Gynecologic Oncology 155 (2019) 112–118

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Endometrial cancer does not increase the 30-day risk of venous thromboembolism following hysterectomy compared to benign disease. A Danish National Cohort Study☆

Henriette Strøm Kahr [a,b,c,d,*], Ole Bjarne Christiansen [a,c], Claus Høgdall [e], Anni Grove [f], Rikke Nørmark Mortensen [g], Christian Torp-Pedersen [h,i], Aage Knudsen [a,c], Ole Thorlacius-Ussing [b,c,d]

[a] Department of Gynecology and Obstetrics, Aalborg University Hospital, Denmark
[b] Department of Surgical Gastroenterology, Aalborg University Hospital, Denmark
[c] Department of Clinical Medicine, Aalborg University, Denmark
[d] Clinical Cancer Research Center, Aalborg University Hospital, Denmark
[e] Department of Gynecology, Rigshospitalet, University of Copenhagen, Denmark
[f] Institute of Pathology, Aalborg University Hospital, Denmark
[g] Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Denmark
[h] Department of Cardiology, Aalborg University Hospital, Denmark
[i] Department of Cardiology and Clinical Investigation, Nordsjaellands Hospital, Hilleroed, Denmark

HIGHLIGHTS

- Surgery for endometrial cancer carries a low 30-day risk of venous thromboembolism (VTE).
- Risk of VTE following hysterectomy for endometrial cancer was comparable to hysterectomy for benign condition.
- Risk factors were open surgery, lymphadenectomy, BMI > 40 and previous VTE.

ARTICLE INFO

Article history:
Received 11 June 2019
Received in revised form 18 July 2019
Accepted 22 July 2019
Available online 1 August 2019

Keywords:
Endometrial cancer
Venous thromboembolism
Deep venous thrombosis
Pulmonary embolism

ABSTRACT

Objectives. We aimed to clarify if endometrial cancer patients are at higher risk of venous thromboembolism (VTE) following hysterectomy, compared to patients undergoing hysterectomy for benign gynecological disease.

Methods. In a nationwide registry-based cohort study, patients undergoing hysterectomy for endometrial cancer or benign disease were followed 30 days after surgery. The Danish Gynecological Cancer Database (DGCD) and the Danish National Patient Register (DNPR) were linked with four other administrative registries to describe the population and retrieve data on venous thromboembolism and mortality.
Multivariable logistic regression models were used to estimate odds ratios (ORs) for 30-day postoperative VTE.

Results. We identified 5513 patients with endometrial cancer, and 45,825 patients with benign disease undergoing hysterectomy in the period 2005–2014.
The overall incidence of 30-day VTE following hysterectomy was 0.2% (103/51,338). Thirty (0.5%) patients with endometrial cancer and 73 (0.16%) patients with benign disease developed VTE. In a multivariable logistic regression analysis, significant predictors of 30-day OR for VTE were open surgery (minimally invasive surgery vs. open: OR = 0.46; 95% CI, 0.30–0.71; p < 0.001), lymphadenectomy (OR = 4.00; 95% CI, 1.89–8.46; p < 0.001), BMI > 40 (OR = 2.34;95% CI, 1.10–5.01; p = 0.03) and previous VTE (OR = 34; 95% CI, 22.7–51.3; p < 0.001). There was no statistically significant difference in the 30-day OR for VTE in endometrial cancer compared to benign disease (OR = 1.47; 95% CI, 0.74–2.91; p = 0.27).

Conclusions. This study did not identify endometrial cancer to be an independent risk factor for VTE following hysterectomy compared to benign disease. We identified open surgery, lymphadenectomy, BMI above 40 and previous VTE as independent risk factors for 30-day postoperative VTE.

☆ Source of the study: A cohort study using a variety of nationwide Danish patient registers.

* Corresponding author at: Department of Gynecology and Obstetrics, Aalborg University Hospital, 9000 Aalborg, Denmark.
E-mail address: hestje@rn.dk (H.S. Kahr).

https://doi.org/10.1016/j.ygyno.2019.07.022
0090-8258/

1. Introduction

Venous thromboembolism (VTE) is a common complication in cancer patients and is associated with increased morbidity and mortality [1]. The risk of VTE is previously shown to be increased after abdominal and pelvic cancer surgery [2]. Based on randomized controlled trials, extended thrombosis prophylaxis is recommended to such patients, but these trials do not consider differences in VTE risk based on the type of cancer [3]. Most endometrial cancer patients are diagnosed at early stage. The primary treatment is hysterectomy and bilateral salpingo-oophorectomy which can be performed by open laparotomy or minimally invasive surgery (MIS) by laparoscopic (conventional or robotic) or vaginal approach [4]. A large retrospective cohort study with 9948 endometrial cancer patients described an overall 30-day VTE incidence of 1.3% with a significantly lower risk after MIS compared to laparotomy (adjusted odds ratio (OR) 0.36, 95% CI, 0.24–0.53) [5]. Considering the low risk of postoperative VTE following MIS for endometrial cancer it has been questioned if pharmacologic VTE prophylaxis is necessary in these patients [6,7]. The limited utility of VTE risk assessment tools recommended by the American College of Chest Physicians (ACCP) in gynecologic oncology surgery, is addressed by Barber et al. in a recent review [8,9]. They propose an individualized approach to VTE prophylaxis, as the recommended scoring systems categorize most gynecologic oncology patients at high risk of postoperative VTE.

We previously reported the incidence of VTE following hysterectomy for benign disease to be very low, especially after MIS and in-hospital pharmacologic VTE prophylaxis [10]. With similar findings in endometrial cancer surgery it is questionable if extended VTE prophylaxis is necessary for all patients.

The aim of the present study is to identify risk factors and estimate the difference in VTE rate between patients undergoing hysterectomy for benign disease compared to patients undergoing hysterectomy due to endometrial cancer.

2. Methods

2.1. Data-sources

The present study is based on data from nationwide Danish administrative registries. All Danish residents are at time of birth or immigration provided a unique and permanent civil registration number which is used at all contacts with the health care system, and enables linkage between different registries. The Danish National Patient Register (DNPR) holds data on diagnoses and treatments for hospitalization and outpatient visits in Denmark since 1977 [11]. Diagnoses are registered according to the International Classification of Diseases, 10th revision (ICD-10). Registration of surgical procedures follows the Nordic Medico-Statistical Committee's Classification of Surgical Procedures [12]. The nationwide Danish Gynecologic Cancer Database (DGCD) was established in 2005 and holds information on patients undergoing treatment for gynecologic cancers. Data are collected prospectively and comprise of baseline characteristics, clinical findings, treatment and final pathological diagnosis including stage of disease. Data on

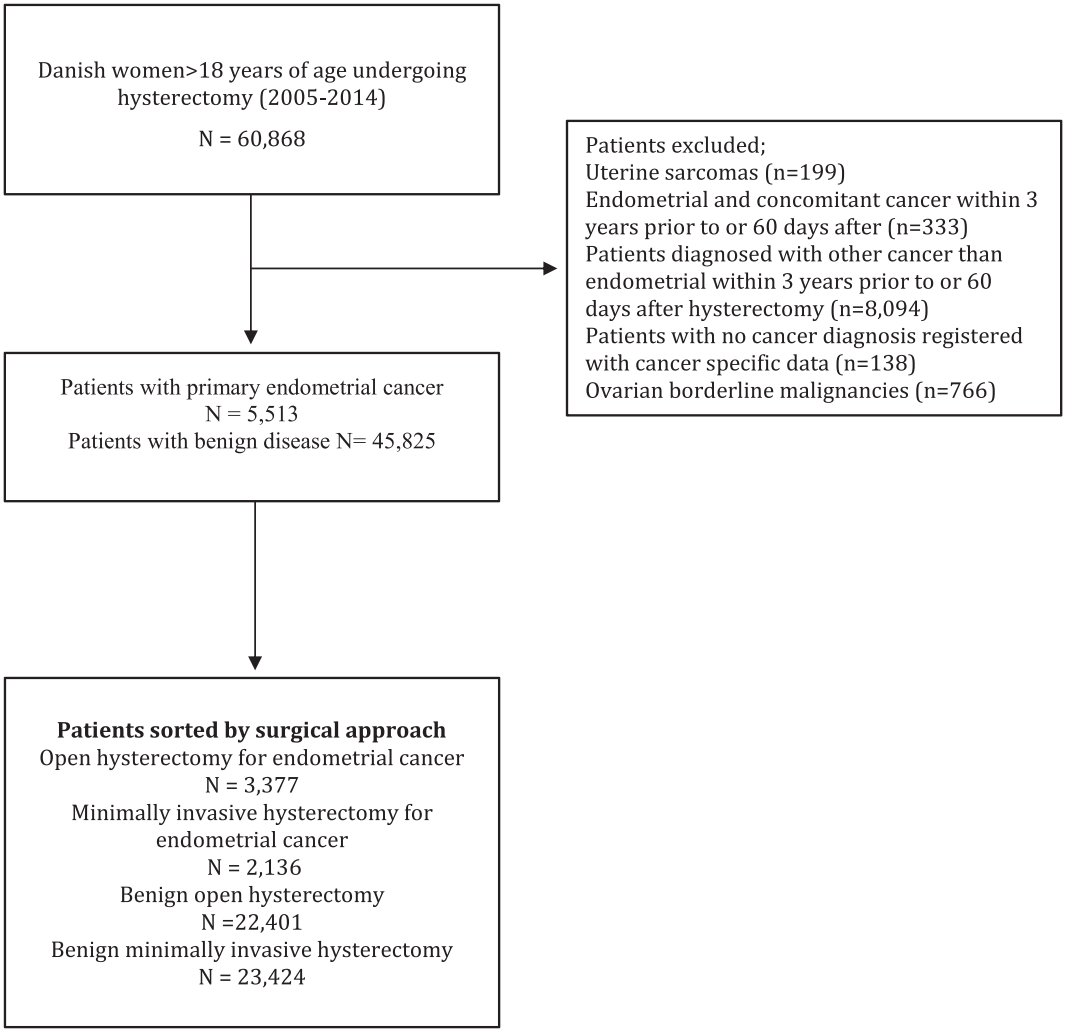

Fig. 1. Flowchart presenting the patient selection using Danish National Registries.

endometrial cancer were validated by ensuring the right cancer diagnosis code in the DNPR. We linked these data with four other nationwide registries.

The Danish Cancer Registry was established in 1942 and holds cancer specific information such as type and stage. Information on vital status, date of birth and death including cause of death was retrieved from The Population Statistics Register and the National Causes of Death Register. Data on diabetic medicine was retrieved from The Danish Register of Medicinal Product Statistics, where data on prescription-based medicine are recorded.

2.2. Study population

Patients undergoing hysterectomy due to endometrial cancer in the period 2005–2014 were identified in the DGCD. For comparison, data on patients undergoing hysterectomy for benign disease in the same period were retrieved from a previously described cohort [10]. The patients were divided into four groups according to indication for surgery and surgical approach: Patients with benign disease undergoing open hysterectomy (subtotal or total abdominal hysterectomy: KLCD00, KLCD96, KLCC10), laparoscopic (total, subtotal, vaginal and robotic assisted laparoscopic hysterectomy: KLCD01, KLCD04, KLCC11, KLCD11, KLCD97 + KZXX00 if robotic assisted) or vaginal (total or subtotal: KLCD10, KLCC20). Endometrial cancer patients were divided into the same groups regarding surgical approach – open or MIS (including radical hysterectomies: KLCD30, KLCD31, KLCD40).

Patients undergoing hysterectomy due to cancers other than endometrial cancer, and patients with concomitant cancer or another cancer within three years prior to or two months after hysterectomy were excluded (ICD10: DC00-DC96 excluding cancer of the corpus uterus, DC54–55 coded as primary diagnoses, and non-melanoma skin cancers, DC44). Patients with ICD10 codes DC54 and DC55 were classified as endometrial cancer, except for tumors that were histopathological classified as uterine sarcomas. Patients were excluded if there was any confusion about allocation to the benign or cancer group, for example when ICD-10 codes were insufficient.

2.3. Outcome

VTE comprised the following ICD-10 codes: I80.1 (phlebitis or thrombophlebitis in the femoral vein), I80.2 (deep phlebitis or thrombophlebitis in other veins in lower extremities), I80.3 (deep phlebitis or thrombophlebitis in other veins in lower extremities without specification), I80.8 (phlebitis or thrombophlebitis at other locations), I80.9 (phlebitis or thrombophlebitis without specification) and I26 (pulmonary embolism). If one of these codes occurred prior to the date of hysterectomy it was registered as a previous VTE; however, data has only been retrieved after 1993 when ICD10 replaced ICD8 coding of diseases in the DNPR.

If the code was assigned to a patient within one month after hysterectomy it was registered as a postoperative VTE.

2.4. Confounders

Danish guidelines for surgical treatment of endometrial cancer do not recommend routine lymphadenectomy in low risk patients, which include endometrioid carcinomas and variant differential grade 1–2 and myometrial invasion of <50%. Treatment decision is based on preoperative endometrial biopsy or resection, and intraoperative macroscopic evaluation of the degree of myometrial invasion. Lymphadenectomy performed at the time of hysterectomy (code KPJD) was registered without distinguishing between pelvic, para-

Table 1
Characteristics of the study population (N = 51,338).

Variable[a]	Open benign hysterectomy (n = 22,401)	MIS benign hysterectomy (n = 23,424)	Open malign hysterectomy (n = 3377)	MIS malign hysterectomy (n = 2136)	Totals (n = 51,338)
Median age, years	47.5 (43–52)	48.0 (43–59)	66.8 (60–75)	67.0 (60–74)	48.7 (44–59)
Median BMI	25.4 (23–29)	25.1 (23–29)	27.1 (24–32)	27.9 (24–33)	25.4 (23–29)
BMI > 40	392 (2.2)	292 (1.6)	232 (7.5)	205 (11.1)	1121 (2.7)
Missing	4431	4729	271	297	9728
Median length of stay, days	2 (2–3)	1 (1–2)	3 (2–5)	1 (1–2)	2 (1–3)
Median operating time, minutes	75 (60–95)	70 (52–97)	80 (60–115)	90 (61–123)	75 (57–100)
Lymphadenectomy	–	–	958(28.4)	554(25.9)	1512(2.9)
Route of MIS					
Laparoscopic	–	8905 (38.0)	–	933 (43.7)	9838 (19.2)
Vaginal	–	14,317 (61.1)	–	88 (4.1)	14,405 (28.0)
Robotic	–	202 (0.9)	–	1115 (52.2)	1317 (2.6)
ASA > 1	4661 (20.8)	5549 (23.7)	2013 (59.6)	1200 (56.2)	13,423 (26.1)
Smoking	4786 (21.4)	4797 (20.5)	497 (14.7)	244 (11.4)	10,324 (20.1)
Previous VTE	402 (1.8)	378 (1.6)	81 (2.4)	59 (2.8)	920 (1.8)
FIGO classification					
Stage I	–	–	2423 (72.6)	1821 (86.3)	4244 (77.9)
Stage II	–	–	404 (12.1)	168 (8.0)	572 (10.5)
Stage III	–	–	409 (12.3)	113 (5.3)	522 (9.6)
Stage IV	–	–	99 (3.0)	8 (0.4)	107 (2.0)
Missing	–	–	42	26	68
Tumor grade					
Grade 1	–	–	1705 (60.9)	841 (71.3)	2546 (64.0)
Grade 2	–	–	693 (24.8)	241 (20.4)	934 (23.5)
Grade 3	–	–	401 (14.3)	98 (8.3)	499 (12.5)
No grading/missing	–	–	578	956	1534
Histopathology					
Endometrioid adenocarcinoma	–	–	2674 (82.1)	1794 (88.7)	4468 (70.1)
Non-endometrioid	–	–	562 (17.3)	192 (9.5)	754 (11.8)
Hyperplasia with atypia	440 (73.6)	371 (73.9)	–	–	811 (12.7)
Hyperplasia without atypia	158 (26.4)	131 (26.1)	–	–	289 (4.5)
Other	–	–	20 (0.6)	36 (1.8)	56 (0.9)
Missing	–	–	121	114	235

Abbreviations: MIS, minimally invasive surgery; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; ASA score, American Society of Anesthesiologists (ASA) score classification.

[a] Data are expressed as n (column %), median (interquartile range).

aortic or complete dissections. Sentinel node assessment was introduced in Denmark for endometrial cancer after the study period ended. Cancer specific data such as FIGO stage, WHO classification of tumor type and grade, were primarily retrieved from DGCD and supplied with data from the DNPR and the Cancer Registry. Classification of disease stage followed the International Federation of Gynecology and Obstetrics 2009 FIGO guidelines [13].

Risk factors for surgical complications were retrieved from DGCD or DNPR, if registered together with the primary disease code at discharge from hospital after hysterectomy for benign disease. These were obesity (DE660, Body Mass Index (BMI) was calculated in cases with registered height and weight-data). American Society of Anesthesiologists (ASA) score classification (EZA + number), and smoking (DVRB02). Discharge diagnosis within one year prior to hysterectomy was used to identify the following comorbidities: Ischemic heart disease (I20, I23–25), cerebral vascular disease (I60–69), acute myocardial infarction (I21), varices of the lower extremities (I83), thrombophilia (D68), heart failure (I50), and diabetes mellitus (E10–14). Dispensing of glucose-lowering agents (Anatomical Therapeutic Chemical Classification A10) was used as a "proxy" for diabetes as in previous publications [14]. The coding of comorbidity and coexisting diseases in DNPR has been validated with a positive predictive value between 82% and 100% [15].

The open-source software, DAGitty was used for evaluation of potential confounders [16]. The Directed Acyclic Graph is included in Supplementary (Fig. S3).

Data are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17].

2.5. Statistics

Cumulative incidence was estimated for the competing risks of VTE and death after open and minimally invasive hysterectomy, in patients with benign disease and endometrial cancer. Time to event was calculated from date of hysterectomy; the follow-up time was 30 days. For descriptive statistics, all continuous variables were compared using analysis of variance and all discrete variables using the chi-squared test (Table 2). Data were analyzed using a multivariable logistic regression model. Odds Ratios (ORs) of VTE after hysterectomy for benign disease and endometrial cancer, were estimated and presented with 95% confidence intervals (CIs). A p value <0.05 was considered statistically significant. The adjusted model included endometrial cancer versus benign disease, patients older than versus younger than 60 years, MIS versus open surgery, BMI higher than 40, lymphadenectomy and previous VTE.

Calculations were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.4.0 (R Core Team, 2017) [18].

2.6. Ethics

The study was approved by The Danish Data Protection Agency (Re: 2008-58-0028, internal reference: 2015-125). Permission from the ethics committee is not required for retrospective register studies in Denmark.

3. Results

We identified 45,825 patients undergoing hysterectomy for benign conditions and 5513 patients who had a hysterectomy due to endometrial cancer in the period from January 2005 to December 2014. A flowchart presenting selection of the study population is illustrated in Fig. 1. Patients were divided into four groups according to the route of hysterectomy (open versus MIS) and the indication (benign versus endometrial cancer). Table 1 shows baseline characteristics of the cohort according to age at time of surgery, BMI, length of hospital stay, ASA score, specifications on surgery, cancer specific data and previous VTE. The median age of patients with endometrial cancer was higher than that of women undergoing hysterectomy for benign conditions. Lymphadenectomy was equally distributed within the open and MIS groups for endometrial cancer surgery (28.4 vs. 25.9%). Comorbidity was higher among endometrial cancer patients (see Table S1 in Supplementary material).

During the 30-day follow up after surgery, 103 patients (0.2%) developed postoperative VTE, 30 cases were observed within the group of endometrial cancer patients (30/5513 = 0.5%), and 73 cases in patients after hysterectomy for benign conditions (73/45,825 = 0.16%). There were 26 deaths (0.5%) in the endometrial cancer group compared to 29 (0.06%) in patients with benign disease.

The cumulative incidence of VTE was calculated within the four groups; Open surgery for benign disease, MIS for benign disease, open surgery for endometrial cancer and MIS for endometrial cancer, and is depicted in Fig. 2A. The highest VTE incidence was observed in open surgery for endometrial cancer. The cumulative incidence for the competing risk of death is illustrated in Fig. 2B and shows highest incidence of death after open surgery for endometrial cancer.

Table 2 shows the results of the univariable analysis whereas Fig. 3 shows the results of the multivariable logistic regression analysis. The incidence of VTE in patients older than 60 was 0.3% compared to 0.2% in younger, there was no difference in adjusted OR (1.04; 95% CI, 0.62–1.74; p = 0.89). The incidence of VTE in early FIGO stages (I–II) was 0.5% versus 1.0% in stages III–IV, but stage was not significantly associated with a higher OR when adjusting for other risk factors (FIGO stage divided in groups is not depicted in Fig. 3, since groups were too small to publish without violation of personal data protection).

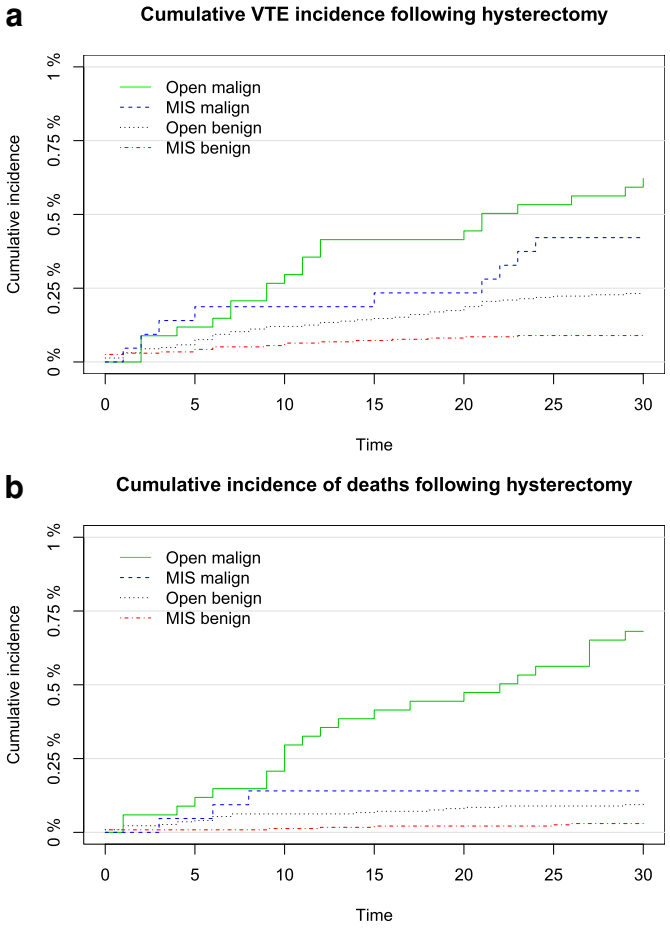

Fig. 2. A. Cumulative incidence of venous thromboembolism 30 days following hysterectomy regarding approach and endometrial cancer vs benign disease. B. Cumulative incidence of death 30 days following hysterectomy regarding approach and endometrial cancer vs benign disease.

Table 2
Univariable associations between different exposures and venous thromboembolism.

Variable[a]	No VTE (n = 51,235)	VTE (n = 103)	Total (n = 51,338)	p-Value
Age ≤ 60	39,215 (76.5)	68 (66.0)	39,283 (76.5)	
Age > 60	12,020 (23.5)	35 (34.0)	12,055 (23.5)	0.016
BM ≤ 40	40,418 (97.3)	71 (89.9)	40,489 (97.3)	
BMI > 40	1113 (2.7)	8 (10.1)	1121 (2.7)	<0.001
Median length of stay, days	2 (1–3)	2 (1–4)	2 (1–3)	<0.001
Median operating time, min	75 (57–100)	80 (60–128)	75 (57–100)	0.009
Cancer surgery				
Benign	45,752 (89.3)	73 (70.9)	45,825 (89.3)	
Cancer	5483 (10.7)	30 (29.1)	5513 (10.7)	<0.001
Route of surgery				
Open	25,705 (50.2)	73 (70.9)	25,778 (50.2)	
Minimally invasive	25,530 (49.8)	30 (29.1)	25,560 (49.8)	<0.001
Lymphadenectomy				
No LND	49,740 (97.1)	86 (83.5)	49,826 (97.1)	
LND	1495 (2.9)	17 (16.5)	1512 (2.9)	<0.001
Non-smoking	40,926 (79.9)	88 (85.4)	41,014 (79.9)	
Smoking	10,309 (20.1)	15 (14.6)	10,324 (20.1)	0.199
No previous VTE	50,355 (98.3)	63 (61.2)	50,418 (98.2)	
Previous VTE	880 (1.7)	40 (38.8)	920 (1.8)	<0.001
FIGO classification				
Benign	45,752 (89.4)	73 (71.6)	45,825 (89.4)	
Stage I–II	4793 (9.4)	23 (22.5)	4816 (9.4)	
Stage III–IV	623 (1.2)	6 (5.9)	629 (1.2)	<0.001
Histopathology				
Endometrioid	4442 (85.5)	26 (89.7)	4468 (85.6)	
Non-endometrioid	751 (14.5)	3 (10.3)	754 (14.4)	0.716
Tumor grade				
Grade 1–2	3464 (87.5)	16 (84.2)	3480 (87.5)	
Grade 3	496 (12.5)	3 (15.8)	499 (12.5)	0.935

Abbreviations: MIS, minimally invasive surgery; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.
[a] Data are expressed as n (column %), median (interquartile range). Column n does not add up to the total n in case of missing data.

Including comorbidities in the multivariable analysis had no effect on the estimates of OR's (Supplementary Fig. S2). Comparing patients undergoing hysterectomy for benign disease with patients undergoing surgery due to endometrial cancer showed no statistically significant difference in adjusted OR (1.47; 95% CI, 0.74–2.91; p = 0.27) (Fig. 3). The incidence of VTE was 0.1% with minimally invasive surgery compared to 0.3% with open surgery and the adjusted OR was 0.46 (95% CI, 0.30–0.71; p < 0.001). VTE incidence was 0.2% in patients with BMI ≤ 40 compared to 0.7% with BMI above 40, adjusted OR was 2.34; (95% CI, 1.10–5.01; p = 0.03). Patients undergoing lymphadenectomy in addition to hysterectomy had a VTE incidence of 1.1% compared to 0.2% in hysterectomy alone (adjusted OR = 4.00; 95% CI, 1.89–8.46; p < 0.001). Previous history of VTE was the strongest predictor of 30-day postoperative VTE risk with a 4.3% incidence compared to 0.1% in patients with no previous VTE and adjusted OR 34.1 (95% CI, 22.7–51.3; p < 0.001).

4. Discussion

In agreement with previous studies, we found an overall low incidence of 30-day postoperative VTE of 0.2% [19]. The risk was highest in open surgery for endometrial cancer (21/3377 = 0.6%), 0.4% (9/2136) in MIS for endometrial cancer, 0.2% (52/22,401) in open surgery for benign conditions, and 0.1% (21/23,424) in MIS for benign conditions. Endometrial cancer patients were more likely to have comorbidities, which was expected since these patients were older. Furthermore BMI and diabetes are recognized risk factors for endometrial cancer [4]. The higher comorbidity did not influence on the OR for VTE. White previously demonstrated a dramatic increase in risk of VTE after the age of 60 and this is commonly used as the cut-off when reporting the incidence of VTE related to age [5,20]. In the present study, age was not associated with VTE in the multivariable model. When adjusting for known risk factors, we found an OR of 1.47 (95% CI, 0.74–2.91; p = 0.27) in endometrial cancer using patients undergoing hysterectomy for benign conditions as the reference. While this difference was not statistically significant it cannot be rejected that a study with higher power could detect an increased risk. Nevertheless, the present study does show convincingly that the risk of VTE after hysterectomy performed for endometrial cancer is low and, at least, not much higher than hysterectomy for a benign condition. Previously, Nick et al. found high-complexity MIS (including patients undergoing lymphadenectomy) to be associated with a higher risk of VTE [21]. We identified lymphadenectomy as a significant risk factor for developing

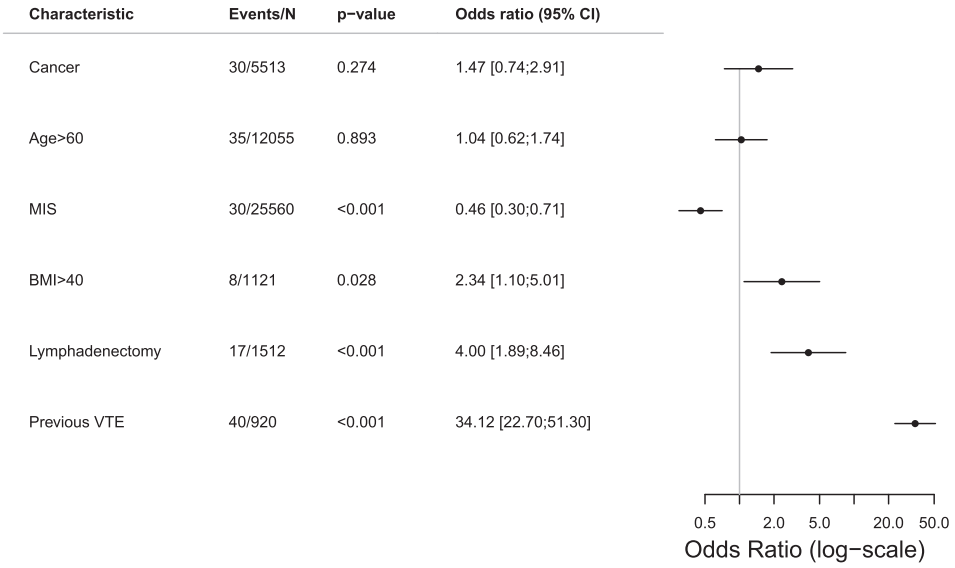

Fig. 3. Odds ratios of venous thromboembolism associated with cancer disease, age, approach to hysterectomy, BMI, lymphadenectomy and previous venous thromboembolism.

postoperative VTE after surgery for endometrial cancer (OR = 4.00; 95% CI, 1.89–8.46; $p < 0.001$). As previously reported, we found that patients with a history of VTE were at high risk of developing a new VTE following surgery [10]. In accordance with the findings by Barber et al. we found that MIS was associated with a lower incidence of VTE, and that BMI higher than 40 increased risk of VTE [5].

A Directed Acyclic Graphs was used to assess the causal relationship between exposure, outcome and potential confounders (Supplemental Fig. S3). Operative time and length of stay were interpreted as intermediary variables between main exposure and outcome and were not included in the multivariable analysis to avoid overadjustment bias [22,23]. Furthermore, length of stay could act as a collider since both the operation and VTE could cause an increased length of stay. Controlling for length of stay would accordingly introduce selection bias [24].

This study was conducted prior to implementation of a recommendation of four weeks extended VTE prophylaxis following major gynecologic oncology surgery in Denmark. National guidelines in the study period recommended low molecular weight heparin (LMWH) in prophylactic dosage, initiated 12 h prior to surgery, once daily hereafter and throughout hospital stay. Patients undergoing hysterectomy for benign disease received LMWH 6 h following surgery, once daily and throughout the hospital stay. Danish guidelines also recommend elastic compression stockings throughout hospital stay, and intermittent pneumatic compression is used during robotic surgery in some of the cancer centers. A report from the Danish Hysterectomy Database presents high adherence to thrombosis prophylaxis guidelines [25].

Rauh-Hain et al. observed a higher rate of VTE in non-endometrioid carcinomas and endometrioid carcinomas grade 3 in a large cohort of 23,122 endometrial cancer patients followed for up to 24 months after diagnosis [26]. In the present study, tumor type and grade of differentiation were not associated with OR of VTE in the univariable analysis (Table 2) and FIGO stage did not significantly influence on the estimates in a multivariable analysis (data not shown). Lymphadenectomy is performed in high-risk patients and could for this reason serve as a "proxy" for some of the cancer specific variables. The low incidence of VTE following surgery for endometrial cancer could be explained by a minor systemic effect of low risk endometrial cancers compared to other cancers with a more aggressive tumor biology such as pancreatic and ovarian cancer [1]. Gade et al. investigated the impact of cancer stage on VTE incidence in different cancer types and found the highest incidence rate difference between localized and advanced disease in uterine cancer [27]. Satoh et al. found advanced disease, non-endometrioid tumors and myometrial invasion>50% associated with asymptomatic VTE before treatment in endometrial cancer, which supports the theory of a systemic effect in metastatic disease and with high-risk tumors [28]. Results from cohort studies investigating risk of VTE in endometrial cancer independent of treatment cannot be directly compared to our results, since some of the patients included would not be considered for surgery due to advanced disease and comorbidities. Furthermore, follow-up periods in such studies are generally longer.

The strength of using Danish national registers is the possibility of investigating the relationship between exposures and outcome in a large population based cohort with prospectively collected, high-quality clinical data [15,29]. VTE diagnoses registered in the DNPR have recently been validated and the positive predictive value is reported high in both cancer-specific subsets (84.4% and 86%) and in the general population (88%) [30–32]. To reduce confounding, we excluded patients with concomitant or previous cancers within three years before surgery, as these could serve as competing risk factors for VTE.

The observational nature of this study allows us only to report cases of symptomatic VTE's and bias could arise from misclassification of both disease and treatment. Another limitation of the study, is that we cannot conclude if any prophylaxis is necessary following MIS in patients without risk factors, since most of the patients in the present study received dual prophylaxis throughout hospital stay.

5. Conclusion

The risk of VTE following surgery for endometrial cancer was very low and not significantly different to the risk after hysterectomy for benign conditions. Risk factors in the present study were open surgery, body mass index higher than 40, lymphadenectomy and previous VTE. Based on our results, we find that extended thrombosis prophylaxis might not be required in all patients following surgery for endometrial cancer. We suggest that risk assessment tools are developed to be able to make individual decisions about thrombosis prophylaxis in gynecological oncology.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.022.

Authorship

Contribution: HSK, AAK, OTU, OBC and CTP designed the study. HSK and RNM performed data merging, analysis and interpretation. HSK wrote the manuscript. CTP and CH provided derived data sets for merging, interpreted the data and reviewed the manuscript. AAK, OTU, AG, RNM and OBC interpreted the data and reviewed the manuscript.

Declaration of Competing Interest

The authors report no conflict of interest.

Acknowledgements

The project was funded by Department of Clinical Medicine, Aalborg University and the Danish Cancer Research Fund. The Danish Gynecological Cancer Database is acknowledged for providing data for the study. Karina Frahm Kirk is acknowledged for English proof reading of the manuscript.

References

[1] T. Wun, R.H. White, Epidemiology of cancer-related venous thromboembolism, Best Pract. Res. Clin. Haematol. 22 (2009) 9–23, https://doi.org/10.1016/j.beha.2008.12.001.
[2] M.S. Rasmussen, L.N. Jørgensen, P. Wille-Jørgensen, Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery, Cochrane Database Syst. Rev. (1) (2009) 1–19, https://doi.org/10.1002/14651858.CD004318.pub2 Art. No.: CD004318.
[3] A. Fagarasanu, G.S. Alotaibi, R. Hrimiuc, A.Y.Y. Lee, C. Wu, Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: a systematic review and meta-analysis, Ann. Surg. Oncol. 23 (2016) 1422–1430, https://doi.org/10.1245/s10434-016-5127-1.
[4] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, A. González-Martín, J. Ledermann, C. Marth, R. Nout, D. Querleu, M.R. Mirza, C. Sessa, ESMO-ESGO-ESTRO consensus conference on endometrial cancer, Int. J. Gynecol. Cancer 26 (2015) 2–30, https://doi.org/10.1097/igc.0000000000000609.
[5] E.L. Barber, P.A. Gehrig, D.L. Clarke-pearson, Venous thromboembolism in minimally invasive compared with open hysterectomy for endometrial cancer, Obstet. Gynecol. 128 (2016) 121–126, https://doi.org/10.1097/AOG.0000000000001492.
[6] A.H. Freeman, A. Barrie, L. Lyon, R.D. Littell, C. Garcia, C. Conell, C.B. Powell, Venous thromboembolism following minimally invasive surgery among women with endometrial cancer, Gynecol. Oncol. 142 (2016) 267–272, https://doi.org/10.1016/j.ygyno.2016.06.002.
[7] S. Sandadi, S. Lee, A. Walter, G.J. Gardner, N.R. Abu-rustum, Y. Sonoda, C.L. Brown, E. Jewell, R. Parameswaran, R.R. Barakat, M.M.L. Jr, Incidence of venous thromboembolism after minimally invasive surgery in patients with newly diagnosed endometrial cancer, Obstet. Gynecol. 120 (2012) 1077–1083.
[8] E.L. Barber, D.L. Clarke-pearson, Prevention of venous thromboembolism in gynecologic oncology surgery, Gynecol. Oncol. 144 (2017) 420–427, https://doi.org/10.1016/j.ygyno.2016.11.036.
[9] M.K. Gould, D. a Garcia, S.M. Wren, P.J. Karanicolas, J.I. Arcelus, J. a Heit, C.M. Samama, Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2012) e227S–e277S, https://doi.org/10.1378/chest.11-2297.
[10] H.S. Kahr, O. Thorlacius-Ussing, O.B. Christiansen, R.K. Skals, C. Torp-Pedersen, A. Knudsen, Venous thromboembolic complications to hysterectomy for benign disease: a nationwide cohort study, J. Minim. Invasive Gynecol. 25 (2018) 715–723, https://doi.org/10.1016/j.jmig.2017.11.017.
[11] http://www.ssi.dk/Sundhedsdataogit/Registre/Landspatientregisteret.aspx, (n.d.).

[12] N.M.S. Committee, NOMESCO classification of surgical procedures, https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf 2010.
[13] S. Pecorelli, Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium, Int. J. Gynecol. Obstet. 105 (2009) 103–104, https://doi.org/10.1016/j.ijgo.2009.02.012.
[14] C. Andersson, S. Lyngbæk, C.D. Nguyen, M. Nielsen, G.H. Gislason, L. Køber, C. Torp-Pedersen, Association of clopidogrel treatment with risk of mortality and cardiovascular events following myocardial infarction in patients with and without diabetes, JAMA 308 (2012) 882–889, https://doi.org/10.1001/2012.jama.10779.
[15] S.K. Thygesen, C.F. Christiansen, S. Christensen, T.L. Lash, H.T. Sørensen, The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients, BMC Med. Res. Methodol. 11 (2011), 83. https://doi.org/10.1186/1471-2288-11-83.
[16] J. Dextor, J. Hardt, S. Knüppel, A graphical tool for analyzing causal diagrams, Epidemiology 22 (2011) 745.
[17] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, J. Clin. Epidemiol. 61 (2008) 344–349, https://doi.org/10.1016/j.jclinepi.2007.11.008.
[18] R Development Core Team, R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2017 (R A Lang. Environ. Stat. Comput. (2017).
[19] E.M. Jorgensen, H.C. Hur, Venous thromboembolism in minimally invasive gynecologic surgery: a systematic review, J. Minim. Invasive Gynecol. 26 (2019) 186–196, https://doi.org/10.1016/j.jmig.2018.08.025.
[20] R.H. White, The epidemiology of venous thromboembolism, Circulation 107 (2003) I4–I8, https://doi.org/10.1161/01.CIR.0000078468.11849.66.
[21] A.M. Nick, K.M. Schmeler, M.M. Frumovitz, P.T. Soliman, W. a Spannuth, J.K. Burzawa, R.L. Coleman, C. Wei, R. dos Reis, P.T. Ramirez, Risk of thromboembolic disease in patients undergoing laparoscopic gynecologic surgery, Obstet. Gynecol. 116 (2010) 956–961, https://doi.org/10.1097/AOG.0b013e3181f240f7.
[22] E. Vittinghof, D.V. Glidden, S.C. Shiboski, C.E. McCulloch, Predictor selection, Regres. Methods Biostat, Second EdiSpringer 2012, pp. 395–429.
[23] E.F. Schisterman, S.R. Cole, R.W. Platt, Overadjustment bias and unnecessary adjustment in epidemilogic studies, Epidemiology 20 (2009) 488–495, https://doi.org/10.1097/EDE.0b013e3181a819a1.Overadjustment.
[24] S. Greenland, J. Pearl, J.M. Robins, Causal diagrams for epidemiologic research, Epidemiology 10 (1999) 37–48, https://doi.org/10.1097/00001648-199901000-00008.
[25] C.T. Hansen, H. Kehlet, C. Møller, L. Mørch, J. Utzon, B. Ottesen, Timing of heparin prophylaxis and bleeding complications in hysterectomy a nationwide prospective cohort study of 9,949 Danish women, Acta Obstet. Gynecol. Scand. 87 (2008) 1039–1047, https://doi.org/10.1080/00016340802419384.
[26] J.A. Rauh-Hain, E. Hariton, J. Clemmer, R.M. Clark, T. Hall, D.M. Boruta, J.O. Schorge, M.G. Del Carmen, Incidence and effects on mortality of venous thromboembolism in elderly women with endometrial cancer, Obstet. Gynecol. 125 (2015) 1362–1370, https://doi.org/10.1097/AOG.0000000000000866.
[27] I.L. Gade, S.K. Braekkan, I.A. Naess, J.-B. Hansenx, S.C. Cannegieter, K. Overvad, H. Jensvoll, J. Hammerstrøm, K. Blix, A. Tjønneland, S.R. Kristensen, M.T. Severinsen, The impact of initial cancer stage on the incidence of venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort, J. Thromb. Haemost. 38 (2017) 42–49, https://doi.org/10.1111/jth.13752.
[28] T. Satoh, K. Matsumoto, K. Uno, M. Sakurai, S. Okada, M. Onuki, T. Minaguchi, Y.O. Tanaka, S. Homma, A. Oki, H. Yoshikawa, Silent venous thromboembolism before treatment in endometrial cancer and the risk factors, Br. J. Cancer 99 (2008) 1034–1039, https://doi.org/10.1038/sj.bjc.6604658.
[29] C.S. Juhl, E.S. Hansen, C.K. Høgdall, G. Ørtoft, Valid and complete data on endometrial cancer in the Danish Gynaecological Cancer Database, Dan. Med. J. 61 (2014) 1–5.
[30] I.L. Gade, S.J. Riddersholm, I. Christiansen, A. Rewes, M. Frederiksen, L. Enggaard, C.B. Poulsen, O.J. Bergmann, D.B. Gillström, R.S. Pedersen, L. Nielsen, H.H. Eriksen, C. Torp-Pedersen, S.R. Kristensen, M.T. Severinsen, Venous thromboembolism in chronic lymphocytic leukemia: a Danish nationwide cohort study, Blood Adv 2 (2018) 3025–3034, https://doi.org/10.1182/bloodadvances.2018023895.
[31] A. Drljevic, M. Borre, M. Høyer, V. Ehrenstein, M. Nguyen-Nielsen, Quality of venous thromboembolism diagnoses among prostate cancer patients in the Danish National Registry of Patients, Clin. Epidemiol. 6 (2014) 351–357, https://doi.org/10.2147/CLEP.S65681.
[32] J. Sundbøll, K. Adelborg, T. Munch, T. Frøslev, H.T. Sørensen, H.E. Bøtker, M. Schmidt, Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study, BMJ Open 6 (2016) 1–11, https://doi.org/10.1136/bmjopen-2016-012832.