

VTEs can also be classified as either symptomatic or asymptomatic, the latter observed after examination e.g. in relation to clinical trials or incidental findings on radiological imaging performed for other indications than clinically suspected VTE.[7]

Virchow (1856) proposed a theory to describe the pathogenesis behind the development of venous thrombosis. In an up-to-date terminology, Virchow's triad describes an unbalance between endothelial damage, venous stasis and a hypercoagulant state.[8] It will often be possible to explain the causation of VTE by Virchow´s triad, as depicted in Figure 1.

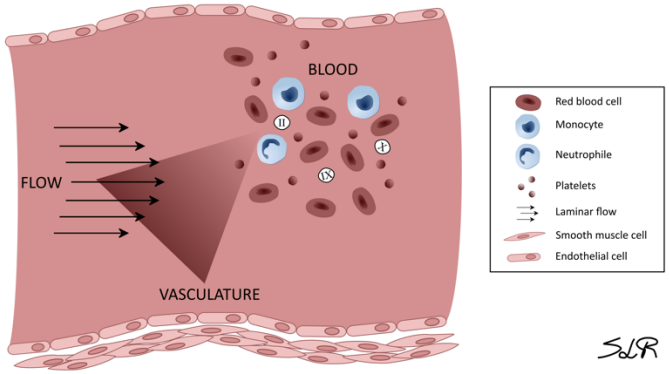


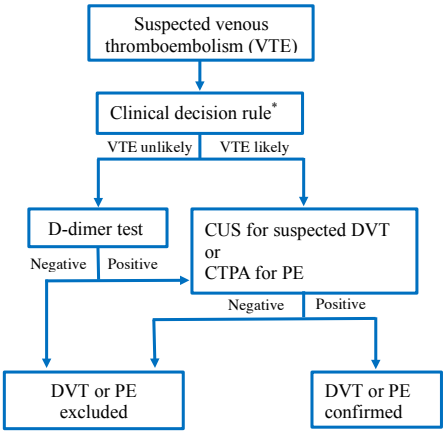
Figure 1 Components of Virchow's triad: Blood flow, vascular function and blood composition. Bleeding or thrombosis occurs in case of unbalance in the regulation of coagulation. II, IX, and X are coagulation factors.

Symptoms of PE are dyspnoea, tachycardia, chestpain, haemoptysis, or sudden death. Acute symptoms of DVT are leg swelling, redness, pain and warmth. A DVT can progress to a PE or manifest as post-thrombotic syndrome.[9] These symptoms are not exclusive for VTE, and therefore, diagnostic tools are important to rule out other underlying pathology.

1.2. DIAGNOSIS, TREATMENT AND PREVENTION OF VTE

The fibrin degradation product D-dimer can be used to assess the probability of VTE in symptomatic patients. The test has a 91 % sensitivity for DVT and 55 % specificity, but the performance is influenced by the assay used, as well as patient characteristics. Cancer and pregnancy can increase D-dimer levels.[10] Furthermore, D-dimer increases naturally with age and an age-adjusted threshold has been proposed.[9]

Clinical decision rules (CDR) are available to help guide clinicians in the diagnosis of VTE. The Wells score is widely used for this purpose in combination with D-dimer.[11,12] Figure 2 illustrates how CDR and D-dimer testing can safely rule out patients with a low probability of VTE, without concurrent imaging.



Wells score for DVT†	**Points**
Cancer	+1
Paralysis or recent plaster cast	+1
Bed rest >3 days or surgery <4 weeks	+1
Pain on palpation of deep veins	+1
Swelling of entire leg	+1
Diameter difference on affected calf >3 cm	+1
Pitting Oedema (affected side only)	+1
Dilated superficial veins (affected side)	+1
Alternative diagnosis at least as probable as DVT	-2
Wells score for PE‡	
Previous PE or DVT	+1.5
Heart rate >100 beats per min	+1.5
Recent surgery or immobilisation	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3
Haemoptysis	+1
Cancer	+1

Figure 2 Diagnostic algorithm for suspected venous thromboembolism. Modified from[12–14]
*Clinical decision rule e.g. Wells score as illustrated in corresponding table to assess probability of VTE;
†DVT probability; ≤1 point: Unlikely, >1point: Likely.
‡PE probability; ≤4 points: Unlikely, >4 points: Likely.

Venography for the diagnosis of DVT is a very sensitive test and has been used as the reference standard, but for practical use, it has been replaced by the non-invasive ultrasonography, which has a high sensitivity (94 %) for particular proximal DVT

whereas much lower (64 %) for distal DVT with a 94 % specificity.[15] The simplest technique for ultrasound scan is performed in grey scale (B-mode) with intermittent compression of the deep veins.[16] In the presence of a DVT, the vein will be incompressible (Figure 3).

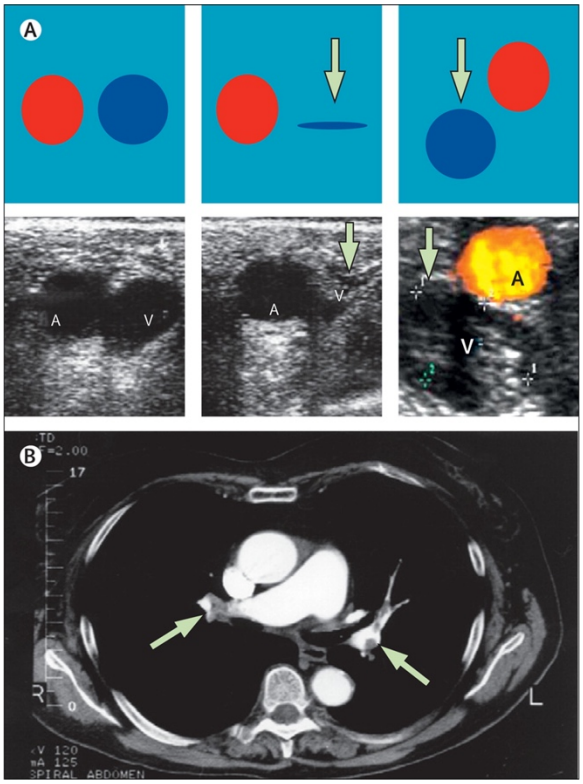


Figure 3 Diagnostic imaging for venous thromboembolism. A: Upper series demonstrate the configuration of the veins in a patient undergoing CUS with the corresponding ultrasound image below. From left to right: The arterial and venous femoral blood vessels are depicted without compression from the transducer in the first image, the second image demonstrates total compressibility of the femoral vein in the absence of DVT. The third image illustrates increased diameter/lumen, incompressibility and no blood-flow in the presence of an occlusive DVT. Picture B shows a central PE in the right pulmonary artery and a segmental PE in a branch from the left pulmonary artery. A= Artery, V=Vein. From S.Z. Goldhaber, H. Bounameaux, Pulmonary embolism and deep vein thrombosis, Lancet. 379 (2012) 1835–1846.[13] Reprinted with permission from Elsevier.

Compression ultrasound scan (CUS) can be supplied with modalities such as color flow and power Doppler imaging, in order to increase sensitivity.[17] The sensitivity in asymptomatic cohorts is reported to be 66.7 % for proximal DVT, while only 39 % for distal DVT.[10] Computed Tomography Pulmonary Angiography (CTPA) has become the first-line imaging modality for confirmation of suspected PE, as it has a

high diagnostic accuracy and is widely available. The disadvantages of CTPA are the exposure to iodized radiation and infusion of contrast medium, which can be contraindicated in case of renal impairment.[9,12] Improvement of imaging techniques has resulted in the detection of smaller pulmonary emboli with potentially no clinical relevance.[18–20] Clinical surveillance is recommended instead of anticoagulant treatment in low-risk patients with sub segmental PE, in the absence of proximal DVT by CUS screening.[21]

The clinical significance of isolated distal DVT has been subject to discussion, since this condition reports lower morbidity and mortality compared to proximal DVT, while also having a lower recurrence rate.[22] For these patients, clinical surveillance is recommended over anticoagulant treatment, to control for proximal extension in case of isolated distal DVT in low-risk patients.[21]

Before initiating antithrombotic treatment, it should be considered if the VTE is unprovoked or provoked by a transient or permanent risk factor, since this should guide clinicians in choice of drug and treatment duration.[5] The American College of Chest Physicians (ACCP) Antithrombotic guidelines provide definite recommendations for VTE treatment, regarding anticoagulant drugs and duration, in non-cancer patients.[21] Non-vitamin K oral anticoagulants (NOACs) are safe and efficient for long-term VTE-treatment in non-cancer patients, and are preferred over Vitamin K antagonists (VKA) and low molecular weight heparin (LMWH). Guidance regarding VTE in cancer patients is less clear; In the absence of major risk of bleeding, anticoagulant treatment is recommended as long as cancer is active, but in risk of bleeding, complications could possibly outweigh the benefits. Active, solid cancer is defined as cancer diagnosed within six months of the VTE event, non-curable cancer, active antineoplastic treatment, metastatic or recurrent cancer.[23] LMWH is preferred over VKA as it has proved to be more effective in the prevention of recurrent VTE in patients with active cancer without increasing risk of bleeding complications.[24] Safety and efficacy of NOACs in cancer patients remains uncertain, and routine use is not recommended for treatment of VTE.[25] NOACs might be implemented for thrombosis prophylaxis during non-surgical cancer treatment in high-risk patients, after the CASSINI and AVERT studies proved safety and efficacy for this purpose.[26] Evidence to guide the decision of the optimal duration is not clear, AY Lee suggests a personalized recommendation for every patient, based on current evidence and personal preferences.[27] Discontinuation of anticoagulant treatment after PE could be guided by D-dimer levels, in patients with a low recurrence risk, as suggested by Palareti et al. [28]

1.3. THE RISK OF VENOUS THROMBOEMBOLISM IN THE GYNECOLOGIC PATIENT

Hospitalized patients are generally at increased risk of developing venous thromboembolic complications, described as the most common preventable cause of hospital death.[29] Different factors influencing risk of VTE, can be divided into patient-related (e.g. gender, age, thrombophilia, obesity, smoking), disease-related (e.g. malignancy, inflammatory disease), and treatment-related (e.g. estrogen-containing oral contraceptives or hormone therapy, surgery, chemo- and radiotherapy).[3,30,31] Early studies reporting an incidence of DVT between 15-40 % following major gynecologic surgery, used sensitive diagnostic tools such as venography and radioactive labelled fibrinogen leg-scanning.[32,33] Randomized controlled trials concluded that many of these symptomatic, as well as asymptomatic VTE cases, could be prevented with proper thrombosis prophylaxis.[34,35] Recent observational studies based on data from clinical databases report incidences of symptomatic VTE between 0.1-2.2 % after gynecologic surgery for benign conditions and cancer.[36–39] Surgical technique has been reported to be associated with risk of VTE, with the highest incidence in open abdominal- and pelvic surgery and lowest incidence in minimally invasive surgery (laparoscopic or vaginal approach). A large cohort study from gastrointestinal surgery with 138,595 patients treated for benign conditions found a higher risk of VTE in open surgery (0.59 % VTE cases) compared to laparoscopy (0.28 % VTEs) with Odds ratio (OR) at 1.8 (95 % CI, 1.3-2.5).[40] One reason that minimally invasive surgery (MIS) minimizes the risk of VTE might be early mobilization and ambulation of patients, which is suggested to play an important role in the prevention of VTE.[41]

1.4. CANCER PATIENTS AND RISK OF VTE

Approximately 20% of incidental venous thromboembolic events are cancer related.[9] The impact of VTE on survival was demonstrated by Sørensen et al in a Danish cohort study showing overall 1-year survival rates of 12 % in cancer patients diagnosed within a year of a VTE event, compared to a survival rate of 36 % in matched cancer patients without VTE.[42] Some cancer types carry a higher risk than others, these being tumors of the pancreas, ovary, brain and bone.[43] The effect of advanced stage on VTE risk also differs within different cancer types, most evident in uterine cancer. [43,44] Another important factor associated with risk of VTE is time since cancer diagnosis, with the highest incidence observed within the first few months, possibly associated to the aggressiveness of tumor biology and initiation of cancer treatment.[45] In pancreatic cancer, Larsen et al. found that 9 % of patients had VTE upon first

admission to hospital in a prospective cohort study with systematic examination for both symptomatic and asymptomatic VTE.[46] Using the same setup, Stender et al. observed 8 % preoperative VTE events in patients with colorectal cancer.[47] The 30-day incidence of VTE following cancer surgery varies from 0.3 % after breast resection to 7.3 % after oesophagectomy.[48] Patients undergoing chemotherapy are at increased risk of VTE[43], but evidence to support VTE prophylaxis in the outpatient setting is scarce. [49,50] There are divergent reports on the risk of VTE in relation to treatment with vascular endothelial growth factor(VEGF)-inhibitor, but a systematic review concluded that risk of arterial, but not venous thrombosis, was increased in patients exposed to this therapy.[51] Central vein catheters induce endothelial damage and inflammation, which can lead to deep vein thrombosis at the catheter site. This is a common complication in patients undergoing chemotherapy, especially in patients with peripherally inserted central catheters or prior history of VTE.[52]

1.5. ENDOMETRIAL CANCER

With almost 100.000 new cases per year in Europe, endometrial cancer is the most common gynecological cancer in developed countries, with approximately 800 new cases in Denmark annually.[53,54] Endometrial cancer primarily occurs in postmenopausal women, with a median age of 63 years at diagnosis. The initial symptoms are abnormal bleeding or spotting. The primary risk factor is estrogen exposure associated with early menarche, late-onset menopause, nulliparity, obesity, diabetes, polycystic ovary syndrome, radiation therapy and tamoxifen use.[55,56] Patients with a germline mutation in DNA mismatch repair genes (Lynch Syndrome) have an up to 60 % life-time risk of developing endometrial cancer.[57] Endometrial carcinomas have been classified according to histopathology and molecular biology. Most tumors (80-90 %) are classified as type I endometrioid estrogen-dependent adenocarcinomas with a favorable prognosis compared to type II tumors comprising non-endometrioid carcinomas (e.g. serous, clear cell, undifferentiated).[53] Genetic mutations are diversely distributed within the two tumor types and molecular insight could potentially influence future treatment guidelines and provide targeted medical development opportunities.[57,58] Most endometrial carcinomas are diagnosed in early stage (80 % in International Federation of Gynecology and Obstetrics (FIGO) stage I) in which the five-year survival is more than 95 %, in advanced disease survival rates are much lower[53]. Primary treatment is surgical removal of the uterus, salpinges and ovaries which can be performed as either open surgery (laparotomy) or MIS, by vaginal or laparoscopic (conventional or robotic) access. The indication for more extensive surgery including e.g. lymphadenectomy, is guided by stage of disease and a preoperative pathological examination of an endometrial biopsy. Lymph node dissection (LND) is not indicated in case of endometrioid histotype, differential grade 1 and 2 and myometrial invasion <50 %.[53]

In two large cohort studies with up to 24 months of follow-up, risk of VTE in endometrial cancer was correlated to advanced disease, non-endometrioid histopathology, and endometrioid grade 3 carcinomas.[59,60] Publications on the 30-day postoperative risk of VTE, report a low VTE incidence between 0.35-1.3 %, with the lowest risk in patients undergoing MIS.[39,61–63] Given the low VTE incidence following surgery, it has been proposed that four weeks of extended VTE prophylaxis, as recommended by clinical guidelines, is not required for this group of low-risk patients.[35,64–66]

1.6. OVARIAN CANCER; EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT

In 2012, 65.538 women were diagnosed with ovarian cancer in Europe, with the highest incidences in northern Europe.[67] Approximately 550 Danish women are diagnosed with ovarian cancer every year.[68] Patients are typical elderly and postmenopausal with a median age of 63 years.[69]

Non-epithelial ovarian cancer constitutes approximately 10 % of ovarian cancers. These include germ cell-, sex cord stromal and pure stromal tumors, that are further categorized into histopathological subtypes. Non-epithelial tumors are rare, and managed differently from epithelial ovarian cancer (EOC), and will not be discussed in further detail in this thesis.[70] EOC are classified as high-grade serous (~70 %), endometrioid (~10 %), clear cell carcinoma (~5 %), low-grade serous (~5 %) mucinous (~3 %), Brenner and undifferentiated carcinomas (Figure 5).[71,72] Histopathological distribution varies between countries, and the proportion of clear cell carcinomas accounts for 24 % of EOC in Japan.[73] Borderline tumors are tumors of low-malignant potential, managed surgically with a low recurrence rate. In recent years, it has been commonly recognized that tumor classification has important implications on prognosis and treatment. Therefore, it is crucial that histopathological examination is carried out by experts in the field of gynecopathology.[74,75]

Etiology of the cancer is unknown in most patients, germline mutations (in e.g. BRCA or mismatch repair genes) are present in 3-24 %.[76] Other risk factors are endometriosis and obesity.[77] Tubal ligation and factors decreasing ovulations such as pregnancies, breastfeeding and hormonal contraceptives, reduce the risk of EOC.[78]

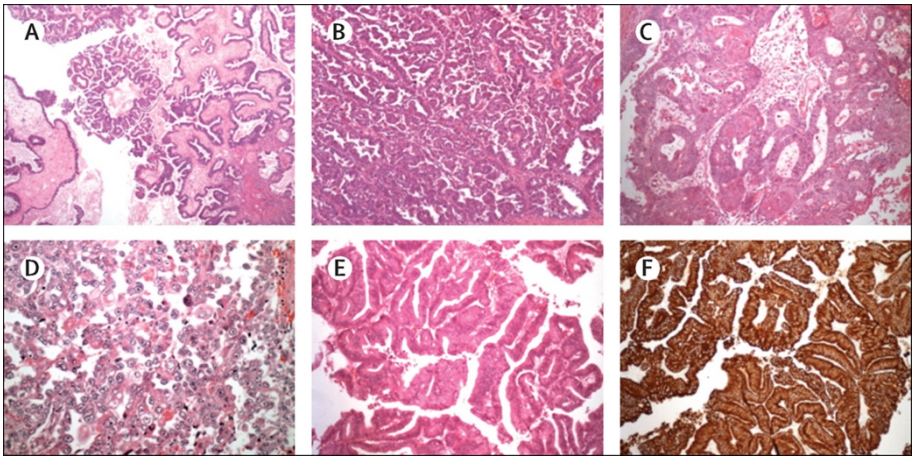


Figure 4 Microscopic images of the major EOC histotypes: A) Serous borderline, B) High-grade serous carcinoma, C) Endometriod carcinoma, D) Clear cell carcinoma, E) Mucinous carcinoma, F) Mucinous carcinoma, cytokeratin 7 staining. From G.C. Jayson et al. Ovarian Cancer, Lancet. 384 (2014) 1376–1388.[78] Reprinted with permission from Elsevier.

Symptoms in early stage ovarian cancer are often vague, which might explain that most ovarian cancers are diagnosed in advanced stage. Recognized symptoms at all stages include abdominal or pelvic pain, vaginal bleeding, affected intestinal function, polyuria, abdominal distention, fatigue and DVT.[69]

Patients with suspected ovarian cancer undergo gynecologic examination including a transvaginal ultrasound scan. Risk of malignancy index (RMI) is calculated based on the ultra-sonographic findings, menopausal status and CA-125 level measured in a blood sample (illustrated in Figure 5). The most commonly recognized RMI was developed by Jacobs et al.[79] With a cut-off at 200, the accuracy of RMI in correctly diagnosing EOC was previously validated with a 71 % sensitivity, 92% specificity and a positive predictive value of 69 % and negative predictive value at 92 % in women> 30 years of age, referred with a pelvic mass.[80] A slightly different RMI was proposed by Tingulstad et al. with a 80 % sensitivity and 92 % specificity.[81]

Ultrasound criteria (U score)		Menopausal status (M score)	
Multilokular cyst	1	Premenopausal or prior hysterectomy and age < 50 years	1
Solid areas	1		
Bilateral lesions	1	Postmenopausal or prior hysterectomy and age ≥ 50 years	3 or 4*
Ascites	1		
Intraabdominal metastases	1		

Total U-score; 0-1: U=1, 2-5: U=3 or 4*

Formula RMI=U x M x s-CA-125
Interpretation: RMI < 200: Most likely benign ovarian tumor. RMI ≥ 200: Suspected ovarian cancer
*Jacobs et al.[79] proposed U and M score at 1 or 3, whereas Tingulstad et al.[81] described U and M score at 1 or 4.

Figure 5 Risk of malignancy index (RMI) score

In order to stage the tumor, Computed Tomography (CT), Positron Emission Tomography (PET) or magnetic resonance (MR) imaging is performed preoperatively in most patients, but is not mandatory.[82] An example of a ^{18}F-labeled Fluoro-2-deoxyglucose (^{18}F-FDG) PET-CT scan in a patient with FIGO stage IV disease is depicted in figure 6.

Figure 6 Whole body PET-CT scan; Illustrating ^{18}F-FDG-uptake throughout the abdominal cavity consistent with advanced epithelial ovarian cancer.

The primary treatment of EOC is surgical resection of all visual tumor tissue. In case of advanced disease, neoadjuvant chemotherapy (NACT) followed by secondary debulking surgery is optional. This treatment algorithm is supported by recent publications with long term follow-up data that demonstrated non-inferiority to upfront surgery[83]. The primary intention should be complete resection of visual tumor tissue, since clinical trials have demonstrated this to be the most important prognostic factor.[84] Adjuvant chemotherapy with paclitaxel and carboplatin is indicated for the majority of patients except in the earliest stages of low-grade tumors.[82] Based on beneficial effects on overall survival in poor-prognosis patients, the angiogenesis inhibitor bevacizumab is added in cases of incomplete resection of tumor tissue in patients with FIGO stages III/IV.[85] A recently published clinical trial, demonstrated an increase in progression free survival in EOC patients, treated with a Poly ADP Ribose Polymerase (PARP)-inhibitor. Maintenance therapy after concluding chemotherapy, is recommended in patients with FIGO stage III/IV high-grade serous/endometrioid EOC with BRCA mutations, and complete/partial response to platinum-based chemotherapy.[86]

Recurrence in EOC patients usually occurs within the first three years after diagnosis and the overall five-year survival was 41% in Denmark in the period from 2012-2016.[68]

1.7. OVARIAN CANCER AND RISK OF VTE

A large number of studies have investigated a proposed procoagulant state that causes changes in the constituents of the blood in ovarian cancer patients, and thereby increase the risk of VTE[87–90] There is a great variation in the reported incidence of VTE, which in part can be explained by the study designs. Observational studies obviously report lower incidences than prospective clinical trials that use sensitive imaging tools to examine for the presence of both symptomatic and asymptomatic events. Rodriguez et al investigated VTE incidence in a cohort of 13,031 ovarian cancer patients (borderline tumors, epithelial and stromal cancers) based on retrospective data retrieved from the California Cancer Registry from 1993-99.[91] The two-year cumulative incidence of VTE was 5.2 %. Risk factors included disease stage, histopathology and degree of comorbidity. Thirty percent of cases were observed during the 90-day postoperative period, but the multivariate analysis showed that patients who did not undergo surgery were at higher risk, indicating that tumor burden is of great importance. VTE incidence at time of diagnosis was reported to be 3.3 % in a German study by von Tempelhoff et al using impedance plethysmography for DVT screening[92], whereas Satoh et al found 25 % VTE cases in a Japanese cohort using CUS.[93] Both studies included EOC and borderline tumors. Ovarian cancer diagnosed in near relation to a VTE episode is associated with a poorer prognosis compared to patients with no VTEs.[94,95] In one study, neoadjuvant chemotherapy was associated with a 11.6 % VTE incidence during treatment period.[96] Pant et al. observed a 12.5 % VTE incidence in a retrospective cohort of 128 EOC patients undergoing first-line chemotherapy after surgery. There was a great variation in treatment regimens according to chemotherapy, making comparison to other studies difficult.[97]

Coagulation markers are often elevated in cancer patients without VTE, indicating that the coagulation system is activated even in the absence of a detectable thrombus.[98] Cancer cells are capable of activating the coagulation system in different ways including expression of tissue factor, and shedding of procoagulant factors into the blood stream (Figure 7).[99] Swier et al. reviewed the literature regarding the association between ovarian cancer and VTE, and addressed several mechanisms of the coagulation components involved in VTE occurrence and cancer progression, including possible biomarkers.[100] Tissue factor is assumed to play a central role in the pathogenesis behind the hypercoagulant state observed in ovarian cancer patients. VTE risk varies between different histopathologic subtypes of EOC with the highest incidence observed in clear cell carcinomas even in early FIGO stage.[101] Elevated interleukin-6, increased expression of tissue factor, and shedding of tissue factor

bearing microparticles has been observed in clear cell carcinomas and are considered to play a role in the increased coagulant activity.[102–104]

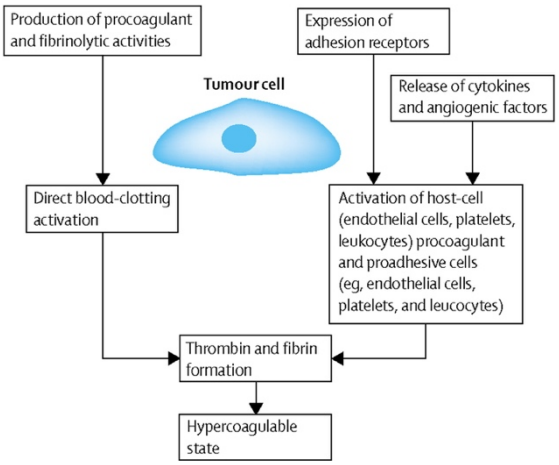


Figure 7 Different ways tumor cells induce a hypercoagulant state. From Prandoni et al. Cancer and venous thromboembolism, Lancet Oncol. 6 (2005) 401-410.[98] Reprinted with permission from Elsevier.

1.8. BIOMARKERS FOR VTE PREDICTION

D-dimer is the only biomarker that is routinely used in clinical practice to assess the probability of VTE in symptomatic patients. There are several commercially available assays that by different techniques localize different epitopes at the D-dimer molecule, and the threshold indicating an elevated level vary, making comparison of studies difficult.[105,106] Performance of the test can be influenced by different factors and Schaefer et al. proposed that D-dimer might not be appropriate in certain patient groups, including cancer.[107] A broad panel of other biomarkers are subject to investigation as predictors of VTE. One of the more promising biomarkers to predict VTE is P-selectin, a molecule that mediates platelet adhesion to the endothelium and induces tissue factor expression on the surface of monocytes.[8,108] Cancer cells increase the expression of P-selectin on certain cells including endothelial cells. This enhances interaction with neoplastic cells, thought to play an important role in the metastatic spreading of cancer cells.[109]

Different laboratory tests have been investigated by Ay et al. in the Vienna Cancer and thrombosis study, with the aim of improving risk stratification in cancer patients.[110] Soluble p-selectin and thrombin-generation are suggested as promising predictors of cancer-associated thrombosis.[109,111]

HYPOTHESES AND AIMS

Early studies have indicated an association between major pelvic surgery and significant venous thromboembolic complications. Hysterectomy is a common procedure in gynecology and is performed for a variety of conditions. However, only few studies have focused on the risk of a VTE event following hysterectomy indicated for benign disease.

Paper I: To investigate the 30-day risk of VTE in a large population based cohort of women undergoing abdominal, laparoscopic and vaginal hysterectomy for benign conditions.

Endometrial cancer is the most common gynecologic cancer in developed countries with the majority of cases diagnosed in early stages for whom the prognosis is good after treatment with hysterectomy. Clinical guidelines on thrombosis prophylaxis in gynecologic oncology surgery have recently implied recommendations to extend prophylaxis for all patients for four weeks following major surgery. The null-hypothesis of study 2 was a similar risk of VTE between patients undergoing hysterectomy for endometrial cancer, compared to benign disease.

Paper II: To determine the incidence of postoperative VTE in endometrial cancer patients compared to patients undergoing hysterectomy for benign disease.

Ovarian cancer is among the cancers with the highest risk of venous thromboembolic complications. Many studies have investigated the incidence of VTE in ovarian cancer and the impact of person-, tumor- and treatment related risk factors. However, no study has focused on exact timing of VTE episodes associated to both person-, tumor- and treatment related risk factors.

Paper III: To determine at which time epithelial ovarian cancer patients are at highest risk of developing venous thromboembolic events.

The incidence of VTE has primarily been studied in retrospective cohorts. A few prospective cohorts, mostly from Japan, report high VTE incidences in ovarian cancer even prior to surgery. We hypothesized that the main proportion of VTEs would be present at time of first referral for ovarian cancer as asymptomatic events, that could become symptomatic after surgery.

Paper IV: To examine the incidence of symptomatic and asymptomatic venous thromboembolism in patients with suspected epithelial ovarian cancer from time of diagnosis and throughout the first year, in a prospective, consecutive cohort study.

METHODS

3.1. REGISTERS USED IN STUDY I-III

CPR: The Danish Civil Personal Registration System; Every Danish resident is provided a unique personal civil registration number (CPR-number) at time of birth or immigration. The CPR-number is used at all contacts with the health care system, which enables linkage of different Danish registers.[112]

DNPR: The Danish National Patient Registry covers all hospitalizations in Denmark since 1977 and outpatient visits since 1995.[113] Accessible information includes dates of admission and discharge. Coding of disease follows ICD-8 (international Statistical Classification of Diseases, eighth revision) until 1994, where it was replaced by the tenth revision (ICD-10). Surgical treatment is registered according to the Nordic Medico-statistical Committee's Classification of Surgical Procedures.[114] In 2001, it became mandatory to report many medical treatments including cancer treatment. The validity of the coding of chemotherapy and bevacizumab was previously validated in colorectal cancer with an overall high sensitivity (94-100 %, specificity: 88-100 %).[115]

DGCD: The Danish Gynecologic Cancer Database was established in 2005 and contains information on all patients diagnosed with any type of gynecologic cancer at Danish hospitals. Data is entered prospectively and contains information on patient demographics, surgical treatment, final cancer stage and histopathology. Compulsory data entering is published in annual reports after audit by the engaged hospitals. The coverage rate compared to patients registered in the Danish National Patient Register is reported to be 97 % in most years since initiation of the DGCD.[116] A validation study regarding endometrial cancer reported 97.3 % completeness for the coverage of pathological and surgical variables.[117] Completeness of data concerning epithelial ovarian cancer was 94.2 % in a validation study covering the first two years after the database was established.[118]

DAD: The Danish Anesthesia Database was established in 2004 and comprises information obtained in relation to surgical procedures such as body mass index (BMI), American Society of Anesthesiologists (ASA) score and smoking status. DAD has not covered all departments throughout the period since 2004, which reduces the utility in nationwide studies. The database was used in study I for analysis in a sub cohort.

The Population Statistics Register: Contains information on vital and civil status, and migration in and out of Denmark since 1971. Data is retrieved from the Danish Civil Registration System.

The Register of Causes of Death: Contains information on time, age, cause, manner and place of death of Danish citizens since 1970. Data is based on death certificates completed by physicians. Such certificates, stating the underlying cause of death are mandatory for all deceased Danish residents.[119]

The Danish Cancer Register: Has since 1942 collected information on newly diagnosed cancer cases from clinical and pathology departments in Denmark.[120] Cases are coded with cancer type and staging level according to the TNM classification of tumors.

The Danish National Prescription Registry: Is a subset register under the Danish Register of Medicinal Products, where data on all prescription-based medicine claimed at Danish Pharmacies since 1994 is registered. Data contains CPR number, Anatomical Therapeutic Chemical (ATC) classification, total prescription dosage and date of dispensing.[121,122]

The Danish Pathology Register: Established in 1997**.** Holds information on histopathological diagnoses obtained from pathologic examination of cell and tissue samples, including date and type of sampling procedure.[123] Pathologic-anatomical diagnoses follow SNOMED pathology.[124]

3.2. STUDY POPULATIONS

Study I is based on data retrieved from the DNPR and linked with other national registers. Study II-III are primarily based on data from the DGCD. Linkage of different registers using encrypted CPR numbers provided us with unique datasets with various variables allowing us to study the causal relationships between gynecologic cancers and VTE. Study IV is based on a local prospectively included cohort of patients with suspected ovarian cancer, referred to the Department of Gynecology and Obstetrics at Aalborg University Hospital for diagnosis and treatment.

3.2.1. LOCAL COHORT FROM AALBORG UNIVERSITY HOSPITAL (STUDY IV)

Patients referred to the Department of Gynecology and Obstetrics at Aalborg University Hospital in the period from Dec 2014 - May 2017 were evaluated for inclusion in the clinical trial. Inclusion criteria were suspected ovarian cancer

(pathologic pelvic mass and RMI ≥200 calculated with the formula suggested by Tingulstad et al.[81]) and written informed consent. Exclusion criteria were connective tissue disease, previous (within three years) or concomitant cancer, and current treatment with anticoagulant medicine. Baseline data was obtained by the gynecologic oncologist at time of first referral. Patients underwent systematic VTE examination within a few days after their first visit in the outpatient clinic. Patients were routinely examined with a ^{18}F-FDG PET-CT for diagnostic and preoperative evaluation. CT of the thorax was performed in arterial phase ensuring state of the art diagnosis of possible pulmonary embolisms. Objective examinations for DVT with CUS were performed at time of diagnosis, on day 1 or 2 after surgery and repeated 1, 6 and 12 months after inclusion. Extra CUS and/or CTPA was performed if indicated by symptoms, and/or elevated D-dimer levels.

Per-operative frozen section was undertaken by expert gyneco-pathologists for initial diagnosis. Fractions of fresh frozen as well as paraffin embedded tumor tissue were collected and stored in the DCB and reserved for later analysis of protein profiling of different histotypes and a possible link to risk of VTE risk.

Blood samples were collected at time of diagnosis, 1-2 days postoperatively, and after 1,3,6 and 12 months. Cubital venipuncture followed European Concerted Action on Thrombosis (ECAT) procedures.[125] Routine blood analyses were performed on the day of attendance (infection parameters, hematology, liver-enzymes, CA-125 and coagulation markers). D-dimer analysis was carried out with the BCS XP system from Siemens using the MediRox reagent (D-dimer cut-off level used was 0.3 mg/l). Whole blood was distributed in 2 mL EDTA plasma, 4 mL EDTA whole blood, 2 mL serum and 10 mL citrate plasma. Blood samples for storage in the DCB were centrifuged at 2500 x g for 15 minutes before the supernatant was transferred to another tube followed by a second centrifugation, and the supernatant was transferred to micro tubes and frozen immediately at -80°C.

For comparison, data on patients referred to the department in the same period, but not included in the study, was retrieved from the patient files with approval from the local ethics committee. The two cohorts are referred to as participants and non-participants in the clinical trial.

3.2.2. SOURCES OF INFORMATION IN STUDY I-III

Benign indications for hysterectomy by ICD-10 codes: Uterine myomas (D25), Abnormal uterine bleeding (N92), pelvic organ prolapse (N81), endometriosis (N80), benign ovarian neoplasm (D27), pelvic pain (N94, R10), endometrial hyperplasia

(N850), urinary incontinence (R329), cancer predisposition (Z815, Z803), cervical intraepithelial neoplasia (N87) if coded at discharge following hysterectomy.

Comorbidities by ICD-10 codes: Ischemic heart disease (I20, I23-25), cerebrovascular disease (I60-69), history of acute myocardial infarction (I21), thrombophilia(D68), varicose disease(I83), heart failure (I50), chronic obstructive lung disease (J44), diabetes (E10-14) if registered at discharge within 365 days before hysterectomy.

Cancer diagnosis by ICD-10 codes: Cancer diagnosis (C00-96) were retrieved in order to exclude cancer patients. For validation and date of diagnosis in ovarian cancer (C48, C56-57) and cancer corpus uteri (C54-55).

Cancer stage: Data was primarily retrieved from the DGCD, endometrial cancer stage followed the FIGO-2009, whereas ovarian cancer was coded according to FIGO-2014[126,127]. In case of missing data in the DGCD, data on TNM stage was collected from the Cancer register and translated into FIGO stage (algorithm provided in appendix).

Histopathology and differential grade: Retrieved from the Pathology Register in case of missing data in DGCD.

Medicine by ATC codes: Use of specific pharmacotherapeutics within 180 days before surgery was based on at least one prescription of: Estrogen containing oral contraceptives (G03A, G03CB), hormone therapy with estrogen, oral and transdermal but not vagitories, (G03F, G03CX, G03CA, G03CB), antiplatelet drugs (B01AC), anticoagulating drugs (B01 except B01AC), glucose-lowering agents (A10).

Postoperative LMWH: DNPR registration (BOHA03C).

Surgery based on NOMESCO classification: Abdominal hysterectomy (KLCD00, KLCD96, KLCC10), laparoscopic hysterectomy (KLCD01, KLCD04, KLCC11, KLCD11, KLCD97, robotic-assisted +KZXX0), vaginal hysterectomy (KLCD10, KLCC20), radical hysterectomies (KLCD30, KLCD31, KLCD40), laparotomy (KJAH00), laparotomy with biopsies (KJAA10), lymphadenectomy (KPJD), extensive peritoneal exenteration (KJAQ00).

Chemotherapy and VEGF-inhibitor registered in DNPR: Basic chemotherapy (BWHA1), BWHA (complex chemotherapy), VEGF-inhibitor (BOHJ19B).

BMI by ICD-10 code or registered in a database: Overweight/obesity (DE660).

Outcome by ICD-10 code: PE (I26), DVT (I80.1-I80.9) were registered as an event in study I and II if registered in the 30-day period following hysterectomy and in study

III if VTE occurred after EOC diagnosis. VTE episodes occurring before these dates were registered as previous VTEs.

3.3. POTENTIAL CONFOUNDING

An open-source software DAGitty, was used to visualize the causal assumptions and identify confounders that should be controlled for.[128] The use of Directed Acyclic Graphs (DAGs) in epidemiologic research was introduced by Greenland et al. as a tool for visualization of causal assumptions.[129] This can serve as a help to identify possible confounders present in observational studies as no test exists that can determine if a variable is a confounder. Three criteria should be fulfilled; The variable should be 1) a risk factor for the outcome of interest, 2) associated with the main exposure, 3) not on the causal pathway between main exposure and outcome.[130] Examples of simple DAGs are depicted in figure 8 and 9. Arrows indicate causal pathways between different factors, arrows and their directions are based on existing knowledge, interpretation and beliefs of the researcher.[131] No factors can be self-causal; thus, closed loops cannot be formed. A backdoor path is formed when an arrow head points from a confounder to exposure and from confounder to outcome. A backdoor path should be closed by controlling for the confounder, in DAG terminology "conditioning" on the confounder.[132] A collider is a common effect indicated by two arrowheads pointing from outcome and exposure to the collider, this blocks the path. Conditioning on a collider opens the backdoor path and introduces selection bias.[133] All other paths than the directed path between exposure and outcome should be blocked to avoid confounding. It should be kept in mind that a DAG is subject to the personal assumption of the researcher, but still a useful tool for identification of confounders to control for.

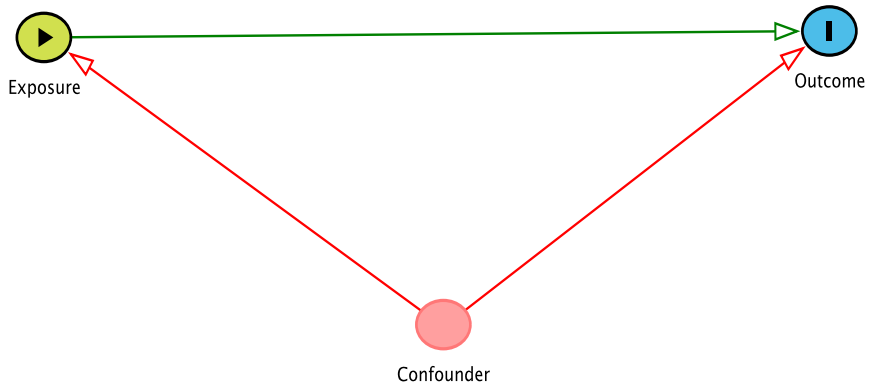


Figure 8 DAG example 1: Main exposure of interest is illustrated by the green circle, the green arrow represents the causal relations we want to investigate between exposure and outcome (blue circle). The red arrows illustrate a backdoor pathway that we need to block to avoid confounding, this means we have to adjust for the confounder (red circle) in our analysis.

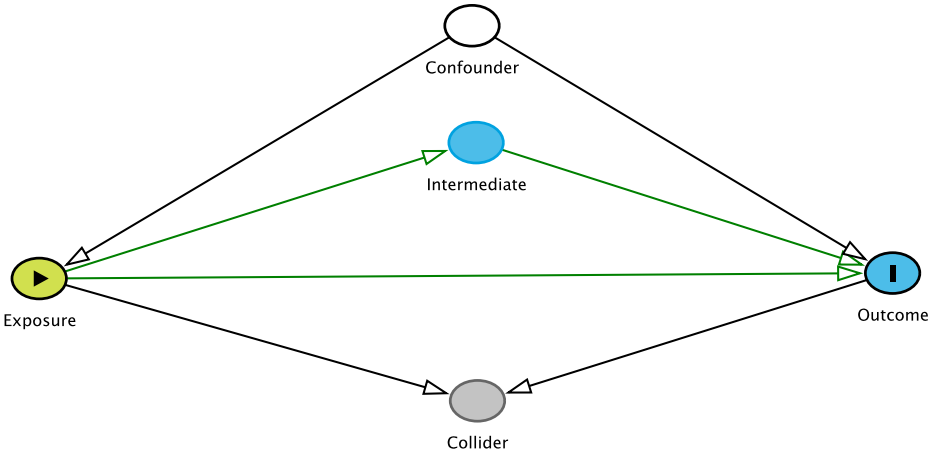


Figure 9 DAG example 2: Illustrating two causal path ways (green arrows) from exposure to outcome with an intermediate variable on one of them, this pathway should be kept open as conditioning on the intermediate would introduce over adjustment bias. The confounder is already adjusted for, indicated by the white circle and black arrows. The grey circle represents a collider on a blocked pathway (black arrows pointing in the direction of the collider), conditioning on the collider would open this pathway, thus introducing selection bias.

3.4. STROBE

Publication of the results from the four studies included in the PhD thesis adhered to the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[134]

3.5. STATISTICS

Data management in study I-III was carried out using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). Calculations were performed using R version 3.4.0 (R Core Team, 2017).[135] Stata version 13 was used in study IV. Estimates in regression analysis were presented with 95 % confidence intervals. P-values ≤ 0.05 were considered statistically significant. The Aalen-Johansen estimator was used to depict the cumulative incidence of VTE considering death as competing risk.

STUDY I

Patients entered the study at the date of hysterectomy for benign disease and were followed for 30 days after surgery or until VTE event or death occurred. The cumulative incidence of VTE according to open, laparoscopic and vaginal hysterectomy was calculated considering the competing risk of death. Cox proportional hazard regression was used for univariable and multivariable analysis. The proportionality assumption was examined using plots of Schoenfeld residuals. Interaction between the presence of fibromyomas and approach to hysterectomy was tested using analysis of variance. Linearity between the outcome and the continuous variable age was tested.

STUDY II

Patients were followed from the date of hysterectomy for endometrial cancer or benign disease until time of VTE event, death or 30 days after surgery. Cumulative incidence of the competing risks of VTE and death was calculated and depicted in the four exposure groups: Open hysterectomy for cancer, MIS for cancer, open hysterectomy for benign disease and MIS for benign disease. Descriptive statistics were carried out using analysis of variance for continuous variables and the chi-squared test for categorical variables. Odds ratios of VTE were estimated using a multivariable logistic regression model. The adjusted model included assumed confounders primarily assessed by a directed acyclic graph and afterwards analyzed in a univariable model.

STUDY III

Patients were followed from the date of ovarian cancer diagnosis until VTE, death, emigration or end of follow-up (Dec 31st, 2018). Person-time at risk was calculated and baseline characteristics were expressed as person years, crude numbers and percentages. The 2-year incidence rate of VTE was estimated using Poisson regression analysis and presented as events per 1000 person years.

Age and treatment for ovarian cancer were considered as time-varying exposures in time-to-event analyses. The impact of patient-, tumor-, and treatment related exposure on the risk of VTE was analyzed in a Cox proportional hazard regression model. The proportionality assumption was examined using plots of Schoenfeld residuals.

STUDY IV

When planning the study, we calculated a sample size to ensure statistical significance. Based on a previous study in the Northern Jutland Region, we assumed that 1/3 of patients with suspected ovarian cancer based on RMI score ≥ 200, would be diagnosed with a benign tumor.[136] Two Japanese studies using CUS for preoperative DVT screening found 3.5 % VTE cases in patients with benign ovarian tumors and 25 % VTE cases in EOC and borderline patients respectively.[13793] Considering the high prevalence of clear cell carcinomas in the Japanese cohort, our null hypothesis was 3.5 % VTE events in patients with benign ovarian tumors vs. 20 % VTE events in patients with EOC and borderline tumors. We used Fisher's exact test to calculate the sample size with a power of 0.80 and a two-sided significance level at 0.05 and concluded that we should include at least 47 with benign tumors and 94 with malignant tumors. Inclusion was discontinued after a 2.5-year long inclusion period, at which point 97 patients had entered the study. The reason for discontinuation was primarily that the Department of Nuclear Medicine replaced their PET-CT equipment and would not be able to run the CTPA protocol for several months. Furthermore, interim results revealed that recruitment was slow and VTE incidence much lower than expected, indicating that we would need a much longer inclusion period and a larger cohort to achieve statistical power.

Differences within the EOC cohort was tested using Fisher's exact test for discrete variables and Wilcoxon rank sum for numerical variables. Cumulative incidence was graphical depicted for the competing risks of VTE and death.

3.6. ETHICS

Study I-III were carried out using encrypted personal data in the research environment of Statistics Denmark, permission from the ethics committee is not required for this type of study.

The Danish Data Protection Agency approved study I with the reference (Re: 2007-58-0015, int.ref: GEH-2010-001) and study II and III with the reference (Re: 2008-58-0028, internal reference: 2015-125).

The local Committee on Health Research Ethics, Northern Jutland Region (re: N-20140009) and The Danish Data Protection Agency (re: 2008-58-0028) approved Study IV which was also registered at ClinicalTrials.gov (identifier: NCT02480790).

RESULTS

STUDY I

A total cohort of 89,931 women undergoing hysterectomy for a benign disease in the period Jan 1st 1996 to Dec 31st 2015 were included in the study.[138] Three different exposure groups were examined with regards to route of hysterectomy: Open (n=59,231), laparoscopic (n=9,198), and vaginal (n=21,502). There was an increasing tendency to perform MIS in favor of open hysterectomy during the study period. Venous thromboembolic complications in the 30-day postoperative period were rare, with an overall incidence at 0.19 %. Lowest was with a vaginal approach (0.10 %) vs. 0.13 % with laparoscopy and 0.24 % with open hysterectomy. When adjusting for assumed confounders in a multivariable Cox regression model, the risk of VTE was significantly lower in laparoscopic (HR=0.51; 95 % CI, 0.28-0.92, p=0.03) and vaginal (HR=0.39; 95 % CI, 0.24-0.63, p<0.001) compared to open hysterectomy. A sub-cohort of patients undergoing hysterectomy after 2003 was investigated to estimate the effect of LMWH thrombosis prophylaxis which was introduced in the national guideline for hysterectomy, published by the Danish National Board of Health in 2003[139]. The HR of VTE in patients receiving LMWH prophylaxis was 0.63 (95 % CI, 0.42-0.96, p=0.03) compared to non-exposed. Crude and adjusted HRs of VTE in different exposure groups are provided in Table 1.

Table 1 Cox proportional hazards models for venous thromboembolism in different exposure groups.[138]

	VTE events/N total	HR, Crude (95 % CI)	HR, multivariable (95 % CI)
Main exposures			
Abdominal hysterectomy	142/59,231	Reference	Reference
Laparoscopic hysterectomy	12/9,198	0.54(0.30-0.98)	0.51(0.28-0.92)
Vaginal hysterectomy	21/21,502	0.41(0.26-0.64)	0.39(0.24-0.63)
Confounders			
Age (by decade)	175/89,931	1.16(1.02-1.31)	1.06(0.93-1.21)
Benign ovarian tumors	11/5,391	1.05(0.57-1.94)	0.75(0.40-1.40)
Uterine fibroids	76/43,051	0.83(0.62-1.13)	0.82(0.60-1.13)
Hormone therapy	24/12,931	0.95(0.62-1.46)	1.10(0.69-1.74)
Contraceptives	13/6,596	1.01(0.58-1.78)	1.35(0.75-2.40)
Anticoagulant drugs	31/918	21.5(14.6-31.7)	2.22(1.40-3.53)
Previous AMI	6/573	5.7(2.5-12.8)	2.57(1.12-5.94)
Previous VTE	67/1,540	36.7(27.1-49.8)	26.8(18.6-38.7)
Surgery after 2003	105/53,566	1.02(0.75-1.38)	0.93(0.68-1.28)
Postoperative VTE prophylaxis	43/31,391	0.49(0.33-0.72)	0.63(0.42-0.96)

Abbreviations: VTE, venous thromboembolism; AMI, acute myocardial infarction.

STUDY II

A study population consisting of 45,825 patients with benign gynecological disease and 5,513 patients with endometrial cancer undergoing hysterectomy in the study period from Jan 1st 2005 to Dec 31st 2014, were included.[140] The incidence of VTE in four different exposure groups was calculated: Open hysterectomy for endometrial cancer (21/3,377~0.6 %), MIS for endometrial cancer (9/2,136~0.4 %), open hysterectomy for benign disease (52/22,401~0.2 %) and MIS for benign disease (21/23,424~0.1 %). Variables to fit a logistic regression model were selected based on DAGs, as depicted in Figures 10 and 11.

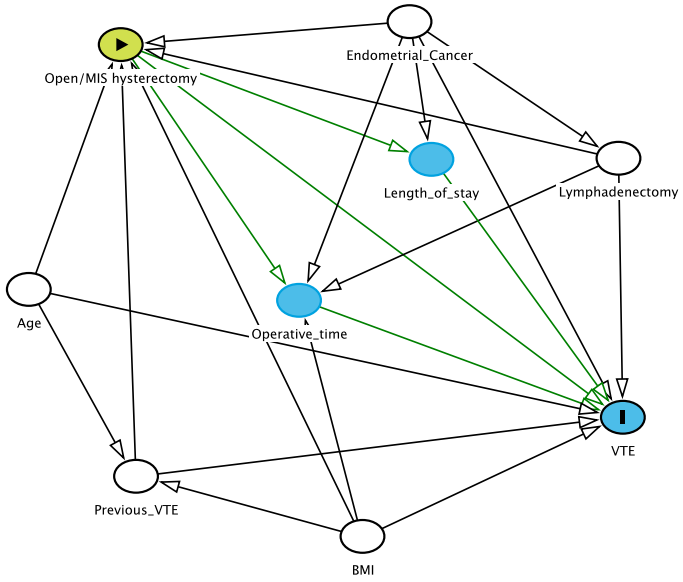


Figure 10 DAG illustrating causal pathways highlighted in green color with operative time and length of hospital stay as intermediate variables. Black arrows illustrate backdoor pathways.

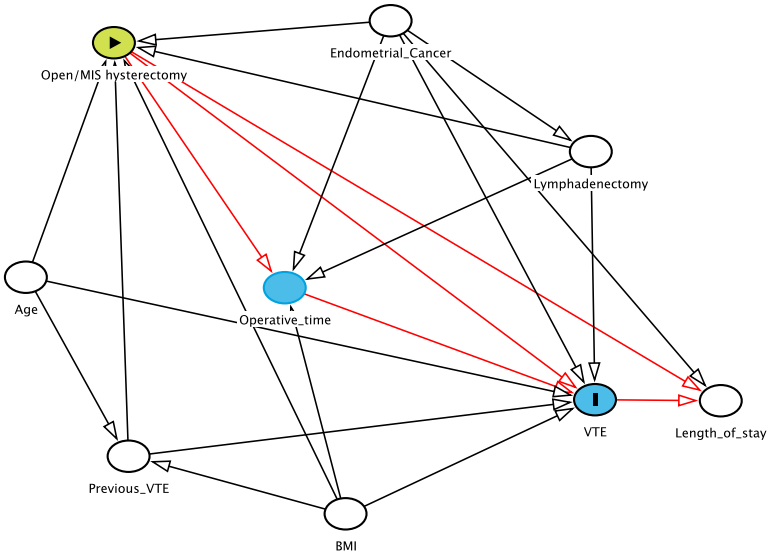


Figure 11 DAG illustrating colliderbias in a situation where length of stay is a collider, thus introducing bias if controlled for.

The adjusted OR of VTE was not significantly higher in endometrial cancer patients compared to patients undergoing hysterectomy for benign disease (1.47; 95 % CI,

0.74-2.91; p=0.27). Independent risk factors associated with 30-day risk of VTE were: open hysterectomy, BMI>40, lymphadenectomy and previous VTE (Fig. 12).

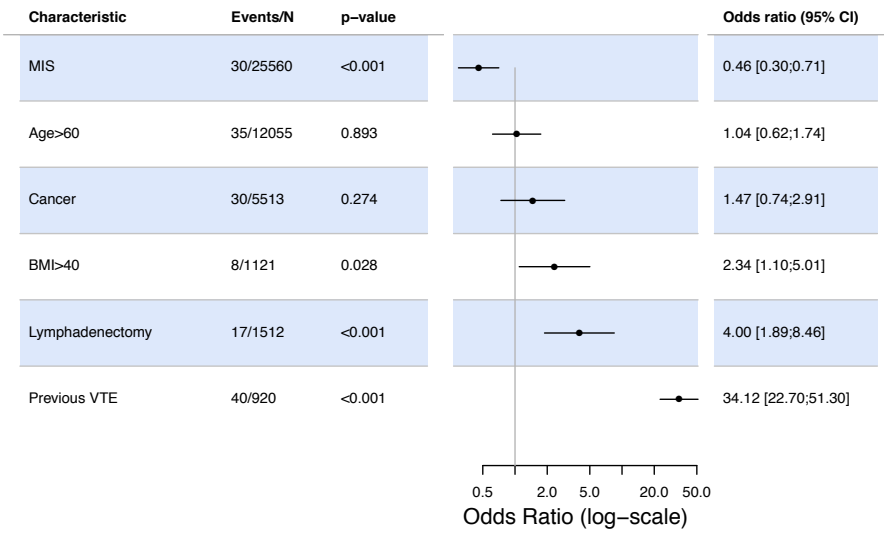


Figure 12 Odds ratios of venous thromboembolism in relation to potential risk factors. Modified from[140]

STUDY III

A cohort of 4,991 patients diagnosed with EOC were included and followed in this trial, collectively contributing with 20,214 person years from time of diagnosis till VTE event, death or right censoring.[141] Patient selection is illustrated in figure 13.

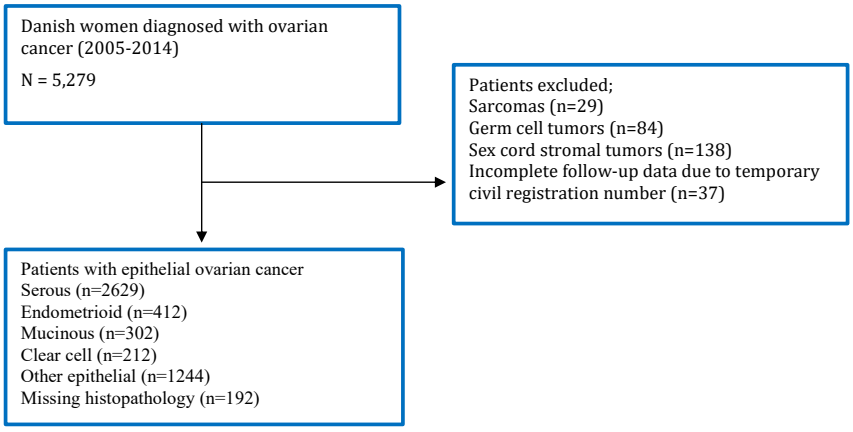


Figure 13 Flowchart for patient selection using nationwide Danish registries. Modified from[141]

During a median follow-up of 2.9 years 551 VTE events were observed corresponding to 27 VTEs per 1000 person years (95 % CI, 25-29). Risk of VTE was associated with increasing age, previous VTE, advanced FIGO stage, clear cell histopathology, surgery and chemotherapy (Figure 14).

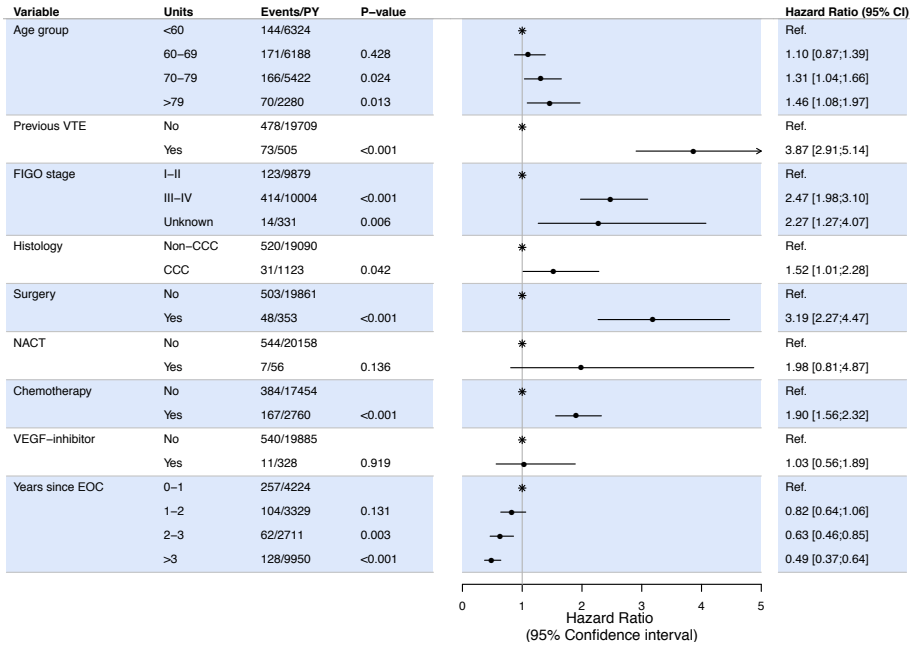


Figure 14 Hazard ratios associated with patient-, tumor- and treatment related risk factors. From[141]

STUDY IV

During the inclusion period from Nov 2014 to May 2017 a total of 221 patients referred to the department of Gynecology and Obstetrics, Aalborg University Hospital on suspicion of ovarian cancer were assessed for inclusion in the trial.[142] Written informed consent was obtained from 97 patients, of whom 33 were later diagnosed with benign ovarian tumors, 11 with borderline malignancies and 53 with epithelial ovarian carcinomas. Non-participants tended to be older and had more co-morbidities. In EOC participants 3.8 % had VTE at time of diagnosis, whereas 4.2 % of non-participants had pre-treatment VTE. One-year cumulative incidence of VTE in EOC patients was 20.8 % in the cohort that underwent systematic objective VTE examination (participants) and 18 % in non-participants (fig. 15 and 16). Mortality was highest in non-participants. Median time to VTE was 87 (0-358) and 71 (0-184) days, respectively. Information on presentation and timing of VTE events in relation to treatment is provided in table 2.

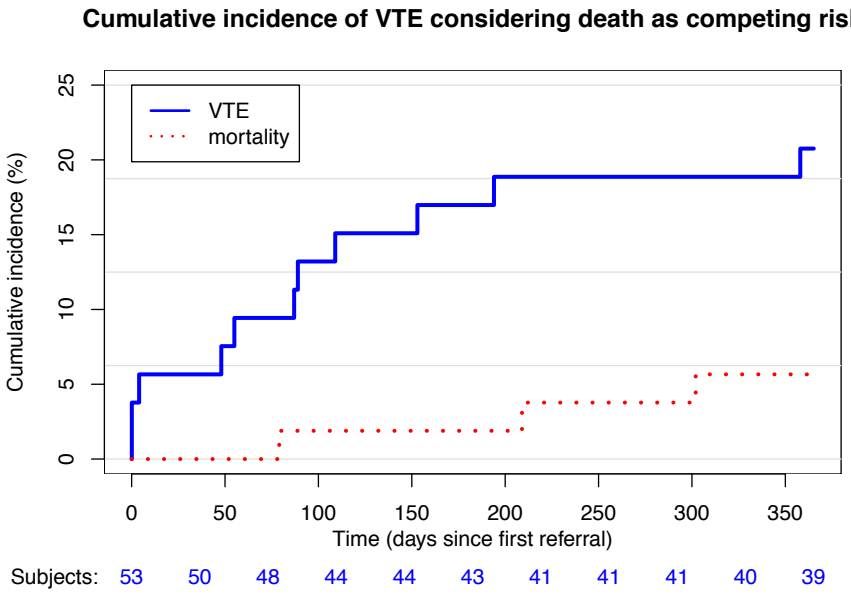


Figure 15 Cumulative incidence of VTE in EOC patients participating in the clinical trial with consequent examination for VTE, death is competing risk. Modified from[142].

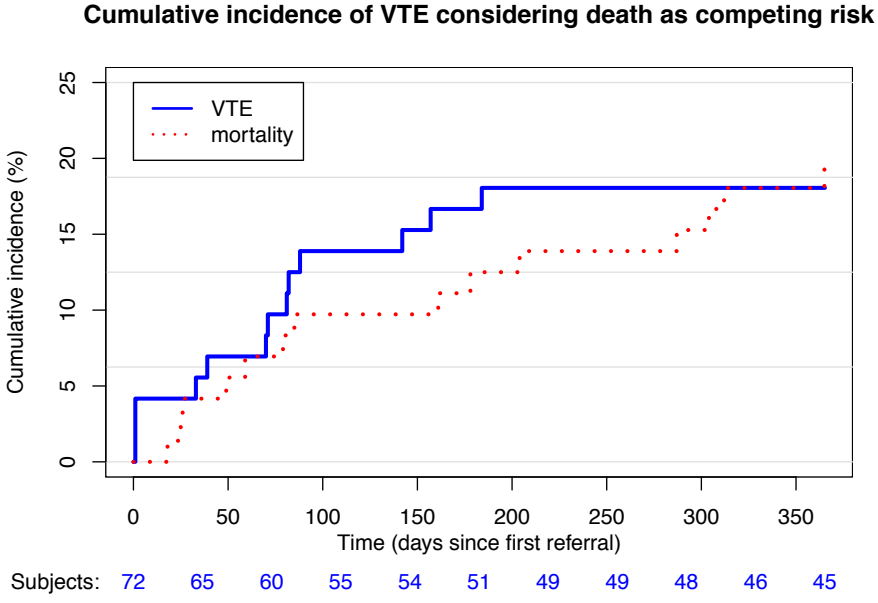


Figure 16 Cumulative incidence of VTE and death in non-participants. Unpublished plot from [142]

Table 2 Comparison of participants and non-participants according to localization and timing of VTE. Modified from[142]

Variable[a]	Participants (11)	Non-participants (13)
VTE location		
Proximal DVT	4(36.3)	4(30.7)
Central and segmental PE	-	2(15.4)
Subsegmental PE	3(27.3)	3(23.1)
DVT + PE	3(27.3)	2(15.4)
VTE at central vein catheter site	1(9.1)	1(7.7)
Ovarian vein thrombus	-	1(7.7)
Symptomatic vs. incidental		
Symptomatic	5(45.5)	7(53.8)
Incidental	6(54.5)	6(46.2)
Timing of VTE		
Median time to VTE, days (range)	87 (0-358)	71(0-184)
Before treatment	2(18.1)	3(23.1)
Postoperative VTE	1(9.1)	1(7.7)
During neoadjuvant chemotherapy	3(27.3)	4 (30.8)
During adjuvant chemotherapy	3(27.3)	2(15.4)
During palliative chemotherapy	1(9.1)	3 (23)
During randomized trial with PARP-inhibitor/placebo	1(9.1)	-

Abbreviaions: VTE, Venous thromboembolism; DVT, Deep vein thrombosis; PE, Pulmonary embolism; PARP, Poly ADP Ribose Polymerase
[a] Data are expressed as No. (%) unless otherwise indicated.

Baseline D-dimer levels measured in blood samples collected before treatment was initiated are depicted in Figure 17. D-dimer levels were normal in most patients with benign ovarian tumors and elevated in the majority of EOC patients independent of the presence of current or future VTE event.

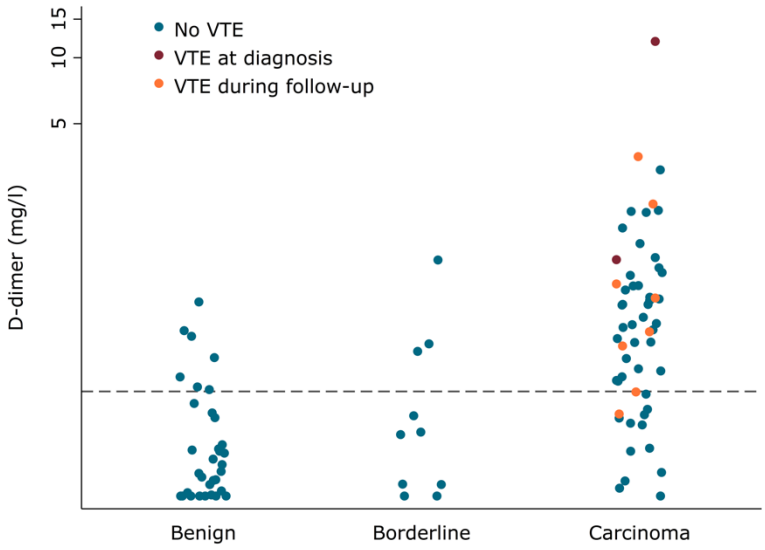


Figure 17 Differences in pretreatment D-dimer levels in benign and malignant tumors. Blood samples collected from patients participating in study IV[142]. Dashed line indicates normal D-dimer level at 0.3 mg/l. Results previously presented at the 9th International Conference on Thrombosis and Hemostasis Issues in Cancer, April, 2018.[143]

GENERAL DISCUSSION

5.1. MAIN FINDINGS

In the first study[138], we found a low overall incidence of postoperative VTE following hysterectomy when indicated for benign disease, especially if the procedure was performed as MIS. In study II[140], we investigated if the risk of VTE was higher in patients undergoing hysterectomy due to endometrial cancer compared to a sub-cohort of patients from study I. There was no statistically significant difference.

Study III confirmed previous reports of a high incidence of VTE in epithelial ovarian cancer. We were able to investigate several recognized risk factors in a multivariable time-dependent analysis by including a large cohort from a national database.[141] The results give a good indication of the impact of the various risk factors in a Caucasian cohort.

We objectively assessed occurrence of VTE in study IV with the aim of clarifying if asymptomatic VTE was present at time of diagnosis and followed by progression to symptomatic VTE after anticancer treatment.[142] The study revealed a low incidence (3.8%) of pre-treatment VTE but a high cumulative incidence of VTE (20.8 %) throughout the first year after diagnosis. Median time to VTE was 87 days, with most events occurring during chemotherapy. In comparison, patients diagnosed with EOC at our department within the study period, but not included in the clinical trial, had a similar high one-year VTE incidence of 18 %.

5.1.1. POSTOPERATIVE VTE (STUDY I, II AND III)

Guidelines in gynecology and obstetrics recommended thrombosis prophylaxis in relation to surgery for several years. The American College of Gynecologists and obstetricians (ACOG) recommends a risk stratification, with LMWH administered to the majority except for healthy patients younger than 40 years of age, undergoing surgery for less than 30 min.[144] In Denmark, LMWH prophylaxis was implemented for all patients undergoing hysterectomy after recommendations by the Danish National Board of Health in 2003.[139] Recommendations are primarily based on RCTs including patients undergoing open surgery for various diseases.[144–146] An early multicenter study by Kakkar et al. (1975) observed a difference in postoperative DVT incidence of 8 % vs. 25 % in patients exposed to low-dose heparin from two hours before surgery and 7 days after surgery compared to the control group.[147] Patients in this study underwent open surgery for different benign and malignant conditions and VTEs were diagnosed by phlebography, radioactive fibrinogen screening test, chest

X-ray or autopsy in case of death. Furthermore, currently updated guidelines recommend four weeks of extended prophylaxis for all patients undergoing surgery for solid cancers. Despite clear recommendations of thrombosis prophylaxis, observational studies based on data from clinical registries reveal a low adherence to the guidelines. Two studies showed no significantly higher VTE incidence in patients who did not receive pharmacologic prophylaxis, compared to those who did.[65,148] However, nearly half of the patients in the study by Ritch et al. did receive mechanical prophylaxis with elastic compression stockings or intermittent pneumatic compression, giving rise to an expectation that VTE incidence would have been higher with no prophylaxis at all.[148] Another study by Bouchard-Fortier et al. found a 30-day VTE incidence of 0.57 % following MIS for gynecologic cancer even though 84 % of patients did not receive any kind of prophylaxis.[149] An editorial by Clarke-Pearson and Barber addressed the lack of knowledge regarding proper VTE prophylaxis in gynecologic oncology surgery since current recommendations are mainly extrapolated from other surgical fields.[66] Barber et al. propose the development of a risk assessment model for use in gynecologic oncology surgery as the available tools from general surgery are not very applicable in gynecology.[150]

In all studies, we defined the postoperative period as the first 30 days after surgery, so our results were comparable with similar studies.[39,151] We chose this approach, even though surgery is categorized as a major transient risk factor that increase risk of VTE for 12 weeks following surgery.[5,13]

The incidence of 30-day postoperative VTE was very low in study I, especially when performed as MIS.[138] Patients exposed to LMWH prophylaxis had a significantly lower risk of VTE. A prior VTE was associated with a substantial increased risk of VTE in study I, II and III, illustrating the importance of including this factor in the risk assessment. Risk of VTE was not significantly higher in patients undergoing hysterectomy for endometrial cancer compared to benign disease in study II.[140] This cancer type is associated with risk factors that could also increase risk of VTE such as high age and BMI, hence the results have been controlled for these factors.[13] Crude results showed higher VTE incidence in endometrial cancer patients while adjusted results showed no significantly higher risk. Surgery was the most important treatment-related risk factor in study III.

5.1.2. OVARIAN CANCER AND RISK OF VTE (STUDY III+IV)

Several risk factors, including biological mechanisms and timing of events, have been proposed regarding VTE in ovarian cancer.[100,152–155] Results from our research group have suggested that some postoperative VTE cases reported in clinical trials were present before surgery, induced by the cancer itself rather than the surgical trauma[46,47]

Satoh et al. revealed a very high (25 %) preoperative VTE incidence in patients with ovarian cancer and borderline tumors.[93] Other studies from Japan have reported similar high pre-treatment incidences of VTE.[156–158] The incidence of pre-treatment VTE was lower than expected in study IV, compared to recently published studies from Japan, but similar to an older German study with objective assessment of DVT incidence [92]. Analyzing the data from study III and IV revealed that a Danish cohort of EOC patients is not comparable to Japanese cohorts, since the distribution of histopathologic subtypes is vastly different[73,141,142], greatly impacting VTE risk. Furthermore, definitions of DVT vary between studies, resulting in overestimation of the VTE risk as some studies include intramuscular, and even superficial vein thrombosis in their definition of DVT. These thrombi do not carry the same risk of progression or recurrence as deep vein thrombosis. Accordingly, they are treated differently in existing clinical guidelines.[159,160] Study IV was underpowered and could not elucidate differences in the risk of VTE between recognized risk factors, but gave a good implication of the timing of VTE events in relation to treatment. D-dimer levels measured in patients in study IV confirmed the poor accuracy of this test to rule out a VTE event in EOC patients.[93] In study III, we were able to investigate the association between EOC and VTE controlling for recognized risk factors. Among tumor-related risk factors we found that advanced FIGO stage was stronger associated with VTE than clear cell histopathology. Regarding treatment related VTE, EOC patients had a more than three-fold risk of VTE in the 30-day post-operative period and a two-fold risk during chemotherapy.

5.2. METHODOLOGICAL CONSIDERATIONS

5.2.1. SYSTEMATIC ERRORS

SELECTION BIAS

Selection bias occurs when the investigated sample is not representative of the target population. This is rarely a problem in population based cohort studies with complete follow-up as it was the case in study I-III. We investigated the risk of VTE after hysterectomy in study I and II and noticed that other studies on the same subject included length of hospital stay (LOS) in the multivariable analyses. [39,151] We did not control for LOS in study I and II as DAGs (Fig. 10 and 11) illustrated that LOS could act as either an intermediate or a collider if the increased LOS was actually a result of a postoperative VTE. Conditioning on LOS would then introduce selection bias. Selection bias is likely present in study IV, since EOC patients agreeing to participate, had a lower mortality than non-participants. This phenomenon was previously described by Larsen et al.[161]

INFORMATION BIAS

Information bias arises if subjects included in a study are misclassified with regard to exposures, target disease or confounders. This type of bias is reduced in study I-III by use of validated register data of high quality. A high proportion of EOC non-participants (18 %) in study IV were diagnosed with VTE during the study period, even though these patients were not systematically screened. An explanation for this finding could be that both clinicians and radiologists were more aware of this complication in EOC patients, due to the ongoing trial.

CONFOUNDING

Confounding is present when exposed and non-exposed individuals in a study are incomparable to differences in disease risk, because other risk factors are differently distributed within exposed and non-exposed. Knowledge about the associations between exposures and outcome is important, in order to determine which confounders to control for, since no test for confounding exists.[162] We used DAGs in study I-III to guide the selection of confounders to control for in the multivariable analyses.[129]

There are different ways to control for confounding in the design and analysis stages: One option is randomization, which is rarely possible in epidemiological studies, another is narrowing the number of potential confounders.[130] We used the latter approach in study I, II and IV by excluding patients with malignant diseases other than the ones of interest within a certain time-frame, to minimize the effect from other cancers on VTE risk. Further exclusion criteria were defined in study IV, potentially contributing to not reaching our calculated sample size, since many patients did not meet the inclusion criteria. Furthermore, the generalizability of the results decreases with many exclusions, which was illustrated by the fact that mortality was considerably higher in EOC non-participants, diagnosed at the same department within the study period. Another way to control for confounding in the study design, is to match on specific variables to ensure the same proportion of exposed and unexposed subjects in the cohort. Control for confounding in the analysis can be carried out by stratification in case of few confounding factors, or by multivariable regression analysis allowing to control for several confounding factors limited by the number of events. In cases where data on a confounding variable is lacking e.g. type II diabetes mellitus treated in general practice, another variable might serve as “a proxy”. Dispensing of glucose-lowering agents was used in study II to ensure correct classification of diabetes patients included in a sub-analysis to estimate the effect of comorbidities, as it has been done previously.[163]

Despite adjusting for known confounders, there might still be residual confounding from unmeasured or unknown factors.[113]

5.2.2. RANDOM ERRORS

Observational studies investigate associations between exposures and outcome based on a sample from a population, assuming that we can draw conclusions about the causal inference regarding the entire population. A random error may lead to inaccurate estimates of disease frequency and associations between exposures and outcome. A method of reducing this type of error is to increase the study population, which is not always possible in epidemiologic studies where sample size is based on the available data. Confidence limits to the estimates indicate the degree of precision.[130] We were able to include large nationwide cohorts in the epidemiological studies (I-III) and our findings are not likely to be subject to chance. Study IV was underpowered to estimate associations between recognized risk factors and VTE within EOC patients.

CONCLUSIONS AND IMPLICATIONS OF THE THESIS

STUDY I

In conclusion, we found a low risk of VTE in a large cohort of women undergoing hysterectomy for benign disease. Risk factors were open surgery, treatment with anticoagulant drugs and previous venous and arterial thromboembolic events. Exposure to postoperative prophylactic LMWH was associated with a significant lower risk of VTE.

STUDY II

The risk of VTE was low after hysterectomy for endometrial cancer and statistically not significantly different from the risk when hysterectomy was performed for benign disease. Independent risk factors were open surgery, BMI>40, lymphadenectomy, and previous VTE.

STUDY III

The risk of VTE was high among EOC patients especially within the first year after diagnosis. Advanced FIGO stage was associated with a higher VTE risk than clear cell histopathology in a Danish EOC cohort. Major surgery was associated with a 3-fold increase of VTE, while chemotherapy was associated with a 2-fold higher risk compared to non-exposed.

STUDY IV

The cumulative incidence of VTE within the first year after diagnosis was 20.8 % in EOC patients undergoing systematic examination for VTE. Pretreatment VTE incidence was lower (3.8 %) than expected, based on recent Asian publications. Median time to event was 87 days, with the majority of VTEs occurring during non-surgical anti-cancer treatment.

The studies in the thesis investigated the risk of VTE in gynecologic patients treated for various benign and malignant diseases. The studies give a good indication that the risk of postoperative VTE is low after hysterectomy for benign conditions and endometrial cancer. Epithelial ovarian cancer carries a high risk of VTE, particularly in the first year after cancer diagnosis. Future research should focus on elucidating subgroups of patients that would benefit from further extension of prophylaxis.

PERSPECTIVES

The findings in study I and II indicate that the risk of VTE is very low after hysterectomy for benign conditions and endometrial cancer. With an apparently insignificant difference in the risk of postoperative VTE in endometrial cancer patients compared to patients undergoing hysterectomy for benign conditions, it might not be necessary to prescribe extended LMWH prophylaxis to all patients. Further investigations should clarify if patients could be additionally stratified further into risk categories regarding risk of postoperative VTE. A randomized controlled trial would be ideal in order to clarify if pharmacologic VTE prophylaxis is indicated to all patients undergoing MIS. A large sample size is required and fund raising for such a project would probably be difficult, as the results might not be beneficial to the medicinal industry.

Molecular biology research will potentially lead to better understanding of the hypercoagulant state observed in at least some histopathologic subtypes of EOC. Tumor tissue was collected from patients included in study IV and proteomic analysis was performed in cases with VTE events and a control group, consisting of nine patients with clear cell carcinomas from the Danish Cancer Biobank, nine cancer patients and ten patients with benign ovarian tumors, included in the clinical trial. The interpretation of bioinformatics data is currently underway, and the study group expects to be able to publish the results in the near future.

Blood samples collected from patients in study IV will be analyzed to evaluate the utility of novel coagulation markers to diagnose clinical and subclinical VTE in EOC patients.

The knowledge gained within the field of epidemiologic research has prompted the author's involvement in other research collaborations. One research project aims to describe the distribution of birth weight in a Danish national birth cohort and analyze the result in relation to international birth weight references.

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APPENDIX

Supplementary table 1 Algorithm for translating FIGO classification to TNM SKS codes[55,69,126,164]

FIGO	Description	TNM	SKS T stage
I	Tumor confined to the corpus uteri	T1N0M0	AZCD13
IA	Tumor limited to endometrium or myometrial invasion < 50 %	T1aN0M0	AZCD13A
IB	Myometrial invasion ≥ 50 %	T1bN0M0	AZCD13B
II	Invasion of cervical stroma, but no extension beyond the uterus	T2N0M0	AZCD14
III	Local and/or regional spreading	T3N0M0	AZCD15
IIIA	Invasion of serosa of the corpus uteri and/or adnexae	T3aN0M0	AZCD15A
IIIB	Involvement of vagina and/or parametrium	T3bN0M0	AZCD15B
IIIC	Pelvic and/or para-aortic lymph node metastases	T1-T3, N1, N1mi,or N1a, M0	AZCD15C
IIIC1	Positive pelvic nodes	T1-T3, N2, N2mi,or N2a, M0	AZCD15C
IIIC2	Positive para-aortic nodes with/without positive pelvic nodes	T1-T3, N2, N2mi,or N2a, M0	AZCD15C
IV	Invasion of bladder and/or bowel mucosa, and/or distant metastases	T4N0M0	AZCD16
IVA	Invasion of bladder and/or bowel mucosa	T4, Any N, M0	AZCD16A
IVB	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes	Any T, Any N, M1	AZCD16B

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