Thrombosis Research 156 (2017) 177–183

Contents lists available at ScienceDirect

Thrombosis Research

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

Elevated plasma vitamin B12 levels and risk of venous thromboembolism among cancer patients: A population-based cohort study☆

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ARTICLE INFO

Article history:
Received 1 February 2017
Received in revised form 1 June 2017
Accepted 20 June 2017
Available online 23 June 2017

Keywords:
Cohort studies
Neoplasms
Registries
Venous thromboembolism
Vitamin B12

ABSTRACT

Introduction: Both venous thromboembolism (VTE) and high plasma vitamin B12 levels (cobalamin, Cbl) are markers of occult cancer and aggressive cancer with a poor prognosis. In this population-based cohort study, we assessed VTE risk among cancer patients with high plasma Cbl levels.

Materials and methods: We used Danish health registries to identify a Cb1 cohort of 25,310 cancer patients with a plasma Cbl measurement prior to cancer diagnosis. The cohort was subdivided according to Cbl levels (pmol/L): 200–600 (population reference range), 601–800 and >800. All VTE events were considered provoked and categorised as either cancer-associated if no other provoking factors were present before VTE or provoked by other risk factors (surgery, trauma, or pregnancy). We calculated cumulative incidence proportions and adjusted hazard ratios computed from Cox regression analysis (reference: plasma Cbl of 200–600 pmol/L) for the risk of VTE before and after the cancer diagnosis date (index date).

Results: The risk of cancer-associated VTE 30 days after index date increased with higher Cbl levels. The cumulative incidence (95% CI) by Cbl levels was: 200–600 pmol/L: 0.24 (0.18–0.31); 601–800 pmol/L: 0.63 (0.34–1.09); >800 pmol/L: 0.86 (0.49–1.40). Adjusted hazard ratios (95% CI) were: 601–800 vs. 200–600: 2.55 (1.32–4.92); >800 vs. 200–600: 2.36 (1.19–4.71). We found similar results for VTE provoked by other risk factors and for VTE occurring before index date, but scarcity of events produced uncertain risk estimates.

Conclusion: We demonstrated an association between high plasma Cbl levels and risk of VTE in cancer patients. Any clinical implications warrant further study.

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1. Introduction

Venous thromboembolism (VTE) is a recognised marker of occult cancer and a complication to cancer [1–4], especially advanced, aggressive cancer. This is reflected in the poor prognosis of cancer patients who develop VTE [5–7].

We have recently shown that elevated levels of vitamin B12 (cobalamin, Cbl) are associated with increased cancer risk [8] and with high mortality among cancer patients [9]. These associations showed a dose-response effect. A number of other studies have reported that elevated Cbl levels are associated with both increased cancer risk [10–13] and poor prognosis among cancer patients [14–18]. Thus far, the mechanisms underlying these associations have not been studied. Interestingly, some of the same cancer types are associated with both VTE and high Cbl levels, such as cancers of the stomach, lung, and pancreas and haematological malignancies [2,3,8].

The association between elevated Cbl levels and VTE was recently shown in a cross-sectional study by Grossfeld et al. [19] conducted among patients undergoing major orthopaedic surgery of the lower limb. The study showed that patients who experienced a VTE event had higher plasma Cbl levels than patients without VTE. The odds ratio for high plasma Cbl levels, defined as levels above 500 pg/mL (370 pmol/L), was 3.1 among patients with VTE. Grossfeld et al. [19] speculated that increased inflammatory response to the surgical procedure was the common underlying factor for both high Cbl levels and VTE.

Since both high Cbl levels and VTE are associated with elevated cancer risk and poor cancer prognosis, we undertook this study to examine VTE risk among cancer patients with high Cbl levels. We hypothesised that high Cbl levels are associated with susceptibility to VTE, and thereby could serve as a potential marker for VTE risk in cancer patients.

Abbreviations: Cbl, Cobalamin, vitamin B12; CCI, Charlson Comorbidity Index; CI, Confidence interval; CPR, Civil Personal Registration; CRS, Civil Registration System; DCR, Danish Cancer Registry; DNPR, Danish National Patient Registry; DVT, Deep venous thrombosis of the lower limbs; HR, Hazard ratio; ICD, International Classification of Diseases; LABKA, Laboratory Information Systems Research Database; PE, Pulmonary embolism; VTE, Venous thromboembolism.

☆ Parts of this work were presented as an oral presentation at the 10th International Conference on Homocysteine and One Carbon Metabolism, Nancy, France, July 10 2015

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http://dx.doi.org/10.1016/j.thromres.2017.06.022
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2. Materials and methods

2.1. Study design and data sources

We used Danish health registries covering Northern Denmark to conduct a population-based cohort study. Northern Denmark has a catchment population of approximately 1.8 million residents (≈one-third of the Danish population). The Danish medical system provides tax-paid health care for the entire population. Upon birth or immigration, all residents receive a unique personal identification code (Civil Personal Registration, CPR number), recorded in the Danish Civil Registration System (CRS) [20]. The CPR number allows for individual-level linkage among Danish health registries. The CRS also maintains data on date of death or emigration for each resident and these events were included for censoring during follow-up. For codes used in this study, please see Supplementary Table S1.

The Danish Cancer Registry (DCR) [21], established in 1943, contains information on all Danish cancer patients. The *International Classification of Diseases*, *Seventh Revision* (ICD-7) and The *International Classification of Diseases for Oncology (ICD-O)* were used for coding in DCR until 2003. In 2004, all new cancers were coded according to ICD-10 and previous ICD-7 and ICD-O codes were converted to ICD-10. The data in the DCR are considered complete and valid, since all Danish physicians are required to register cancer diagnoses. The current study included patients with a first-time cancer diagnosis in the DCR between January 1, 2001 and November 30, 2013.

The Clinical Laboratory Information System Research Database (LABKA) [22] contains data on biochemical analyses performed on biological specimens in Danish hospital laboratories in Northern Denmark since 1997. The LABKA database is considered complete for the entire study area from 2000. Each record contains the patient's CPR number, the date and time of the analysis, the test result, unit and reference range, and the type of analysis with a corresponding Nomenclature for Properties and Units code or local analysis code. To include a Cbl cohort in this study, we identified patients with a plasma Cbl measurement of >200 pmol/L (>271 pg/mL, lower reference limit in Northern Denmark [23]) up to one year prior to cancer diagnosis during the period from January 1, 2000 to November 30, 2013 (see Study cohort for cohort description).

The Danish National Patient Registry (DNPR) [24] has collected data on all hospital admissions since 1977 and on all emergency clinic and hospital outpatient clinic visits since 1995. Each record contains the patient's CPR number, dates of admission and discharge or outpatient visit, a code for the treating physician/department, and up to 20 discharge diagnoses. One discharge diagnosis is coded as the primary reason for the hospital contact. Diagnoses are coded according to ICD-8 from 1977 to 1993 and according to ICD-10 from 1994 and on. We obtained data from the DNPR on first-time diagnoses of VTE from January 1, 2000 to November 30, 2014. These included deep venous thrombosis of the lower limb (DVT), pulmonary embolism (PE), and other VTE events. We also used the DNPR to obtain data on covariates in order to assess comorbidity and hospital treatment with Cbl drugs prior to the cancer diagnosis date.

We used the Aarhus University Prescription Database to obtain data on prescriptions for Cbl drugs from January 1, 1998 to November 30, 2013 [25]. This database contains records of all prescription costs reimbursed to patients from community pharmacies in Northern Denmark since 1998. Each record contains the patient's CPR number, date of dispensing, the Anatomical Therapeutic Chemical code, a code for the prescribing physician/department, and the name, dose, pack size, and drug manufacturer.

2.2. Study cohort

We defined the Cb1 cohort as persons with a first-time cancer diagnosis from January 1, 2001 to November 30, 2013 who had at least one plasma Cbl measurement up to one year prior to diagnosis. The date of cancer diagnosis served as the index date. If multiple plasma Cbl measurements were available, we used the result obtained closest to the index date. Patients who were treated with a Cbl drug up to two years prior to plasma Cbl measurement were excluded (n = 3125).

We sampled a comparison cohort of cancer patients residing in Northern Denmark from the DCR. Up to three comparison cohort members were selected per member of the Cb1 cohort. Comparison cohort members were matched to Cb1 cohort members by age (10-year intervals), sex, calendar period (5-year intervals), and cancer type. A flowchart of the study cohorts is shown in Fig. S1.

2.3. Statistical analysis

The outcome was defined as a first-time VTE event recorded in the DNPR up to one year prior to or up to one year after the index date. All VTE events were considered provoked, and we distinguished between two sets of provoking factors: 1. If no other predisposing factors than cancer were found, the VTE event was considered to be potentially associated with cancer and categorised as cancer-associated; 2. If a patient had a record of trauma, surgery, or pregnancy recorded in the DNPR up to 90 days before the VTE event, we categorised the VTE event as provoked by other risk factors.

We stratified the Cb1 cohort into three groups according to plasma Cbl levels: one group with normal/reference range levels [23]: 200–600 pmol/L (271–813 pg/mL), and two groups with high Cbl levels: 601–800 pmol/L (814–1084 pg/mL) and >800 pmol/L (>1084 pg/mL). As a measure of absolute VTE risk, we calculated: (1) cumulative incidence proportions, i.e. the number of VTE events in a specified time period divided by the number of persons at risk, and (2) incidence rates, i.e. the number of VTE events in a specified time period divided by the person-years at risk during that period. These estimates were calculated in the three Cbl level groups and in the comparison cohort. The time periods were 365–91 days, 90–31 days, and 30–1 days before the index date and 0–30 days, 31–90 days, and 91–365 days after the index date. We further stratified our analyses according to VTE category (cancer-associated/other risk factors), type of VTE event (DVT, PE, other VTE events), cancer type (haematological or solid tumours), cancer stage (localised, non-localised), and year of diagnosis (3–5-year intervals).

We used a Cox proportional hazards regression analysis to compute hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Using patients with Cbl levels of 200–600 pmol/L as reference, we computed adjusted HRs to assess the relative VTE risk in Cb1 cohort members with high Cbl levels. In the regression model, we adjusted for age (continuous), sex, cancer stage, year of diagnosis, and comorbidity. Comorbidity was scored using the Charlson Comorbidity Index [26] (CCI), and categorised as follows: low: CCI score = 0; medium: CCI score = 1–2; high: CCI score = ≥3. Patients were censored if they died or emigrated during follow-up. The model assumption of proportional hazards was assessed by log-log plots and the model fit was assessed by plotting Schoenfeld residuals. Both were considered satisfactory. Using the same categories of plasma Cbl levels as described above, we also computed HRs in the Cb1 cohort stratified by length of follow-up, VTE category, VTE type, cancer type, cancer stage, and year of diagnosis.

We performed a spline regression analysis to better assess any dose-response pattern in the association between plasma Cbl levels and 1-year cumulative VTE incidence. We disaggregated the analysis according to VTE category and according to their occurrence before or after the index date.

In our study cohorts, a high proportion of patients had missing cancer stage in the DCR. Previous studies have shown that using multiple imputations is a valid approach to account for missing data [27], yielding less biased estimates for missing cancer stage in registries [28]. Therefore, we used multiple imputations with chained equations to account for missing cancer stage. We imputed 30 datasets and combined the estimates from each dataset into one estimate (and corresponding 95% CIs) using

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