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Family history of venous thromboembolism and risk of hospitalized thromboembolism in cancer patients: A nationwide family study

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ABSTRACT

Background: The importance of family history of venous thromboembolism (VTE) in cancer patients is unclear. We conducted a nationwide study to determine whether family history of VTE is a risk factor for hospitalized VTE in cancer patients.
Methods: The Swedish Multi-Generation Register was linked to the Swedish Hospital Discharge Register and the Swedish Cancer Registry. Familial (sibling/parent history of VTE) hazard ratios (HRs) for VTE in 20 cancer types were determined by cause-specific Cox regression for 258877 cancer patients in 1987–2010 without previous VTE. Familial HRs were also determined in 7644203 individuals without cancer or VTE before 1987, with follow-up in 1987–2010.
Results: Significant familial HRs for VTE in cancer patients were observed for the following cancer types: cancers of the breast (HR = 1.79), lung (HR = 1.21), colon (HR = 1.30), prostate (HR = 1.46), testis (HR = 2.02), nervous system (HR = 1.31), stomach (HR = 1.73), and rectum (HR = 1.77), as well as melanoma (HR = 1.71), non-Hodgkin lymphoma (HR = 1.32), myeloma (HR = 1.69), and leukemia (HR = 1.44). In a time-dependent analysis the familial HRs for VTE were significant before diagnosis of cancer (p-values <0.0001). After diagnosis of cancer the familial HRs VTE were weaker, with significant HRs for 12 cancer types. On an additive scale, the joint effect of cancer and family history was significantly increased compared to separate effects in four cancer types. However, for certain cancers the familial VTE cases were limited.
Conclusions: Family history of VTE is a risk factor for VTE in several cancer types. However, familial factors are relatively more important in non-cancer than in cancer patients.

1. Introduction

An association between cancer and venous thromboembolism (VTE) has been recognized since at least 1865 [1]. Cancer increases the risk of VTE 4- to 7-fold [2–4]. Cancer-associated thrombosis is a major clinical problem and is associated with increased morbidity, mortality, and cost of care [2]. The prothrombotic state generated by cancer is multifactorial and a number of mechanisms have been proposed [3]. Thromboprophylaxis is challenging in cancer patients and benefits must be weighed against the bleeding risk [3–5]. The thrombotic risk is related to tumor type and ranges from 1% in certain cancer types to 20% or more in the most prothrombotic tumor types [5]. Other acquired thrombotic risk factors in cancer patients are metastatic disease, prolonged bed rest, surgical interventions, and chemotherapy [2–5]. However, inherited risk factors may also play a role in cancer-associated thrombosis [3].

Family studies have shown that susceptibility to VTE has a heritable basis and is transmitted in part by mutations in several identified candidate genes, i.e. antithrombin, protein C, Protein S, factor V (rs6025 called Factor V Leiden), and prothrombin (rs1799963) [6–11]. However, few studies have determined the importance of these major genetic risk factors in cancer patients [12,13]. In a population-based case–control study, cancer patients who were carriers of factor V Leiden had an odds ratio (OR) of 12.1 (95% confidence interval [CI] 1.6-88.1) for VTE compared with those without cancer and factor V Leiden [14]. However, cancer patients who were carriers of factor V Leiden had no significantly increased risk compared to cancer patients without factor V Leiden (adjusted OR = 2.2, 95% CI 0.3-17.8) [14]. Moreover, carrying the prothrombin 20210 mutation was not significantly associated with thrombosis in cancer patients (OR = 4.1, 95% CI 0.3-60.8). To determine the importance of inherited thrombophilic factors in cancer patients, a clue could come from analysis of families. A key concept in the framework of genetic epidemiology is whether there exists evidence for

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phenotypic aggregation in families [15]. Familial aggregation of a trait is necessary, but insufficient, to infer that genetic susceptibility is important, because environmental influences may also aggregate in families, thus increasing familial risks [15]. However, the familial aggregation of VTE is more related to genetic than non-genetic causes [16,17]. Family history of VTE was found to be associated with an increased risk of VTE in myeloma patients [18,19]. In a study by Kristinsson et al. myeloma patients with a family history of VTE had an OR for VTE of 2.2 (95% CI 1.8-2.7) compared to myeloma patients without a family history of VTE [18]. In a study by Srkalovic et al. the hazard ratio (HR) for VTE was even higher in myeloma patients with a family history of VTE compared with those without a family history (HR = 9.59, 95% CI 1.29-71.20), although the confidence interval was wide [19]. In another study of 507 patients with different cancer types family history of VTE was suggested to be a risk factor for VTE, with an approximately two-fold increased OR of borderline significance (p = 0.0498) [20]. Mili et al. found an association between family history of deep venous thrombosis (DVT) and VTE in black but not white cancer patients (OR = 6.4, 95% CI 1.3-31.9 and OR = 2.0, 95% CI 0.72-5.4) [21].

We hypothesized that the prothrombotic state associated with a family history of VTE may increase the risk of hospitalized VTE in cancer patients [11–17]. In the present nationwide study, the risk of VTE in cancer patients with a family history of VTE in siblings and parents was analyzed with the aim of determining whether family history of VTE is a risk factor (genetic or non-genetic) for VTE in cancer patients. The study used the Swedish Cancer Registry; the Swedish Hospital Discharge Register, which contains data for all hospitalizations in Sweden since 1987; and the Swedish Multi-Generation Register, a validated source that has been proved to be reliable in the study of many familial diseases, including VTE [15,22].

2. Methods

The dataset contained data from Statistics Sweden (Multi-Generation Register and National Census data) and the National Board of Health and Welfare (Swedish Hospital Discharge Register, Swedish Cancer Registry, and Swedish Cause of Death Register) [15,23–26]. The Multi-Generation Register covers persons born in Sweden in 1932 or later, linked to their siblings. Offspring born in 1932 or later with information on both parents and with their first malign cancer diagnosis in 1987–2010 constituted the study population. Data were linked using the individual national identification number that is assigned to each resident in Sweden for their lifetime [27]. This number was replaced by a serial number in order to preserve anonymity. The study was approved by the Ethics Committee of Lund University, Sweden.

The follow-up period started on January 1, 1987 and proceeded until hospitalization for VTE, death, emigration, or the end of the study period (December 31, 2010). Individuals with a VTE diagnosis before their first cancer diagnosis were excluded (n = 4362) in order to determine incident VTE. Only adults were included, and individuals who were under the age of 20 at their first cancer diagnosis were excluded. Individuals with more than one cancer diagnosis were also excluded (except in a sensitivity analysis where second cancers were analyzed as a competing event). In total, the study population consisted of 258877 individuals with their first cancer diagnosis in 1987–2010 at age 20+ years and without a previous VTE diagnosis. Of these individuals, 8578 (3.3%) had a VTE diagnosis and 43699 (16.9%) had a family history (siblings/parents) of VTE. For definition of outcome variable and exposure variable see below.

A population with no cancer diagnoses was added when we analyzed time-dependent cancer diagnosis. This population consisted of individuals who were 20 years or older in 1987 and had no malign cancer diagnosis and no VTE diagnosis before 1987. This population consisted of 7644203 individuals, of whom 47372 (0.6%) had a VTE diagnosis and 596742 (7.8%) had a family history of VTE.

2.1. Outcome Variable

The outcome variable was time (in years) from cancer diagnosis to first VTE diagnosis (study period 1987–2010). VTE was defined as primary and secondary diagnoses in the Hospital Discharger Register and Cause of Death Register using the following ICD codes [9,11]: ICD-9: 415B, 416W, 451, 452, 453, 437G, 671C, 671D, 671E, 671F, 671X, 673C, and 639G; and ICD-10: I26, I80, I81, I82, I636, O222, O223, O225, O228, O229, O870, O871, O873, O879, O882, O082, and O087.

2.2. Exposure Variable

The exposure variable was family history of VTE (relatives identified with the multi-generation register), dichotomized as (0) no family history of VTE and (1) family history of VTE (a mother, father and/or sibling with a VTE diagnosis at any time between 1964 and 2010). VTE was defined as above and using the same ICD-codes, as well as the ICD-7 codes 463, 464, 465, 466, 583.00, 334.40, 334.50, 682, and 684, and the ICD-8 codes 321, 450, 451, 452, 453, 671, and 673.9.

2.3. Explanatory Variables

Age at cancer diagnosis: a continuous variable. Sex: male/female. Education level: (0) completion of compulsory school or less (≤9 years), (1) practical or theoretical high school (10–12 years), or (2) college or university (>12 years). For individuals aged <25 years at the last observation, their parents' highest education level was used instead. Comorbidity: (0) no comorbidity during the follow-up period or (1) any of the following diagnosis during follow-up period: chronic obstructive pulmonary disease (COPD) (ICD-9: 490–494, and 496; and ICD-10: J40-J47), alcoholism (ICD-9: 291, 303, and 571A-571D; and ICD-10: F10 and K70), obesity (ICD-9: 278A and 278B; and ICD-10: E65 and E66), hypertension (ICD-9: 401–405; ICD-10: I10-I15), diabetes (ICD-9: 250; ICD-10: E10,E11, coronary heart disease (CHD) (ICD-9: 410–414; ICD-10: I20-I25), and stroke (ICD-9: 430–438; ICD-10: I60-I69).

2.4. Strata Examined

Cancer diagnoses: the following 20 cancer diagnoses were examined using data from the Swedish Cancer Registry (at least 20 outcome events in the exposure group): cancers of the breast (ICD-7: 170), lung (ICD-7: 162 and 163), colon (ICD-7: 153), ovary (ICD-7: 175), prostate (ICD-7: 177), testis (ICD-7: 178), urinary bladder (ICD-7: 181), nervous system (ICD-7: 193), stomach (ICD-7: 151), rectum (ICD-7: 154), liver (ICD-7: 155 and 156), pancreas (ICD-7: 157), cervix (ICD-7: 171), endometrium (ICD-7: 172 and 174), kidney (ICD-7: 180), and endocrine glands (ICD-7: 195), as well as melanoma (ICD-7: 190), non-Hodgkin lymphoma (ICD-7: 200 and 202), myeloma (ICD-7: 203), and leukemia (ICD-7: 204–209).

2.5. Statistics

STATA version 12 (Stata Corp LP) was used for all statistical analyses. Distributions of characteristic variables (sex, age, education level, and comorbidity) are shown separately for the exposure groups (no family history of VTE versus family history of VTE). Age was truncated at 20 years, but mean and standard deviation described the variable well according to histograms.

Incidence rates were determined for the two exposure groups by calculating the number of events per 1000 person-years at risk from first cancer diagnosis until first VTE diagnosis or censoring because of death, migration, or the end of the study period (December 31, 2010).

Cumulative incidence graphs, stratified by exposure group, were calculated for each cancer diagnosis but are only shown for breast and