Published in final edited form as:
J Thromb Haemost. 2012 April ; 10(4): 708–711. doi:10.1111/j.1538-7836.2012.04646.x.

Psoriasis is associated with greater risk of incident venous thromboembolism: The Iowa Women's Health Study

Pamela L. Lutsey[*], **Anna E. Prizment**[*], and **Aaron R. Folsom**[*]
[*]Division of Epidemiology and Community Health, University of Minnesota

Psoriasis is a common chronic skin disease, afflicting approximately 2% of the U.S. population[1]. The condition is characterized by autoimmune dysregulation, and systemic inflammation[2]. As such, psoriasis can serve as a model for studies of mechanisms of chronic inflammation[2].

Recently there has been considerable interest in whether systemic inflammation is a risk factor for VTE, as inflammation is associated with a procoagulant state[3, 4]. Most research exploring this relation has been observational, and has utilized blood markers of systemic inflammation, such as C-reactive protein (CRP) and cytokines. Results have been mixed, but overall suggestive of a positive association between inflammatory markers and VTE[4]. There has also been active inquiry into whether medical conditions characterized by chronic systemic inflammation, such as rheumatoid arthritis[5, 6], psoriasis[6–8] and inflammatory bowel disease[9–11], may be associated with elevated VTE risk. To date, studies of psoriasis and VTE include 2 case-reports[8], a medical record-linkage study based on hospital admissions and deaths[6], and a prospective cohort of the entire Danish population from 1997 through 2006[7].

We used data from the Iowa Women's Health Study (IWHS) to test the hypothesis that psoriasis is associated with elevated risk of incident VTE, after adjustment for several potentially confounding variables.

Methods

The IWHS cohort commenced in January 1986 when a questionnaire was mailed to 99,826 Iowa women aged 55–69, who were randomly sampled from the State driver's list. The 41,836 women who responded to this initial questionnaire constitute the IWHS cohort. The questionnaire collected information on characteristics such as age, educational attainment, smoking habits, height, weight, diabetes status, and hormone replacement therapy use. Information on behaviors and physiologic characteristics were queried again in 1992.

As detailed previously[12, 13], the IWHS data were linked to Centers for Medicare Services (CMS) enrollment and health care utilization data from 1986 through 2004. Medicare provides payment for all or part of health care for most U.S. residents aged 65 and older[14, 15], and data stemming from the payment of Medicare bills is now used widely as a population-based data source for clinical occurrences[16]. Of IWHS cohort members surviving to 65 years, 98% (40,377 of 40,997) met our CMS inclusion criteria and were therefore followed for incident VTE events[12]. Information about Medicare enrollees was collected from four files (Denominator, MedPar, Carrier and Outpatient). Information about

Corresponding author: Pamela L. Lutsey, PhD, MPH Assistant Professor Division of Epidemiology and Community Health University of Minnesota lutsey@umn.edu Phone: (612) 624-5812 Fax: (612) 624-0315 Post: 1300 South 2nd St; Suite 300 Minneapolis, MN 55454.

Medicare enrollment and inpatient services, including discharge codes, has been available since 1986, whereas data about outpatient services, including diagnosis codes, have been available since 1991 (Outpatient and Carrier files).

Psoriasis diagnoses were identified using the International Classification of Diseases (ICD-9) diagnosis code 696.1 in Medicare claims data[13]. Psoriasis was defined as ≥1 claim from a dermatologist or ≥2 claims from any Medicare file. IWHS participants were considered to have had a VTE if any of the following VTE ICD-9 codes occurred on their Medicare MedPAR (hospitalization) discharge diagnosis records[12]: 415.1×, 451.1×, 451.2, 451.81, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4×, 453.8, 453.9.

Psoriasis is typically treated in an outpatient setting, and most psoriasis claims are found in the Medicare Carrier file available in 1991–2004. Thus, our analytical sample included only participants who, since 1991, were enrolled in at least 1 month of fee-for-service Part A and Part B Medicare coverage after reaching 65 years (n = 38,608). Person-years accumulated from the date participants met the enrollment criteria until the occurrence of VTE, death, fee-for-service part A or B disenrollment, or the end of December 2004.

Characteristics of women with and without psoriasis were described using means and proportions. Body mass index (BMI) was calculated as weight over height squared (kg/m^2). Cox proportional hazards regression was used to evaluate the relation between psoriasis and incident VTE, with psoriasis modeled as a time-dependent covariate. Our first model adjusted only for age (continuous). Model 2 additionally adjusted for characteristics which have been associated with both psoriasis and VTE in previous analyses of the IWHS cohort[12, 13]: age, education (< high school, high school, > high school), smoking status (current, former, never), body mass index (continuous), diabetes (yes, no) and HRT use (current, former or never). Covariate information collected in 1992 was utilized. In instances of missing values, data from the baseline (1986) survey was carried forward. In sensitivity analyses, results were similar when baseline data was not carried forward.

Results

Our analytic cohort included 38,608 women who were followed for a median of 11.3 years (maximum: 14.0 years). At baseline, the women were on average 68.1 years old (min: 65.0, max: 84.6), and were almost exclusively Caucasian.

Through follow-up, 859 women, who constitute 2.2% of the cohort, were diagnosed with psoriasis. Women who developed psoriasis were more likely to be younger, more highly educated, smokers, have higher BMI, diabetic, and be HRT users (Supplemental Table 1).

A total of 1,825 incident VTE events occurred over 435,065 person-years of follow-up. 37 of these VTEs were preceded by psoriasis. In time-dependent analyses, the age-adjusted hazard ratio (HR) for VTE among individuals who developed psoriasis was 1.40 (95% CI: 1.00, 1.94) versus those who did not develop psoriasis (Supplemental Table 2). The association was similar [HR: 1.39 (1.00, 1.93)] after additional adjustment for education, smoking status, BMI, diabetes, and HRT use.

Discussion

A diagnosis of psoriasis was associated with a 40% increased risk of incident VTE in this prospective, population-based study of nearly 40,000 older women. These results corroborate recent work which has suggested that psoriasis is associated with increased VTE risk.

Among the three manuscripts exploring the relation between psoriasis and VTE, all of which were published in 2011[6–8], the Danish manuscript has the strongest study design[7]. However it too was limited in that it was unable to adjust for lifestyle characteristics and anthropometrics. These characteristics, particularly obesity, are associated with both psoriasis and VTE, and may have confounded that study's observed associations. Furthermore, psoriasis was defined on the basis of psoriasis hospitalizations and claims for prescriptions for vitamin D derivatives. The authors were, therefore, unable to identify outpatients treated with topical corticosteroids alone, the most common topical medication for psoriasis The IWHS associations we observed were similar in magnitude to the Danish study's. Further, our results extend previous work in that we were able to control for lifestyle and anthropometrics, and identify outpatient psoriasis cases.

The implications of this research are two-fold. Our findings contribute to ongoing discussions about whether chronic systemic inflammation causes VTE[4]. Notably, a genome-wide association scan recently identified as a susceptibility locus for VTE HIVEP1 on chromosome 6p24.1, which codes for a protein that participates in the transcriptional regulation of inflammatory target genes[17]. Additionally, the JUPITER trial showed that statins, whose pleiotropic effects include reducing levels of CRP, reduced VTE risk[18].

From a clinical perspective, our findings suggest that psoriasis patients may be at elevated, albeit modestly elevated, risk of VTE. Given the modest hazard ratio and relatively low incidence of VTE a diagnosis of psoriasis would not justify special VTE prevention. Individuals with moderate and severe psoriasis are also at elevated risk of atherosclerotic cardiovascular disease[19, 20]. Thus psoriasis patients may already be targeted for cardiopreventive therapies, such as weight loss and statins, which may also lower VTE risk.

Strengths of this analysis are the population-based sample, prospective design, identification of outpatient psoriasis cases, and ability to adjust for behavioral characteristic and obesity. There are also several limitations. First, we did not validate cases of psoriasis or VTE. However, validation studies comparing Medicare data to medical records for other autoimmune conditions[21] and VTE[22–26] have shown high positive predictive values. Furthermore, as we have reported previously, rates of both psoriasis[13] and venous thromboembolism[12] were in accordance with what one would expect in the general population. Related, the precise date of psoriasis onset is unknown. Second, since we were looking at interrelations between two relatively rare conditions stratifying by psoriasis severity or VTE type (i.e. provoked versus unprovoked) was not viable. Lastly, the generalizability of our finding may be limited, as our study was conducted among elderly women living in Iowa.

To conclude, this study compliments existing work suggesting a relation between chronic, systemic inflammation and risk of VTE, and suggests that patients with even mild-to-moderate psoriasis may be at elevated risk of a VTE event.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This Iowa Women's Health Study was supported by the National Cancer Institute (grant R01 CA39742). We thank the other investigators, the staff, and the participants in the Iowa Women's Health Study for their valuable contributions.

References

1. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clinical and Experimental Dermatology. 2001; 26:314–320. [PubMed: 11422182]
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. New England Journal of Medicine. 2009; 361:496–509. [PubMed: 19641206]
3. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation. 2004; 109:2698–2704. [PubMed: 15184294]
4. Lippi G, Favaloro EJ, Montagnana M, Franchini M. C-reactive protein and venous thromboembolism: Causal or casual association? Clinical Chemistry and Laboratory Medicine. 2010; 48:1693–1701. [PubMed: 20704541]
5. Matta F, Singala R, Yaekoub AY, Najjar R, Stein PD. Risk of venous thromboembolism with rheumatoid arthritis. Thromb Haemost. 2009; 101:134–138. [PubMed: 19132199]
6. Ramagopalan S, Wotton C, Handel A, Yeates D, Goldacre M. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: Record-linkage study. BMC Medicine. 2011; 9:1. [PubMed: 21219637]
7. Ahlehoff O, Gislason GH, Lindhardsen J, Charlot MG, Jorgensen CH, Olesen JB, Bretler DM, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis carries an increased risk of venous thromboembolism: A danish nationwide cohort study. PloS one. 2011; 6:e18125. [PubMed: 21464995]
8. Zhao YX, Chen G, Zhao RZ, Zhang XG. Psoriasis complicated with venous thromboembolism: Report of two cases and a literature review. Chinese medical journal. 2011; 124:1593–1596. [PubMed: 21740826]
9. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: A cohort study. The Lancet. 2010; 375:657–663.
10. Saleh T, Matta F, Yaekoub AY, Danescu S, Stein PD. Risk of venous thromboembolism with inflammatory bowel disease. Clinical and Applied Thrombosis/Hemostasis. 2011; 17:254–258. [PubMed: 20211927]
11. Novacek G, Weltermann A, Sobala A, Tilg H, Petritsch W, Reinisch W, Mayer A, Haas T, Kaser A, Feichtenschlager T, Fuchssteiner H, Knoflach P, Vogelsang H, Miehsler W, Platzer R, Tillinger W, Jaritz B, Schmid A, Blaha B, Dejaco C, Eichinger S. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. Gastroenterology. 2010; 139:779–787. e771. [PubMed: 20546736]
12. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR Jr. Folsom AR. Correlates and consequences of venous thromboembolism: The iowa women's health study. Am J Public Health. 2010; 100:1506–1513. [PubMed: 19910349]
13. Prizment A, Alonso A, Folsom A, Ahmed R, Virnig B, Warshaw E, Anderson K. Association between psoriasis and incident cancer: The iowa's women's health study. Cancer Causes and Control. 2011; 22:1003–1010. [PubMed: 21553077]
14. Gornick ME, Warren JL, Eggers PW, Lubitz JD, De Lew N, Davis MH, Cooper BS. Thirty years of medicare: Impact on the covered population. Health Care Financ Rev. 1996; 18:179–237. [PubMed: 10173021]
15. Virnig BA, Marshall McBean A, Kind S, Dholakia R. Hospice use before death: Variability across cancer diagnoses. Med Care. 2002; 40:73–78. [PubMed: 11748429]
16. Virnig BA, McBean M. Administrative data for public health surveillance and planning. Annu Rev Public Health. 2001; 22:213–230. [PubMed: 11274519]
17. Morange P-E, Bezemer I, Saut N, Bare L, Burgos G, Brocheton J, Durand H, Biron-Andreani C, Schved J-F, Pernod G, Galan P, Drouet L, Zelenika D, Germain M, Nicaud V, Heath S, Ninio E, Delluc A, Münzel T, Zeller T, Brand-Herrmann S-M, Alessi M-C, Tiret L, Lathrop M, Cambien F, Blankenberg S, Emmerich J, Trégouët D-A, Rosendaal FR. A follow-up study of a genome-wide association scan identifies a susceptibility locus for venous thrombosis on chromosome 6p24.1. American journal of human genetics. 2010; 86:592–595. [PubMed: 20226436]
18. Glynn RJ, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM. A

randomized trial of rosuvastatin in the prevention of venous thromboembolism. New England Journal of Medicine. 2009; 360:1851–1861. [PubMed: 19329822]

19. Friedewald VE, Cather JC, Gelfand JM, Gordon KB, Gibbons GH, Grundy SM, Jarratt MT, Krueger JG, Ridker PM, Stone N, Roberts WC. Ajc editor's consensus: Psoriasis and coronary artery disease. The American Journal of Cardiology. 2008; 102:1631–1643. [PubMed: 19064017]
20. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, Gelfand JM. Attributable risk estimate of severe psoriasis on major cardiovascular events. The American Journal of Medicine. 2011; 124:775.e771–775.e776. [PubMed: 21787906]
21. Katz JN, Barrett J, Liang MH, Bacon AM, Kaplan H, Kieval RI, Lindsey SM, Roberts WN, Sheff DM, Spencer RT, Weaver AL, Baron JA. Sensitivity and positive predictive value of medicare part b physician claims for rheumatologic diagnoses and procedures. Arthritis and rheumatism. 1997; 40:1594–1600. [PubMed: 9324013]
22. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: The longitudinal investigation of thromboembolism etiology. The American Journal of Medicine. 2004; 117:19. [PubMed: 15210384]
23. White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in california. Ann Intern Med. 1998; 128:737–740. [PubMed: 9556467]
24. Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, Gaziano JM, Frishman WH, Curb JD. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the women's health initiative. Am J Epidemiol. 2004; 160:1152–1158. [PubMed: 15583367]
25. Kniffin WD Jr. Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med. 1994; 154:861–866. [PubMed: 8154949]
26. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of icd-9-cm codes for identifying cardiovascular and stroke risk factors. Med Care. 2005; 43:480–485. [PubMed: 15838413]