Risk factors for venous thromboembolism in patients treated for differentiated thyroid carcinoma

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Abstract

Although cancer in general is a strong risk factor for developing venous thromboembolism (VTE), the risk factors for venous thromboembolic events in patients with differentiated thyroid carcinoma (DTC) have never been assessed. This is remarkable, as several parts of the treatment comprise a hypercoagulable state that could in subgroups of DTC patients lead to an increased risk of VTE. The aim of this study was to assess which risk factors could cause DTC patients to develop VTE. We performed a nested case–control study, involving cases of DTC patients treated between 1980 and 2014 with confirmed VTE after diagnosis of DTC. Controls were defined as DTC patients without VTE. In all subjects, we collected information about thyroid cancer characteristics, treatment characteristics, traditional risk factors for VTE and additional clinical data, and we performed univariable and multivariable regression analyses. We included 28 cases and 56 controls matched for age at DTC diagnosis, sex and date of DTC diagnosis. In the univariable regression analysis, histology, distant metastases, DTC risk classification, recent surgery and other active malignancy were associated with VTE. In the multivariable analysis, distant metastases (odds ratio 7.9) and recent surgery (odds ratio 6.1) were independently associated with VTE. In conclusion, surgery and presence of distant metastases are independent risk factors for developing VTE in DTC patients. The risk factors identified in this study could be considered when making decisions regarding thromboprophylaxis for patients with thyroid cancer.

Key Words

- ▶ differentiated thyroid carcinoma
- ▶ venous thromboembolism
- ▶ risk factors

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Introduction

Cancer is a strong risk factor for developing venous thromboembolism (VTE), and VTE is an important cause of death in cancer patients (Lyman 2011, Deng *et al.* 2014). The risk of developing VTE varies among subgroups

of cancer, depending mostly on the growth rate and the presence of metastases (Khorana & Rao 2007, Lyman 2011).

Thyroid carcinoma is the most common endocrine malignancy with an estimated 56,870 new

cases in the United States each year (<https://seer.cancer.gov/statfacts/html/thyro.html>). Moreover, the incidence rate of thyroid cancer is rising, with an average annual increase of 5.3% (95% confidence interval (CI), 4.8–5.7%) over the last two decades (Magreni *et al.* 2015).

Differentiated thyroid carcinoma (DTC) comprises papillary and follicular thyroid carcinomas (PTC and FTC). DTC patients have a favorable prognosis after treatment with total thyroidectomy, iodine-131 ablation and subsequent thyroid hormone suppression therapy (THST) (Schlumberger 1998). In low-risk patients, there is a tendency to use less aggressive treatment (ATA *et al.* 2009). The rationale for THST, advocated in high-risk patients, is to minimize potential tumor growth (Pujol *et al.* 1996). However, the downside of this therapy is that it results in (subclinical) hyperthyroidism, which is associated with adverse cardiovascular effects and mortality (Klein Hesselink *et al.* 2013, Danzi & Klein 2014).

Walker and coworkers assessed the incidence of VTE in 83,203 cancer patients and 577,207 controls. The study included 503 thyroid cancer patients in whom an absolute increased incidence of VTE was not found (Walker *et al.* 2013). However, as histological subgroups of thyroid cancer were not defined, a subgroup of thyroid cancer patients may have increased the risk of VTE. DTC patients may have an increased risk of developing VTE as known (treatment-related) risk factors for VTE, including surgery (Bates *et al.* 2012) and (subclinical) hyperthyroidism, are inevitable during treatment of DTC. Although hypothyroidism is associated with increased bleeding risk, hyperthyroidism is associated with a hypercoagulable state (Franchini *et al.* 2011, Kootte *et al.* 2012, Horacek *et al.* 2015). In overt hyperthyroidism, increasing levels of FT₄ are a risk factor for VTE (van Zaane *et al.* 2010). In contrast to patients with overt hyperthyroidism, patients on THST are maintained in a less toxic state of hyperthyroidism, but potentially for a much longer time. Horne and coworkers found that DTC patients on THST have an increased thrombin production and reduced plasminogen activation. This would suggest that patients on THST are predisposed to VTE (Horne *et al.* 2004, Franchini *et al.* 2011, Horacek *et al.* 2015). In conclusion, certain subgroups of DTC patients, depending on the histological findings, metastases, THST and recent surgery, may be more at risk than others of developing VTE. Therefore, the aim of this study was to identify the risk factors for VTE in patients with DTC.

Materials and methods

Patients and controls

We performed a nested case–control study in patients with DTC. Data were retrieved from a document pertaining thyroid cancer patients treated and/or in follow-up at the University Medical Center Groningen (UMCG) between January 1980 and December 2014. Deceased patients were eligible. At the UMCG, patients are treated with total thyroidectomy and lymph node dissection when indicated. They are subsequently treated with Iodine-131 ablation therapy after thyroid hormone withdrawal. Recombinant human (rh)TSH ablation is performed only if withdrawal is contraindicated.

Cases were defined as patients with PTC or FTC, with confirmed VTE after DTC diagnosis. VTE was defined as deep venous thrombosis or pulmonary embolism confirmed by compression ultrasonography, computed tomography (CT) angiography, magnetic resonance imaging (MRI) or digital subtraction angiography (DSA). Controls were defined as DTC patients without VTE after diagnosis of DTC. Controls were derived from the same patient cohort as cases. Cases and controls were excluded if younger than 18 years old when diagnosed with DTC, and when follow-up records, thyroid cancer characteristics, or treatment modalities were not present in the electronic patient files. In general, follow-up visits of DTC patients took place at least once a year. Correspondence from both the UMCG and regional hospitals regarding outpatient clinic visits was available in the electronic patient files. Each case was matched to two controls. First, for each case, the period between DTC diagnosis and VTE diagnosis was calculated. A patient was eligible to be matched to a case if he or she had clinical follow-up records for at least the DTC-VTE duration of the case. Second, cases and controls were matched according to sex. Third, to correct for evaluating treatment strategies and standard of care between 1980 and 2014, the difference in date of DTC diagnosis between cases and controls was not allowed to exceed 10 years. Finally, we chose the control whose age at DTC diagnosis was closest to that of the case upon DTC diagnosis. We calculated an index date for each control; we used the date as long after their DTC diagnosis as the length of time between the corresponding case's DTC diagnosis and VTE diagnosis.

Data collection

Data on tumor histology (papillary or follicular thyroid carcinoma, including Hürthle) and TNM classification

Table 1 Characteristics of cases and controls at DTC diagnosis.

Parameter	Cases (n=28)		Controls (n=56)	
	No./median	%/IQR	No./median	%/IQR
Sex (male)	10	35.7	20	35.7
Age (years)	58	43–67	58	43–67
Histology				
Papillary	13	46.4	37	66.1
Follicular	15	53.6	19	33.9
Hürthle	4	14.2	6	10.7
TNM stage				
Tx–T2	6	21.4	14	25
T3–T4	22	78.6	42	75
Nx–N0	19	67.9	14	25
N1	9	32.1	42	25
Mx–M0	20	71.4	51	91.1
M1	8	28.6	5	8.9
DTC risk classification				
Low (Tx–T2, Nx–N0, Mx–M0)	9	32.1	28	50
Intermediate (any T3 or N1 tumor)	9	32.1	13	23.2
High (any T4 or M1 tumor)	10	35.7	15	26.8
History of VTE before DTC diagnosis	1	3.6	1	1.8

DTC, differentiated thyroid carcinoma; IQR, inter quartile range; VTE, venous thromboembolism.

were collected upon VTE diagnosis/index date. All subjects were scored according to the postoperative TNM classification. Until 2006, the fifth edition of TNM Classification of Malignant Tumors was used. Between 2006 and 2010, the sixth edition was used, and thereafter, the seventh edition. Subjects were classified according to the risk of recurrence: low (Tx–T2, Nx–N0 and Mx–M0), intermediate (any T3 or N1 tumor) or high (any T4 or M1 tumor).

Thyrotropin (TSH) values closest to VTE diagnosis or index date were collected. TSH values were regarded as missing if no TSH value was available within 2 years of VTE diagnosis or index date. Different TSH assays were used over time (Klein Hesselink *et al.* 2013). Iodine-131 dose was defined as the cumulative dose of iodine-131 before VTE diagnosis or index date. In addition, we collected data about the use of targeted therapy for DTC and about systemic therapy (targeted and chemotherapy) for other malignancies. Recent radiotherapy was defined as radiotherapy within two months prior to VTE or index date.

Recent surgery was defined as any surgery with general or regional anesthesia occurring within four weeks prior to VTE diagnosis or index date. Recent trauma was defined as trauma occurring in the same period. Recent immobilization was defined as immobilization by plaster-cast or immobilization for longer than three days in the four weeks prior to VTE diagnosis or index date. Furthermore, we evaluated the use of exogenous estrogens and pregnancy at the time of VTE diagnosis or index date and assessed the presence of active

malignancies other than thyroid cancer. Body mass index (BMI) was collected as closely as possible to the time of VTE diagnosis or index date. Smoking was scored at VTE diagnosis or index date as never, former, current and not recorded. Additionally, we collected data about the use of antithrombotics (anticoagulant and antiplatelet drugs) in cases and controls. Finally, we assessed the history of VTEs prior to DTC diagnosis.

According to Dutch law, i.e. Medical Research Involving Human Subjects (WMO), no ethical review was necessary for retrospective data collection. Data sets were encrypted during data analysis.

Statistical analysis

All data were shown as number (percentage) for categorical variables, median (inter quartile range, IQR) for skewed variables and as mean ($\pm$ standard deviation (s.d.)) for variables with a normal distribution. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable.

To find the best model to describe the relationship between VTE and the exposure variables, a binary logistic regression model was used. As this case–control study was matched, the model parameters were estimated with conditional maximum likelihood. In this binary logistic regression model, each determinant was added separately. TSH, log-transformed, was included in the univariable logistic regression. Variables with a significance of $P < 0.15$ in the univariable model were added to the multivariable

Table 2 Characteristics and risk factors of cases and controls at VTE diagnosis or index date.

Parameter	Cases (n=28)		Controls (n=56)	
	No./median	%/IQR	No./median	%/IQR
Age (years)	67	56–73	67	56–74
Sex (male)	10	35.7	20	35.7
Years between DTC diagnosis and VTE diagnosis or index date	5	0.5–14.9	5	0.5–14.9
Use of antithrombotics ^a	3	10.7	7	12.5
TNM stage				
Tx–T2	6	21.4	14	25
T3–T4	22	78.6	42	75
Nx–N0	18	64.3	38	67.9
N1	10	35.7	18	32.1
Mx–M0	17	60.7	51	91.1
M1	11	39.3	5	8.9
DTC risk classification				
Low (Tx–T2, Nx–N0, Mx–M0)	7	25	26	46.4
Intermediate (any T3 or N1 tumor)	8	28.6	15	26.8
High (any T4 or M1 tumor)	13	46.4	15	26.8
TSH (U/L) geometric mean, 95% CI	0.0761	0.035–0.164	0.138	0.080–0.237
Missing	1		1	
Cumulative I-131 dose (mCi)	125	50–263	65	50–200
Targeted therapy	1	3.6	0	0
Recent radiotherapy	2	7.1	0	0
Recent surgery	8	28.6	4	7.1
Recent immobilization	2	7.1	1	1.8
Other active malignancy	5	17.9	2	3.6
Systemic therapy (in patients with other active malignancy)	4	80	0	0
Use of exogenous estrogens (in woman)	2	11.1	2	5.6
Smoking status				
Current	2	7.4	9	16.7
Former	13	48.1	10	18.5
Never	12	44.4	35	64.8
Not recorded	1			
Missing	2		11	
BMI (kg/m ²)	27	23.9–29.2	26.1	23.8–30.1

^aAntithrombotics consist of anticoagulant and antiplatelet drugs; Patient characteristics and risk factors at time of VTE diagnosis or index date. BMI, body mass index; CI, confidence interval; DTC, differentiated thyroid carcinoma; IQR, inter quartile range; TSH, thyrotropin; VTE, venous thromboembolism.

model. Subsequently, each variable that did not contribute with a significance of $P < 0.10$ was incrementally removed from the multivariable model.

A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the IBM Statistical Package for Social Science (SPSS, version 23).

Results

Cases and controls

We evaluated 955 DTC patients treated at the UMCG between January 1980 and December 2014. Twenty-eight patients who were diagnosed with a VTE after the diagnosis of DTC were matched to 56 controls (defined as DTC patients who did not develop a VTE), derived

from the same patient cohort. Patients underwent standard surgery, and none of the patients received rhTSH for ablation therapy. Thereafter, patients were treated with levothyroxine and/or liothyronine. Of the 28 cases, 12 (42.9%) had a deep venous thrombosis and 16 (57.1%) were diagnosed with a pulmonary embolism. A total of five (18.5%) cases and two (3.6%) controls had an active malignancy other than thyroid carcinoma upon VTE diagnosis or index date (two colon, one breast and one each of multiple myeloma, adrenal, lung and prostate). We found three (11.1%) cases who were current users of antithrombotics upon VTE diagnosis. All three cases were using carbasalate calcium for cardiovascular prevention (after myocardial infarction, cerebral infarction and unknown). A total of seven (12.5%) controls were current users of antithrombotics

Table 3 Univariable logistic regression model.

Parameter		Odds ratio	95% CI	P
Histology	Follicular vs papillary (ref)	2.2	0.9–5.7	0.087
Lymph node metastases	N1 vs Nx–N0 (ref)	0.7	0.3–1.6	0.399
Distant metastases	M1 vs Mx–M0 (ref)	3.5	1.2–10.2	0.020
DTC risk classification	High vs low-intermediate (ref)	1.8	1.0–3.1	0.040
TSH (U/L) Ln-transformed		0.9	0.8–1.1	0.206
Cumulative I-131 dose (mCi)		1.0	1.0–1.0	0.332
Recent surgery		5.2	1.4–19.2	0.013
Recent immobilization		4.2	0.4–48.8	0.248
Other active malignancy		5.9	1.1–32.5	0.043
Use of exogenous estrogens (in woman)		2.1	0.3–16.5	0.471
History of VTE before DTC diagnosis		2.0	0.1–33.8	0.620
Smoking status	Current vs never and former (ref)	0.4	0.1–2.0	0.400
BMI (kg/m ²)		1.0	0.9–1.1	0.625

BMI, body mass index; CI, confidence interval; DTC, differentiated thyroid carcinoma; TSH, thyrotropin; VTE, venous thromboembolism. Bold indicates $P < 0.05$.

at the index date; three controls used acetylsalicylic acid (two after cerebral infarction and one after myocardial infarction), three controls used a vitamin K antagonist (after cerebral infarction, for atrial fibrillation and unknown) and the remaining control used carbasalate calcium for cardiovascular prevention.

Characteristics of cases and controls

Characteristics of cases and controls at DTC diagnosis are provided in [Table 1](#). A total of 15 (53.6%) cases had FTC, including 4 (14.2%) with Hürthle cell carcinoma. There were 19 (33.9%) controls with FTC, including 6 (10.7%) with Hürthle cell carcinoma. Characteristics and risk factors at VTE diagnosis or index date are shown in [Table 2](#). As a result of the matching procedure, in both groups, the median age at VTE diagnosis or index date was 67 years (inter quartile range (IQR) 56–73 and 56–74 years), and 36% of patients were male. Cases underwent surgery within four weeks prior to VTE diagnosis more often than controls within four weeks prior to the index date ($n=8$ (28.6%) vs 4 (7.1%)) ($P=0.013$). Surgery included total and hemithyroidectomy (seven patients), lymph node dissection (one patient), metastasectomy (two patients) and surgery for malignancy other than thyroid cancer (two patients).

Distant metastases present at VTE diagnosis were more common in cases than in controls, 39.3% vs 8.9% ($P=0.001$). Distant metastases per patient are described in [Supplementary Table 1](#) (see section on [supplementary data](#) given at the end of this article). More cases than controls were classified as high DTC recurrence risk, 46.4% vs 26.8% ($P=0.073$). There were more cases than controls with other active malignancies, 17.9% vs 3.6% ($P=0.026$).

TSH values in cases at VTE diagnosis ranged from 0.004 to 2.800 U/L. In controls, TSH values at index date ranged from 0.005 to 9.200 U/L. In one case and one control, we were not able to identify a TSH value closer than two years to VTE diagnosis. There were no cases or controls pregnant upon VTE diagnosis or index date. Furthermore, no trauma was reported within four weeks prior to VTE diagnosis or index date either in cases or controls. Other cancer and treatment characteristics and traditional VTE risk factors did not differ between cases and controls ([Table 2](#)).

Risk factors for developing VTE in patients with DTC

Univariable regression analysis showed that histology, distant metastases, DTC risk classification, recent surgery and other active malignancy are associated with VTE ($P < 0.15$), as shown in [Table 3](#).

Table 4 Multivariable logistic regression model.

Parameter		Odds ratio	95% CI	P
Distant metastases	M1 vs Mx–M0 (ref)	7.9	2.2–28.1	0.001
Recent surgery		6.1	1.5–25.2	0.012
Other active malignancy		4.9	0.7–32.3	0.097

CI, confidence interval; DTC, differentiated thyroid carcinoma; TSH, thyrotropin.

Multivariable regression analysis (Table 4) showed that patients with distant metastases have an OR of 7.9 (95% CI 2.2–28.1, $P=0.001$) for developing a VTE as compared to patients without distant metastases. Recent surgery is an independent risk factor for VTE, with an OR of 6.1 (95% CI 1.5–25.2, $P=0.012$). The presence of other active malignancy is independently associated with VTE with an OR of 4.9 (95% CI, 0.7–32.3, $P=0.097$).

Discussion

In this case–control study, we identified the risk factors for VTE in patients treated for DTC. Patients with distant metastases or recent surgery have an independent increased risk of developing VTE. The presence of other active malignancy was associated with VTE in the multivariable regression model, although its P value was higher than 0.05.

To our knowledge, this is the first study to assess risk factors of VTE in DTC patients. It is well known that cancer is associated with a higher incidence of VTE (Walker *et al.* 2013). Especially cancer types with a short survival time and early metastatic spread, such as lung and pancreas carcinomas, have an increased VTE incidence (Wun & White 2009, Walker *et al.* 2013). In our study, the presence of distant metastases in DTC patients was associated with increased risk of developing VTE. This is consistent with studies of other malignancies (Wun & White 2009).

We could not identify TSH as a risk factor for VTE. By comparing blood samples from thyroid cancer patients while on THST and during hypothyroidism, Horne and coworkers confirmed the prothrombotic state of chronic THST. However, the relation between clinical overt VTE and THST was not assessed (Horne *et al.* 2004). For our study, we used different TSH assays over time. However, as cases and controls were matched as to period of DTC diagnosis, the distributions of the different TSH assays between both groups were similar. The results of this study indicate that any possible difference between cases and controls due to TSH is small.

One can argue that we may have missed DTC patients with a VTE, as only patients with clinically registered VTE were included as cases. This may have led to an underestimation of our results, as the control group could have contained patients with subclinical VTE. Cases were matched to controls according to age and sex. Therefore, age and sex could not be assessed as

risk factors for developing VTE. Due to low power, other variables, such as pregnancy, targeted therapy, systemic therapy and radiotherapy, could not be assessed as risk factors for developing VTE. Another limitation is that we could not precisely estimate the amount of increased risk for patients with distant metastases and/or recent surgery as we had only limited power as indicated by the width of the confidence intervals. Although the number of patients in this study was relatively small, we were able to obtain a comprehensive database with only two missing TSH values, one smoking habit and thirteen BMIs. Furthermore, as this is an observational study, it cannot in itself establish that the associations between the identified risk factors and VTE are causal.

Our study contributes to an improved identification of DTC patients at risk of developing VTE. Identification of these high-risk patients is particularly important when considering the use and duration of antithrombotics in patients with DTC after surgery. To assess the clinical impact of VTE in patients treated for DTC, in future cohort studies that assess incidence in cancer patients, attention on thyroid cancer is warranted. This could contribute to developing advice about preventing VTE in DTC patients. The presence of other active malignancies may influence the risk of developing VTE; however, this was not detectable in this study. In a future study, the risk of having more than one malignancy on developing VTE could be clarified.

In summary, we found that surgery and the presence of distant metastases are independent risk factors for developing VTE in DTC patients. The risk factors identified in this study could be considered when making thromboprophylaxis decisions about patients with thyroid cancer.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/ERC-17-0013>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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