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Venous thromboembolism in children with cancer – A population-based cohort study ☆☆

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ABSTRACT

Introduction: Cancer is a known risk factor for venous thromboembolism (VTE) in adults, but population-based data in children are scarce.
Materials and methods: We conducted a cohort study utilising linkage of the Clinical Practice Research Database (primary care), Hospital Episodes Statistics (secondary care), UK Cancer Registry data and Office for National Statistics cause of death data. From these databases, we selected 498 children with cancer diagnosed between 1997 and 2006 and 20,810 controls without cancer. We calculated VTE incidence rates in children with cancer vs. controls, and hazard ratios (HRs) using Cox regression.
Results: We identified four VTE events in children with cancer compared with four events in the larger control population corresponding to absolute risks of 1.52 and 0.06 per 1000 person-years respectively. The four children with VTE and cancer were diagnosed with hematological, bone or non-specified cancer. Childhood cancer was hence associated with a highly increased risk of VTE (HR adjusted for age and sex: 28.3; 95%CI = 7.0-114.5).
Conclusions: Children with cancer are at increased relative risk of VTE compared to those without cancer. Physicians could consider thromboprophylaxis in children with cancer to reduce their excess risk of VTE however the absolute risk is extremely small and the benefit gained therefore would need to be balanced against the risk invoked of implementing such a strategy.
Novelty & Impact Statements: While there is a reasonable level of knowledge about the risk of VTE in adult populations, it is not well known whether this risk is reflected in paediatric patients. We found a substantial increase in risk of VTE in children with cancer compared to a child population without cancer. While this finding is important, the absolute risk of VTE is still low and must be balanced with the risks of anticoagulation.

Introduction

Cancer is a leading cause of death in children in the Western world. In the last 30 years, the survival rate has however improved dramatically, and today the 5-year-survival of both leukemia and Non Hodgkins Lymphoma in children exceeds 85% [1]. With increasing survival rates, health care in these children focuses more on the prevention of complications from cancer and cancer treatment. One such complication is venous thromboembolism (VTE) [2–7]. VTE, defined as deep-vein thrombosis or pulmonary embolism, is a leading cause of non-cancer death in adult patients with cancer [8].

As the treatment strategies for critically ill children have improved, the rate of VTE in children has increased both in the general population [9], and among patients with cancer [10]. VTE is also associated with a substantial excess mortality [9,10] and seems to influence cancer mortality even when tumour stage and cancer regimen have been taken into consideration [11]. In a recent US study [9], Boulet et al. reported that venous catheter use, mechanical ventilation, malignancy, and hospitalization for at least five days were all risk factors for VTE-related hospital admissions. Despite the identification of these risk factors, few studies have quantified the absolute and relative risks of VTE in cancer compared with general population controls. We recently showed that adults with cancer are at a 4-5-fold increased risk of VTE compared to the general population [12]. Guidelines for adults stipulate that thromboprophylaxis is advised for high-risk inpatients including those

Abbreviations: CI, Confidence Interval; CVC, Central venous catheters; HR, Hazard ratio; PE, Pulmonary embolism; VTE, Venous thromboembolism.

☆☆ Details of ethics approval: This project was approved by the CPRD Independent Scientific Advisory Committee (Protocol no. 10–091).

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with cancer. Whilst routine prophylaxis is not advised for outpatients recent updates to U.S. guidelines advise that prophylaxis is recommended for patients with both cancer and additional risk factors for thrombosis providing they are at low risk of bleeding [13,14]. However it is not clear if children with malignancies might benefit from thromboprophylaxis [2].

The aim of the current study was to examine the risk of VTE in children with cancer, using population-based English data.

Materials and Methods

We utilised population-based health registers to investigate the risk of VTE in cancer patients under the age of 18 years from England (such patients are hereby denoted "children"). Our cohort comprised children who had linked data available from all three data sources described below. A more detailed description of our methods, has been published elsewhere [12].

Cancer Registry Data

Information on cancer diagnoses was obtained from the National Cancer Intelligence Network (NCIN), which processes data supplied by all regional cancer registries in the United Kingdom. Two related but separate databases make up the cancer registry data; the Merged Cancer Registry data (1990 to 2006, from English registries only) and the Office of National Statistics (ONS) minimum cancer dataset (1971 to 2006). From these sources, we selected children with cancer diagnosed between April 1997 and December 2006 as this was the period from which data linked to Clinical Practice Research Datalink (CPRD) and Hospital Episodes Statistics (HES) were available. Cancers were classified into 10 categories according to Cancer Research UK incidence data. Cancers diagnosed outside these categories were referred to an 11th non-specified cancer category ("other site").

Clinical Practice Research Datalink (CPRD)

Through the CPRD (formerly known as the General Practice Research Database, GPRD), we were able to ascertain data on VTE. The CPRD is an anonymised primary care database that was started in 1987 and now encompasses some 600 GP UK practices. This database contains all recorded primary care data including clinical diagnoses, treatments and outcomes. Data from the CPRD has been found to be broadly representative of the UK population with regards to sex, age, socio-economic status and geographic location [15], whilst the validity of coding has been demonstrated across a range of medical conditions [16].

Hospital Episodes Statistics (HES)

The third database used in this paper is the Hospital Episodes Statistics (HES) database. This is a secondary care database that enlists all hospital admissions in England. For each inpatient episode we collected data on all diagnoses and procedures. About half of the CPRD practices are linked to the HES and cancer registry databases.

Exclusion Criteria

We excluded patients who (I) were from a CPRD practice that was not linked to the HES and cancer registry databases; (II) had received their cancer diagnosis outside the HES and CPRD registration dates; (III) were diagnosed with cancer within one year of registration at a participating general practice; (IV) had a VTE diagnosis at any point prior to the date of first cancer diagnosis. Finally we excluded (V) all individuals with a non-melanoma skin cancer.

Comparison Cohort

The general population comparison cohort was identified from the CPRD. In order to maximize statistical power, all available controls without a diagnosis of cancer were eligible. Controls then received a pseudo-diagnosis date generated at random within the registration period for each patient. Any control whose pseudo-diagnosis date was after they reached 18 years of age was then excluded.

VTE

Our outcome, VTE; was defined according to relevant ICD codes (I26.0, I26.9, I80, I80.1-I80.9, I81, I82, I82.0-I82.9) in HES and Read codes mapped to these in the CPRD, if supported by any of the following: (I) a prescription for an anticoagulant or evidence of anticoagulation (based on Read codes) between 15 days before and 90 days after the VTE event, or (II) when the VTE was followed by death within 30 days of the VTE diagnosis. We also accepted VTE when listed as the underlying cause of death. Earlier data indicate that VTE defined according to primary care data has a high validity [17].

Statistics

Follow-up started at cancer diagnosis in cases or at pseudo-diagnosis in controls respectively. It ended with either a VTE event, death, emigration from a participating general practice or end of follow-up (Dec 31, 2010), whichever occurred earliest.

We calculated the rate of VTE according to number of VTEs per 1000 person-years of follow-up at risk. Through Cox regression we estimated Hazard ratios for VTE in cancer patients compared to controls, adjusting for sex, age at cancer diagnosis, and calendar year. All analyses were carried out using STATA version 11.2 (Statacorp, 4905 Lakeway Drive, College Station, Texas 77845, USA). P-values <0.05 were considered statistically significant.

Ethics

This study was approved by the CPRD Independent Scientific Advisory Committee (Protocol no. 10–091).

Results

Four hundred and ninety eight (498) children with cancer fulfilled our case criteria and were selected to the study group. The control group comprised 20 810 children. The median age at first cancer diagnosis was 7 years, with controls being 8 years at pseudo-diagnosis, whilst 55% of cases (and 51% of controls) were male. Additional data on participant characteristics, including total and median follow-up, are given in Table 1. Of the 498 individuals with a diagnosis of cancer during childhood, some 143 (28.7%) had leukemia, 80 (16.1%) tumours of the brain and central nervous system, and 68 (13.7%) a lymphoma (Table 2).

Table 1
Characteristics of study participants.

		Cancer patients	% (IQR)	Controls	% (IQR)
Total		498		20 810	
Median age (years)		7	(3–13)	8	(3–12)
Sex	Male	273	54.8	10 694	51.4
	Female	225	45.2	10 116	48.6
Follow up time (years)	Total	2 627		68 761	
	Median	5.0	(2.2-8.0)	2.1	(0.8-5.0)
VTE*	No	494	99.20	20 806	99.98
	Yes	4	0.80	4	0.02

IQR, Interquartile range.
* VTE, Venous thromboembolism.