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Risk of venous thromboembolism in men with prostate cancer compared with men in the general population: a nationwide population-based cohort study in Sweden

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ABSTRACT

Objective To estimate the additional risk of venous thromboembolism (VTE) in men with prostate cancer compared with men without prostate cancer in Sweden.

Design Nationwide cohort study following 92 105 men with prostate cancer and 466 241 men without prostate cancer (comparison cohort) matched 5:1 by birth year and residential region.

Setting The male general population of Sweden (using the Nationwide Prostate Cancer data Base Sweden).

Primary and secondary outcome measures Crude incidence proportion ratios (IPRs) comparing the incidence of VTE in men with prostate cancer and men in the comparison cohort. Cox regression was used to calculate HRs for VTE adjusted for confounders.

Results 2955 men with prostate cancer and 9774 men in the comparison cohort experienced a first VTE during a median of 4.5 years' follow-up. Deep vein thrombosis (DVT) accounted for 52% of VTE cases in both cohorts. Median time from start of follow-up to VTE was 2.5 years (IQR 0.9–4.7) in the prostate cancer cohort and 2.9 years (IQR 1.3–5.0) in the comparison cohort. Crude incidence rates of VTE per 1000 person-years were 6.54 (95% CI 6.31 to 6.78) in the prostate cancer cohort (n=2955 events) and 4.27 (95% CI 4.18 to 4.35) in the comparison cohort (n=9774 events). The IPR decreased from 2.53 (95% CI 2.26 to 2.83) at 6 months to 1.59 (95% CI 1.52 to 1.67) at 5 years' follow-up. Adjusted HRs were 1.48 (95% CI 1.39 to 1.57) for DVT and 1.47 (95% CI 1.39 to 1.56) for pulmonary embolism after adjustment for patient characteristics.

Conclusions Swedish men with prostate cancer had a mean 50% increased risk of VTE during the 5 years following their cancer diagnosis compared with matched men free of prostate cancer. Physicians should be mindful of this marked increase in VTE risk in men with prostate cancer to help ensure timely diagnosis.

Strengths and limitations of this study

- The good quality and national coverage of the linked data sources used mean the results have good internal validity and are generalisable to the male population of Sweden as a whole.
- The focus on one specific cancer type and the near absence of any loss to follow-up are also strengths of the study.
- We included patients with venous thromboembolism (VTE) who were either hospitalised or managed on an outpatient basis, thereby maximising the sensitivity of our case definition.
- Although we were able to adjust our risk estimates for several patient variables, including comorbidities, medications and sociodemographic factors, lack of information on height, weight, smoking status and alcohol intake may have led to residual confounding.
- Some men in the comparison cohort of men without prostate cancer may have developed another cancer during follow-up, thereby increasing their risk of developing a VTE and diluting the relative risk estimates observed.

INTRODUCTION

Individuals with cancer have a higher risk of developing venous thromboembolism (VTE) than those without cancer, the magnitude of which varies by cancer type and disease stage.[1 2] VTE is a leading cause of death in patients with cancer, being second only to death from the cancer itself.[1]

Several factors contribute to an increased hypercoaguable state in patients with cancer, including treatment-related factors, such as cancer therapy and surgery, and patient-related factors, such as age, obesity, history of VTE and other comorbidities.[1–3] Prostate cancer is the most commonly diagnosed cancer in middle aged and older men worldwide,[4] and 5-year relative survival is high, with reported rates of 82% in Europe[5] and 99% in the USA.[6] The high number of men living with prostate

cancer underscores the importance of understanding the magnitude of VTE in this population in order to prevent morbidity and mortality.

Population-based data suggest that the risk of VTE is twofold to threefold higher in men with prostate cancer than among men of similar age without cancer.[7–9] In our previous study published more than a decade ago, we compared observed rates of thromboembolic events that led to hospitalisation in men with prostate cancer with expected rates in the total Swedish male population for the period of 1997–2007.[7] Other studies in this field,[8–10] including another previous study of ours that focused on surgical interventions,[10] have been conducted during comparable time periods. However, there are few other reported estimates on this topic, and there is therefore a need to obtain comparable contemporary data to gain further knowledge in this field for several reasons. These include the dramatic change in the pattern of care for men with prostate cancer and the widespread adoption of direct oral anticoagulants (DOACs) over the last decade, both of which could potentially affect VTE risk. In this present study, conducted during a more recent time period (2007–2017), we aimed to compare the incidence of all VTE events, treated in either an outpatient or an inpatient setting, between men with prostate cancer and men free of prostate cancer from the Swedish general population.

METHODS

Study design and data source

We performed a population-based matched cohort study using information from the Prostate Cancer data Base Sweden (PCBaSe) V.4.0. This is a research database comprising data from the National Prostate Cancer Register (NPCR) of Sweden and several other national healthcare registers; further details of PCBaSe can be found elsewhere.[11 12] Notification of cancer has been mandatory in all Nordic counties for decades, and the NPCR has held information on 98% of incident cases of prostate cancer in the country since 1998. In this study, we used data in PCBaSe from the NPCR and the following registers: the National Patient Register (hospital inpatient/outpatient diagnoses coded using International Classification of Diseases, 10th Revision [ICD-10] codes) with a look-back period to 1998, the National Prescribed Drug Register (medication dispensed from Swedish pharmacies), the Cause of Death Register, the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Register (LISA) with sociodemographic data, and the registries of immigration and emigration. For each man with prostate cancer in PCBaSe, the database also includes a set of randomly selected men from the general population, matched 5:1 by year of birth and geographical region of residence, who were alive and free of prostate cancer at the end of the year of diagnosis for their matched case.[13]

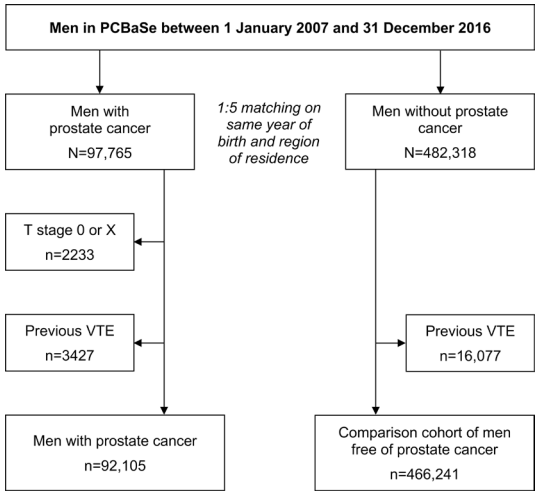

Figure 1 Flowchart depicting the identification of the two study cohorts: men with prostate cancer and men without prostate cancer. PCBaSe, Prostate Cancer data Base Sweden; VTE, venous thromboembolism.

Patient and public involvement

There was no public or patient involvement in the design, conduct, reporting or dissemination plans of our research.

Study cohorts and outcome follow-up

As shown in figure 1, we identified all men in PCBaSe with a first diagnosis of prostate cancer between 2007 and 2016. We excluded men with T stage 0 or X, and those with a previous record of VTE recorded as either a primary or secondary diagnosis (to increase the certainty that only men with a first-ever VTE were identified during follow-up). For each man with prostate cancer, we identified their matched men from the general population from PCBaSe (n=466 241, comparison cohort). The date of prostate cancer diagnosis was the index date for each case and for their respective matched men in the comparison cohort. The two study cohorts were followed up from the index date until the first VTE (primary diagnosis), death or the end of the study period (December 2017), whichever came first. Men in the comparison cohort who were diagnosed with prostate cancer during follow-up were censored at the date of diagnosis (if this occurred earlier than other censoring variables)[13] and subsequently joined the prostate cancer cohort. VTE events occurring during follow-up were categorised as deep vein thrombosis (DVT, ICD-10 I801–802) or pulmonary embolism (PE, I26) or other (ICD-10 I809 or I82).

Covariates

For all men, we obtained information on age, education level and marital status, comorbidities including cardiovascular disease (CVD) and risk factors for CVD, as a main or secondary diagnosis any time before the index date, medications including those for CVD and its risk factors

(from the National Drug Prescription Register in the 120 days before the index date). We also calculated Charlson Comorbidity Index as a marker of general health. For men in the prostate cancer cohort, we extracted data on tumour–node–metastasis stage, prostate cancer risk category and prostate-specific antigen (PSA) level at cancer diagnosis.

Statistical analysis

Patient characteristics at the start of follow-up were described using frequency counts and percentages for categorical variables, and with medians with IQR for continuous variables. We calculated crude incidence proportions as the number of men with a first VTE during follow-up divided by the total number of men at the start of follow-up. We calculated incidence rates per 1000 person-years using the same numerator divided by the total person-years of follow-up. Incidence proportion ratios (IPRs) comparing incidence proportions in the prostate cancer and comparison cohorts were calculated, along with 95% CIs based on the binomial distribution. We used Cox proportional hazard regression to calculate HRs comparing the incidence rate of VTE between the prostate cancer and comparison cohorts, adjusted for confounders. Potential confounders were added sequentially, retaining those that were deemed, on a subjective basis, to not materially change the HR. Variables included in the final model were age, atrial fibrillation, chronic heart failure, hypertension, diabetes, cancer, myocardial infarction and ischaemic stroke. SAS V.9.4 was used for all analyses.

RESULTS

Baseline characteristics

A total of 92 105 men with prostate cancer and 466 241 matched men without prostate cancer were identified after applying exclusion criteria. Apart from previous cancer, which was more common in the prostate cancer cohort than in the comparison cohort (13% vs 7%), patient characteristics were broadly similar between the cohorts (table 1). Over half of men (52%) in the prostate cancer cohort had T2 stage disease; 17% had metastases; and the median PSA was 9 mg/L (IQR 5–20) at the time of the cancer diagnosis (online supplemental table 1).

Incidence of VTE

A total of 2955 men with prostate cancer and 9774 men in the comparison cohort experienced a first VTE during a median of 4.5 years' follow-up (SD ±2.9 years); DVT accounted for 52% of VTE cases in both cohorts. Median time from the index date to VTE was 2.5 years (IQR 0.9–4.7) in the prostate cancer cohort and 2.9 years (IQR 1.3–5.0) in the comparison cohort. Incidence proportions over 60 months' follow-up increased in absolute terms in both cohorts over time and decreased over time in relative terms (figure 2 and online supplemental table 2). For example, incidence proportions in the prostate cancer and comparison cohorts, respectively, were 0.5% and 0.2% at 6 months, 1.4% and 0.8% at 2 years, and

Table 1 Baseline characteristics of men with prostate cancer and randomly selected men free of prostate cancer from the general population matched on birth year and geographical region in PCBaSe V.4.0

	Men with prostate cancer N=92 105	Men without prostate cancer N=466 241
Age (years), median (IQR)	69 (64–76)	69 (64–76)
Educational level		
Low (<9 years)	30 977 (33.6)	166 338 (35.7)
Middle (9–12 years)	36 472 (39.6)	182 575 (39.2)
High (>12 years, university)	23 955 (26.0)	110 787 (23.8)
Missing	701 (0.8)	6541 (1.4)
Marital status		
Married	60 323 (65.5)	286 441 (61.4)
Unmarried	10 714 (11.6)	66 971 (14.4)
Divorced	13 859 (15)	76 631 (16.4)
Widower	7169 (7.8)	36 186 (7.8)
Missing	40 (0.04)	12 (0)
Charlson Comorbidity Index		
0	70 303 (76.3)	341 974 (73.3)
1	11 835 (12.8)	63 565 (13.6)
2	5485 (6)	31 184 (6.7)
3	2213 (2.4)	13 938 (3.0)
≥4	2269 (2.5)	15 580 (3.3)
Mean (SD)	0.5 (1.1)	0.5 (1.2)
Comorbidities*		
Hypertension	22 932 (24.9)	116 690 (25.0)
Valvular heart disease	2795 (3.0)	15 379 (3.3)
Coronary artery disease	13 163 (14.3)	74 009 (15.9)
Angina pectoris	9154 (9.9)	50 474 (10.8)
Myocardial infarction	7633 (8.3)	44 622 (9.6)
Peripheral arterial disease	2989 (3.2)	18 516 (4.0)
Atrial fibrillation	8628 (9.4)	47 540 (10.2)
Chronic heart failure	4642 (5.0)	30 040 (6.4)
Peripheral systemic embolism	261 (0.3)	1570 (0.3)
Haemorrhagic stroke	1077 (1.2)	6647 (1.4)
Ischaemic stroke	4298 (4.7)	26 604 (5.7)
Stroke NOS	1231 (1.3)	8425 (1.8)
TIA	2990 (3.2)	15 721 (3.4)
Diabetes mellitus	7897 (8.6)	51 139 (11)
Hyperlipidaemia	574 (9.3)	46 220 (9.9)
Cancer	12 261 (13.3)	30 942 (6.6)
Obstructive sleep apnoea	1370 (1.5)	7396 (1.6)
COPD	2599 (2.8)	15 250 (3.3)
Bleedings		
Intracranial	1293 (1.4)	7900 (1.7)
Upper gastrointestinal	1904 (2.1)	9787 (2.1)

Continued

Table 1 Continued

	Men with prostate cancer N=92 105	Men without prostate cancer N=466 241
Lower gastrointestinal	626 (0.7)	3061 (0.7)
Urogenital	4251 (4.6)	15 829 (3.4)
Medications†		
Antiarrhythmics	463 (0.5)	2270 (0.5)
Statins	22 355 (24.3)	115 697 (24.8)
Cardiovascular drugs‡	82 267 (89.3)	414 211 (88.8)
Antidiabetics	8364 (9.1)	53 108 (11.4)
NSAIDs	10 875 (11.8)	35 896 (7.7)
Antiplatelet drugs	19 870 (21.6)	105 195 (22.6)
Vitamin K antagonists	4516 (4.9)	24 725 (5.3)
DOACs	604 (0.7)	3320 (0.7)
Parenteral anticoagulant	2073 (2.3)	3346 (0.7)

Data are n (%) unless otherwise stated.
*Comorbidities were identified through International Classification of Diseases, 10th Revision, codes in the National Patient Register as the main or secondary diagnosis any time before the index date.
†Medications were identified by ATC Classification codes in the Drug Prescription Register during the 120 days before the index date.
‡Includes beta blockers, calcium-channel blockers, ACE inhibitors, angiotensin II receptor blockers and diuretics.
ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical Classification; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; NOS, not otherwise specified; NSAID, non-steroidal anti-inflammatory drug; PCBaSe, Prostate Cancer data Base Sweden; TIA, transient ischaemic attack.

2.5% and 1.6% at 5 years. IPRs decreased from 2.53 (95% CI 2.26 to 2.83) at 6 months to 1.59 (95% CI 1.52 to 1.67) at 5 years' follow-up (see online supplemental figures 1 and 2 and tables 3 and 4 for corresponding incidences for DVT and PE separately). Crude incidence rates of VTE were 6.54 per 1000 person-years (95% CI 6.31 to 6.78) in men with prostate cancer and 4.27 per 1000 person-years (95% CI 4.18 to 4.35) in the comparison cohort; the absolute risk difference was 2.27 per 1000 person-years (table 2). Crude incidence rates increased with time (online supplemental table 5). In the Cox regression analysis, the adjusted HR was 1.47 (95% CI 1.41 to 1.53). Findings for DVT and PE separately were only very minimally different: adjusted HR for DVT was 1.47 (95% CI 1.39 to 1.56), and adjusted HR for PE was 1.48 (95% CI 1.39 to 1.57).

DISCUSSION

In our nationwide study in Sweden, men with prostate cancer had a 50% increased risk of a first VTE in the 5 years following cancer diagnosis compared with men free of prostate cancer in the general population, after adjusting for age and other confounders. The risk was mostly increased in the first 6 months of prostate cancer diagnosis, decreasing steadily thereafter, and the average time to develop a first VTE was shorter in men with prostate cancer than in men free of prostate cancer of a similar age (3.1 years vs 3.4 years). Adjusted HRs differed only marginally from crude estimates, indicating that this excess risk is likely due to effects of the prostate cancer itself and/or residual confounding. Additionally, VTE incidence increased in both study cohorts over time, reflecting an increased incidence with age irrespective of cancer status.

Our findings support previous findings on this topic, although the magnitude of increased risk among men with prostate cancer in our study was lower than those in other reports.[7–9] This could be explained by the inclusion of both inpatient and outpatient VTE cases—the latter likely representing less serious events. In a previous study using PCBaSe, incidence rates of DVT and PE were twofold higher in men with prostate cancer (2.5 higher in those on endocrine therapy or who received curative treatment) compared with the expected rates from the general male Swedish population.[7] In a registry study from Denmark, Cronin-Fenton *et al*[9] reported a threefold increased risk of hospitalised VTE among 4457 men with prostate cancer compared with matched general population controls after adjusting for confounders (median follow-up 1.23 and 3.5 years in the all-cancer and general population cohorts, respectively). In a larger study from the UK using linked primary care, secondary care and National Statistic Cause of Death data, Walker *et al*[8] found a 2.6 (95% CI 2.4 to 2.9) increased rate of VTE among 10 238 men with prostate cancer compared with a non-cancer comparison cohort, after adjusting for age and calendar year (median follow-up of 2.0 and 2.6 years in the all-cancer cohort and comparison cohort, respectively). Their exclusion of patients with other cancers in their comparison cohort would have meant this group was probably healthier than our comparison cohort that did not exclude men with other cancers, and thus could also be a reason for their observed higher relative risk. Furthermore, the smaller relative increase in VTE risk seen in our study occurred over a longer follow-up duration (median 4.5 years) than the two aforementioned studies. As we observed a higher relative incidence of VTE in the first 6 months from cancer diagnosis—as seen previously[7 10]—it is logical that higher relative risks would be observed in shorter studies. The higher risk in the months after prostate cancer may reflect the higher risks of VTE associated with surgical interventions such as radical prostatectomy.

In addition to being a leading cause of death in patients with cancer, VTE adversely affects patients' quality of life, bringing anxiety about the risk of recurrence, and potentially interrupting cancer treatment.[2 3 14] Furthermore, decisions about treating the VTE can be challenging, as risks of recurrent VTE and anticoagulant-associated bleeding are higher in patients with cancer. For most

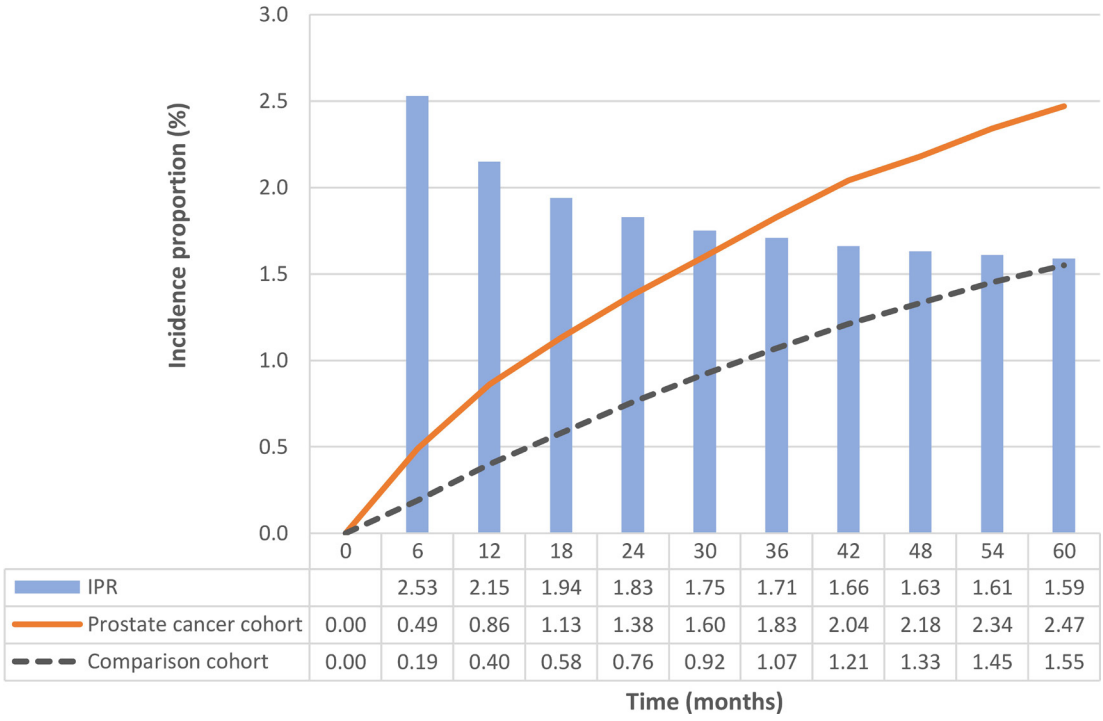

Figure 2 Incidence proportion (%) of first VTE in men with prostate cancer and men without prostate cancer. IPR, incidence proportion ratio; VTE, venous thromboembolism.

Table 2 Incidence rates of first VTE (overall and stratified by DVT and PE) per 1000 person-years (95% CI) in men with prostate cancer and men without prostate cancer, IRRs and HRs (95% CI) comparing rates in the two cohorts

	Men with prostate cancer N=92 1015	Men without prostate cancer N=466 241
VTE		
Incidence rate per 1000 person-years (95% CI)	6.54 (6.31 to 6.78)	4.27 (4.18 to 4.35)
Crude HR (95% CI)	1.53 (1.47 to 1.60)	1.0 (reference)
Adjusted HR* (95% CI)	1.47 (1.41 to 1.53)	1.0 (reference)
PE		
Incidence rate per 1000 person-years (95% CI)	3.12 (2.96 to 3.28)	2.02 (1.96 to 2.08)
Crude HR (95% CI)	1.54 (1.45 to 1.64)	1.0 (reference)
Adjusted HR* (95% CI)	1.48 (1.39 to 1.57)	1.0 (reference)
DVT		
Incidence rate per 1000 person-years (95% CI)	3.38 (3.22 to 3.55)	2.22 (2.16 to 2.80)
Crude HR (95% CI)	1.52 (1.44 to 1.61)	1.0 (reference)
Adjusted HR* (95% CI)	1.47 (1.39 to 1.56)	1.0 (reference)

*Adjusted for age, atrial fibrillation, chronic heart failure, hypertension, diabetes, cancer, myocardial infarction and ischaemic stroke.
DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

patients, clinical guidelines currently recommend long-term anticoagulant therapy with low-molecular weight heparin or a DOAC to help prevent VTE recurrence, although some recommend a duration of at least 3 months,[15] while others recommend 6 months[16] or more.[17 18] Ageing populations with increasing life expectancy means that more men will be living with prostate cancer and at risk of VTE for many years. Our findings quantifying the increased risks of VTE in men with prostate cancer suggest that physicians should be particularly vigilant of these patients in the first 6 months following diagnosis.

Strengths of our study include the large sample size, enabling the calculation of precise incidence estimates, and the good quality and national coverage of the linked data sources,[12] meaning the results have good internal validity and are generalisable to the male population of Sweden as a whole. Other strengths are the focus on one specific cancer type and the near absence of any loss to follow-up. We included patients with VTE who were either hospitalised or managed on an outpatient basis, maximising the sensitivity of our case definition. The use of several linked data sources enabled information on a wide range of potential confounders to be ascertained, including comorbidities, medications and sociodemographic factors; however, lack of adjustment for unknown confounders may have led to residual confounding. Although ICD-10 codes are the standard means of recording clinical data in Swedish clinical practice, information on the accuracy of the code for VTE used across

Sweden are lacking. Furthermore, we were unable to validate the VTE diagnoses because the results of imaging procedures are not routinely recorded in the patient register. The likely under-recording of VTE cases (not capturing those whose imaging results were unobtainable or those who were asymptomatic) would not affect the HRs under the assumption of non-differential misclassification. If, hypothetically, there was an over-recording of VTE cases (inclusion of false positives), this would bias the HRs towards the null, assuming non-differential misclassification. Another limitation is that prostate cancer stage at the time of VTE diagnosis was unknown, and we did not have sufficient information to analyse specific cancer treatments. We did not attempt to define the observed VTE events as 'cancer-associated VTE' due to the fact that this could not be ascertained with confidence. Instead, the aim was to describe the risk of VTE in the unselected total population of men living with prostate cancer. Our prostate cancer cohort consisted of men in different disease risk categories, and in some, the cancer may have been indolent for a long time, making it difficult to attribute VTE events to the cancer itself. Finally, some men in the comparison cohort may have developed cancer during follow-up, thereby increasing their risk of developing a VTE. This would dilute the relative risk estimates observed.

The magnitude of increased VTE risk among men with prostate cancer seen in our study is lower than that seen for other cancer types as seen in previous studies, and is likely attributable to the high proportion of men with localised disease and at low risk of cancer progression.[1 8 9] Notwithstanding this, physicians treating men with prostate cancer should be aware of the marked increase in VTE risk in these men, particularly in the first 6 months following cancer diagnosis, to help ensure timely VTE diagnosis.

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Contributors Study concept and study design: YB, BF and GB; acquisition of the data: PS and HG; analysis of the data: BF; interpretation of the data: YB, BF, GB, PS and HG; reviewing of the manuscript drafts and approval of the final draft to be submitted for publication: all authors. YB is the guarantor.

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Competing interests YL is an employee of Bayer AG. BF and GB were employees of Bayer AB at the time the study was carried out; GB currently works as a paid consultant for Bayer AB. PS declares that Region of Uppsala has, on behalf of National Prostate Cancer Register (NPCR), made agreements on quarterly reports from Patient-Overview Prostate Cancer (part of NPCR) with Astellas, Janssen and Bayer, as well as research projects with Astellas, Bayer and Janssen. HG declares no conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was carried out in accordance with the Helsinki Declaration. There was no requirement for informed consent by the Research Ethics Authority, Uppsala, the ethics committee that approved the study protocol (Dnr 2019-01319). The Research Ethics Authority, Uppsala, approved the use of the opt-out informed consent in National Prostate Cancer Register for which there was no collection of signed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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