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The association of smoking with venous thrombosis in women: a population-based, case-control study

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Abstract

Background—The evidence for association between smoking and venous thrombosis (VT) is inconsistent and its mediation pathways remain to be fully elucidated.

Methods—A population-based, case-control study was conducted in a large, integrated healthcare system in Washington State, USA. Cases were women aged 18-90 years who experienced a validated incident deep vein thrombosis or pulmonary embolism between January 1, 1995, and December 31, 2009. Controls were randomly selected from members of the healthcare system. Smoking status (current, former, never) was assessed from medical records review and, for a subset, also by telephone interview. Multivariable logistic regression was used to estimate odds ratios (OR) associated with smoking status.

Results—We identified 2278 cases and 5927 controls. Subjects comprised mostly postmenopausal white women with a mean age of 66 years and a current smoking prevalence of 10%. Compared to never-smokers, current and former smokers were at higher risk of VT (adjusted OR 1.21, 95%CI 1.02-1.44 and OR 1.15, 95%CI 1.03-1.29, respectively). These associations were attenuated with further adjustment for potential mediators (cardiovascular disease, congestive heart failure, cancer, recent hospitalizations and physical activity): OR 1.02 (95%CI 0.83-1.25) and 0.95 (95%CI 0.83-1.08), respectively.

Conclusion—The modestly increased risk of VT in women who are current or former smokers might be explained by the occurrence of smoking-related diseases and decreased physical activity.

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Our results do not support a direct biological effect of smoking on the risk of VT that is clinically relevant.

Keywords

venous thrombosis; thromboembolism; women; smoking; epidemiology

Introduction

About 900,000 Americans per year experience venous thromboembolism (VT), comprised of pulmonary embolism (PE) and deep-venous thrombosis (DVT) (1). In addition to the deaths caused by PE, VT is responsible for important morbidities including chronic pulmonary hypertension and post-thrombotic syndrome. A precise knowledge of risk factors for incident VT would allow providers to target short-term thromboprophylaxis to high-risk situations, and 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 current smoking during 2004-2010 (2). Smoking increases the risk of arterial cardiovascular disease, but the evidence about its possible association with VT is inconsistent. A meta-analysis of published data through 2006 found a statistically non-significant association (odds ratio (OR) 1.15, 95%CI 0.92-1.44) (3). Subsequently, higher risk of VT among current smokers has been documented in different populations, with relative risks that ranged from 1.3 to 1.5 (4-7). The potential causal mechanisms underlying any association remain unclear, but suggestions include a direct effect of smoking on the coagulation propensity or the development of smoking-related diseases such as cancer or cardiovascular disease that are themselves associated with VT (6,8,9).

Our aim was to compare, among women, the risk of incident VT of current smokers and former smokers with the risk of never-smokers. We hypothesized that current smokers may be at highest risk, and that this risk may be explained by the higher occurrence of cardiovascular disease, cancer, hospitalizations among current smokers and other lifestyle factors such as physical activity.

Methods

This case-control study is part of the Heart and Vascular Health Study (HVH), a population-based case-control study of stroke, myocardial infarction, atrial fibrillation, and VT in Group Health Cooperative (GHC). The initial sub-study on incident VT focused on women's health and men were not enrolled. GHC is a large, integrated healthcare system in Western Washington State, USA, with over 500,000 members (10-13). The study was approved by its Human Subjects Review Committee.

Population

Study participants were women aged 18 to 90 years. Cases were all GHC members who experienced a first DVT and/or PE between January 1, 1995 and December 31, 2009. They were identified from inpatient and outpatient care settings and the Washington state death registry using inpatient ICD-9/ICD-10 discharge codes, outpatient prescription of low-

molecular weight heparin, specific treatment protocols for DVT, or a death certificate diagnosis of PE. VT cases were verified through medical record reviews by trained abstractors on the basis of objective diagnoses with pulmonary angiography, chest computed tomography, or ventilation-perfusion scintigraphy (for PE) and venogram, Duplex/Doppler ultrasound or venous computed tomography (for DVT). Non-objective diagnoses from ICD-9/ICD-10 codes were permitted for fatal PE events or when confirmed by a HVH study physician, and represented less than 5% of all cases.

Controls were randomly selected female GHC members who met the same eligibility criteria as cases but had no history of VT. They were frequency-matched on age, treated hypertension status and calendar year of identification to cases of myocardial infarction (not included in this analysis, but representing the largest group in the HVH study). 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).

The participation rate, defined as at least allowing the review of the medical record, was very high for both cases (90.7%) and controls (84.0%).

Data collection and variable definition

Trained abstractors 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. Except for cancer, which included diagnoses from 5 years prior to 3 months after the index date (for occult cancers), only data from before the index date were abstracted. 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 (58%) were also interviewed by telephone. Data on smoking, race, socioeconomic status (education, occupation) and physical activity 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. The use of hormonal therapy (HT) and oral contraceptives (OC) was determined from the GHC pharmacy database.

Current smokers were defined as those who had ever smoked more than 100 cigarettes and were still smoking on the index date. Former smokers were defined as those who had ever smoked more than 100 cigarettes but who had quit and were not smoking on the index date. All other subjects were classified as never-smokers. Agreement for smoking status between medical record review and telephone interview was excellent (91.4% agreement, unweighted Kappa 0.84). When data from the telephone interview were absent, cigarettes per day and pack-years were computed using all available smoking information in the medical record. The last information about smoking in the medical record was recorded within the year before the index date for more than half of the sample.

Statistical analysis

From the initial population of 2301 cases and 5952 controls, we excluded subjects with completely missing data on smoking (n=45) and subjects who smoked pipes or cigars (n=3). Rates of missing data for other covariates were low (3%), except for educational attainment (25%), recent hospitalizations (17%), occupation (8%), the number of pack-years (17% of current or former smokers) and of cigarettes per day (5% of current smokers). Missing values (except pack-years and cigarettes per day) were imputed with a multivariate normal regression model including the exposure (smoking), the outcome (VT) and multiple covariates such as age, comorbidities, cardiovascular risk factors, or the use of HT / OC. Twenty imputations were generated per missing value with the use of Stata software (14,15).

We used multiple logistic regression to estimate the association between smoking and incident VT. As VT is rare, the resulting OR estimates can be interpreted as estimates of relative risk (16). All regressions were adjusted for the matching factors: age (linear and by decade), index year (categorical), and treated hypertension status. Adjustment variables were chosen *a priori* and included body-mass index (BMI), represented as a natural cubic spline; diabetes; race (white vs. non-white); use of OC, use of HT, and pregnancy at the index date; and socio-economic status as measured by educational attainment and occupation. The primary analysis compared current smokers and former smokers with never smokers.

In secondary analyses, we evaluated the possible mediation of the association between VT and both current and former smoking by further adjusting for smoking-related co-morbidities (a prior diagnosis of cancer (within 5 years before the index date), congestive heart failure, any history of cardiovascular disease (myocardial infarction, angina, coronary artery bypass graft, angioplasty, stroke, carotid endarterectomy, claudication or peripheral vascular bypass)), recent hospitalizations (within 1 month before the index date) and other lifestyle factors (physical activity).

We also divided smokers into categories based on cigarettes per day (current smokers), pack-years (current and former smokers) and recency of quitting (former smokers). In addition, we considered subgroup analyses among groups defined by age and menopausal status and by the type of VT (idiopathic vs. secondary). A secondary VT was defined as occurring in patients with a prior diagnosis of cancer; following a recent hospitalization, surgery, trauma or plaster cast (in the past 30 days); in pregnant women; or in current users of OC or HT. Differences between the association of smoking with idiopathic VT and with secondary VT were assessed using polytomous logistic regression.

A level 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).

Results

The study population comprised 8205 women: 2278 cases and 5927 controls. They were primarily white and postmenopausal with a median age of 69 years (Table 1). About 10% of cases and controls were current smokers and 33% were former smokers. The prevalence of

current smoking among controls decreased on average by 0.3% per year throughout the study period (1995-2009).

The 2278 validated VT events comprised 1134 DVT (49.8%), 804 PE (35.3%) and 340 concomitant PE and DVT (14.9%). The vast majority of isolated DVT were located in the proximal leg (84%), compared to distal DVT (12%) and upper extremity DVT (4%). We defined 38.5 % and 61.5% of all events as idiopathic and secondary, respectively. Ninety cases of PE (7.9%) were fatal.

The primary analysis was adjusted for the matching variables (including age), race, diabetes, pregnancy, BMI, the use of OC and HT, educational attainment and occupation (model 1). After adjustment, current smokers had a 21% greater risk of VT than never-smokers (OR 1.21, 95%CI 1.02-1.44, $p=0.03$; Table 2). Former smokers were also at increased risk of incident VT (OR 1.15, 95%CI 1.03-1.29, $p=0.01$). However, in regression further adjusted for potential mediators such as a recent cancer, any history of cardiovascular disease, congestive heart failure, recent hospitalizations and physical activity, these association disappeared (model 2: OR 1.02 (95%CI 0.83-1.25) for current smokers and OR 0.95 (95%CI 0.83-1.08) for former smokers ; Table 2).

Among former smokers, the risk of VT was highest for women who had stopped smoking in the year prior to the index date (OR 2.79, 95%CI 2.04-3.81), without a significantly increased risk for those who had quit >5 years before the index date (OR 1.04, 95%CI 0.93-1.18, p for trend <0.001, Table 3). Cases of VT who had quit recently (<1 year) had a very high prevalence of recent cancer (38.8%), recent hospitalization (57.10%) and chronic heart failure (11.8%). Their number of physician visits in the year prior to the index date, a quantity that is correlated with comorbidity level (17,18), was also elevated, compared to current smokers. Adjustment for these potential mediators reduced the OR estimate for recent quitters to 1.45 (95%CI 0.98-2.14).

We found evidence of higher VT risk associated with higher pack-years among current and former smokers (p for trend = 0.03 and <0.001, respectively, Table 3), but not with a higher number of cigarettes per day for current smokers (p for trend = 0.49). The risk of idiopathic and secondary VT were not statistically different among current smokers ($p=0.32$) or among former smokers ($p=0.81$, Table 4). There was no significant modification of the risks associated with current or former smoking by age, menopause and education, occupation or physical activity status (data not shown).

Finally, for the purpose of comparison with other studies, we grouped recent quitters with current smokers and found an adjusted OR of 1.44 (95%CI 1.23-1.69), compared to never-smokers.

Discussion

In this large population-based case-control study of women, we demonstrated that current and former smokers had a 21% and 15% higher risk of incident VT than never smokers in a multivariable model adjusted for confounders. However, our data suggest that these associations are explained by the occurrence of smoking-related co-morbidities (cancer,

arterial cardiovascular disease, congestive heart failure), more frequent recent hospitalizations and a decreased physical activity in current and former smokers.

A modestly increased risk for current smokers is consistent with the observation in other studies (4-9). The slightly higher risks reported in some 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) (4-6) may partly be explained by the grouping of recent quitters with current smokers. In our data, the OR increased from 1.21 to 1.44 when we included recent quitters as current smokers. In line with our finding that recent quitters were at higher risk of VT, this may indicate an overestimation of the true relative risk for current smokers.

The nature of the association of smoking with VT is debated. Two recent studies suggest a mediation through the occurrence of cancer (8) or myocardial infarcts (9) among current smokers. Our results also support the hypothesis of an indirect effect of smoking on the risk of VT through the occurrence of more smoking-related co-morbidities, hospitalizations and a diminished physical activity. Interestingly, direct biological effects of smoking on thrombotic propensity have been reported: smokers have higher levels of fibrinogen, factor II, factor VII, and serum C-reactive protein, and have impaired fibrinolysis, compared to non-smokers (19-22). These direct effects may not be important enough to be associated with an increased risk of clinical VT.

To our knowledge, this is the first report of the risk of VT for former smokers according to their recency of quitting. We observed a nearly 3-fold increased risk among recent quitters (within 1 year before the index date) compared to never-smokers. 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 thrombotic or inflammatory markers after smoking cessation: CRP, soluble thrombomodulin and prothrombin fragment 1+2 appear to gradually decrease over time (23,24). Nicotine replacement therapy and bupropion have been used safely in patients with chronic cardiovascular disease for several years without reports of more VT events. An increased cardiovascular risk with varenicline has been subject to debate (25,26), but this drug was only introduced in 2006 and was not prescribed to any of the VT cases within 6 months before their index dates. Therefore, we believe that the high risk among recent quitters is explained by medical conditions that led to the smoking cessation and are risk factors for VT (confounding by the indication for smoking cessation). The decrease in the OR (from 2.79 to 1.45) observed with the adjustment for history of cancer, chronic heart failure, arterial cardiovascular disease, recent hospitalization and health care utilization reinforces this belief. We postulate that the rest of the association is driven by other diseases and conditions that we were not able to capture with the available data, such as recent infections or bed rest.

When translated into clinical implications, our findings suggest decisions on short-term thromboprophylaxis should not rely on individuals' smoking status. This may not be true for specific categories of women, such as those who have recently quit smoking, in whom the reason for the cessation should be explored.

Our study, with its large sample size, has several strengths. All VT events were individually reviewed and validated. The case-control design allowed us to estimate the risk of VT since time from smoking cessation. Model misspecification was reduced by the use of a natural cubic spline to adjust for BMI instead of a simple linear term. The possibility of differential misclassification in smoking status appears minimal in light of the 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 true smoking status (27).

Several limitations also need to be recognized. Our results can only be generalized to a population of white women, and we were not able to assess potential racial differences. As usual with observational studies, we cannot rule out the presence of residual confounding. In particular, we did not have data on individual incomes, and our measure of socioeconomic status (educational attainment and occupation), shown to be associated with VT in prior studies (5,28), was partially imputed. The use of anti-platelet agents, potentially more prevalent among smokers and believed to reduce the risk of VT (29), may confound the associations and bias our results towards the null. Finally, the small proportion of eligible women who refused to participate in our study may still have induced some selection bias that we are unable to assess.

In conclusion, among women, our data support a modest increased VT risk in current smokers that appears to be explained by the presence of smoking-related diseases and decreased physical activity. Former smokers who have quit recently appear to be a high-risk group, likely due to their co-morbidities, and should be distinguished from current smokers in research studies.

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What is known on this topic

- The risk of venous thrombosis is thought to be higher for current smokers than non-smokers.
- Previous evidence suggests that this risk could be explained by a direct effect of cigarette smoking on clotting propensity or an indirect effect through the occurrence of smoking-related diseases, themselves risk factors for VT.

What this paper adds

- A modestly increased risk of incident VT in former and current smokers appears to be explained by a higher occurrence of smoking-related comorbidities (cancer, cardiovascular disease), a higher rate of hospitalization and a lower physical activity, compared to never-smokers.
- No direct (independent) effect of smoking on the risk of VT was observed.
- Former smokers who quit smoking during the previous year were at high risk of VT. Our data suggest that this is due to the presence of the diseases that led to the smoking cessation.
- Future studies should differentiate current smokers from recent quitters.

Table 1
Characteristics of Study Participants

	%	
	VT Cases (n=2278)	Controls (n=5927)
Age, mean (SD), y	65.8 (16.0)	65.3 (14.7)
BMI, mean (SD), kg/m ²	30.1 (8.5)	28.2 (6.7)
White race	91.7 %	88.7%
Peri/postmenopausal	86.3 %	86.9 %
Current smokers	10.2 %	10.4 %
Cigarettes per day, mean (SD)	16.5 (9.6)	16.5 (9.6)
Pack-years, mean (SD)	43.9 (31.6)	39.7 (30.4)
Former smokers	37.1 %	33.8 %
Pack-years, mean (SD)	33.0 (29.9)	23.9 (24.9)
Recency of quitting, y, median	16	19
Current use of contraceptives	6.8 %	3.0 %
Current use of hormone therapy	18.3%	21.5 %
Diagnosis of cancer		
within 5 years before index date	21.9 %	4.7%
within 3 months after index date	3.3%	0.2%
Pregnancy at index date	0.8 %	0.4 %
Diabetes	10.7 %	9.0 %
Hypertension	42.3 %	49.0 %
Hyperlipidemia	14.7 %	14.3 %
History of cardiovascular disease ¹	21.3 %	13.9 %
Myocardial infarction	6.4 %	3.6 %
Stroke	8.7 %	4.0%
Congestive heart failure	7.9 %	3.8 %
Education (High School or less)	36.5 %	35.0 %
Occupation (Blue collar)	13.2 %	15.1 %
Low physical activity (sedentary)	49.2 %	21.6 %

¹ defined as a history of myocardial infarction, angina, CABG, angioplasty, stroke, carotid endarterectomy, claudication or peripheral vascular bypass

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Table 2
Association between smoking and VT

	VT Cases (N=2278)	Controls (N=5927)	Model 1 OR (95%CI)	Model 2 OR (95%CI)
Never smokers	1202	3306	1.0 (ref)	1.0 (ref)
Current smokers	232	617	1.21 (1.02-1.44)	1.02 (0.83-1.25)
Former smokers	844	2004	1.15 (1.03-1.29)	0.95 (0.83-1.08)

Model 1: adjusted for matching factors (age, hypertension, index year), race, diabetes, pregnancy, BMI, the use of oral contraceptives or hormone therapy, education and occupation.

Model 2: further adjusted for a recent diagnosis of cancer (<5 years), any history of cardiovascular disease, congestive heart failure, recent hospitalizations (<1 month) and physical activity.

Table 3
Association between smoking and VT, stratified by dose of smoking or recency of quitting

	VT Cases (N=2278)	Controls (N=5927)	OR 1 (95%CI)	P-value (trend)
Never-smokers	1202	3306	1.0 (ref)	
Current smokers				
Cigarettes/day				
<10	34	103	1.18 (0.78-1.80)	P = 0.49
10-19	76	198	1.16 (0.88-1.55)	
20	114	284	1.28 (1.00-1.63)	
Pack-years				
<10	27	79	1.00 (0.63-1.59)	P = 0.03
10-20	34	91	1.08 (0.71-1.64)	
20-40	58	149	1.21 (0.88-1.66)	
>40	88	213	1.39 (1.06-1.83)	
Former smokers				
Pack-years				
<10	179	604	0.79 (0.65-0.95)	P <0.001
10-20	113	376	0.83 (0.66-1.04)	
20-40	178	376	1.31 (1.07-1.61)	
>40	200	310	1.83 (1.49-2.24)	
Recency of quitting				
1 year	85	98	2.79 (2.04-3.81)	P<0.001
2-5 years	92	198	1.23 (0.93-1.63)	
>5 years	620	1607	1.04 (0.93-1.18)	

OR 1: adjusted for matching factors (age, hypertension, index year), race, diabetes, pregnancy, BMI, the use of oral contraceptives or hormonal replacement therapy, education and occupation.

Numbers may not agree due to missing data.

Table 4
Association between smoking and idiopathic or secondary VT

	VT Cases (N=2278)	Controls (N=5927)	OR1 (95%CI)
Idiopathic VT			
Never-smokers	460	3306	1.0 (ref)
Current smokers	91	617	1.25 (0.96-1.63)
Former smokers	319	2004	1.09 (0.92-1.37)
Secondary VT			
Never-smokers	733	3306	1.0 (ref)
Current smokers	140	617	1.20 (0.97-1.49)
Former smokers	516	2004	1.20 (1.05-1.37)

OR 1: adjusted for matching factors (age, hypertension, index year), race, diabetes, pregnancy, BMI, the use of oral contraceptives or hormonal replacement therapy, education and occupation.

Numbers may not agree due to missing data.