Clinical Epidemiology

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ORIGINAL RESEARCH

Venous Thromboembolism and Risk of Cancer in Patients with Diverticular Disease: A Danish Population-Based Cohort Study

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Purpose: Venous thromboembolism may be a harbinger of cancer. Patients with diverticular disease are suggested to have an increased risk of developing venous thromboembolism compared with the general population, but it remains unclear whether venous thromboembolism is also a marker of occult cancer in these patients. We investigated the risk of cancer after venous thromboembolism among patients with diverticular disease.

Patients and Methods: We used Danish health registries to conduct a nationwide, population-based cohort study during 1996–2017. We identified all venous thromboembolism patients with a diagnosis of diverticular disease and calculated absolute risks of cancer and standardized incidence ratios (SIRs) by comparing observed and expected cancer incidence based on national cancer incidence in the Danish population.

Results: We followed 3406 patients with venous thromboembolism and diverticular disease for a median of 3.0 years (interquartile range: 1.0–6.0). During the first year of follow-up, we observed 212 cancer cases. The corresponding one-year risk of cancer was 6.2% (95% confidence interval [CI]: 5.5–7.1) with a SIR of 2.9 (95% CI: 2.5–3.3). The SIRs were particularly elevated for cancers of the stomach, pancreas, ovary, and kidney. During the second and subsequent years of follow-up, 337 cancers were diagnosed with a SIR of 1.1 (95% CI: 1.0–1.3).

Conclusion: Venous thromboembolism is a harbinger of occult cancer in patients with diverticular disease.

Keywords: epidemiology, pulmonary embolism, deep venous thrombosis, diverticulitis, perforated diverticulitis, cancer

Video abstract

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Introduction

There is compelling evidence that venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), is a complication of cancer.[1,2] On the other hand, among patients diagnosed with VTE, studies have shown a two- to fourfold increased one-year risk of subsequent cancer compared with the general population.[1,3,4] Thus, VTE may be considered a sign of an occult cancer.[1] The pathogenetic mechanisms underlying this association are thought to include hypercoagulability due to activation of clotting by tumor cells, vessel wall injury, and stasis.[1,5]

Diverticular disease (DD), a common condition in the Western world, occurs by herniation of mucosa and submucosa through the muscular layer of the colonic wall.[6] In the western world, the prevalence of DD is reported to be up to 50% of

Received: 5 April 2021
Accepted: 17 July 2021
Published: 20 August 2021

adults aged 60 years and older.[7] The condition remains asymptomatic in most cases; however, around five percent of patients develop complications such as bowel obstruction, inflammation, bleeding, or perforation.[8] The most common complications include diverticular bleeding and diverticulitis.[6] Compared with the general population, patients with both diverticulitis and perforated diverticulitis are suggested to have a 40% increased risk of developing VTE.[9]

Previous studies have shown a two- to threefold increased one-year risk of cancer after VTE among patients with concurrent liver disease, inflammatory bowel disease, rheumatoid arthritis, and diabetes.[10–13] These studies have contributed with evidence that can be used for clinical decision-making when planning the diagnostic workup for occult cancer in patients with VTE and specific comorbidities. However, it remains unknown whether VTE could also be considered a marker of occult cancer in patients with DD. Thus, enhanced understanding of cancer risk after VTE in DD patients is needed.

We, therefore, conducted a population-based cohort study in Denmark to examine the risk of cancer following VTE among patients with DD and compared the observed risk of cancer with the expected based on national cancer incidence rates.

Materials and Methods

Setting

We conducted a population-based cohort study based on the entire Danish population during 1 April 1996–31 December 2017. We obtained prospectively collected data from the Danish National Patient Registry (DNPR) and the Danish Cancer Registry (DCR). Since 1968, all Danish residents are assigned a unique ten-digit civil registration number and registered in the Civil Registration System. This allows exact individual-level linkage between the DNPR and the DCR.[14] All Danish residents are covered by the tax-financed public health insurance.[15] The study was conducted in a setting without specific cancer screening for patients with DD; however, DD patients were invited to the Danish national colorectal cancer screening from 2014–2017 on equal conditions as all other Danes aged 50–74 years.[16]

Venous Thromboembolism and Diverticular Disease Cohort

We searched the DNPR to identify all patients with a first-time hospital-based diagnosis (primary [ie main diagnosis of hospital contact] or secondary [ie diagnoses recorded in addition to the primary diagnosis], excluding emergency room diagnoses) of VTE during 1996–2016. The inclusion ended on 31 December 2016 to ensure at least one year of follow-up after VTE for all included patients. VTE events included both PE and DVT (see Supplementary Table 1 for ICD codes). Since 1977, the DNPR has recorded information on all patients discharged from Danish non-psychiatric hospitals. Since 1995, all psychiatric inpatients, psychiatric and somatic outpatients, and emergency room contacts have been included in the DNPR.[17] The information recorded in the DNPR includes the civil registration number, dates of hospital admission and discharge, treatments, examinations, and up to 20 discharge diagnoses. Diagnoses are coded according to the International Classification of Diseases, Eighth revision (ICD-8) until 31 December 1993 and according to the Tenth revision (ICD-10) thereafter.[17] Since 1996, surgical procedures have been coded according to the Nordic Medico-Statistical Committee (NOMESCO) classification of surgical procedures.

We restricted the VTE cohort to patients with a prior or concurrent diagnosis of DD (Figure 1 illustrates the study population). We applied two methods to further categorize patients with DD, to be able to investigate if the type and treatment of DD could have an impact on the risk of cancer after VTE. First, based on ICD-8 and ICD-10 codes, we categorized DD patients into diverticulitis and perforated diverticulitis (see Supplementary Table 1 for ICD codes). Second, based on ICD-10 and NOMESCO codes, we categorized DD patients into those surgically treated, conservatively treated, and others (see Supplementary Table 1 for ICD codes). The total number of DD patients with VTE were identified from all DD diagnoses codes (ICD-8, ICD-10) while subgroups were identified as described above. Thus, the total number of patients in each subgroup did not correspond to the total number of DD patients included in our study. The groups within the two different DD categorization methods were mutually exclusive. Hence, when multiple DD codes were recorded, patients were assigned to the DD group based on the diagnosis recorded closest to their VTE diagnosis.

Cancer Outcomes

We linked the cohort of VTE patients with DD to the DCR to identify incident cancers recorded after a VTE. The DCR has recorded all cases of cancer in the Danish population since 1978, coded according to ICD-10.[18] Cancers

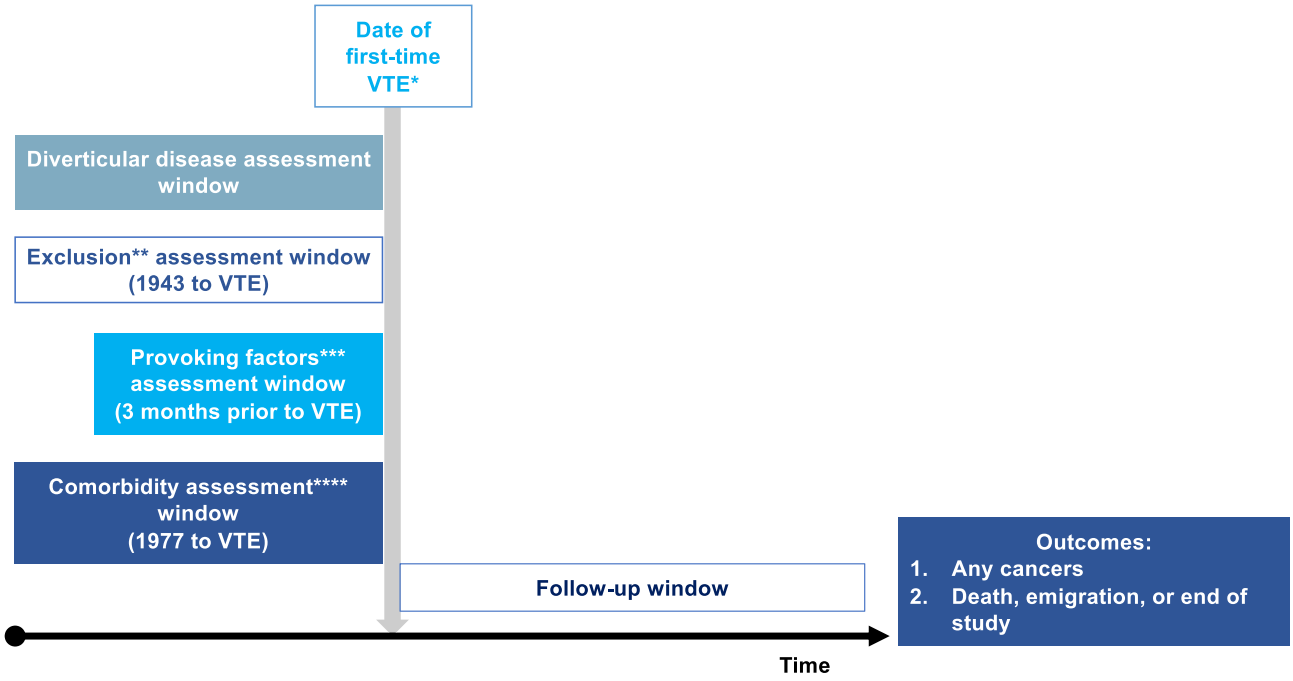

Figure 1 Study flow diagram (*Venous thromboembolism, **Any cancers, ***Fractures/trauma, pregnancy, or surgery, ****According to Charlson Comorbidity Index).

are categorized according to the annual cancer report published by The Danish Health Data Authority in 2018.[19] Using data from the DCR, we excluded all patients with a cancer diagnosis recorded before or at the date of VTE diagnosis (Figure 1).

Covariates

We used the DNPR to ascertain the presence of previous provoking factors for VTE and comorbidities recorded before the date of VTE (Figure 1). We considered fracture/trauma, pregnancy, or surgery recorded in the DNPR within three months prior to the VTE event (admission date) as provoking factors for VTE.[20] VTEs without these conditions recorded prior to diagnosis were considered as unprovoked.[20] Based on hospital discharge diagnoses recorded in the DNPR from 1977 to the date of VTE, we used the Charlson Comorbidity Index (CCI) to measure the burden of comorbidity. The CCI is a scoring system that assigns from one to six points to a range of diseases based on their impact on mortality (see Supplementary Table 2 for ICD codes and assigned weighting).[21] According to the calculated CCI score, we categorized all VTE patients with DD into three subgroups: low (no comorbidity) = CCI score of 0, medium = CCI score of 1–2, or high = CCI score of 3 or more. Of note, we applied a modified CCI excluding any previous tumors before the VTE diagnosis from counting in the index, because any cancers recorded before the index date were excluded initially.

Statistical Analysis

We categorized all VTE patients with a history of DD according to age, sex, year of VTE diagnosis, type of DD, type of treatment for DD, CCI score, and presence of provoking factors. We followed all VTE patients with DD from the date of VTE diagnosis until occurrence of a first-time cancer diagnosis, death, emigration, or administrative end of follow-up (31 December 2017), whichever occurred first. We divided the follow-up period into one year (first year) and more than one year (second and subsequent years) following the VTE diagnosis.

We calculated the absolute risks of cancer after VTE as the cumulative incidence proportions considering death as a competing risk.[22] As a measure of the relative risk, we calculated standardized incidence ratios (SIRs) - the ratio of the observed number of cancers to the expected number of cancers. We used the national cancer incidence rates to calculate the expected number of cancer cases after a first-time hospital-based diagnosis of VTE according to sex, age, and calendar period of diagnosis (one year intervals). Multiplying the number of years of follow-up by the incidence rates yielded the number of expected cancer cases if patients with VTE and DD had the same risk of cancer as the general population. We calculated 95% confidence intervals (CIs) for SIRs under the assumption that the observed number of cases in a specific category followed a Poisson

distribution.[22] When the observed number was less than ten, the exact 95% CIs were used; otherwise Byar's approximation was used.[22] Both SIRs and absolute risks were stratified by sex, age, calendar period, CCI score at the date of VTE, and presence of classic provoking factors for VTE recorded in the DNPR within three months prior to the VTE. We conducted analyses for VTE and for PE and DVT separately. Patients with a simultaneous diagnosis of PE and DVT were considered as having PE.

We conducted all statistical analyses using SAS statistical software package, V.9.4 (SAS Institute, Cary, North Carolina, USA). The study was reported to the Danish Data Protection Agency by Aarhus University (record number 2016–051-000001/811). According to Danish legislation, no approval from an ethics committee or informed consent from patients are required for register-based studies.[23]

Results

Descriptive Data

We followed 3406 incident VTE patients with a diagnosis of DD for a median follow-up time of 3.0 years

Table 1 Characteristics of Patients Having Venous Thromboembolism (VTE) and Diverticular Disease (DD). Denmark 1996–2016

Variable	Patients with DD and VTE	Patients with DD and PE	Patients with DD and DVT
Total number	3406	1696 (49.8)	1710 (50.2)
Median follow-up time (IQR), years	3.0 (1.0–6.0)	2.1 (0.3–4.7)	3.9 (1.7–7.2)
Median age at VTE diagnosis, years	77.2 (68.4–83.7)	77.8 (69.7–83.9)	76.5 (66.7–90.7)
0–69	981 (28.8)	437 (12.8)	544 (16.0)
70–84	1720 (50.5)	895 (26.3)	825 (24.2)
85+	705 (20.7)	364 (10.7)	341 (10.0)
Sex			
Female	2148 (63.1)	1056 (31.0)	1092 (32.1)
Male	1258 (36.9)	640 (18.8)	618 (18.1)
Year of VTE diagnosis			
1996–1999	293 (8.6)	110 (3.2)	183 (5.4)
2000–2004	590 (17.3)	260 (7.6)	330 (9.7)
2005–2009	796 (23.4)	353 (10.4)	443 (13.0)
2010–2014	1157 (34.0)	608 (17.9)	549 (16.1)
2015–2016	570 (16.7)	365 (10.7)	205 (6.0)
Type of DD[a]			
Diverticulitis	213 (6.3)	94 (5.5)	119 (7.0)
Perforated diverticulitis	300 (8.8)	162 (9.6)	138 (8.1)
Type of treatment[b]			
DD surgically treated	50 (1.7)	22 (0.7)	28 (0.9)
DD conservatively treated	2402 (81.0)	1322 (44.6)	1080 (36.4)
Other cases of diverticular disease	512 (17.3)	164 (5.5)	348 (11.7)
Charlson Comorbidity Index (CCI)			
CCI: Low	1227 (36.0)	549 (16.1)	678 (19.9)
CCI: Medium	1501 (44.1)	751 (22.1)	750 (22.0)
CCI: High	678 (19.9)	396 (11.6)	282 (8.3)
Provoking factor[c]			
Absent	2570 (75.5)	1264 (37.1)	1306 (38.3)
Present	836 (24.5)	432 (12.7)	404 (11.8)

Notes: [a]Type of diverticular disease classified according to ICD-10: overall: DK572-9, diverticulitis: 562.11(ICD-8), perforated diverticulitis: 562.12, DK572, DK574, DK578. [b]Type of DD treatment classified according to ICD-10: Surgically treated: DK572-9 and KJF, KJG, or KJAH01, conservatively treated: inpatient diagnoses of DK572-9, other: outpatient diagnoses of DK572-9. [c]VTE provoking factors were classified as fracture/trauma, pregnancy, or surgery recorded in the DNPR within three months prior to the VTE event (admission date). Patients without these were considered to have no previous presence of provoking factors.
Abbreviations: PE, pulmonary embolism; DVT, deep venous thrombosis; IQR, interquartile rage.

(interquartile range [IQR]: 1.0–6.0). Table 1 shows patient characteristics. The median age at VTE diagnosis was 77.2 years (IQR: 68.4–83.7), and more than half of the patients were female (63.1%). Overall, 836 patients (24.5%) had a provoking factor diagnosed within 90 days prior to the VTE, and 1501 (44.1%) had a medium CCI score. Among included VTE patients with DD, 1696 (49.8%) had PE (Table 1). The characteristics at date of VTE were virtually equal across patients with PE and patients with DVT.

First Year of Follow-Up

Within one year after VTE diagnosis, 212 patients were diagnosed with cancer. The corresponding one-year absolute risk was 6.2% (CI: 5.5–7.1) (Figure 2 and Table 2). The total number of expected cancer cases during the first year was 72.7, yielding a SIR of 2.9 (95% CI: 2.5–3.3) (Table 3). The SIR was similar between men and women, across different age groups, calendar periods, CCI scores, and presence of provoking factors. In contrast, the SIR was higher among patients diagnosed with PE (SIR = 3.6 [95% CI: 3.0–4.3]) than among patients with DVT (SIR = 2.3 [95% CI: 1.8–2.8]). SIRs were particularly elevated during the first year of follow-up for cancers of the stomach (SIR = 9.2 [95% CI: 4.2–17.4]), pancreas (SIR = 6.8 [95% CI: 3.5–12.0]), the ovary (SIR = 11.5 [95% CI: 5.7–20.5]), and the kidney (SIR=8.2 [95% CI: 3.6–16.2]) (Table 4).

Second and Subsequent Years of Follow-Up

During the second and subsequent years, a total of 337 cancers diagnoses were observed (Table 3). Overall, the SIR decreased to 1.1 (95% CI: 1.0–1.3). SIRs had point estimates around 1.0 across all stratifications of patient characteristics and cancer sites.

Type and Treatment of Diverticular Disease

We followed 213 (6.2%) VTE patients with a history of diverticulitis and 300 (8.8%) with perforated diverticulitis (Table 1). According to type of treatment, 50 (1.7%) were surgically treated, 2402 (81.0%) were conservatively treated, and 512 (17.3%) were classified as

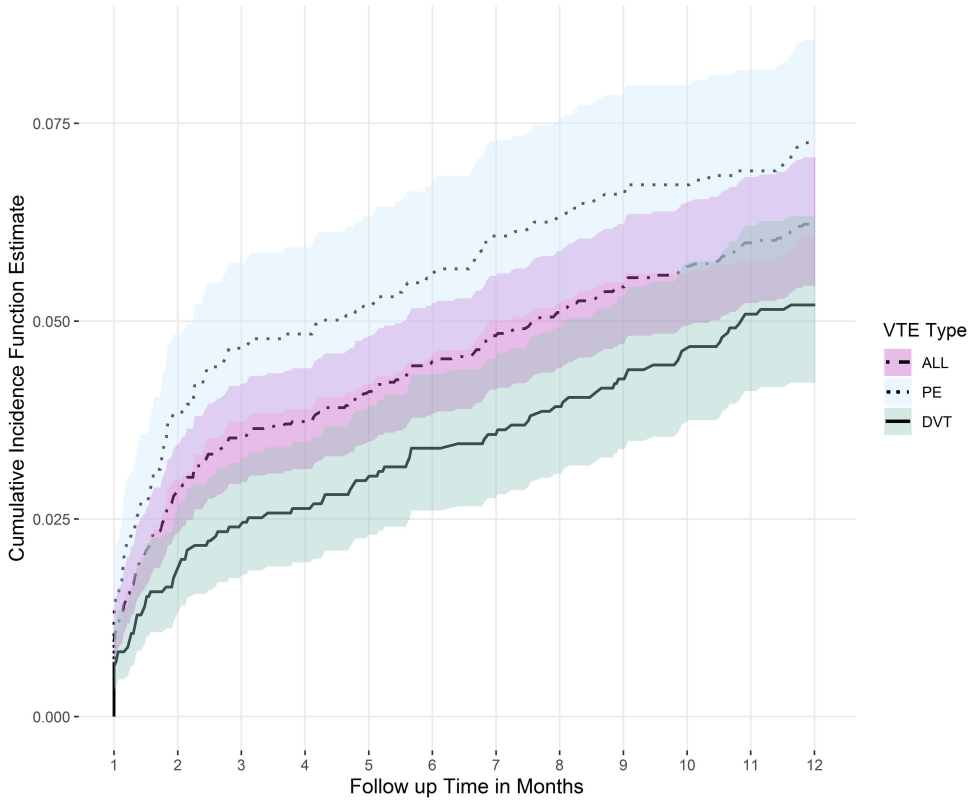

Figure 2 Cumulative incidence proportion of cancer patients with diverticular disease and venous thromboembolism.

Table 2 One-Year Absolute Risks of Cancer and 95% Confidence Intervals (CI's) Among Patients with Venous Thromboembolism (VTE) and Diverticular Disease (DD). Denmark 1996–2017

Variable	Absolute First Year-Risk (95% CI)
All	6.2 (5.5–7.1)
Median age at VTE diagnosis, years	
0–69	4.9 (3.7–6.4)
70–84	7.7 (6.5–9.0)
85+	4.5 (3.2–6.3)
Sex	
Female	5.5 (4.5–6.5)
Male	7.6 (6.2–9.1)
Year of VTE diagnosis	
1996–1999	5.5 (3.3–8.5)
2000–2004	4.6 (3.1–6.5)
2005–2009	6.3 (4.7–8.1)
2010–2014	6.6 (5.2–8.1)
2015–2016	7.5 (5.6–9.9)
VTE Type[a]	
PE	7.3 (6.1–8.6)
DVT	5.2 (4.2–6.3)
Charlson Comorbidity Index (CCI)	
CCI: Low	6.8 (5.5–8.3)
CCI: Medium	5.8 (4.7–7.1)
CCI: High	6.2 (4.6–8.2)
Provoking factors[b]	
Absent	6.5 (5.6–7.5)
Present	5.3 (3.9–6.9)

Notes: [a]ICD-10: pulmonary embolism (PE) DI26, deep venous thromboembolism (DVT) DI80.1–3. [b]VTE provoking factors were classified as fracture/trauma, pregnancy, or surgery recorded in the Danish National Patient Registry (DNPR) within three months prior to the VTE event (admission date). Patients without these were considered to have no previous presence of provoking factors.

"other". During the first year of follow-up, VTE patients with a history of perforated diverticulitis had a higher SIR for cancer (SIR = 5.3 [95% CI: 3.5–7.7]) than patients with a history of diverticulitis (SIR = 3.8 [95% CI: 2.2–6.3]) (Table 5), although 95% CIs were overlapping. Concerning type of treatment, conservatively treated DD patients had the highest SIR of cancer (SIR = 3.2 [95% CI: 2.8–3.8]). In the second and subsequent years of follow-up, the SIR decreased in both patients with diverticulitis (SIR = 1.1 [95% CI: 0.7–1.6]) and perforated diverticulitis (SIR = 1.3 [95% CI: 0.9–1.9]). Also, the SIR in the group of conservatively treated DD patients decreased (SIR = 1.1 [95% CI: 0.9–1.2]).

Discussion

Key Results

In this population-based cohort study of patients with both VTE and DD, the one-year absolute risk of cancer was six percent. Compared with the general population, the one-year risk of cancer after the VTE diagnosis was increased three-fold. Relative risks of cancer were particularly elevated for cancers of the stomach, pancreas, ovary, and kidney. One-year absolute and relative risks of cancer were higher among VTE patients diagnosed with perforated diverticulitis than among patients diagnosed with diverticulitis.

Interpretation

Although DD is suggested as a risk factor for VTE, our study is the first to investigate the risk of cancer following VTE in patients with DD.[9] Our finding of an increased risk of cancer subsequent to VTE in DD patients is in line with previous findings among patients hospitalized with VTE in the general population and indicates that VTE in patients with DD should be regarded as much a harbinger of occult cancer as it is for VTEs in the general population.[1,3,4] Generally, cancer diagnosed within one year after VTE tends to be associated with an advanced stage of cancer and a poor prognosis.[24] Screening for prevalent malignancy following VTE leads to an early detection of occult cancer at an earlier cancer stage, which may be associated with improved treatment.[25,26] However, cancer screening is generally not recommended after VTE.

The increased short-termrisk of cancer after VTE may be explained by heightened diagnostic efforts among patients with VTE or DD.[27] Figure 2 is depicting the cumulative incidence proportion of cancer within the first year after VTE in the DD population. The curve is particularly steep during the first month. This could be explained by a well-known increased risk of cancer after VTE and/or by a higher degree of examinations for potential occult cancer (called detection bias). However, if detection bias had occurred, the period of increased prevalent cancer diagnosis during the first year of follow-up would have been followed by a compensatory

Table 3 Age, Sex, and Calendar Period Standardized Incidence Ratios (SIRs) of Cancer and 95% Confidence Intervals (CI's) Among Patients with Diverticular Disease (DD) and Venous Thromboembolism (VTE). Denmark 1996–2017

Variable	First Year After VTE		>1 Year After VTE	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Total	212/72.7	2.9 (2.5–3.3)	337/300.7	1.1 (1.0–1.3)
Sex				
Female	117/41.5	2.8 (2.3–3.4)	199/176.0	1.1 (1.0–1.3)
Male	95/31.2	3.0 (2.5–3.7)	138/124.6	1.1 (0.9–1.3)
Age at having VTE diagnosis				
0–69 years	48/14.2	3.4 (2.5–4.5)	120/100.6	1.2 (1.0–1.4)
70–84 years	132/43.0	3.1 (2.6–3.6)	178/163.2	1.1 (0.9–1.3)
85+ years	32/15.4	2.1 (1.4–2.9)	39/36.8	1.1 (0.8–1.5)
Year of VTE diagnosis				
1996–1999	16/4.9	3.3 (1.9–5.3)	33/36.3	0.9 (0.6–1.3)
2000–2004	27/10.6	2.5 (1.7–3.7)	96/74.1	1.3 (1.1–1.6)
2005–2009	50/16.7	3.0 (2.2–4.0)	99/93.5	1.1 (0.9–1.3)
2010–2014	76/27.2	2.8 (2.2–3.5)	97/85.1	1.1 (0.9–1.4)
2015–2016	43/13.3	3.2 (2.3–4.4)	12/11.6	1.0 (0.5–1.8)
Type of VTE[a]				
PE	123/33.9	3.6 (3.0–4.3)	126/114.0	1.1 (0.9–1.3)
DVT	89/38.8	2.3 (1.8–2.8)	221/186.7	1.1 (1.0–1.3)
Charlson Comorbidity Index				
CCI: Low	83/25.6	3.2 (2.6–4.0)	150/136.4	1.1 (0.9–1.3)
CCI: Medium	87/33.1	2.6 (2.1–3.2)	132/130.1	1.0 (0.9–1.2)
CCI: High	42/14.0	3.0 (2.2–4.1)	55/34.1	1.6 (1.2–2.1)
Provoking factor[b]				
Absent	168/56.1	3.0 (2.6–3.5)	265/231.0	1.1 (1.0–1.3)
Present	44/16.5	2.7 (1.9–3.6)	72/69.7	1.0 (0.8–1.3)

Notes: [a]ICD-10: pulmonary embolism (PE) DI26, deep venous thromboembolism (DVT) DI80.1–3. [b]VTE provoking factors were classified as fracture/trauma, pregnancy, or surgery recorded in the Danish National Patient Registry (DNPR) within three months prior to the VTE event (admission date). Patients without these were considered to have no previous presence of provoking factors.

Abbreviations: CCI, Charlson Comorbidity Index; O, observed; E, expected.

decrease in the following follow-up period.[1,27] We did not see such a pattern.

The analysis concerning type of DD showed an increased risk of cancer following VTE independently of type of DD and type of treatment. Especially, patients diagnosed with perforated DD had a high one-year absolute and relative risk of cancer. Although our analyses were unable to explore the underlying mechanism, it is likely that immobilization, disease activity, and surgical treatment may play a role in this particularly high risk.[28]

Relative risks of cancer were particularly elevated for cancers of the stomach, pancreas, ovary, and kidney. This was in line with previous studies that found a two- to threefold increased one-year risk of cancer after VTE.[10–13]

Limitations

Strengths of the current study includes the population-based design in a setting with free access to healthcare and the high quality and continuously updated data on VTE, comorbidities, and cancer diagnoses. Further, the Danish national registries allowed us to study the entire population for a long period of time with complete follow-up minimizing the potential for selection and referral bias. The DNPR contains hospital diagnoses only and we did not have accessible data on diagnoses made by general practitioners. Fortunately, the majority of patients suspected for a VTE would be referred to a hospital department for further diagnosis and treatment by their general practitioner. Hence, they will be captured in the DNPR and included in our study.

Table 4 Age, Sex, and Calendar Period Standardized Incidence Ratios (SIRs) of Cancer and 95% Confidence Intervals (CI's) Among Patients with Venous Thromboembolism (VTE) and Diverticular Disease. Denmark 1996–2017. Numbers and SIRs Below Five are Marked with <5 to Secure Anonymity According to Danish Legislation

Cancer Groups	First Year After VTE		>1 Year After VTE	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)
All	212/72.7	2.9 (2.5–3.3)	337/300	1.1 (1.0–1.3)
Stomach	9/1.0	9.2 (4.2–17.4)	6/3.9	1.5 (0.6–3.3)
Large intestine incl. Colon rectosigmoid	24/6.1	3.9 (2.5–5.9)	35/24.9	1.4 (1.0–2.0)
Rectum	<5	NA	9/10.3	0.9 (0.4–1.7)
Pancreas	12/1.8	6.8 (3.5–12.0)	9/7.2	1.3 (0.6–2.4)
Lung, bronchi and trachea	25/7.1	3.5 (2.3–5.2)	48/28.2	1.7 (1.3–2.3)
Malignant melanoma	<5	NA	7/7.3	1.0 (0.4–2.0)
Other skin cancer (excl. Basal cell carcinoma)	5/4.4	1.1 (0.4–2.7)	33/20.5	1.6 (1.1–2.3)
Breast	7/6.8	1.0 (0.4–2.1)	19/28.1	0.7 (0.4–1.1)
Uterus	<5	NA	7/5.7	1.2 (0.5–2.5)
Ovary	11/1.0	11.5 (5.7–20.5)	<5	NA
Prostate	21/6.1	3.5 (2.1–5.3)	22/24.1	0.9 (0.6–1.4)
Kidney	8/1.0	8.2 (3.6–16.2)	<5	NA
Urinary bladder	7/3.3	2.1 (0.8–4.3)	12/13.2	0.9 (0.5–1.6)
Non-Hodgkin malignant lymphoma	10/2.4	4.2 (2.0–7.7)	7/9.9	0.7 (0.3–1.5)
Metastases and non-specified cancer in lymph nodes	20/1.6	12.8 (7.8–19.8)	5/6.2	0.8 (0.3–1.9)
Basal cell carcinoma	16/15.8	1.0 (0.6–1.6)	71/68.1	1.0 (0.8–1.3)

Abbreviations: O, observed; E, expected.

Table 5 One-Year Absolute Risks and Age, Sex, and Calendar Period Standardized Incidence Ratios (SIRs) of Cancer and 95% Confidence Intervals (CI's) Among Patients with Venous Thromboembolism (VTE) and Diverticular Disease (DD) According to Type and Treatment of DD. Denmark 1996–2017. Numbers and SIRs Below Five are Marked with <5 to Secure Anonymity According to Danish Legislation

Variable	Absolute First Year-Risk (95% CI)	First Year After VTE		>1 Year After VTE	
		O/E	SIR (95% CI)	O/E	SIR (95% CI)
Type of DD[a]					
Diverticulitis	7.5 (4.5–11.6)	16/4.2	3.8 (2.2–6.3)	27/24.1	1.1 (0.7–1.6)
Perforated diverticulitis	9.3 (6.4–13.0)	28/5.3	5.3 (3.5–7.7)	32/24.3	1.3 (0.9–1.9)
Type of treatment[b]					
DD surgically treated	2.0 (0.2–9.4)	<5	NA	9/5.6	1.6 (0.7–3.1)
DD conservatively treated	6.8 (5.8–7.8)	163/50.5	3.2 (2.8–3.8)	210/197.8	1.1 (0.9–1.2)
Other cases of DD	4.1 (2.6–6.1)	21/12.5	1.7 (1.0–2.6)	59/48.2	1.2 (0.9–1.6)

Notes: [a]Type of diverticular disease classified according to ICD-10: overall: DK572-9, diverticulitis: 562.11(ICD-8), perforated diverticulitis: 562.12, DK572, DK574, DK578. [b]Type of diverticular disease treatment classified according to ICD-10: Surgically treated: DK572-9 and KJF, KJG, or KJAH01, conservatively treated: inpatient diagnoses of DK572-9, other: Outpatient diagnoses of DK572-9.

Limitations of our study include the potential misclassification of diagnostic coding of VTE, DD, cancer, and other comorbidities. However, the positive predictive value has been found to be sufficiently high for both VTE (75–90%),[29] DD (98%),[30] cancer (95–98%),[31] and other comorbidities (98%).[21] To circumvent some potential misclassification of the VTE diagnosis, we excluded patients diagnosed in emergency departments, because these often are based only on clinical suspicion.[29] Further, the diagnostic coding of DD in the DNPR does not differentiate between patients with diverticulosis and diverticulitis as well as between patients with uncomplicated diverticulosis or with specific diverticular complications.[30] Instead, we combined subgroups of diagnostic codes to categorize the type of DD to investigate the risk of cancer following VTE in specific groups of DD patients. Patients conservatively treated had a higher cancer incidence rate, than patients surgically treated. Surgical resection of an inflamed bowel segment may secure a lower degree of intestinal and systemic inflammation, in turn decreasing the risk for subsequent cancer development. The cohort includes all patients with a history of prior DD, irrespective of treatment status. Therefore, some patients underwent surgery and might no longer have active DD at the time of VTE diagnosis. This detail should be kept in mind when interpreting our findings. Lastly, it should be noted that the grouping of treatment for DD was conducted on other codes than type of DD. Hence, it is not possible to directly compare the estimates showed for different treatment of DD (ie surgical, conservative, or other) and different type of DD (ie diverticulitis or perforated diverticulitis).

Conclusion

In conclusion, compared with the general population, VTE patients with DD had a three-fold increased risk of cancer within the first year following VTE. Our results suggest that VTE may be a harbinger of occult cancer in patients with DD.

Acknowledgments

The Department of Clinical Epidemiology is involved in studies with funding from various companies in the form of research grants to and administered by Aarhus University. None of these studies are related to the present study.

Disclosure

The authors report no conflicts of interest in this work.

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