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ORIGINAL ARTICLE

Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis

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Summary. *Background*: Venous and arterial thrombotic complications exhibit a seasonal variation, with risk peaking in winter and dropping to a nadir in summer. We sought a possible correlation between sun exposure habits and venous thromboembolism (VTE) events. *Methods*: This was a cohort study comprising 40 000 women (1000 per year of age from 25 to 64 years) who were drawn from the southern Swedish population registry for 1990 and followed for a mean of 11 years. Seventy-four per cent answered an inquiry at the inception of the study (n = 29 518), and provided detailed information on their sun exposure habits. Cox regression analysis was used with the presence of VTE as a dependent variable and selected demographics as independent variables. The main outcome was the relationship between VTE and sun exposure habits. *Results*: Swedish women who sunbathed during the summer, on winter vacations, or when abroad, or used a tanning bed, were at 30% lower risk of VTE than those who did not. Risk estimates did not change substantially after adjustment for demographic variables. The risk of VTE increased by 50% in winter as compared to the other seasons; the lowest risk was found in the summer. *Conclusions*: Women with more active sun exposure habits were at a significantly lower risk of VTE. We speculate that greater ultraviolet B light exposure improves a person's vitamin D status, which in turn enhances anticoagulant properties and enhances the cytokine profile.

Keywords: sun exposure habits, venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) events constitute a major cause of female morbidity and mortality. The risk of VTE increases with advancing age, the presence of inherited or acquired thrombophilias, hypofibrinolysis, surgery, hormonal use [combined oral contraceptives (COCs) or hormone replacement therapy (HRT)], immobilization, overweight, pregnancy, and malignancy [1,2]. There are several studies indicating that the risk of VTE is greater in the winter months than in the summer months [3–6]. Coronary heart disease (CHD) and other arterial thrombotic complications have shown a similar seasonal pattern [7–10]. No plausible explanation has yet been given for the seasonal variations in thrombotic complications.

Vitamin D levels have been demonstrated to have a similar seasonal variation, with a nadir occurring in winter [11]. Humans obtain vitamin D from exposure to sunlight, diet, or dietary supplements [12]. Most dietary products are low in vitamin D. Therefore, the major source of vitamin D is ultraviolet B (UVB) radiation (wavelength between 290 and 315 nm), which penetrates the skin and converts 7-dehydrocholesterol to 25-hydroxycholecalciferol vitamin D_3 (25-OH-VitD) via previtamin D [12]. The hydroxylation of 25-OHVitD into its active form, 1α,25$(OH)_2$ vitamin D_3 (1,25VitD), takes place mainly in the kidney [12].

In our study, the Melanoma Inquiry of Southern Sweden (MISS), we followed 40 000 women prospectively for a mean period of 11 years, obtaining detailed information on their sun exposure habits, as well as such established risk factors for VTE as age, malignancy, number of births, and hormonal treatment. This longitudinal cohort study was carried out in order to assess how women's sun exposure habits influence their risk of VTE.

Material and methods

The study was approved by the Ethics Committee of Lund University (LU 632-03). In 1990 the MISS study was initiated. One thousand native-born Swedish women per year of age, from 25 to 64 years (n = 40 000), with no history of malignancy, were chosen from the general population registry of the South Swedish Health Care Region by computerized random selection. Twenty-seven women could not be contacted, leaving 39 973 as the study cohort, representing 20% of the south Swedish female population in the selected age groups. The women were invited to complete a standardized written questionnaire concerning risk factors for malignant melanoma. The initial inquiry was made between 1990 and 1992, and a written follow-up was conducted between 2000 and 2002. The questionnaire inquired into several items of potential interest for thrombosis risk, such as number of births, marital status, and educational level, and included detailed questions regarding sun exposure habits. The sun exposure questions at the inception of the study were: (i) how often do you sunbathe during the summer? (never, 1–14 times, 15–30 times, > 30 times); (ii) do you sunbathe during the winter, such as during vacations to the mountains or the Alps? (never, 1–3 days, 4–10 days, > 10 days); (iii) do you use a sun bed? (never, 1–3 times, 4–10 times, > 10 times per year); (iv) do you work outdoors during the summer (no, yes); and (v) do you go abroad on vacation to swim and sunbathe? (never, once every year or two, once a year, two or more times a year). For analysis, the five questions were dichotomized into negatives (no/never) and affirmatives (varying positive frequencies). All data regarding risk factors, apart from cancer diagnosed during the study period, were collected from the initial written inquiry. At the follow-up interview, women were asked about long-term medications that they may have taken and the presence of other diseases (including VTE). In order to determine whether there was a dose–response relationship, a new categorized three-part dummy variable was created (no/never, sometimes, or more often).

The unique personal identification number assigned to each Swedish resident allowed us to ascertain all deaths and causes of death from the National Cause of Death (NCD) register. The incidence of VTE was determined both through responses to the follow-up questions regarding disease and long-term medication, and by means of entries in the National Patient Registry (NPR), which records all women who have been hospitalized.

Those women who were invited to participate in the MISS study were sought by ICD 9 code numbers for VTE – 634G or 634H, 635G or 635H, 636G or 636H, 637G or 637H, 638G or 638H, 639G or 639H, 671D, 671E, 671F, 673C, 451B, 452, 325, 437G, 572B, 453 (C, D, W, or X) or 415B – or the corresponding ICD 10 codes O082, O087, O223, O871, O873, O879, O225, O229, O882, I802, I803, I81*, I82*, I636, I676, K550, or I26*. The personal identification number and the above-mentioned diagnosis codes were cross-matched in the NCD and NPR. Thus, the registered cases, and dates, of VTE events were established for all women in the cohort, that is, both those included and those not included in the analysis of risk factors. From the register, we collected all VTE events up to 31 December 2002. Malignancy was defined as the diagnosis of any type of malignancy during the study period prior to 31 December 2002. Information was gathered from both Regional and National Cancer Registries. Vital statistics were determined up to 31 December 2002.

Hormone use at the inception of the study, that is, use of COCs or HRT, was introduced as a dichotomized variable [never use (reference), ever use]. The question posed was: have you used/are you using combined oral contraceptives? Women not answering the question were considered never to have used COCs.

Smoking habits were also recorded at the inception of the study. They were categorized into the following subgroups: non-smokers (reference); those who had smoked fewer than 100 000 cigarettes in their lifetime; and those who had smoked 100 000 cigarettes or more (based on how participants had characterized their cigarette smoking in mean consumption at 5-year intervals).

Drinking habits were noted at the time of the initial questionnaire by quantity of beer, wine and spirits consumed per month. Alcohol intake was categorized into five subgroups by equivalent amounts of alcohol consumed: no consumption (reference); < 5 g day^{-1}; 5 to < 10 g day^{-1}; 10–15 g day^{-1} (moderate consumption); and > 15 g day^{-1}.

Weight and height were recorded at the second interview, and body mass index (BMI) was calculated as kg m^{-2}. BMI was classified into three groups: < 25 (reference); 25 to < 30 (overweight); and ≥ 30 (obese).

The level of regular exercise was estimated at the second interview by answers to the question – 'In addition to your usual work, do you exercise regularly?': No, Do you go for a walk once a week? Do you go for a walks several times a week? Do you bicycle, swim, participate in gymnastics, dancing, or similar activities one or more times a week (i.e. strenuous exercise)? Physical exercise was then divided into three categories: none, take walks one or more times a week, or strenuous exercise.

Statistics

Analysis of characteristics of selected variables were performed with Cox regression analysis using 95% confidence intervals. The presence of VTE was used as a dependent variable, and 'time-at-risk' as a time variable. Time-at-risk was defined as time from initial participation in the study to VTE, death, or 31 December 2002, whichever came first. As increasing age is a strong risk factor for VTE, it was introduced as a categorized variable and included for adjustment in all risk estimates. All calculations were performed using SPSS software (Statistical Package for the Social Sciences, SPSS Inc., Chicago IL, USA), and *P*-values < 0.05 were considered to be statistically significant.

Results

In Table 1, we present the characteristics of the women in the study cohort. There was an increased incidence of VTE among women with less than 9 years of schooling, unmarried women, and widows. As compared with those who had given birth on one or two occasions, nulliparous and multiparous women were at increased risk. Women who were diagnosed with cancer

Table 1 Demographic characteristics of women with and without venous thromboembolism (VTE) from inquiry at inclusion

Women's characteristics and habits*	Women with VTE (n = 312)	Women without VTE (n = 29 205)	Age-adjusted	
			RR	95% CI
Education				
≤ 9 years	95	5488	1.6	1.2–2.2
9 years	39	2734	1.3	0.9–2.0
10–12 years	65	7594	1.3	0.9–1.8
≥ 12 years	74	9623	1.0	Reference
Other	39	3767	1.1	0.7–1.6
Marital status				
Unmarried	30	2533	1.6	1.1–2.4
Married	226	22 784	1.0	Reference
Divorced	22	2645	0.8	0.5–1.2
Widow	32	1121	1.7	1.2–2.6
Number of births				
0	58	4914	1.6	1.2–2.2
1–2	144	16 313	1.0	Reference
≥ 3	110	7979	1.4	1.1–1.8
Menarche				
≤ 10	6	471	1.7	0.7–3.8
11–13	141	15 793	1.0	Reference
≥ 14	149	12 426	1.1	0.9–1.4
Combined oral contraceptives				
Never use	176	10 811	1.0	Reference
Ever use	136	18 395	0.7	0.5–0.9
Hormone replacement therapy				
Never use	262	25 595	1.0	Reference
Ever use	50	3611	0.9	0.6–1.2
Cancer during study period				
No	242	27 602	1.0	Reference
Yes	70	1604	4.2	3.2–5.5

CI, confidence interval; RR, relative risk. All information, except that for cancer (follow-up data), was gathered at study inclusion and analyzed with Cox regression analysis with age adjustment.
*Some women did not answer all questions.

during the study period were at four-fold increased risk of VTE. At the initial interview, data were gathered from 29 518 women of the 39 973 in the total cohort (74%), representing 317 290 woman-years; 24 098 women answered the follow-up inquiry.

Table 2 shows the age-adjusted analysis of sun exposure habits and VTE risk. Those who used a sun bed, sunbathed during winter vacations or during the summer, or who sunbathed abroad, were all at about 30% reduced risk of VTE. There were only minor changes in risk estimates when adjusting for demographic characteristics (model 1). In model 2, an adjustment for smoking habits and alcohol consumption was added, and in model 3, exercise and BMI were added by means of data obtained from those answering the follow-up inquiry (i.e. retrospective information). The relative risks (RR) for smoking habits, moderate alcohol consumption, obesity and strenuous exercise were 1.4, 0.4, 2.5, and 0.5, respectively. All differed significantly from the reference groups. A dose–response relationship was not found between sun exposure habits and risk of VTE. The risk among those sunbathing 1–14 times during summer was almost identical to that for those sunbathing ≥ 15 times. Women using sun beds one to three times during the course of a year were at similar risk as those using them at least four times per year. The risk to those who frequently sunbathed abroad or during winter vacations was not significantly lower than the risk to those who did not.

Figure 1 shows the mean hours of sunlight per month by season and the number of VTE events annually for the whole study population (n = 39 973). It is notable that the risk of VTE in the winter is between 40% and 60% greater than in other seasons. As compared to winter, the risk is lower in spring [30% lower, odds ratio (OR) = 0.7], in summer (OR = 0.6), and in autumn (OR = 0.7).

Table 2 Sunbathing habits and risk of venous thromboembolism (VTE); bivariate age-adjusted analysis

Sunbathing habits	Women with VTE	Women without VTE	Age-adjusted		Model 1		Model 2		Model 3	
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Use of sun beds										
No	214	15 218	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	93	13 483	0.6	0.5–0.8	0.7	0.5–0.9	0.7	0.5–0.9	0.8	0.6–1.0
Sunbathing during winter vacation										
No	277	23 339	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	33	5420	0.6	0.4–0.9	0.7	0.5–1.0	0.7	0.5–1.0	0.7	0.4–1.0
Working outdoors in summer										
No	221	21 580	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	77	6791	1.1	0.8–1.4	1.1	0.8–1.4	1.1	0.8–1.4	1.0	0.7–1.3
Sunbathing during summer										
No	38	1527	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	269	27 105	0.6	0.4–0.8	0.7	0.5–0.9	0.7	0.5–1.0	0.6	0.4–0.9
Sunbathing during vacation abroad										
No	165	12 201	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Yes	147	16 717	0.7	0.6–0.9	0.7	0.6–0.9	0.8	0.6–1.0	0.8	0.6–1.0

CI, confidence interval; RR, relative risk. Data were analyzed with Cox regression analysis with age adjustment. Model 1: Adjusted for age, education, marital status, number of births, and cancer during study period. Model 2: Adjusted for age, education, marital status, number of births, cancer during study period, alcohol consumption, and smoking habits. Model 3: Adjusted for age, education, marital status, number of births, cancer during study period, body mass index, and physical activity, including those who answered the follow-up inquiry.

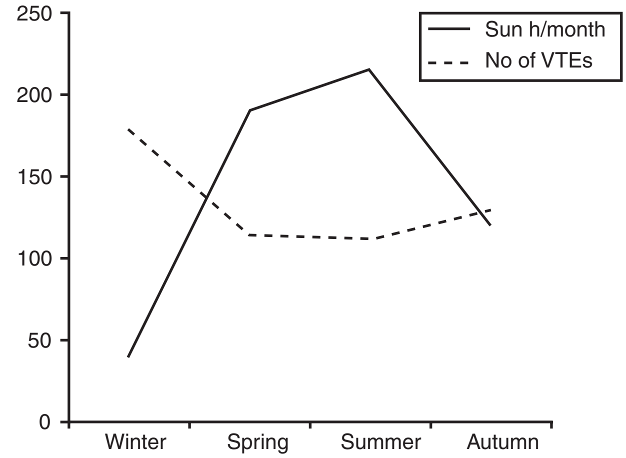

Fig. 1. Number of women with venous thromboembolism (VTE) and mean hours of sunlight per month by season.

Discussion

We found women with active sun exposure habits to be at significantly lower risk of VTE. This finding was constant after adjustment for demographic variables. It was also constant after adjustment for smoking habits, alcohol consumption, BMI, and physical exercise. The results for these lifestyle variables were recently reported [13]. Furthermore, a seasonal pattern was noted in the risk of VTE: it increased by about 50% in winter, when the hours of sunlight were few. We believe that our finding of reduced risk of VTE with increased sun exposure might offer a plausible explanation for the seasonal variation in the incidence of VTE [3–6] Women who exposed themselves more often to the sun or to artificial UVB light presumably improved their vitamin D status [14]. As women with more active sun exposure habits were at lower risk of VTE, we speculate that variations in vitamin D status might be a possible cause for the seasonal variations in thromboembolic complications. This study lends support to the previously reported health benefits of sun exposure [12]. In the past, the effect of cold has been proposed as a cause of the seasonal variation in these risks [7]. With more hours of sunlight, there will be less cold weather and improved vitamin D status. Thus, our hypothesis is in agreement with the correlation between cold and thrombotic complications [7], but not with cold weather as the causative mechanism.

By what mechanism might sun exposure lower the risk of VTE?

The active metabolite of vitamin D is 1,25VitD. It has been shown to have anticoagulant properties by upregulating thrombomodulin and downregulating tissue factor [15], Thus, the decreased vitamin D levels during winter move the coagulation balance towards hypercoagulation, as compared with summer. Levels of 25-OHVitD have been shown to be inversely related to plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator antigen (t-PA Ag) levels *in vivo*. PAI-1 is a marker of fibrinolytic activity, and the level is positively associated with cardiovascular risk. The t-PA Ag level is useful as a marker of endothelial dysfunction. Endothelial cells show 1,25VitD receptor activity together with a 1α-hydroxylase enzyme for local 1,25VitD production from 25-OHVitD. In patients with type 2 diabetes mellitus with low 25-OHVitD status, supplementation with vitamin D (vitamin D_2, 100 000 units, single dose) resulted in decreased blood pressure and improved flow-mediated vasodilatation (i.e. improved endothelial function) [16]. There are several possible mechanisms by which vitamin D may improve endothelial function: indirectly, by reducing blood pressure [16,17]; by decreasing vascular resistance [16]; by acting as an immunomodulator, preventing excessive expression of inflammatory cytokines (tumor necrosis factor-α, interleukin-6) [18,19]; and by increasing interleukin-10 expression [20]. Thus, there seems to be a role for vitamin D in maintaining the integrity of the vascular endothelium.

Several factors affect the ability to form 25-OHVitD via the skin. Clothing and sunscreen are effective in preventing vitamin D synthesis [21,22]. Sun block with sun protection factor (SPF) 15 absorbs 99% of the incident UVB radiation, thus preventing most of the 25-OHVitD synthesis [23]. Melanin is extremely efficient in absorbing UVB radiation: increased skin pigmentation markedly reduces 25-OHVitD synthesis in the skin [19,22]. African Americans with very dark skin have an equivalent SPF of 15; that is, their ability to synthesize vitamin D is reduced by 99% [19]. A large cohort study in the USA reported a 60% increased risk of VTE among blacks, as compared with whites [24]. Thus, our hypothesis might be relevant in explaining some of the racial differences concerning VTE. Sunbathers using a sun bed have been shown to have robust 25-OHVitD levels [14]. In addition, the angle at which the sun shines upon the earth has a major effect on the amount of UVB light that reaches the surface [19]. Therefore, not much vitamin D is synthesized in the morning or late afternoon. Furthermore, the capacity to synthesize 25-OHVitD in the skin declines with age (a 70-year-old person has about 25% of the capacity of a young adult) [19].

We have found no trials designed to test the ability of vitamin D to prevent VTE. However, a randomized controlled study of 250 patients with prostate cancer, half of whom were given 45 μg of calcitriol (1,25VitD) weekly, found an unexpected significantly lower risk of thrombotic events (two vs. 11 events) [25].

Strengths and weaknesses

Strengths of the present study are its use of an unselected large cohort drawn from the national population registry and the fact that the information was obtained at the inception of the study. The combination of administrative data and the questions put to women at follow-up about diseases and long-term medication is a strength; we are confident that most outpatient VTE events have been recorded. However, we have no data on the incidence of misclassification among the diagnosis numbers. We also lack data on familial thrombosis or prior thromboembolic events. There is a possibility that women with prior VTE events travel less, and thus have a lower level of sunbathing. An additional weakness is that we lack information on other established risk factors, such as surgery, injury, and immobility. The assumption was made that sun exposure habits did not change over time and, consequently, information from one assessment alone was used in the models. This is a common assumption in cohort studies, and it tends to lead to underestimation of the risk. Another potential shortcoming is that we lack data on what method was used for diagnosing a VTE event. However, the employment of objective methods is widespread in Sweden, as the cost of verifying VTE events is borne by the Swedish social security system. Thus, we do not believe there is a substantial 'overdiagnosis'. Clinically unrecognized VTE events might have been missed (for example, a sudden death caused by pulmonary embolism might have gone undetected without an autopsy). However, in order to minimize this shortcoming, the study population was cross-matched against the cause of death registry.

Women with one or two prior deliveries are at lower risk of VTE than are nulliparous women. Those who have made it through one or two high-risk periods without a VTE event have shown themselves not to be at high risk. The few who have had a prior VTE event are presumably treated with thromboprophylaxis in high-risk situations. This may account for the low risk among those with one or two prior deliveries. Our finding of increased risk among nulliparous women is in agreement with studies previously conducted in Sweden [26], but in partial opposition to the generally accepted view that a high number of prior births is a risk factor for VTE. A longitudinal cohort study using data from inception is not the most appropriate design for studying the relationship between hormonal use and the acute precipitation of a disease such as VTE, where the highest risk occurs shortly after initiation of therapy. Thus, the estimates for ever-users of COCs at inception of the study should not be regarded as valid estimates of present use: because of the age distribution in the present study, over 80% were prior users. Prior users are expected to be less likely to have a VTE event during the study period, for the same reason as above. In addition, a longitudinal cohort study with data from inception will tend to underestimate the risk of current use. A nested case–control design would have been more appropriate.

The SunSmart program promoted by Cancer Research UK (spend time in the shade between 11 a.m. and 3 p.m., make sure that you never burn, aim to cover up with a T-shirt, hat, and sunglasses, remember to take extra care with children, and then use factor 15+ sunscreen) has been subject to revision; new recommendations from the UK SunSafe program advocate that people should sun themselves often but for brief intervals, without burning, preferably at mid-day, and without sunscreen [27]. The US economic burden due to vitamin D deficiency from inadequate exposure to solar UVB irradiation largely surpasses the cost of excess UV radiation [28]. This is largely due to the beneficial effects of vitamin D on the cardiovascular system, and the lower risk of malignant cancers other than melanomas [12].

Future studies could be designed to differentiate between the effects of cold and sunlight regarding the risk of thrombotic complications. In a case–control set-up, it would be possible to determine 25-OHVitD levels in cases and controls.

We believe that our study offers novel epidemiologic data together with an etiologic hypothesis regarding the cause of seasonal variations in the risk of thrombotic complications. Our findings indicate that women who described themselves as having more active sun exposure habits were at a significantly lower risk of VTE than those who did not.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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