Malignancies, Prothrombotic Mutations, and the Risk of Venous Thrombosis

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Context Venous thrombosis is a common complication in patients with cancer, leading to additional morbidity and compromising quality of life.

Objective To identify individuals with cancer with an increased thrombotic risk, evaluating different tumor sites, the presence of distant metastases, and carrier status of prothrombotic mutations.

Design, Setting, and Patients A large population-based, case-control (Multiple Environmental and Genetic Assessment [MEGA] of risk factors for venous thrombosis) study of 3220 consecutive patients aged 18 to 70 years, with a first deep venous thrombosis of the leg or pulmonary embolism, between March 1, 1999, and May 31, 2002, at 6 anticoagulation clinics in the Netherlands, and separate 2131 control participants (partners of the patients) reported via a questionnaire on acquired risk factors for venous thrombosis. Three months after discontinuation of the anticoagulant therapy, all patients and controls were interviewed, a blood sample was taken, and DNA was isolated to ascertain the factor V Leiden and prothrombin 20210A mutations.

Main Outcome Measure Risk of venous thrombosis.

Results The overall risk of venous thrombosis was increased 7-fold in patients with a malignancy (odds ratio [OR], 6.7; 95% confidence interval [CI], 5.2-8.6) vs persons without malignancy. Patients with hematological malignancies had the highest risk of venous thrombosis, adjusted for age and sex (adjusted OR, 28.0; 95% CI, 4.0-199.7), followed by lung cancer and gastrointestinal cancer. The risk of venous thrombosis was highest in the first few months after the diagnosis of malignancy (adjusted OR, 53.5; 95% CI, 8.6-334.3). Patients with cancer with distant metastases had a higher risk vs patients without distant metastases (adjusted OR, 19.8; 95% CI, 2.6-149.1). Carriers of the factor V Leiden mutation who also had cancer had a 12-fold increased risk vs individuals without cancer and factor V Leiden (adjusted OR, 12.1; 95% CI, 1.6-88.1). Similar results were indirectly calculated for the prothrombin 20210A mutation in patients with cancer.

Conclusions Patients with cancer have a highly increased risk of venous thrombosis especially in the first few months after diagnosis and in the presence of distant metastases. Carriers of the factor V Leiden and prothrombin 20210A mutations appear to have an even higher risk.

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In 1868, Trousseau described the relationship between malignancy and venous thrombosis.[1] Recent studies showed a 4% to 20% prevalence of malignancy in patients with deep venous thrombosis or pulmonary embolism.[2,3] Although the risk of venous thrombosis in patients with cancer is evidently increased, studies that identify patients at highest risk of thrombosis are scarce. It is unclear what risks are for various types and stages of cancer.[4,5]

In the last 2 decades, several hereditary risk factors for venous thrombosis have been identified.[6] The factor V Leiden mutation, a mutation of the *F5* gene (gene ID: 2153), causes partial resistance of this coagulation factor to the inactivating effects of activated protein C, a protein encoded by the *PROC* gene (gene ID: 5624).[7,8] Approximately 5% of the population carries this mutation and it is present in 20% of unselected patients with a first venous thrombotic event.[6,8] The risk of venous thrombosis is 3- to 8-fold increased in the presence of this mutation.[6] In 1996, the prothrombin 20210A mutation was identified and found to be associated with elevated prothrombin levels.[9] The prothrombin 20210A mutation has a lower frequency, with 2% occurring in healthy individuals and 6% in unselected patients with a first venous thrombotic event. The relative risk of thrombosis associated with this mutation is approximately 2.0.[9]

Venous thrombosis is a multicausal disease.[10] The presence of more than 1 risk factor can lead to the development of deep venous thrombosis or pulmonary embolism. The risk of venous thrombosis in patients with cancer with the factor V Leiden or prothrombin 20210A mutation may be increased compared with patients with cancer without these hereditary risk factors. Determination of the magnitude of this risk may identify high-risk groups that will benefit from prophylactic anticoagulant therapy.

The Multiple Environmental and Genetic Assessment (MEGA) of risk fac-

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tors for venous thrombosis study is a large population-based, case-control study, which evaluated the risk of venous thrombosis in the presence of various different risk factors. We studied the risk of thrombosis for different types of cancer and stage of disease, and also investigated the joint effect of cancer and the factor V Leiden or prothrombin 20210A mutation.

METHODS

Selection of Participants

We identified 4300 consecutive patients aged 18 to 70 years, with a first deep venous thrombosis of the leg or a first pulmonary embolism between March 1, 1999, and May 31, 2002, at 6 anticoagulation clinics in the Netherlands. The anticoagulation clinics monitor the anticoagulant therapy of all patients in a well-defined geographical area, which allowed the identification of consecutive and unselected patients with venous thrombosis. Patients with severe psychiatric problems or patients who could not speak Dutch were excluded (n=178). Partners of participating patients were invited to take part as control participants. The same exclusion criteria applied for patients and control participants.

Data Collection

All participants were asked to complete a questionnaire on acquired risk factors of venous thrombosis. We used the date of diagnosis of thrombosis as reported by the participant as the index date for patients. For control participants, the index date was the same as the index date of their partner (the patient). All items in the questionnaire referred to the period before the index date. One of the questions asked was whether the participant had ever been diagnosed with cancer and if so, the date of diagnosis, the type of cancer diagnosed, and the kind of treatment received. Also, the presence or absence of known metastases at the time of the index date was reported. When the participant was unable to fill in the questionnaire, we asked questions by telephone, using a standard mini-questionnaire (4%). This mini-questionnaire was introduced December 15, 1999. Three months after discontinuation of the anticoagulant therapy, we interviewed both patient and control participant. Patients with an indication for life-long treatment with anticoagulant therapy were interviewed 1 year after the index date. Information on cancer diagnosed after the index date was obtained. A blood sample was taken and DNA was isolated to ascertain the factor V Leiden and prothrombin 20210A mutations. Participants who were unable to visit the anticoagulation clinic were interviewed by telephone, using a standard mini-interview. In these instances, a buccal swab was sent to replace the blood sample. The use of mini-interview and buccal swab also started on December 15, 1999.

We verified the diagnosis of cancer in the patients who died soon after the venous thrombosis, who were in the end-stage of disease, and who refused to participate in the full study, by telephone or information from the anticoagulation clinic. For these patients, we did not have a date of cancer diagnosis or details about type of cancer and stage of disease.

Discharge letters from participating patients with cancer who participated in the full study were collected from their primary physician or from the hospital in which they were being treated. From these letters, we verified the cancer diagnosis and abstracted more detailed information about the origin of the cancer, the stage of disease, and treatment received. Patients with non-invasive skin cancer were not registered as cancer patients.

All participants who filled in a questionnaire also filled in an informed consent form and gave written permission to obtain information about their medical history. This study was approved by the ethics committee of the Leiden University Medical Center, Leiden, the Netherlands.

Validation Study of Thrombosis Diagnosis

Discharge letters or diagnostic reports of the venous thrombotic event were obtained for a sample of 742 patients who had their first thrombosis between March 1, 1999, and February 29, 2000. The diagnostic management of the patients was compared with the diagnostic procedure as described in the Dutch consensus.[11] Diagnosis of clinically suspected deep venous thrombosis of the leg is based on a clinical score, serial compression ultrasonography, and D-dimer assay. Objective testing of clinically suspected pulmonary embolism is based on perfusion and ventilation scintigraphy, ultrasonography of the leg veins, or pulmonary angiography. Of 395 patients with a deep venous thrombosis of the leg, 384 (97%) were objectively diagnosed; of 347 patients with a pulmonary embolus, 271 (78%) had been confirmed with objective testing.

Blood Collection and Laboratory Analysis

Blood samples were drawn into vacuum tubes containing 0.1-volume 0.106-mol/L trisodium citrate as anticoagulant. The blood sample was separated into plasma and cells through centrifugation. Using a salting-out method, high–molecular-weight DNA was extracted.[12] This was stored at –20°C until amplification. DNA analysis for the factor V Leiden (G1691A) mutation and the prothrombin (G20210A) mutation was performed using a combined polymerase chain reaction method. The status of the factor V Leiden and the prothrombin variant was determined by the presence of *Mnl*I and *Hind*III restriction sites in the polymerase chain reaction fragment.[13]

Three large cotton swabs in a total of 6-mL sodium dodecyl sulfate–proteinase K solution (homemade solution: 100-mM sodium chloride, 10-mM EDTA, 10-mM *tris*-hydrochloride acid, pH=8.0, 0.5% sodium dodecyl sulfate, 0.1-mg/mL proteinase K) were obtained from each person who did not provide a blood sample. The proteinase K concentration was increased to 0.2 mg/mL and the sample was incubated for 2 hours at 65°C. Subsequently, the suspension was recovered by centrifugation. Potassium acetate was

added to the supernatant for a final concentration of 1.6 M. After 15-minute incubation on ice, proteins were removed using chloroform/isoamylalcohol (24:1) treatment. The water-phase DNA was subsequently ethanol precipitated. After centrifugation, the pellet was resuspended in 200-µL 10-mM tris-hydrochloride acid, 10-mM EDTA, pH=8.0, and frozen at –20°C until further analysis. Assessment of factor V Leiden and prothrombin 20210A mutations in DNA retrieved from the buccal swabs was performed identically to the method for DNA from whole blood.

Statistical Analysis

Odds ratios (ORs) were calculated as an approximation of relative risks, which indicated the risk of venous thrombosis in the presence of a risk factor relative to the absence of that risk factor, and 95% confidence intervals (CIs) were calculated according to the method of Woolf.[14] With a multiple logistic regression model, ORs were adjusted for age and sex (adjusted OR). SPSS for Windows version 12.0.1 (SPSS Inc, Chicago, Ill) was used for all statistical analyses.

In the analysis of the effects of different types of cancer, advanced stage of cancer, or the joint presence of cancer and the factor V Leiden mutation or the prothrombin 20210A mutation, participants were only categorized as patients with cancer if the period between the diagnosis of malignancy and the index date was 5 years or less. This was performed under the assumption that this group consists mainly of patients with active cancer. The reference group consisted of participants without a history of cancer. Thus, patients with cancer diagnosed longer than 5 years ago were excluded in this particular analysis.

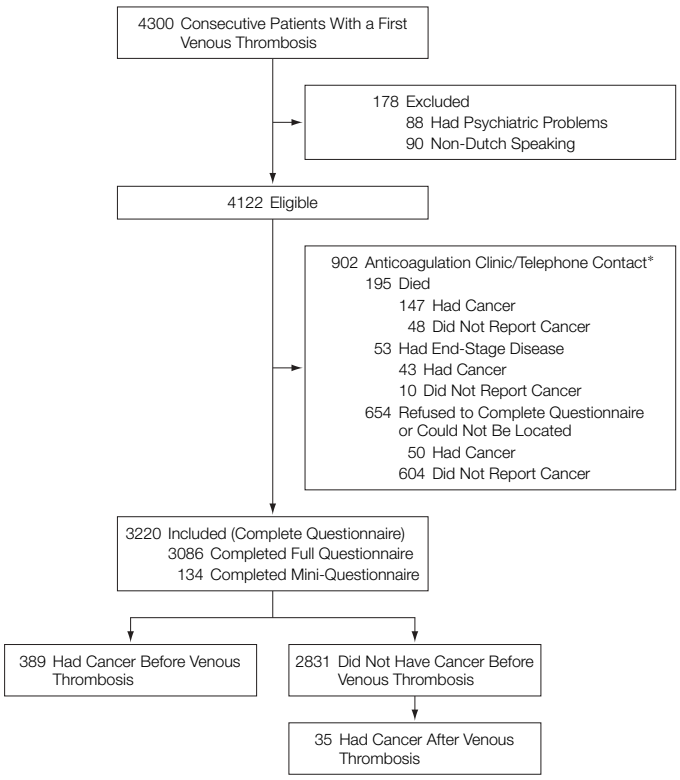
To assess the joint effect of malignancy and the factor V Leiden or prothrombin 20210A mutations, ORs were calculated in the presence of only 1 risk factor and in the presence of both risk factors, both relative to those patients with neither risk factor present. We also performed a case-only analysis. The resulting estimates from the case-only analysis can be interpreted as a synergy index (SI) on a multiplicative scale (indicates evidence of more than a multiplicative effect between the exposure and the genotype when SI >1).[15] The SI indicates the departure from multiplicativity for the joint effect of 2 risk factors (if factor A has an OR of 4 and factor B, an OR of 3, an SI = 0.5 indicates an OR for A + B = $4 \times 3 \times 0.5 = 6$). An SI of 1 or more indicates multiplicativity of effects and less than 1 of a joint effect that is less than multiplicative. In the latter case, the joint effect may still be supra-additive (exceed the sum of the separate effects), which is usually indicative of the presence of interaction or synergy. The underlying assumption of the SI is independence between exposures.

RESULTS

Among the 4122 eligible patients, 195 died soon after the venous thrombosis. All other 3927 patients were invited to participate. Fifty-three patients did not take part because they were in the end stage of a disease, such as cancer or autoimmune disease (FIGURE 1), and of the remaining 3874 patients, 654 could not be located or refused to participate. A total of 3220 patients participated in the study by filling in a questionnaire. Information about malignancy for the patients who did not fill in a questionnaire was obtained from data already available at the anticoagulation clinic or during the first contact by telephone. Partners of participating patients were invited to take part as control participants (n=2131) (FIGURE 2). The response among patients and control participants was 82% and 78%, respectively. An interview or mini-interview was obtained from 2575 of 3220 patients and 1798 of 2131 control participants.

A total of 3220 patients with venous thrombosis and 2131 control par-

Figure 1. Participation of Patients With Venous Thrombosis



*Information about malignancy obtained from anticoagulation clinic or during the first telephone contact.

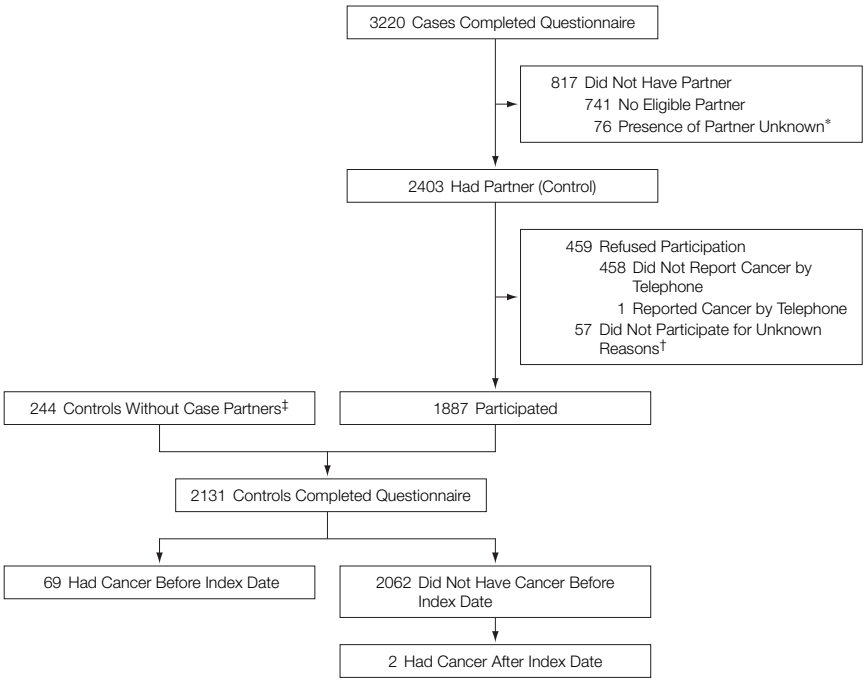
ticipants took part in the study, with similar median (5th-95th percentile) ages of 49.8 (25.7-68.0) and 50.5 (28.1-66.4) years, respectively. There were 1754 women (54.5%) in the patient group and 1073 women (50.4%) in the control group. A total of 1865 patients (57.9%) had deep venous thrombosis of the leg, 983 (30.5%) had a pulmonary embolism, and 372 (11.6%) were diagnosed with both.

According to the information about cancer from the questionnaire, 389 participants (12.1%) with venous thrombosis had a malignancy diagnosed before the index date compared with 69 (3.2%) of the control participants. Adjusted for age and sex, the overall OR of venous thrombosis for malignancy was 4.3 (95% CI, 3.3-5.6) compared with persons without malignancy (**TABLE 1**). For deep venous thrombosis of the leg alone, the OR was 4.0 (95% CI, 3.0-5.3) and for a pulmonary embolism with or without a deep venous thrombosis of the leg, the OR was 4.6 (95% CI, 3.6-6.4).

In the interview, 35 patients and 2 control participants reported cancer diagnosed within 6 months after the venous thrombosis or index date. Assuming that malignancy diagnosed within 6 months of the thrombotic event was already present at the time of the event and including these individuals as cancer cases and controls, the overall OR of venous thrombosis for malignancy was similar (adjusted OR, 4.6; 95% CI, 3.6-6.0). Taking into account patients with cancer (240 cases and 1 control) among nonparticipants (902 cases and 459 controls) (Figure 1 and Figure 2), the overall risk of venous thrombosis for cancer vs noncancer was increased 7-fold (OR, 6.7; 95% CI, 5.2-8.6).

The risk of venous thrombosis was highest in the first few months after the diagnosis of malignancy (adjusted OR, 53.5; 95% CI, 8.6-334.3). As time progressed, the risk of a thrombotic event decreased (Table 1). This tendency was

Figure 2. Participation of Partners of Patients With Venous Thrombosis



*For 76 patients, it remained unknown whether they had a partner or not.
†For 57 control participants, no information about the presence of cancer was available.
‡Participating partners of patients who initially participated but were later excluded for various reasons (history of venous thrombosis, index date before March 1, 1999) remained in the study.

Table 1. Effect of Malignancy on the Risk of Venous Thrombosis Depending on the Duration Between Diagnosis of Cancer and Venous Thrombosis

Duration Between Malignancy and Venous Thrombosis	No. of Individuals (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Patients (n = 3220)	Control Participants (n = 2131)		
No malignancy	2831 (87.9)	2062 (96.8)	1.00	1.00
All malignancies	389 (12.1)	69 (3.2)	4.1 (3.2-5.3)	4.3 (3.3-5.6)
Time after index date (diagnosis)†				
0 to ≤3 mo	80 (20.6)	1 (1.5)	58.2 (8.1-419.1)	53.5 (8.6-334.3)
>3 mo to ≤1 y	92 (23.7)	5 (7.6)	13.4 (5.4-33.0)	14.3 (5.8-35.2)
>1 to ≤3 y	67 (17.2)	14 (21.2)	3.5 (2.0-6.2)	3.6 (2.0-6.5)
>3 to ≤5 y	43 (11.1)	11 (16.7)	2.8 (1.5-5.5)	3.0 (1.5-5.7)
>5 to ≤10 y	47 (12.1)	14 (21.2)	2.4 (1.3-4.5)	2.6 (1.4-4.7)
>10 to ≤15 y	19 (4.8)	6 (9.0)	2.3 (0.9-5.8)	2.3 (0.9-5.8)
>15 y	23 (5.9)	15 (22.7)	1.1 (0.6-2.1)	1.1 (0.6-2.2)

Abbreviation: CI, confidence interval.
*Adjusted for age and sex.
†Eighteen patients and 3 control participants did not report a date of diagnosis.

similar in patients with only a deep venous thrombosis of the leg and in patients with a pulmonary embolism with or without thrombosis of the leg. During the first year after a diagnosis of malignancy when the risk of venous thrombosis was highest, 16.9% of the patients with cancer received chemotherapy, 4.1% received radiotherapy, 23.8% underwent surgery, and 36.6% had a combination of these therapies.

When we defined cancer as active if the diagnosis was less than 1 year ago or when patients visited the clinic more than once a year because of the malignancy, the same decrease in risk of venous thrombosis over time could be shown. Only the group of patients diagnosed more than 15 years ago had a higher risk (adjusted OR, 3.0; 95% CI, 0.6-13.9).

Patients with hematological malignancies had the highest risk of venous thrombosis (adjusted OR, 28.0; 95% CI, 4.0-199.7), followed by lung cancer (adjusted OR, 22.2; 95% CI, 3.6-136.1) and gastrointestinal cancer (adjusted OR, 20.3; 95% CI, 4.9-83.0) (TABLE 2).

The analysis of the risk of venous thrombosis associated with advanced stage of cancer was performed in patients with solid tumors. The risk of venous thrombosis for patients with distant metastasis was greatly increased compared with patients without distant metastasis (adjusted OR, 19.8; 95% CI, 2.6-149.1) (TABLE 3). Adjustment for time since diagnosis of cancer increased the risk (adjusted OR, 23.8; 95% CI, 3.1-185.7).

DNA samples were available for 2706 patients and 1757 control participants, excluding patients with cancer diagnosed more than 5 years ago. The allele frequency of the factor V Leiden mutation among patients and control participants was 8.1% and 2.8%, respectively. The heterozygous variant of the factor V Leiden mutation was found in 400 (14.8%) of 2706 patients and 92 (5.2%) of 1757 control participants. Nineteen homozygous carriers (0.7%) were found among patients and 4 (0.2%) among control participants. Overall, the risk of venous thrombosis in the presence of the factor V Leiden mutation was 3-fold in-

Table 2. Risk of Venous Thrombosis per Type of Malignancy for Patients With a Diagnosis of Malignancy Within 5 Years Before Diagnosis of Venous Thrombosis

Type of Malignancy	No. of Patients	No. of Control Participants	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
No malignancy			1.00	1.00
Men	1279	1038		
Women	1552	1024		
All malignancies†				
Lung	34	1	24.8 (3.4-181.1)	22.2 (3.6-136.1)
Hematological malignancies				
Non-Hodgkin lymphoma	13	1	9.5 (1.2-72.4)	10.2 (1.4-76.9)
Hodgkin disease	7	0	ND	ND
Leukemia	5	0	ND	ND
Multiple myeloma	12	0	ND	ND
All hematological cancer	37	1	26.2 (3.6-191.4)	28.0 (4.0-199.7)
Gastrointestinal malignancies				
Bowel	46	2	16.8 (4.1-69.1)	16.4 (4.2-63.7)
Pancreas	2	0	ND	ND
Stomach	2	0	ND	ND
Esophagus	2	0	ND	ND
All gastrointestinal cancer	52	2	18.9 (4.6-77.8)	20.3 (4.9-83.0)
Urinary/prostate malignancies				
Kidney	8	1	5.8 (0.7-46.6)	6.2 (0.8-46.5)
Bladder	10	0	ND	ND
Prostate‡	25	6	3.4 (1.4-8.3)	2.2 (0.9-5.4)
Female malignancies				
Breast‡§	43	8	3.5 (1.7-7.6)	4.9 (2.3-10.5)
Cervix‡	5	1	3.3 (0.4-28.3)	2.9 (0.3-25.3)
Ovarium‡	7	2	2.3 (0.5-11.1)	3.1 (0.6-15.3)
Endometrium‡	4	0	ND	ND
Brain	11	1	8.0 (1.0-62.1)	6.7 (1.0-45.4)
Skin (melanoma, squamous) cell	15	3	3.6 (1.1-12.6)	3.8 (1.1-12.9)
Ear, nose, and throat	6	3	1.5 (0.4-5.8)	1.6 (0.4-6.4)
Other	18	2	6.6 (1.5-28.3)	6.9 (1.6-29.6)

Abbreviations: CI, confidence interval; ND, not determined due to 0 control participants.
*Adjusted for age and sex, when applicable.
†Seven patients had more than 1 malignancy.
‡Reference group: only men or only women.
§A total of 12 patients and 0 control participants used hormone therapy.

Table 3. Effect of Distant Metastases on the Risk of Venous Thrombosis in Patients With Solid Tumors and Diagnosis of Malignancy Within 5 Years Before the Diagnosis of Venous Thrombosis

Malignancy	Distant Metastases	No. of Patients (n = 3050)*	No. of Control Participants (n = 2088)*	OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
No	No	2831	2062	1.00	1.00	
Yes	No	126	25	3.7 (2.4-5.7)	3.9 (2.5-6.0)	1.00
	Yes	93	1	67.7 (9.4-486.6)	58.0 (9.7-346.7)	19.8 (2.6-149.1)

Abbreviations: CI, confidence interval; OR, odds ratio.
*A total of 37 cases and 1 control participant had a hematological malignancy; 26 cases and 4 control participants did not provide information about stage of disease.
†Adjusted for age and sex; reference group is patients with no malignancy.
‡Adjusted for age and sex; reference group is patients with malignancy but without distant metastases.

Table 4. Malignancy Within 5 Years Before Venous Thrombosis, Presence of Factor V Leiden or the Prothrombin 20210A Mutation, and the Risk of Venous Thrombosis

Mutation	Malignancy	Patients (n = 2706)	Control Participants (n = 1757)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Factor V Leiden					
No	No	2125	1635	1.00	1.00
	Yes	162	26	4.8 (3.2-7.3)	5.1 (3.3-7.7)
Yes	No	403	95	3.3 (2.6-4.1)	3.3 (2.6-4.1)
	Yes	16	1	11.9 (1.6-86.6)	12.1 (1.6-88.1)
Prothrombin 20210A					
No	No	2410	1694	1.00	1.00
	Yes	164	27	4.3 (2.8-6.4)	4.5 (3.0-6.8)
Yes	No	118	36	2.3 (1.6-3.4)	2.3 (1.6-3.3)
	Yes	14	0	ND	ND

Abbreviations: CI, confidence interval; ND, not determined due to 0 control participants.
*Adjusted for age and sex.

creased compared with noncarriers (OR, 3.2; 95% CI, 2.5-4.0). The OR for individuals with only the factor V Leiden mutation without a malignancy was 3.3 (95% CI, 2.6-4.1) (TABLE 4). Individuals with only malignancy had an OR of 5.1 (95% CI, 3.3-7.7) compared with noncarriers without malignancy. Carriers of the factor V Leiden mutation who also had cancer had an OR of 12.1 (95% CI, 1.6-88.1). This implies that patients with cancer with factor V Leiden had a 2-fold increased risk of venous thrombosis compared with noncarriers with cancer (adjusted OR, 2.2; 95% CI, 0.3-17.8).

The allele frequency of the prothrombin 20210A mutation among patients was 2.5% and among control participants was 1.0%. The heterozygous (20210 AG) variant was found in 131 patients (4.8%) compared with 36 control participants (2.0%). One homozygous carrier was found among patients and none among control participants. Overall, the risk of thrombosis in the presence of the prothrombin 20210A mutation was 2.5-fold increased compared with noncarriers (OR, 2.5; 95% CI, 1.7-3.6). The OR for prothrombin 20210A carriers without malignancy was 2.3 (95% CI, 1.6-3.3). In the absence of control participants with cancer and with the prothrombin 20210A mutation, we were unable to directly estimate the risk for cancer patients carrying the prothrombin 20210A mutation; however, we used 2 approaches to estimate the risk. First, under the assumption that in the population of control participants, cancer and the prothrombin 20210A mutation are not associated, we estimated the expected number of control participants with both factors. When we applied the proportion of prothrombin 20210A carriers among control participants without cancer {[36/(1694+36)] =0.0208} to the 27 control participants with cancer, we expected [(0.0208×27)=0.562] control participants with both risk factors. The calculated crude OR of venous thrombosis for these patients compared with patients without malignancy and without the mutation was then 17.5 (95% CI, 1.2-252.0). Compared with patients with cancer without the prothrombin 20210A mutation, the calculated crude OR was 4.1 (95% CI, 0.3-60.8). As a second approach, we calculated the SI in a case-only analysis for the prothrombin 20210A mutation and malignancy. This calculation [(2410×14)/(164×118)] yielded an SI of 1.7 (95% CI, 1.0-3.0), which indicates that there is a multiplicative effect for this mutation and malignancy. The indirectly estimated OR of prothrombin 20210A carrier status in the presence of malignancy compared with the absence of both risk factors is 18.0, which is 1.7 times the product of the separate ORs.[15]

COMMENT

In this large case-control study of venous thrombosis, we found that the overall 7-times increased risk for venous thrombosis in patients with a malignancy depends on type of cancer and time since the cancer diagnosis, whereas advanced stage of disease is associated with a further increase in risk. The risk is approximately 12- to 17-fold increased for patients with cancer who have the factor V Leiden or the prothrombin 20210A mutation.

The overall 4-fold increased risk for patients with cancer to develop venous thrombosis is similar to previously reported relative risks.[3,16] We found that the risk for thrombosis increased 7-fold when persons who did not participate in the study by filling in a questionnaire were included. This relative risk is higher than risks mentioned in other studies. For instance, a study from the United States reported a relative risk of 4.1 (95% CI, 1.9-8.5) for patients with cancer who did not have chemotherapy and 6.5 (9.5% CI, 2.1-20.2) for patients with cancer who had chemotherapy.[3] In this study, *cancer* was defined as "active cancer mentioned in the medical records and documented in the 3 months prior to the thrombotic event."[3] In our MEGA study, all diagnosed cancers were taken into account, leading to a higher relative risk.

Information was collected by questionnaire as well as by telephone and records from the anticoagulation clinic. Due to our ability to collect information about patients who did not fill in a questionnaire and those who died, we could ensure complete information of all consecutive patients with venous thrombosis. The selection of partners of patients as control participants made it possible to receive information about disease in partners who did not fill in a questionnaire. We showed that those patients who died and those who were unwilling to participate preferentially included patients with cancer, which implies that studies on survivors[16] lead to underestimation.

Gastrointestinal cancer, lung cancer, and hematological cancer were the malignancies associated with a very high relative risk of venous thrombosis. This is in agreement with findings in other studies. Several studies evalu-

ating the occurrence of cancer after a venous thrombotic event reported an increased incidence of pancreatic cancer, gastrointestinal cancer, hematological cancer, brain cancer, and lung cancer in the first year after the thrombosis.[17,18] A prospective cohort study reported malignancies of the kidney, stomach, pancreas, brain, ovary, and lymphoma as being associated with the highest incidence of venous thrombosis.[19] Although our study is a large population-based, case-control study, certain types of malignancy were not found in control participants, precluding the calculation of the relative risks. The risk of thrombosis in these rare cancers needs to be studied in cohort studies of such patients with cancer. For some types of malignancy, we had relatively few control participants and as a result the CIs were wide, so the estimates of the ORs should be interpreted with caution. However, if we define *active cancer* as cancer diagnosed until 10 years before the index date, the ranking of tumor types according to increasing risk of venous thrombosis remains the same.

We found that the risk to develop thrombosis was highest when the diagnosis of malignancy was made recently. In the first 3 months after the diagnosis of cancer, the risk was 53-fold increased and declined thereafter. After 2 years, the relative risk had decreased considerably but was still increased compared with individuals without cancer. Only after 15 years, did the risk subside. Mechanisms by which cancer may cause activation of the clotting system comprise effects of the tumor, such as humoral and mechanical effects,[20] and are likely to be highly active in recently diagnosed cancer. Additionally, cancer therapy is often associated with a hypercoagulable state.[21] The more recent the diagnosis of cancer, the more likely it is that cancer therapy plays a role in the development of thrombosis. Because we had no information about the date of therapy, we could not analyze the direct effect of the different treatment modalities on the risk of venous thrombosis.

The presence of distant metastases in solid tumors increases the risk of venous thrombosis 58-fold compared with patients without cancer, which is much higher than the risk for patients with cancer without distant metastases (4-fold). This is in accordance with earlier findings.[4,22] The presence of metastases is associated with increased hypercoagulability, as the hemostatic system seems to play a key role in the metastatic capacity of solid tumors.[23]

We evaluated the effect of malignancy in association with either the factor V Leiden or prothrombin 20210A mutation. In either case, the joint effect appeared slightly higher than the sum of the single effect, with a 12- to 17-fold increased risk compared with the absence of both risk factors. In agreement with our findings, a retrospective cohort study among unselected patients in a hematology-oncology clinic and a cohort study of patients with gastrointestinal carcinoma reported a relative risk of venous thrombosis of 3.1 (95% CI, 0.63-14.73) and 4.4 (95% CI, 1.3-14.9), respectively, for patients with cancer and the factor V Leiden mutation compared with patients with cancer and without the factor V Leiden mutation.[24,25] A relative risk of 2.4 (95% CI, 0.6-9.9) was reported for patients with cancer with the prothrombin 20210A mutation compared with patients with cancer but without the prothrombin 20210A mutation, also in agreement with our study.[25]

From a case-control study, one cannot directly infer absolute risks or derive statements about treatment strategies. Nevertheless, with the use of well-established background incidences of thrombosis, information useful to the clinician can be obtained. Assuming a baseline risk of 1 to 4 patients with venous thrombosis per 1000 per year, a 5% prevalence of factor V Leiden and a 2% prevalence of the prothrombin 20210A mutation, among 10 000 patients with cancer, we would expect 8 to 34 patients with venous thrombosis due to factor V Leiden or the prothrombin 20210A mutation. Screening for factor V Leiden and the prothrombin 20210A mutation and subsequent prophylactic anticoagulant therapy with an effectivity of 80% would prevent annually 7 to 27 venous thrombotic events per 10 000 patients with cancer screened (numbers needed to screen: 700-2700), which does not make screening a useful strategy. Rather than screening for factor V Leiden or the prothrombin 20210A mutation, it may be more cost-effective to consider prophylactic anticoagulant therapy for patients with cancer who have an increased risk to develop venous thrombosis.

Prophylactic anticoagulant treatment of cancer is effective during chemotherapy and perioperatively and also as secondary prevention after a venous thrombotic event.[26] Future studies could address the issue of giving prophylactic anticoagulant therapy to patients with cancer in the first months after the diagnosis of cancer or in the presence of distant metastases. However, since these patients also have an increased risk of hemorrhage,[27] this needs to be cautiously evaluated.

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Study concept and design: Blom, Doggen, Rosendaal.
Acquisition of data: Blom, Doggen.
Analysis and interpretation of data: Blom, Doggen, Osanto, Rosendaal.
Drafting of the manuscript: Blom, Doggen, Rosendaal.
Critical revision of the manuscript for important intellectual content: Blom, Doggen, Osanto, Rosendaal.
Statistical analysis: Blom, Doggen, Rosendaal.
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