The association of smoking with venous thrombosis in women and its modification by exogenous hormones

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Abstract

Background: The evidence for an association between smoking and venous thrombosis (VT) remains inconsistent. In particular, the nature of this association has not been reported among users of hormone therapy (HT).

Methods: We studied 2125 women with validated VT and 5749 controls from a large healthcare system in Washington State. Smoking status (current, former, never) was assessed from medical records review and, for a subset, also by telephone interview. The agreement between the 2 measures was excellent (Kappa 0.84). Current hormone use was calculated from pharmacy databases. We used multivariate logistic regression to evaluate the association between smoking and VT, and its modification by the use of HT. Adjustment variables included BMI, race, diabetes and pregnancy.

Results: Our sample comprised mostly postmenopausal white women, with a mean age of 65 years and a smoking prevalence of 10%. Current smokers were at higher risk of VT than non-smokers (OR 1.21, 95%CI 1.02-1.46). This risk did not differ between women not using and using HT: OR 1.2 (95%CI 1.0-1.5) and 1.2 (95%CI 0.8-1.9), respectively (p for interaction = 0.73). A subgroup analysis among women in their first year of use of HT suggested a higher risk for current smokers, compared to non-smokers, however without evidence of an interaction (OR 3.3, 95%CI 0.9-12.6, p for interaction = 0.13). In former smokers, an association between smoking and VT was only present during the first year after smoking cessation (OR 2.7, 95%CI 2.0-3.8), without suggestion of an increased risk thereafter.

Conclusion: Among women in the US, smoking was a weak risk factor for VT and was not modified in women who had used HT for >1 year. Further studies are needed to elucidate the association of smoking with VT during the first year of treatment with HT.

Introduction

Venous thromboembolism (VT), comprised of pulmonary embolism (PE) and deep-venous thrombosis (DVT), is thought to occur in 900,000 events annually in the United States.[1] In addition to the deaths caused by PE, VT is responsible for an important morbidity including chronic pulmonary hypertension and post-thrombotic syndrome. Thromboprophylaxis can prevent incident VT, but should be targeted to high-risk situations.[2] A precise knowledge of risk factors for VT and their potential interactions is therefore of considerable public health importance.

Although the prevalence of smoking has decreased in the United States, about 1 out of 5 working adults still reported currently smoking during 2004-2010.[3] Smoking increases the risk of arterial cardiovascular disease, but the evidence of its association with VT remains inconsistent. A meta-analysis through 2006 found a statistically insignificant association (odds ratio (OR) 1.15, 95%CI 0.92-1.44).[4] Increased risks of VT among smokers have been documented in three subsequent studies (OR 1.4, 95%CI 1.2-1.6 in the largest case-control study[5]), with even higher risks for heavy smokers.[6,7] The potential causal mechanisms underlying any association also remain unclear, but suggestions include an effect of smoking on the coagulation pathways, or the development of smoking-related diseases, such as cancer that are themselves related to VT.[7,8]

A strong evidence supports an increased risk of VT for women taking exogenous hormonal treatments, comprising oral contraceptives (OC) and hormone replacement therapy (HT).[9,10] Both treatments are composed of an estrogen and/or a progestin, albeit with smaller doses in HT. A synergic action between OC and smoking on the risk of VT has been suggested in a large case-control study.[5] The extent to which HT and smoking act synergistically on VT has not been studied for VT, and their joint effect also remains unknown.

Our aim was to estimate the association between smoking and VT in women, and its

modification by hormone treatments. We hypothesized that HT and smoking, when combined, might act synergistically to create a high risk of VT. We also hypothesized that a large proportion of the risk associated with smoking would be due to the development of cancer.

Methods

This study is part of the Heart and Vascular Health Study (HVH), a population-based case-control study of stroke, myocardial infarction and venous thrombosis in Group Health Cooperative (GHC), a large integrated healthcare system in Western Washington State, with over 500,000 members.

Population

Study participants were women aged 18 to 89 years. Cases were all GHC members who experienced a first deep venous thrombosis (DVT) and/or pulmonary embolism (PE), from January 1, 1995, until December 31, 2008 (n=2147). Potential VT cases were identified from inpatient and outpatient care settings and the Washington state death registry. All suspected cases based on ICD-9 codes, prescription of low-molecular weight heparin, specific treatment protocols for DVT, or death were ascertained through medical record reviews by trained medical record abstracters. Ascertainment criteria included objective diagnoses with pulmonary angiography, chest computed tomography or ventilation-perfusion scintigraphy (PE) and venogram, Duplex/Doppler ultrasound or venous computed tomography (DVT). Non-objective diagnoses from ICD-9 codes were permitted for fatal events or when confirmed by a HVH study physician, and represented less than 5% of all cases.

Controls were randomly selected GHC members who met the same eligibility criteria but had no history of VT (n=5674). They were frequency-matched to cases of myocardial infarction, representing the largest group in the HVH study, with matching on sex, age (within decades), hypertension status, and calendar year of identification. The index date was defined as the date of diagnosis of VT or of hospitalization (cases) or a random date within the year of selection (controls).

We excluded subjects with missing data for smoking (n=44) and subjects who smoked pipe or cigar (n=3), resulting in a final sample of 2125 cases and 5649 controls. Rates of missing data for other covariates were low (<2%), except for educational attainment (25% missing). Missing values were imputed with a multivariate normal regression model including other exposures, covariates and the outcome (20 imputations per missing value), with the use of Stata software.[11]

Data collection and variable definition

Trained abstracters collected information on demographics (age, race, education, occupation), smoking, body-mass index (BMI), past medical history and the index VT event (for cases) through standardized reviews of the entire GHC ambulatory medical record, including only information from before the index date. These records contain notes from primary care and specialty physician visits, emergency department visit notes, discharge summaries from hospitalizations, notes from telephone contacts, and laboratory and diagnostic tests reports. All consenting living participants were also interviewed by telephone (n=4511, 58%) by trained interviewers. Data on smoking, race, and socioeconomic status (education, occupation) were taken from the telephone interview when available, and from the medical record review otherwise. GHC administrative files provided information on previous hospitalizations and surgeries, which supplemented information abstracted from the medical record. Finally, current therapies with HT and OC were determined from the GHC pharmacy database, which records the drug, dose and quantity of every prescription dispensed from a GHC pharmacy. Ninety-five percent of participants in the study report that they fill all their prescriptions through GHC pharmacies. A subject was considered a current drug user when her last prescription had enough pills to last until the index date with 80% compliance (HT), and to last until 15 days prior to the

index date, with 100% compliance (OC). Women using non-oral forms of HT (n=11) and non-oral forms of contraceptives (n=3) were not considered non-users of HT or OC. Current smokers were defined as those who had ever smoked more than 100 cigarettes and still smoking on the index date. Participants who reported smoking less than 1 cigarette per day with less than 1 pack-year were considered never-smokers (n=24). We defined former smokers as having smoked >100 cigarettes in their lifetime and having quit smoking at some time prior to the index date. All other subjects were classified as never-smokers. When data from the telephone interview was absent, cigarettes per day and pack-years were computed using all available smoking information in the medical record. Agreement for smoking status between medical record review and telephone interview was excellent (92% agreement, unweighted Kappa 0.85). The median delay between the recorded smoking information in the medical record and the index date was less than 6 months.

Statistical analysis

Multivariate logistic regression was used to estimate the association between smoking and incident VT. As VT is rare, the resulting OR can also be interpreted, to a good approximation, as estimates of relative risks. All regressions were adjusted for the matching factors: age (linear and by decade), index year (categorical), and treated hypertension status. Potential confounding variables were chosen *a priori* and included body-mass index (BMI), modeled as a natural cubic spline, pregnancy, race (white vs. non-white), use of OC, use of HT, and socio-economic status as measured by educational attainment.
Primary analyses compared current smokers and former smokers with never smokers. Effect modification (on a logistic scale) was assessed for current use of OC or HT by adding an interaction term with current smoking, in addition to their main effects. In secondary analyses, we evaluated the possible mediation of the association between current smoking and VT by further adjusting our regression for diagnosis of cancer (within 5 years of the

index date). Further analyses stratified smokers in categories of cigarettes per day (current smokers), pack-years (current and former smokers) and recency of quitting (former smokers). We also considered subgroup analyses among groups defined by age and menopausal status, by the type of VT (idiopathic vs. secondary), and interactions between smoking and HT among recent starters of HT (first year of treatment), when the thrombotic risk associated with HT is the highest.[9] A secondary VT was defined as occuring in patients with cancer, following a recent hospitalization, surgery, trauma or cast (in the past 30 days), in pregnant women, or in current users of OC or HT.

An alpha of 0.05 determined statistical significance. P-values were obtained by Wald tests with robust standard errors. Analyses were conducted using Stata 11 (StataCorp LP, College Station, Texas).

In case of a significant finding for the association between smoking and VTE, we planned to calculate the attributable risk percent (AR%) and the population attributable risk percent (PAR%).

The study was approved by the GHC Human Subjects Review Committee.

Results

The study population comprised 7774 women (2125 cases and 5649 controls). These were primarily white and postmenopausal (Table 1), with a median age of 69 years. About 10% of cases and controls were current smokers, and one third were former smokers. The prevalence of current smokers among controls decreased on average by 0.3% per year throughout the study period (1995-2008, P value <0.001). The use of HT among postmenopausal controls also diminished, from 37.8% in 2000 to 7.4% in 2008 (P<0.001). The 2125 validated VT events comprised 1057 DVT (49.7%), 760 PE (35.8%) and 308 concomitant PE and DVT (14.5%). We defined 40.2 % and 59.8% of these events as idiopathic and secondary, respectively. Eight percent of PE resulted in fatalities.

The primary multivariate regression was adjusted for the matching variables, race, diabetes, pregnancy, BMI and the use of OC and HT. Educational attainment was not associated with VTE (Table 1) and did not modify the results when added to the regression. In the primary analysis, current smokers had a 20% greater risk of VT than never-smokers (OR 1.21, 95%CI 1.02-1.46, P=0.003, Table 2). Secondary analyses did not suggest modification (on the logistic scale) of this risk by age or menopausal status (Table 3). Among smokers, we found no significant dose-response relationship between risk of VT and number of cigarettes per day or cumulative dose (pack-years), although the greatest odds of VT was found among smokers with >40 pack-years (OR 1.40, 95%CI 1.06-1.86).

To investigate possible pathways between active smoking and VT, we further adjusted our logistic regression for any recent diagnosis of cancer (<5 years). The OR decreased only slightly, from 1.21 to 1.17 (95%CI 0.97-1.42).

Our data was compatible with an association between former smoking and VT (OR 1.13, 95%CI 1.01-1.27), as presented in Table 2. However, this association appears to be due almost exclusively to women who had stopped smoking in the year prior to the index date

(OR 2.72, 95%CI 1.97-3.75), with little suggestion of an increased risk for those who had quit before then (OR 1.06, 95%CI 0.94-1.19). Further adjustment for potential mediators (cancer, chronic heart failure and a history of arterial cardiovascular disease) decreased the OR for those who had quit within the past year to 2.05 (95%CI 1.45-2.90).

We did not find any significant interaction between smoking and exogenous hormone treatments (Table 4). There was a low positive risk associated with current smoking, compared to never-smoking, in the subgroups of women who were users of OC, HT or who were non-users. Among users of HT who were in their first year of treatment, the OR associated with current smoking appeared to be higher (OR of 3.33, 95%CI 0.88-12.6), compared with never smoking. However, there was no statistical evidence that this was different than the risk associated with current smoking for women who were non-users of HT (p=0.13).

Table 5 summarizes the relative risks due to the combination of smoking and OC or HT. The increased rate of VT risk associated with OC was three-fold in non-smoking women but five-fold in current smokers. The increased rate of VT associated with HT (OR 1.2) did not differ by smoking status in chronic users of HT (>1 year of treatment). On the contrary, we observed a high risk for smoking women who had started HT recently (OR 3.6), compared to non-smoking women who started HT recently (OR 1.2).

Finally, the AR% for VT among smokers was 17% (95%CI 2-32) and the PAR% for VT among the population was 2% (95%CI 0-3), using a smoking prevalence of 10%.

Discussion

In this large population-based case-control study, we demonstrated a statistically significant, albeit weak (OR 1.2), association between current smoking and the risk of VT. This result is consistent with the results of the meta-analysis summarizing the case-control and cohort studies published before 2006 (OR 1.15, 95%CI 0.9-1.4).[4] Slightly higher risks for current smokers have since been reported in two Danish cohort studies (HR up to 1.5, 95%CI 1.1-1.9) and in a large Dutch case-control study (OR 1.4, 95%CI 1.2-1.6), but with a large overlap in confidence intervals.[5-7]

The nature of the association between smoking and VT remains largely undetermined. A causal relationship is uncertain, as observational data may be subject to unmeasured confounding, especially for weak associations. We adjusted our logistic models for the most important variables (weight, race, diabetes, pregnancy, use of HT or OC), but some unmeasured behaviors could be associated with both smoking and VT, such as physical inactivity or diet.[12,13] However, the consistency of the association across studies and the presence of dose-responses between the grams of tobacco smoked per day and the risk of VT in other studies support a causal relationship.[6,7]

Smoking may influence the propensity to clot or increase the risk of diseases that are themselves risk factors for VT. Numerous studies have demonstrated an effect of smoking on coagulation factors, on thrombus strength and on inflammation markers. In particular, smokers have higher levels of fibrinogen, of other coagulation factors (II, VII), of serum C-reactive protein, and an impaired fibrinolysis (as reflected by an increase in plasminogen activator inhibitor type 1 (PAI-I)), compared to non-smokers.[14-17] By itself, however, a high fibrinogen does not appear to mediate an important part of the association.[5] A recent study suggested that an association between smoking and VT was only present among subjects with cancer.[8] In our logistic regression, however, we found that the OR associated with

smoking decreased only slightly after further adjustment of our regression for a recent diagnosis of cancer, and observed no difference in the associations between smoking and idiopathic or secondary VT.

Our results support a 3-fold increased risk of VT for former smokers who had quit smoking in the prior year, but no elevation of risk for those who had quit before then. A direct effect of smoking cessation or its pharmacological treatments on the VT risk is unlikely. Biomarker studies do not provide evidence of a rebound effect of smoking cessation on thrombotic or inflammatory markers: CRP, soluble thrombomodulin and prothrombin fragment 1+2 appear to gradually decrease over time.[18,19] Nicotine replacement therapy and buproprion have been used safely in patients with chronic cardiovascular disease for several years, without reports of VT events. An increased arterial cardiovascular risk has been suggested with varenicline,[20] but this drug was introduced only in 2006, and could not account for the observed risk. We believe that the high risk among recent quitters may be explained by medical conditions that led to the smoking cessation and are risk factors for VT. The decrease in the OR (from 2.7 to 2.0) observed with the adjustment for cancer, chronic heart failure and arterial cardiovascular disease reinforces this hypothesis, and we postulate that the rest of the association was driven by other diseases and conditions we did not account for. This finding is unique to our study, because previous cohort studies were not be able to capture the early risk after smoking cessation, and other case-control studies have grouped recent quitters with current smokers.[5] This mix of subjects should be avoided in future studies, as it might lead to an overestimation of the risk for current smokers.

To our knowledge, this is the first report of the risks due to smoking, HT and their combination. In the Women's Health Initiative, the authors stated the absence of multiplicative interaction between both factors, but their sample was very limited (13 VT events in smokers).[9] Similarly, we found no statistical interaction between OC or HT and smoking, based on logistic-linear regressions. In other words, there was no evidence of a

difference in the odds ratio due to active smoking between users of OC, HT or non-users. Further study should focus on the OR associated with smoking in women who recently started HT, as our results were compatible with a high risk, but lacked precision (OR 3.3, 95%CI 0.9-12.6). In our sample, women who smoked and were treated with OC had a more than five-fold increase in their risk of VT, compared to non-smokers without OC or HT. Similar to previous studies,[5,7] this result supports the current caution of guidelines and clinicians in the prescription of OC among smoking women.

HT itself was associated with a 20% increase in the risk of VT in our sample. This is lower than the 2-fold increase in large randomized clinical trials of HT,[9,21] and several explanations can be advanced. In our sample, about half of HT users were taking estrogen without progestin, with a smaller risk of VT.[22] The treatment was composed of esterified estrogens in a vast proportion, which is known to be less prothrombotic than conjuguated equine estrogens.[23] Finally, most women in our sample had started HT several years before the index date, and the VT risk decreases gradually after the start of therapy.[9]

We explored the possible consequences of current smoking on public health. If we assume a causal mechanism between smoking and VT, our results suggest that it may be responsible for 17% (95%CI 2-32%) of the VT among smokers (attributable risk percent), and for 2% (95% 0-3) of all VT events (population attributable risk percent). This latter estimate is low partly due to the low prevalence of current smokers in our population (10%), which is concordant with the reported smoking prevalence for mostly postmenopausal insured women in the Northwest.[3]

Our study has several strengths. First, all VT events were individually reviewed and validated, and we benefited from a high quality of the exposure measurements on current treatments. Second, the design of a case-control study is appropriate for a relatively rare outcome and a potentially modifying exposure, and allowed us to estimate the risk of VT since time from smoking cessation. Third, the possibility of differential misclassification in

smoking status was minimal, due to an excellent agreement between our prospective (chart review) and retrospective (telephone interview) measures. Furthermore, self-reported smoking has been shown to be a very good measure of the true smoking status.[24] Fourth, the large sample allowed us to distinguish a relatively weak association from noise. Several limitations also need to be recognized. First, our results can only be generalized to a population of white women, and we were not able to assess potential racial differences. Second, there may be some degree of non-differential misclassification in the detailed smoking exposure variables, abstracted from the medical records (cigarettes per day for example). This could explain the lack of dose-response in our results, when it was found in other studies. Third, limited conclusions can be inferred from the analyses of interaction, due to the restricted power for subgroup analyses. Fourth, we cannot rule out the presence of residual confounding in this observational study. In particular, our measure of socioeconomic status (educational attainment) was suboptimal and had to be imputed, and physical activity, a potential confounder, was not adjusted for. Finally, the threshold of significance for P values was not corrected for the multiple secondary analyses, which have to be considered exploratory.

In conclusion, we found that current smoking was a weak but statistically significant risk factor for VT, with effects that did not differ between women who had taken HT for >1 year and those without HT. Elevated risk among smokers during their first year of HT treatment remains possible, and should be further investigated. Until then, the potential risks associated with a new prescription of HT among smokers should be carefully balanced against the expected benefits, mainly on climacteric symptoms. Future studies should also focus on the effect of smoking on VT recurrence, as smoking may represent a modifiable risk factor.

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Table 1. Characteristics of Study Participants.

	% [1]	
	Cases (n=2125)	Controls (n=5649)
Age, mean (SD), y	65.6 (16.0)	65.5 (14.7)
BMI, mean (SD)	30.0 (8.5)	28.2 (6.6)
White race	91.7%	88.9%
Peri/postmenopausal	86.1%	87.3%
Current smokers	10.3%	10.4%
Cigarettes per day, mean (SD)	16.8 (8.6)	16.8 (9.6)
Former smokers	36.4%	33.7%
Current use of oral contraceptives[2]	39.8%	21.0%
Current use of hormonal replacement therapy[3]	22.8%	25.8%
Cancer within 5 years of index date	25.2%	0.8%
Pregnancy at index date	0.8%	0.3%
Diabetes	10.4%	9.0%
Hypertension	41.0%	49.4%
History of cardiovascular disease[4]	21.1%	14.1%
Education (High School or less)	36.7%	35.3%

[1] unless otherwise specified ; percentages are calculated on non-missing data.
[2] Among premenopausal women
[3] Among postmenopausal women
[4] Defined as: myocardial infarction, angina, stroke, claudication, CABG, angioplasty, carotid endarteriectomy and peripheral vascular bypass.

Table 2. Association between smoking and VT

	Cases (N=2125)	Controls (N=5649)	Unadjusted OR[1]	Adjusted OR[2]
Never smokers	1132	3156	1.0 (ref)	1.0 (ref)
Current smokers	219	588	1.10 (0.92-1.30)	1.21 (1.02-1.46)
Former smokers	774	1905	1.17 (1.05-1.31)	1.13 (1.01-1.27)
Smoking cessation ≤1y	78	91		2.72 (1.97-3.75)
Smoking cessation >1y	696	1814		1.06 (0.94-1.19)

[1] Model including the matching variables (age, hypertension and index years)
[2] Model further adjusted for race, diabetes, pregnancy, BMI, and the use of oral contraceptives or hormonal replacement therapy

Table 3. Exploratory analyses of the association between current smoking and VT among subgroups.

	Cases Current/Never smokers, No.	Controls Current/Never smokers, No.	OR (95%CI)	Interaction P value
Menopausal status				
Premenopausal	48/176	119/457	1.10 (0.75-1.63)	0.60
Peripostmenopausal	170/952	467/2690	1.24 (1.01-1.51)	
Age				
<40y	39/94	63/238	1.68 (0.99-2.85)	0.50
40-55y	58/211	153/524	1.20 (0.82-1.74)	
55-70y	61/282	189/810	1.01 (0.72-1.41)	
70-80y	44/281	156/1167	1.31 (0.89-1.91)	
>80y	17/264	27/417	1.03 (0.53-1.99)	
Cigarettes/day				
1-9 cig	32/1132	95/3156	1.22 (0.79-1.87)	0.65[1]
10-19 cig	69/1132	184/3156	1.14 (0.84-1.53)	
≥20 cigs/day	110/1132	278/3156	1.30 (1.02-1.66)	
Pack-years				
<10 pack-years	23/1132	72/3156	0.90 (0.55-1.49)	0.16[1]
10-20 pack-years	33/1132	84/3156	1.14 (0.74-1.49)	
20-40 pack-years	54/1132	140/3156	1.21 (0.87-1.68)	
>40 pack-years	84/1132	209/3156	1.40 (1.06-1.86)	
VT type				
Idiopathic VT	92/444	588/5649	1.31 (1.01-1.71)	0.48
Secondary VT	125/677	588/5649	1.17 (0.94-1.46)	

[1] test for trend

Table 4. Association of smoking with VT, stratified by hormone status.

	Cases No.	Controls No.	OR (95%CI)	P values for interaction
Non-OC non-HT				
Never smoker	818	2329	1.0 (ref)	
Current smoker	167	470	1.18 (0.96-1.45)	
OC user				
Never smoker	95	124	1.0 (ref)	
Current smoker	15	12	1.74 (0.74-4.08)	0.41
HT user				
Never smoker	219	703	1.0 (ref)	
Current smoker	37	106	1.22 (0.81-1.85)	0.73
HT started ≤1 year prior to the index date				
Never smoker	12	41	1.0 (ref)	
Current smoker	7	7	3.33 (0.88-12.6)	0.13
HT started >1 year prior to the index date				
Never smoker	207	662	1.0 (ref)	
Current smoker	30	99	1.06 (0.68-1.66)	0.68

Table 5. Combined effect of smoking and OC or HT

Smoking status	OC or HT	Cases	Controls	OR (95%CI)*
Never	none	818	2329	1.0 (ref)
Never	OC	95	124	3.11 (2.23-4.32)
Never	HT ≤1y	12	41	1.24 (0.64-2.40)
Never	HT >1y	207	662	1.20 (0.99-1.46)
Current	none	167	470	1.13 (0.91-1.40)
Current	OC	15	12	5.38 (2.28-12.7)
Current	HT ≤1y	7	7	3.61 (1.13-11.5)
Current	HT >1y	30	99	1.22 (0.79-1.91)

* adjusted for matching variables (age, hypertension, index years), race, diabetes, pregnancy, BMI, and recent cancer.