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Incidence of venous thromboembolism in patients with cancer – A cohort study using linked United Kingdom databases

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Abstract ***Background:*** Accurate population-based data are needed on the incidence of venous thromboembolism (VTE) in patients with different cancers in order to inform guidelines on which hospitalised and ambulatory cancer patients should receive VTE prophylaxis.
Methods: We conducted a cohort study using data from the Clinical Practice Research Datalink, linked to Hospital Episode Statistics, Cancer Registry data and Office for National Statistics cause of death data. We determined the incidence rates (cases per 1000 person–years) of VTE separately for 24 cancer sites. To determine relative risk, incidence rates were compared to frequency-matched controls (by age) with no record of cancer.
Findings: We identified 83,203 cancer patients and 577,207 controls. New cases of VTE were diagnosed in 3352 cancer patients, and 6353 controls. The absolute rate of VTE in all cancers was 13.9 per 1000 person–years (95% confidence interval [CI] 13.4–14.4), corresponding to an age, sex and calendar year adjusted hazard-ratio of 4.7 (CI 4.5–4.9) between cancer patients and the general population. Rates varied greatly by cancer site (range; 98 (CI 80–119) in pancreatic cancer to 3.1 (CI 1.5–6.5) in thyroid cancer), age (range; 16.9 for patients over 80 years to 4.9 for those under 30 years) and time from diagnosis (range; 75 in the first three months to 8.4, >1 year after diagnosis).
Interpretation: VTE is strongly linked to cancer, but the annual rate varies greatly by cancer site, proximity to diagnosis and age. Prophylaxis guidelines should take account of cancer site and such intervention should also be targeted towards the three months following diagnosis.

1. Introduction

It is long established that the risk of venous thromboembolism (VTE), which incorporates deep vein thrombosis (DVT) and pulmonary embolism (PE) is increased substantially in cancer patients, with 20% of

Abbreviations: DVT; deep vein thrombosis; CPRD; Clinical Practice Research Datalink; HES; Hospital Episode Statistics; PE; pulmonary embolism; VTE; venous thromboembolism.

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VTE events occurring in people with cancer.[1] Cancer patients are also known to be at substantially higher risk of death if they have a concurrent VTE diagnosis.[2] Various factors are known to influence risk of VTE in cancer and non-cancer patients, including age, immobility, surgery and trauma.[3] The reasons for the increase in incidence of VTE in cancer patients are myriad, but include pathophysiological changes occurring in cancer treatments and the decreased mobility often associated with cancer diagnosis.[4]

Current United Kingdom (UK) guidelines, published by the National Institute for Health and Clinical Excellence (NICE)[5] indicate use of thromboprophylaxis in cancer patients with on-going cancer or cancer treatment, but only routinely to those with reduced mobility, and not ambulatory patients. United States (US) guidelines from the National Clinical Cancer Network (NCCN)[6] are similar in their treatment of inpatients, but have a more detailed assessment of VTE risk factors and suggest that some outpatient chemotherapy patients could also benefit from prophylaxis. The recent American College of Chest Physicians guidelines have also recently changed to suggest thromboprophylaxis in outpatients at high risk of VTE.[7] While general guidelines may be effective in some cases, potential variation in risk between different patient groups with cancer means that some patients in high risk groups may benefit from VTE prophylaxis while ambulant, whereas some at low risk may suffer net harm from prophylaxis and its associated adverse effects.

While a number of previous attempts have been made to characterise the risk of VTE in cancer in more detail,[8–12] these are limited in the number of cancer types studied, the length of patient follow-up or their assessment of VTE. This study uses the recently linked UK Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), National Cancer Intelligence Network Cancer Registry data and Office of National Statistics (ONS) death certificate data to provide a more comprehensive and accurate view of risk of VTE in a cancer population, in comparison with a control population.

2. Methods

2.1. Patients and data sources

We conducted a cohort study using linked data from four sources. The CPRD, formerly the General Practice Research Database, is a prospectively gathered, anonymised primary care database using data from more than 600 GP practices in the UK from 1987 onwards. It provides all recorded primary care data on patients including clinical diagnoses, treatments and outcomes. Its validity has been tested in numerous studies[13–16] and it is thought to represent the UK population well in terms of age, sex, socioeconomic and geographic distribution.[17] Hospital Episodes statistics is a secondary care database containing data for all hospitalisations in England, including diagnoses and procedures. 50% of CPRD practices are linked to at least one other database, from April 1997 onwards. Cancer registry data are provided by the National Cancer Intelligence Network and consist of two databases; the Merged Cancer Registry data (1990–2006, from English registries only) and the ONS minimum cancer dataset (1971–2006). Death certificate data from the ONS which are linked to patients within these HES linked practices provide information on dates of death, as well as underlying cause and up to 15 other causes of death.

We selected patients who had a first cancer diagnosis in the registry data (ICD-10 Chapter II, C00–C97) between 1st April 1997 and 31st December 2006, as this was the period from which cancer registry data linked to the CPRD were available. Patients were followed up until they developed a VTE event, died, left a participating GP practice or 31st December 2010, whichever was earliest.

Patients were excluded if they were:

- Under 18 years of age
- Not in a linked general practice
- Diagnosed with cancer outside of CPRD and HES registration dates
- Diagnosed in the first year of registration at a participating practice
- Had a VTE prior to first cancer diagnosis
- Diagnosed with non-melanoma skin cancer

ICD-10 codes were used to classify patients into the 24 most common cancer sites (based on 2007 Cancer Research UK incidence data). Cancer sites outside of these were placed in a miscellaneous category. Metastatic cancers with no known primary cancer site (C77–C80) were classified as 'Unknown primary'. Only the first occurring cancer was considered for the purposes of this classification and the earliest date was used to determine date of diagnosis.

The general population comparison cohort were selected from the CPRD on the basis that they had no code for cancer at any time in any of the databases. We aimed to select all available controls. A pseudo-diagnosis date was generated as a random date within the registration period for each patient. Controls were frequency matched to all cancer cases by age at diagnosis within 25 year age bands. This reduced control numbers due to the redistribution of age frequencies (patients were dropped at random).

2.2. Outcomes

VTE diagnosis was determined in the first instance from medical codes in the CPRD and HES. These were considered to be a valid VTE event if supported by either: a prescription for an anticoagulant or other evi-