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ORIGINAL ARTICLE

The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma

J. W. BLOM,* S. OSANTO‡ and F. R. ROSENDAAL*†

**Department of Clinical Epidemiology, †Hemostasis and Thrombosis Research Center, ‡Department of Oncology, Leiden University Medical Center, the Netherlands*

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Summary. *Background:* Only limited data on the incidence of venous thrombosis in different types of malignancy are available. Patients with adenocarcinoma are believed to have the highest risk of developing venous thrombosis. *Objectives:* To study the incidence of thrombosis in patients with lung cancer, with an emphasis on the comparison between adenocarcinoma and squamous cell carcinoma, we have performed a cohort study of patients with non-small-cell lung cancer. In addition the risk associated with treatment and extent of disease was assessed. *Patients/methods:* A total of 537 patients with a first diagnosis of lung carcinoma were included. Patient and tumor characteristics as well as venous thrombotic events were recorded from the medical records and from the Anticoagulation Clinic. *Results:* Thrombotic risk in lung cancer patients was 20-fold higher than in the general population (standardized morbidity ratio (SMR): 20.0 (14.6–27.4). In the group of patients with squamous cell cancer we found 10 (10/258) cases (incidence: 21.2 per 1000 years) of venous thrombosis whereas in the group of patients with adenocarcinoma 14 (14/133) cases (incidence: 66.7 per 1000 years) occured. The crude adjusted hazard ratio was 3.1 (95% CI: 1.4–6.9). The risk increased during chemotherapy and radiotherapy and in the presence of metastases. *Conclusions:* The risk of venous thrombosis in lung cancer patients is increased 20-fold compared to the general population. Patients with adenocarcinoma have a higher risk than patients squamous cell carcinoma. During chemotherapy or radiotherapy and in the presence of metastases the risk is even higher.

Keywords: adenocarcinoma, lung cancer, squamous cell carcinoma, venous thrombosis.

Correspondence: Professor F.R. Rosendaal, Department of Clinical Epidemiology, C9-P, Leiden University Medical Center, PO Box 9600, Leiden, the Netherlands. 2300 RC Leiden, Netherlands.
Tel.: +31 070 5264037; fax: +31 070 5266994; e-mail: F.R.Rosendaal@lumc.nl

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Introduction

Venous thrombosis has an incidence in the general population of 1–3 in 1000 per year [1,2]. Risk factors for thrombosis have been identified and may be either genetic or acquired, or have a combined origin [3]. Among the risk factors for venous thrombosis, cancer is an important and well-established risk factor, leading to a 2- to 4-fold increased risk [4,5]. Eighteen per cent of cancer patients have been reported to die of pulmonary embolism (PE) [6].

Several factors may contribute to venous thrombosis in cancer patients, such as immobilization, surgery, procoagulant factors produced by the tumor cells [7], endothelial damage caused by chemotherapy or stimulation of endothelial cells to produce procoagulant material [8]. Patients with adenocarcinoma are believed to have the highest risk of developing venous thrombosis during the course of their disease. In 1865 Armand Trousseau described patients with 'thrombophlebitis saltans et migrans' as well as deep venous thrombosis (DVT) as a first symptom of gastric carcinoma. He concluded 'there exists a particular condition of the blood which predisposes it to spontaneous coagulation' [9].

In 1938 Sproul [10] conducted a postmortem study and suggested a relation between pancreatic cancer and venous thrombosis. She found thrombosis in 20% of the most common malignancies and in 56% of the pancreas carcinomas. This relationship between pancreatic cancer and venous thrombosis has been confirmed in many postmortem studies [11–13]. Among malignancies presenting with venous thrombosis as a first clinical manifestation, prostate and colorectal cancer are the most commonly identified (50% of the total number of patients with occult cancer) [14]. Also cancers of the pancreas, stomach and bladder are frequently reported to cause venous thrombosis, in about 20–30% of the patients with these malignancies [15,16]. Hence, because of the high frequency of adenocarcinomas in patients with venous thrombosis it has become a widespread belief that the risk of thrombosis is paramount in adenocarcinomas.

We searched for data in the literature that support this belief, but found strikingly few papers on the incidence of

symptomatic DVT in patients with different histological types of cancer. To further investigate the concept that adenocarcinomas are associated with a higher risk for venous thrombosis, we investigated the incidence of venous thrombosis in a patient group with non-small-cell lung cancer, in particular with the two major histological types of cancer, squamous cell carcinoma and adenocarcinoma. This enabled us to compare patients with adenocarcinoma vs. patients with squamous cell carcinoma in a patient group with tumors arising in the same organ.

We performed a follow-up study in consecutive patients with non-small-cell lung cancer treated in one center over a 10-year period and estimated the effect of therapy and extent of disease on the risk of venous thrombosis.

Methods

From the oncology registration database of the hospital, we identified 678 consecutive patients who were admitted with non-small-cell lung cancer to the Leiden University Medical Center between January 1990 and December 2000. The oncology registration database is a dedicated database of our hospital, in which information on all patients diagnosed with and admitted for cancer in our hospital, are registered. The database has been set up in 1970 and is staffed by specialized oncology data managers. Fifty-seven medical records could not be traced. Fifty patients were not included because they only briefly visited the Leiden University Medical Center for laser therapy and 34 patients were not included because they had a diagnosis of lung cancer before 1990 or a primary diagnosis of lung cancer could not be confirmed. Five hundred and thirty-seven patients with a first diagnosis of lung cancer established in the Leiden University Medical Center or with a first diagnosis within 2 months before referral to Leiden University Medical Center were selected for the analysis.

From the medical records we recorded clinical characteristics, such as demographic data, use of anticoagulants, treatment (chemotherapy, radiotherapy, surgery). Chemotherapy usually consisted of a combination therapy of various cytotoxic agents including carboplatin, cisplatin, gemcitabine or taxotere. In addition, tumor characteristics were recorded: the histological or cytological classification of the tumor and the extent of the disease. For 391 patients the diagnosis of lung cancer was based on histological examination, whereas in 131 cases only a cytological diagnosis was available. In 15 cases referred by other hospitals no information was available whether the diagnosis was based on histological or cytological analysis was available.

For the classification of the extent of disease we used three stages. Patients without lymph node spread were classified as having only local tumor growth (any T, N0, M0). Patients with tumor growth in regional lymph nodes were classified as local regional tumor growth (any T, N +, M0), as well as patients with unknown T and N, but with M0. The third group was formed by the patients with distant metastases (any T, any N, M +). Whenever a postoperative staging was known, this staging was used. In 28 cases staging was not performed due to lack of treatment options.

We ascertained the occurence of a venous thrombotic event (VTE) since diagnosis of cancer either by examining the medical records of the Leiden University Medical Center and the records of the anticoagulation clinic of the region where the patient was living, or by consulting the general practitioner of the patient. In the Netherlands, anticoagulation clinics monitor all patients receiving treatment with oral anticoagulant therapy in a specific region. Outcome events were DVT or PE, occurring after the first diagnosis of lung cancer. Diagnosis of venous thrombosis was made in the Leiden University Medical Center or in a hospital near the patients' home.

Information on the date of death was obtained from the medical records, the registration offices of the municipalities where the patients lived or from their general practitioner. Three patients whose medical records were not available at the anticoagulation clinic or general practitioner were lost to follow up resulting in a loss of 1.5 person-years.

Statistical analysis

We counted person-years of follow-up for each subject from the date of first contact until the date of a thrombotic event, the date of death, or the end of the study period (31 December 2000), whichever occured first. A total of 879 person-years accrued with maximally 1.5 person-years lost to follow up (0.2%). We computed the incidence rates by dividing the number of thrombotic events by the number of person-years. A standardized morbidity ratio was calculated using the incidence rate of DVT of the leg and PE in the Dutch population of 1994 [17].

We used Cox proportional hazard regression to adjust for age, sex and other putative confounding variables. For the analysis of the effect of therapy we used a Cox proportional hazard model with time-dependent covariates. We constructed a model which compared therapy vs. no therapy:

$$h(t, X(t)) = h_0(t) \exp[\beta_1 \text{therapy}(t)],$$

where therapy(t) is 1 when $t >=$ start date of therapy and $t <=$ end date of therapy, 0 when $t <$ start date of therapy and when $t >$ end date of therapy.

To investigate the effect of duration of therapy we set up an extended Cox model with time-dependent variables which allowed a cumulative increase in risk with the duration of therapy:

$$h(t, X(t)) = h_0(t) \exp[\beta_1 \text{therapy}(t) + \beta_2 \text{duration}(t)],$$

where the therapy(t) 1 when $t >=$ start date of therapy and $t <=$ end date of therapy, 0 when $t <$ start date of therapy and when $t >$ end date of therapy; duration(t) = amount of days of therapy at each t.

The hazard ratio is then calculated per day as:

$$HR = \exp[\beta_1 \text{therapy}(t) + \beta_2 \text{duration}(t)].$$

This model was compared to the simpler model that compared only therapy vs. no therapy. The addition of the duration of therapy to this simpler model was assessed by comparing the −2 ln likelihood of the two models. The underlying assumptions for the Cox proportional hazard model were tested by visual inspection of the log-log survival curves for the time-independent variables. The relative risk associated with surgery was analyzed by introducing a time-dependent covariate in the model indicating the time of surgery plus 1 month for the postoperative period, as an arbitrarily chosen time-window of increased risk.

Effect modification by extent of disease was assessed in a subgroup of patients for whom data on the stage of disease were available. We used a Cox proportional hazards model with a time-dependent covariate to account for changes in stage during the course of the disease.

Analysis of the difference between squamous cell carcinoma and adenocarcinoma was performed in a subgroup of patients of whom the diagnosis of lung cancer was based on histological and not cytological examination of the tumor in order to minimize the probability of misclassification of diagnosis.

For the survival analysis of patients who develop a venous thrombosis after diagnosis of lung cancer we used a Cox proportional hazards model with the thombotic event as a time-dependent covariate.

Results

Characteristics of the cohort of 537 patients are shown in Table 1. The mean age of the patients was 65 years and their median survival 0.9 years. We observed 39 events of DVT over 879 years of follow-up (Table 2) for an overall incidence of DVT of the leg or PE of 44.4 per 1000 person-years (95% CI: 31.3–57.5). Based on age- and sex-specific incidence rates from the general Dutch population, two cases (incidence 2.0 per 1000 person-years) were expected for a cohort of this age- and sex-distribution. Adjusted for age and sex, thrombotic risk in lung cancer patients was 20-fold higher than in the general population (standardized morbidity ratio (SMR): 20.0 (14.6–27.4). The median time from first admittance for lung cancer until development of the VTE was 5.3 months (range 0.0–56.4 months). The incidence of VTE in the first 6 months after the diagnosis of lung cancer was 112.9/1000 person-years (95% CI: 69.8–166.1), i.e. 4-fold higher than in the subsequent time period. Sixteen patients had a previous VTE in their medical history, and of these three patients also developed a VTE after the diagnosis of lung carcinoma (incidence 93.8 per 1000 person-years [95% CI: 17.7–231.3]). Among those without a history of venous thrombosis, the incidence after lungcancer diagnosis was 42.6/1000 person-years (95% CI: 28.7–56.6). Two patients had a VTE before the diagnosis of lung cancer, which was the trigger to search for occult malignancy. These two thrombotic events were not included in the analysis.

Among 258 patients with a histological confirmed squamous cell carcinoma we found 10 VTEs. In the group of 133 patients with a histological confirmed adenocarcinoma 14 VTEs occurred. The incidence of venous thrombosis for patients with squamous cell carcinoma was 21.2 per 1000 person-years (95% CI:10.1–36.2) and for patients with an adenocarcinoma 66.7 per 1000 person-years (95% CI: 36.2–106.2) resulting in a lower venous thrombosis-free survival in patients with adenocarcinoma as compared to patients with squamous cell carcinoma (Fig. 1). The risk was 3-fold increased for patients with adenocarcinoma vs. patients with squamous cell carcinoma (crude hazard ratio 3.1 [95% CI: 1.4–6.9]). In a regression model we adjusted for age, sex, chemotherapy and radiotherapy. This yielded a hazard ratio of 2.8 (95%

Table 1 Patient characteristics

		Total group	Squamous cell carcinoma* ($n = 258$)	Adeno carcinoma* ($n = 133$)
Tumor types	squamous cell carcinoma	311		
	adenocarcinoma	158		
	other non-small cell carcinomas	68		
Men:women		429 : 108	222 : 36	97 : 36
Mean age (range)		65 (29–94)	67 (38–94)	63 (29–84)
Extent of disease	any T N0 M0	142 (26%)		
	any T N +M0	163 (30%)		
	any T any N M +	204 (38%)		
	no staging	28 (5%)		
Therapy	Surgery	188 (35%)	108 (42%)	51 (38%)
	Chemotherapy	81 (15%)	25 (10%)	25 (19%)
	Radiotherapy	300 (56%)	148 (57%)	69 (52%)
Anticoagulants during follow up > ½ year for reasons other than VTE		70 (12%)	47 (18%)	12 (9%)
Second malignancy		64 (12%)	42 (16%)	10 (8%)
Median survival after diagnosis (year) (range)		0.9 (0.0–11.4)	1.0 (0.0–11.4)	0.8 (0.0–10.7)

*Histological confirmed diagnosis.

Table 2 Incidence of venous thrombosis in the total group of lung cancer patients

DVT	17
PE	15
DVT + PE	7
Total	39
Person years of follow up	879
Incidence DVT/PE (per 1000 person-years)	44.4

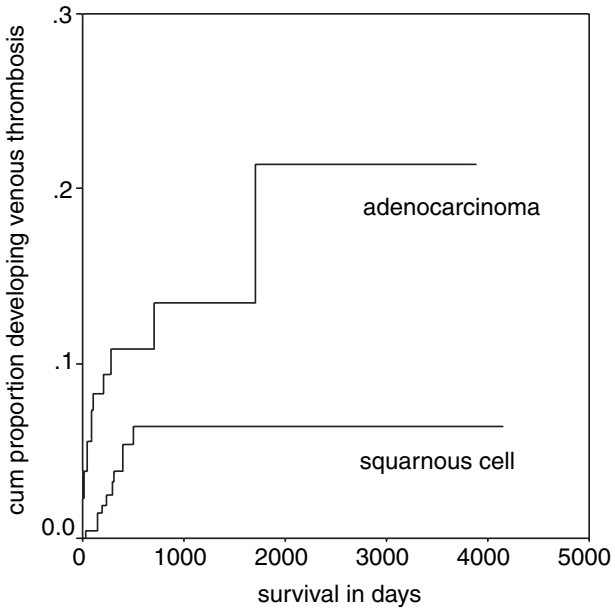

Fig. 1. Cumulative proportion of venous thrombosis in patients with a squamous cell carcinoma vs. patients with an adenocarcinoma.

CI: 1.2–6.4) for patients with adenocarcinoma vs. patients with squamous cell carcinoma. Adjustment for all these variables and for spread of disease led to a hazard ratio of 2.1 (95% CI: 0.9–4.9). The same analysis was performed including patients of whom only a cytological diagnosis was available. The crude hazard ratio as well as the adjusted hazard ratios were slightly lower (crude hazard ratio: 2.4 [95% CI: 1.2–5.0]) than for histological confirmed cases, which means there probably was some misclassification of diagnosis due to the lower accuracy of cytologically made diagnoses.

Analysis of the effect of cancer therapy and extent of disease was performed for the total group. In 13 out of the 25 patients with venous thrombosis who received chemotherapy or radiotherapy as treatment for lung cancer, the symptoms of VTE arose during or within 4 weeks after ending their therapy, resulting in an incidence during or within 1 month after chemotherapy or radiotherapy, of 279.4 per 1000 person-years (95% CI: 111.7–522.8) and 110.2 per 1000 person-years (95% CI: 40.4–216.9), respectively. In a Cox proportional hazards model we estimated the effect of chemotherapy while taking the duration of therapy into account. This model gave the best fit to the data when we considered this therapy to have a prothrombotic effect to persist until 70 days in the post-therapy stage. The coefficients were for therapy$(t)_{\beta 1} = 1.168$ and for duration$(t)_{\beta 2} = 0.005$, adjusted for age and sex. According to our model the risk of venous thrombosis increases 3-fold when chemotherapy is started (HR 3.2, 95% CI: 2.1–4.3) compared to the time when no chemotherapy is given. With increasing duration of chemotherapy, the risk increases even further. At the median duration of 58 days the risk is increased 4-fold (HR 4.3, 95% CI: 3.4–5.2) (Table 3). Adjusting for stage of disease only slightly reduced these relative risks. Similarly, we analyzed the effect of radiotherapy in a Cox proportional hazards model. We used the simpler model, as the model taking the duration of radiotherapy into account did not lead to a better fit of the data. The risk for patients who had received radiotherapy was increased (HR 2.1, 95% CI: 0.6–7.1) compared to patients without radiotherapy. Surgery was not identified as a risk factor (HR 0.9, 95% CI: 0.1–6.6). Adjusting for stage of disease did not alter this relative risk (HR 1.3, 95% CI: 0.2–10.1). One patient presented with venous thrombosis in the postoperative stage, i.e. within 1 month after operation. All surgery patients were receiving thrombosis prophylaxis according to the protocol of the hospital.

We evaluated the effect of distant metastases in a Cox proportional hazards model, adjusting for age, gender and therapy. The risk for patients with loco regional tumor growth was not increased compared to patients with only local tumor growth (HR 1.2, 95% CI: 0.4–3.3, adjusted for age, sex and therapy). Patients with distant metastases had a 6-fold increased risk compared to patients with only local tumor growth (HR 6.5, 95% CI: 2.6–16.5, adjusted for age, sex and therapy). The incidence rate in the presence of distant

Table 3 The risk of venous thrombosis during cancer therapy compared to time without receiving therapy

		Crude HR	Adjusted for age and sex	+ Adjusted for stage of disease*
Chemotherapy	no	1		
	start	4.2 (3.1–5.3)	3.2 (2.1–4.3)	2.9 (1.8–4.0)
	58 days (median duration)	5.3 (4.4–6.2)	4.3 (3.4–5.2)	3.3 (2.4–4.2)
	83 days (mean duration)	5.9 (5.1–6.7)	4.9 (4.1–5.7)	3.4 (2.5–4.3)
Radiotherapy	no	1		
	yes	2.1 (0.6–7.3)	2.1 (0.6–7.1)	1.9 (0.5–6.3)
Surgery	no	1		
	yes	0.9 (0.4–7.4)	0.9 (0.1–6.6)	1.3 (0.2–10.1)

*In subgroup of whom extent of disease was known.

Table 4 Risk of dying after a venous thrombotic event in patients with or without distant metastasis

			Hazard ratio (95% CI)*
no distant metastasis	venous thrombosis	no	1
		yes	3.2 (1.6–6.2)
distant metastasis	venous thrombosis	no	1
		yes	4.5 (2.8–7.3)

*Adjusted for age, sex and therapy.

metastases was very high at 220.5 per 1000 person-years (95% CI: 157.1–355.9).

Survival time till death of patients who developed a VTE during the course of their disease was decreased compared to the survival of patients who did not develop a VTE. At any moment after a VTE the risk of dying was 3-fold increased (HR 3.1, 95% CI: 2.2–4.4, adjusted for age, sex, therapy and extent of disease). For both patients with distant metastasis at the start of follow-up as well as for patients without distant metastasis at the start of follow-up we found an increased risk of dying after a venous thrombotic event (Table 4).

Discussion

This large cohort study of 537 lung cancer patients shows that the incidence of venous thrombosis is 20-fold increased compared to the general population at 44.4 per 1000 patient-years. The incidence is increased 3-fold in patients with adenocarcinoma compared to patients with squamous cell carcinoma. After adjustment for age, sex, therapy and distant metastasis the hazard ratio of an adenocarcinoma vs. squamous cell carcinoma was 2.1.

Since Trousseau, attention has been focused on the high risk of venous thrombosis associated with adenocarcinomas. We indeed found a 3-fold increased risk of venous thrombosis for patients with an adenocarcinoma compared to patients with a squamous cell carcinoma. The difference in incidence could not be explained by the difference in treatment. Patients with an adenocarcinoma more frequently received chemotherapy, but adjusting for therapy did not change the hazard ratio to a great extent, nor did adjustment for the presence of distant metastasis change the hazard ratio substantially.

Only one cohort study previously, assessed the incidence of venous thrombosis in lung cancer patients. This study concerned 280 patients with lung cancer and reported results similar to ours [18]. Three per cent of the patients with a squamous cell carcinoma and 8% of the patients with an adenocarcinoma developed a 'clotting disorder', which could also be types of venous thrombosis other than DVT of the leg or PE.

Recent research has shown that carcinoma mucins can activate platelets and generate microthrombi in mice, most likely through interaction with leukocyte L-selectin and platelet P-selectin because this pathology was markedly diminished in P- or L-selectin deficient mice. Heparin (which potentiates antithrombin and blocks P- and L-selectin) ameliorated this platelet aggregation whereas recombinant hirudin (inhibition of thrombin) did not. Thus interaction of circulating carcinoma mucins with leukocyte L-selectin and platelet P-selectin without requiring accompanying thrombin generation is a probable molecular explanation for the increased incidence of venous thrombosis in patients with adenocarcinoma [19].

Although many studies have shown an increased risk of thrombosis in cancer [4,20], few studies describe the absolute risk as incidence rates of venous thrombosis for cancer patients. In our study we found an incidence rate of 44.4 per 1000 person-years for lung cancer patients. This annual rate of over 4% is a 20-fold increase compared to the general population.

A cohort study of cancer patients using a Medicare database [21] reported the highest cumulative incidence in patients with cancer of the ovaries, brain tumors, pancreatic tumors and lymphoma. This was followed by gastro-intestinal tumors, leukemia and lung cancer. Lung cancer patients had a cumulative incidence of 61 per 10 000 during the 183 days of follow-up after initial diagnosis. We found 21 cases in the first half-year of follow up resulting in a approximately six times higher cumulative incidence of VTE of 391 per 10 000. This difference may be explained by the difference in verification of the thrombotic event. We verified the thrombotic event by checking the medical records of the hospital and the anticoagulation clinics, whereas verification in the Medicare database study was done by record linkage of Medicare data which have been shown to underreport hospitalizations by 10–27% [22]. Furthermore, we excluded all non-primary lung cancer whereas these may have been included in the Medicare database study.

The incidence of venous thrombosis as observed in our cohort of lung cancer patients may even be underestimated as venous thrombosis causing sudden death at home, may not have been diagnosed and registered in the medical records.

Our data also showed that the risk for venous thrombosis continues to be increased for about 2 months after the discontinuation of chemotherapy whereas radiotherapy did not show this effect. Thus far the main mechanisms of thrombogenesis ascribed to chemotherapeutic agents are: release of procoagulants and cytokines from damaged tumor cells, a toxic effect on vascular endothelium, the fall of naturally occurring anticoagulants due to hepatotoxicity [8]. Radiotherapy probably mainly has a thrombogenic effect by release of procoagulants and cytokines from damaged tumor cells. The cumulative damage of vascular endothelium and liver caused by chemotherapy might take longer to recuperate and thus cause an increased risk of venous thrombosis with increasing duration of therapy. Chemotherapy and radiotherapy have previously been shown to be associated with an increased risk of VTE [4,23,24].

We did not find an increased risk of venous thrombosis related to surgery, which is likely to be due to adequate prophylaxis given to all patients who underwent surgery.

In conclusion, our study shows a high incidence of venous thrombosis in lung cancer patients with a much higher incidence in patients with adenocarcinoma as compared to patients with squamous cell carcinoma. Because the incidence

of venous thrombosis significantly increases during chemotherapy or radiotherapy and in the presence of distant metastases, and exceeds the incidence of major bleeding (54 per 1000 person-years [25] and 125 per 1000 person-years [26]), prophylactic anticoagulant treatment during the period of treatment or in the presence of distant metastases may be warranted to prevent development of venous thrombosis and related morbidity and mortality. We suggest this should be studied further in clinical trials.

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