Arthritis & Rheumatology
DOI 10.1002/art.39494

THE INCIDENCE AND RISK FACTORS FOR PSORIATIC ARTHRITIS IN PATIENTS WITH PSORIASIS – A PROSPECTIVE COHORT STUDY

Running Title: **INCIDENCE AND RISK FACTORS FOR PSORIATIC ARTHRITIS**

AUTHORS:

Lihi Eder[1], Amir Haddad[1], Cheryl F. Rosen[2], Ker-Ai Lee[3], Vinod Chandran[1], Richard Cook[3], Dafna D. Gladman[1]

AFFILIATION:

[1]Centre for Prognosis Studies in the Rheumatic Diseases - Toronto Western Hospital, Toronto, ON, Canada

[2] Division of Dermatology, Toronto Western Hospital, Toronto, ON, Canada

[3]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

GRANTS AND FINANCIAL SUPPORT:

Lihi Eder is supported by the Krembil Foundation and a Canadian Institutes of Health Research (CIHR) fellowship award. The Psoriatic Arthritis Program is funded in part by The Arthritis Society, CIHR and the Krembil Foundation.

AUTHOR FOR CORRESPONDENCE:

Dr. Dafna D. Gladman

Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital

399 Bathurst St., 1E-410B, Toronto, Ontario, M5T 2S8.

Tel: 416-603-5753; fax: 416-603-9387; Email: dafna.gladman@utoronto.ca

Key Words: Psoriatic arthritis, epidemiology, risk

Word Count: 3,960

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/art.39494

Received: May 21, 2015; Revised: Oct 07, 2015; Accepted: Oct 27, 2015

ABSTRACT

Objectives: To estimate the incidence of PsA in patients with psoriasis and to identify risk factors for its development.

Methods: A prospective cohort study involving psoriasis patients without arthritis at study entry. Information was collected about lifestyle habits, co-morbidities, psoriasis activity and medications. Patients who developed inflammatory arthritis or spondylitis were classified as PsA if they fulfilled the CASPAR criteria. The annual incidence of PsA was estimated using an event per person-years analysis. Cox proportional hazard models, involving fixed and time-dependent explanatory variables were fitted to obtain estimates of relative risk (RR) for the onset of PsA in multivariate models stratified by sex and controlling for age at onset of psoriasis.

Results: The results of the 464 patients who were followed for 8 years were analyzed. A total of 51 patients developed PsA since enrollment. The annual incidence rate was 2.7 (95% confidence interval (CI) 2.1, 3.6) PsA cases per 100 psoriasis patients. The following baseline variables were associated with the development of PsA in multivariate analysis: severe psoriasis (RR 5.4, p=0.006), low level of education (college/university vs. high school incomplete RR 4.5, p=0.005, high school education vs. high school incomplete RR 3.3, p=0.049), use of retinoid medications (RR 3.4, p=0.02); time-dependent variables included psoriatic nail pitting (RR 2.5, p=0.002) and uveitis (RR 31.5, p<0.001).

Conclusions: The incidence of PsA in patients with psoriasis is higher than previously reported. Severe phenotype of psoriasis, nail pitting, low level of education and uveitis predict the development of PsA in patients with psoriasis.

Psoriasis is a chronic immune mediated skin disease affecting approximately 2% of the general population (1). Psoriatic arthritis (PsA) is an inflammatory arthritis that affects approximately 20-30% of the patients with psoriasis attending dermatology clinics (2). Despite major advances in the therapy of PsA over the past decade, many patients with PsA still suffer from decreased quality of life, disability, co-morbidities and extra-articular manifestations related their disease. Early diagnosis and treatment are critical in the prevention of adverse disease-related outcomes. The relationship between psoriasis and PsA is not well understood. Epidemiologic studies have found that the majority of PsA patients first develop psoriasis and only later develop PsA (3). Therefore, patients with psoriasis may serve as a preferred target population for investigating the epidemiology of PsA and for identifying markers of high risk for the disease. Such information may contribute to the understanding of the pathophysiology of PsA and can also be used to develop clinical prediction algorithms for dermatologists to identify psoriasis patients who are at high risk for developing PsA.

There is limited information about the incidence of PsA and risk factors for the disease in patients with psoriasis. The estimated cumulative incidence of PsA in psoriasis patients ranged widely from 5.1% at 20 years (4) to 20.5% at 30 years (5) following the onset of psoriasis. Our group reported an annual incidence rate of 1.87% in a prospective cohort study of patients with psoriasis who did not have arthritis at baseline (6). This estimate was much higher than previous reports and may reflect the systematic assessment of the cohort participants, which likely allowed the detection of milder cases. However, this study was based on a relatively short follow-up period and small number of incident cases.

Screening for symptoms and signs of PsA in patients with psoriasis is recommended by dermatology guidelines (7,8). Therefore, the identification of markers for an increased risk of developing PsA in this patient population is highly desirable. The presence of psoriatic nail lesions and severe psoriasis, as indicated by more extensive body surface area affected, were associated with a higher risk of having PsA (4,9-11). Involvement of certain body sites, particularly the scalp and intergluteal area, was associated with an increased risk of developing PsA in a retrospective cohort study (4). Obesity predicted the development of PsA in two large population-based studies (12,13). Other suggested environmental risk factors that have been associated with the development of PsA include: trauma and physically demanding occupations, bacterial infections, smoking and a family history of PsA (14-17). However, the evidence to support a link between PsA and these environmental risk factors is weaker and the results were often conflicting. Furthermore, previous studies concerning risk factors for PsA were limited by their retrospective nature, cross-sectional study design, small sample size, a failure to use classification criteria for PsA and by the lack of a comprehensive assessment of psoriasis patients for detection of inflammatory arthritis which may have led to misclassification of the two groups.

A prospective cohort study of patients who are at high risk for developing a condition can serve as an ideal setting for the investigation of pre-clinical phases of a disease. In this study we report the results of 8 years of follow-up of a prospective cohort of patients with psoriasis who were free of psoriatic arthritis at baseline. The objectives of this analysis were a) to estimate the annual incidence of development of PsA in patients with psoriasis and b) to identify markers of high risk for PsA in psoriasis patients.

PATIENTS AND METHODS

Setting

The Toronto Psoriasis Cohort was established in 2006 and forms the basis of a long term prospective study aimed at assessing risk factors for the development of PsA in patients with psoriasis. All potential study subjects have a diagnosis of psoriasis confirmed by a dermatologist. The sources of recruitment are varied and include patients with a range of psoriasis types (primarily chronic plaque psoriasis) and severity. Patients are mainly recruited from dermatology clinics and phototherapy centres in the Greater Toronto Area and also from family practice clinics and through advertisement in flyers posted in several hospitals and local media. The cohort includes different ethnic groups although most of the patients (77.3%) are Caucasians. The inclusion criteria require a diagnosis of psoriasis confirmed by a dermatologist. The exclusion criteria are the presence of inflammatory arthritis or spondylitis in the past or at the time of the assessment. All subjects are evaluated by rheumatologists with expertise in assessment of PsA patients to exclude inflammatory arthritis and spondylitis before enrollment. Each subject undergoes a comprehensive musculoskeletal examination that includes joint assessment for tenderness, swelling and deformities, evaluation for the presence of enthesitis, tendonitis and dactylitis, and assessment for restriction of movement in the spine. If there are definite clinical findings of inflammatory arthritis, enthesitis or spondylitis, the patient is excluded from the study. In cases of doubt, imaging studies, including radiographs, ultrasound or MRI, are performed as indicated to investigate the nature of the abnormality. Patients thus diagnosed with psoriasis that have no current evidence or past history of PsA are eligible for the study. If a non-inflammatory condition,

such as osteoarthritis, is diagnosed, the subject is included in the study. This process ensures that all participants do not have clinical inflammatory arthritis at enrollment.

Case Definition

All study participants were re-assessed annually regardless of whether they had developed musculoskeletal symptoms. The process of incident case ascertainment for patients who developed musculoskeletal symptoms was similar to that described above for the baseline visit. The diagnosis of PsA was determined by at least 2 rheumatologists from the PsA research team after reviewing the clinical, laboratory and imaging data. Participants were classified as having PsA if they fulfilled the CASPAR criteria (referred herein as "confirmed PsA").

Patients who failed to return for the yearly assessment were requested by telephone or by mail to complete the Toronto Psoriatic Arthritis Screen (ToPAS-II) questionnaire, a screening questionnaire designed to detect PsA among patients with psoriasis as well as the general population (18). The ToPAS-II was validated in different populations of patients with skin conditions other than psoriasis, PsA and healthy subjects (18). Subjects scoring $\geq$8 points on the ToPAS-II screen were considered as suspected cases of PsA (referred herein as "suspected PsA").

Data Collection

Study participants were assessed according to a standard protocol at each visit. The subjects provided information about their demographics, lifestyle habits, family history of psoriasis and rheumatic diseases, co-morbidities and extra-articular manifestations of spondyloarthritis (SpA), injuries, infections, musculoskeletal symptoms and the use of medications. The general physical examination included measurement of height and weight, assessment of

psoriasis severity by Psoriasis Area and Severity Index (PASI), assessment of the presence and type of psoriatic nail lesions (pitting or onycholysis). A comprehensive musculoskeletal assessment of 66/68 joints for swelling and tenderness, respectively, was conducted. The presence and the number of dactylitic digits were recorded. The presence of enthesitis in 16 sites was assessed by the Spondyloarthritis Research Consortium of Canada (SPARCC) index (19). The following patient-reported outcomes were assessed: Health Assessment Questionnaire (HAQ), the Medical Outcome Study Short Form Health Survey (SF-36) and Dermatology Life Quality Index (DLQI) to estimate the effect of psoriasis and/or PsA on function and quality of life. Assessment of radiographic joint damage was performed at the time of diagnosis in the majority of the confirmed incident cases of PsA. Radiographic damage in the hands and feet was assessed according to the modified Steinbrocker score. Axial radiographs were scored according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). MRI of the spine was performed in patients with inflammatory back pain and negative or inconclusive findings on radiographs.

Statistical Analysis

Descriptive statistics were computed with continuous variables summarized by their means and standard deviation and categorical variables summarized by proportions.

The number of person-years at risk was calculated as the time between the diagnosis of psoriasis and last contact date (follow-up visit, date of ToPAS-II questionnaire completion, or death) or the date of PsA diagnosis, whichever came first. This duration was used to estimate the cumulative incidence of PsA among patients with psoriasis. Patients who did not have any follow-up visits or ToPAS-II questionnaire assessments after their initial screening visit were excluded since they did not contribute any time at risk. Two parametric models

were used to evaluate whether the risk of developing PsA, as modeled by the hazard function, changes over time. A time homogeneous exponential model (with a constant hazard function) was used to estimate the rate of PsA among psoriasis patients. This model was compared to a Weibull model that accommodates a trend in the hazard. A likelihood ratio test of the two models was taken as lack of evidence for a time-dependent risk. A nonparametric estimate of the cumulative incidence function conveyed the risk of PsA over time.

For the analysis of predictors for PsA, only subjects with complete information about all of the assessed predictors were included. For the primary analyses the outcome included incident cases of PsA (confirmed and suspected). Last observation carried forward strategy was used to handle missing covariates data during the follow-up period. Cox proportional hazard models were used to assess predictors for the development of PsA. A total of 22 predictors were assessed that were selected based on knowledge from prior literature about the epidemiology and pathogenesis of PsA. Since this was considered an exploratory analysis we did not account for multiple testing. Explanatory variables included a family history of psoriasis in a first or second degree relative, family history of PsA or ankylosing spondylitis (AS) in a first or second degree relative, uveitis, depression, hypo/hyperthyroidism, diabetes, presence of diarrhea, being in menopause (women only), alcohol consumption (daily, social, none), smoking status (current, past, never), injury (within a year), infection (within a year), infection that required an antibiotic therapy (within a year), Body Mass Index (BMI), nail pitting, onycholysis, psoriasis severity (severe PASI>20, moderate PASI 10-20, mild PASI<10), level of education (university/college, high school education, high school incomplete), use of methotrexate, use of TNFα blockers and use of retinoids. As a screening phase, each of the above mentioned variables was included in a separate regression model

controlled for age at onset of psoriasis, stratified by sex and used the duration of psoriasis as the left-truncation time. Each explanatory variable was assessed twice: as a time-varying co-variate and as a fixed variable at baseline. All variables that achieved 10% significance level were included in single multivariate Cox regression model controlled for age at onset of psoriasis and stratified by sex with duration of psoriasis as left-truncation time. Backward elimination was used to eliminate non-significant covariates at 5% significance level from the multivariate regression model. Sensitivity analyses were carried out considering only confirmed cases of PsA as an outcome. Suspected cases of PsA were censored at their last clinic visit.

RESULTS

A total of 631 patients with psoriasis were screened. Of those, 60 and 13 patients were excluded due to the presence of PsA and other rheumatic conditions at baseline, respectively. The characteristics of the excluded patients with baseline PsA were similar to the baseline characteristics of the study population, except for a higher proportion of males and psoriatic nail lesions (The characteristics of the excluded patients are summarized in supplementary Table 1). A total of 558 patients who were followed from January 1, 2006 to September 5, 2014 were enrolled in the Toronto psoriasis cohort. Of those, 94 subjects were excluded from the analysis since they only had a single assessment and did not contribute any follow-up period (81 lost to follow-up, 13 declined to return for a follow-up visit or to complete the ToPAS-II questionnaire). The patients who were excluded tended to be younger than the remaining study population, but were similar to the study population with respect to other characteristics. Of the 464 patients who were included in the final analysis, 51 patients

developed PsA that was confirmed by a rheumatologist (confirmed cases) and an additional 9 patients were considered as suspected cases based on a high score on the ToPAS-II questionnaire. The subjects in the latter group however, declined to return for follow-up; therefore the diagnosis of PsA could not be confirmed. The remaining 404 were free of PsA at their last assessment. This cohort had a total of 1880.9 person-years of follow-up, with a mean of 4.1 (SD 2.1) years per person. The study outcome of the participants is summarized in Figure 1.

Characteristics of the Study Population

The sources of recruitment were largely from phototherapy centers (66.4%). The rest were recruited from local advertisement (19.2%), dermatology clinics (11.2%) and from a general rheumatology clinic (3.2%). The latter group included patients who were referred to rheumatology for assessment of musculoskeletal abnormalities but were found to have a non-inflammatory musculoskeletal condition. The characteristics of the study population are summarized in Table 1. Their mean age at baseline was 47.2±13.3 years, 56.2% were males. Their mean duration of psoriasis at baseline was 16.4±14.4 years and 74.4% had early onset psoriasis (prior to the age of 40). The majority of the participants were not taking any systemic medications for their psoriasis.

Characteristics of PsA Patients at Diagnosis

The clinical features of the 51 confirmed PsA cases are presented in Table 2. The mean age at the time of diagnosis was 49.9±12.8 years. The most frequent pattern of musculoskeletal inflammation at presentation was peripheral arthritis (64.7%) followed by axial (17.6%), axial + peripheral (15.7%) and enthesitis (2%). The majority of the patients with peripheral

involvement (32/42, 76.2%) had oligoarthritis (4 or less actively inflamed joints) at the time of diagnosis. 41.4% of the patients had signs of sacroiliitis or spondylitis on imaging (radiographs or MRI). 25% of patients were found to have radiographic sacroiliitis (bilateral grade 2 or unilateral grade 3 sacroiliitis) while in 4 of the 9 (44.4%) patients who presented with inflammatory back pain without peripheral arthritis, the diagnosis was confirmed by MRI of the spine (non-radiographic axial SpA). Radiographs of the hands and feet were performed in 39 patients. Of these, 23% were found to have at least one periarticular joint erosion and 10.2% had periarticular new bone formation.

Incidence of PsA

The annual incidence rate was 2.7 (95% confidence interval (CI) 2.1-3.6) PsA cases per 100 psoriasis patients when only confirmed cases were included. The incidence rate increased to 3.2 (95% CI 2.5 – 4.1) when both confirmed and suspected cases were included. The cumulative incidence function for PsA onset with death as a competing event and the estimated cumulative probability of PsA based on the exponential model are shown in Figure 2. Tests for trend did not suggest a departure from the constant hazard, so there is insufficient evidence to claim that the risk of developing PsA in patients with psoriasis changes over time.

Predictors of PsA in patients with psoriasis

Baseline Predictors

The following baseline variables were associated with an increased risk of developing PsA in univariate analysis (each model was controlled for age at onset of PsA, stratified by sex and used the duration of psoriasis as a left-truncation time): nail pitting (relative risk (RR) 2.21, p=0.007), psoriasis severity (severe: RR 3.87, moderate: RR 1.35, p_{global} =0.05), low level of

education (university/college: RR 0.36, high school graduate: RR 0.54, p_{global} =0.08) and use of systemic retinoids (RR 2.80, p=0.04). After multivariate regression analysis only psoriasis severity (severe RR 5.39, p=0.006), low level of education (university/college: RR 0.22, p=0.005, high school education: RR 0.30, p=0.049) and the use of systemic retinoids (RR 3.42, p=0.02) remained independent predictors for PsA. The complete multivariate Cox regression models are presented in Table 3. A sensitivity analysis considering only confirmed PsA as the study outcome, showed similar results. The following variables remained independent predictors of PsA in the multivariate regression analysis: Severe psoriasis (RR 4.59, 95% CI 1.2, 17.5, p=0.025), low level of education (university/college: RR 0.20, 95% CI 0.06, 0.62, p=0.005, high school education: RR 0.27, 95% CI 0.07, 1.05, p=0.059) and use of systemic retinoids (RR 3.28, 95% CI 1.06, 10.2, p=0.04).

Time-dependent Predictors

The same variables were then assessed as time-dependent covariates in regression models. The following variables were associated with an increased risk of developing PsA in univariate analysis (each model was controlled for age at onset of PsA, stratified by sex and used the duration of psoriasis as a left-truncation time): nail pitting (RR 2.20, p=0.005), uveitis (RR 25.3, p=0.0001), thyroid disease (RR 2.27, p=0.04) and psoriasis severity (severe: RR 4.02, p =0.03). Multivariate regression analysis yielded nail pitting (RR 2.51, 95% CI 1.37, 4.49, p=0.002) and uveitis (RR 31.5, 95% CI 5.06, 195.8, p=0.0002) as independent predictors of PsA. Obesity, that was found to predict the development of PsA in previous studies, showed only a borderline association with PsA in univariate analysis (RR 2.02, p=0.06). A sensitivity analysis considering only confirmed cases as the study outcome,

showed similar results, however, the 95% CI were wider due to reduction in the number of events and reduced precision. Nail pitting (RR 2.39, 95% CI 1.27, 4.53, p=0.007) and uveitis (RR 55.7, 95% CI 6.99, 442.9, p=0.0001) were independent predictors of PsA.

DISCUSSION

In this study we summarize 8 years of follow-up of a prospective cohort of psoriasis patients who did not have arthritis at baseline. This unique cohort was used to investigate the incidence and markers of high risk for PsA. The estimated annual incidence was 2.7 cases of PsA per 100 psoriasis patients, an estimate that is higher than previous reports in the literature. Furthermore, there was no evidence to suggest that the rate of developing PsA changes over time. Several risk markers for PsA were identified. These can be classified into factors related to psoriasis phenotype (nail pitting, severe psoriasis and use of systemic retinoids), extra-articular manifestations (uveitis) and demographics (low level of education).

It is widely accepted that psoriasis and PsA are tightly linked, however, the nature and underlying mechanisms connecting these conditions remain poorly understood. Most studies that assessed the occurrence of PsA in patients with psoriasis estimated the point prevalence of PsA using cross-sectional study designs. Based on these reports the prevalence of PsA in psoriasis patients ranged widely, largely depending on the source of recruitment, with population-based studies reporting a prevalence of approximately 8% and hospital-based studies that recruited patients from dermatology clinics reporting a prevalence of approximately 30% (2,11,20-22). In line with the latter estimates, in our study, where participants were carefully assessed for any sign of arthritis, the estimated incidence of PsA was much higher than previous population-based reports. We have found that the annual

incidence of PsA was 2.7% compared to only 5.1% at 20 years in a retrospective study from Rochester, MN (4). This wide variation in estimates of PsA occurrence across different studies has several causes. First, methods of case-ascertainment vary and range from self-report or screening questionnaire to rheumatologic assessment. This may explain the variation, as it has been shown that a significant proportion of psoriasis patients suffer from unrecognized PsA that is diagnosed only by a careful rheumatologic assessment (2,22). Therefore, a significant proportion of patients with PsA, who may possibly have milder disease, escape medical attention and may lead to underestimation of the occurrence of PsA in population-based studies that rely mostly on administrative databases for case ascertainment. Additionally, differences in the source population may also account for the higher rate in hospital-based studies where participants tend to have more severe psoriasis, which has been linked to a higher risk of developing PsA in the present study as well as in other studies.

There is great interest in identifying risk markers for PsA in psoriasis patients. These may assist in the understanding of the underlying pathophysiologic mechanisms of PsA and facilitate the development of a prediction algorithm for PsA. In this study we confirmed two of the previously suggested risk markers of PsA, psoriatic nail lesions and psoriasis severity. Nail psoriasis has been consistently associated with a higher risk of having PsA among psoriasis patients (4,9,10). The close anatomic link between the nail and a network of entheses fibers connecting to the extensor tendon and collateral ligaments along with the 'enthesis organ' hypothesis suggested by McGonagle and colleagues may explain this association (23). A previous study suggested a stronger association between onycholysis (24) and PsA. In contrast, in our study, only the presence of nail pitting predicted the development

of PsA. Severe psoriasis was associated with a higher risk of having PsA in previous studies (4,11). Our results confirm that association. Additionally, the use of systemic retinoids, that also predicted the development of PsA in our study, may be considered as a marker of more severe skin disease. Psoriasis and PsA share several pro-inflammatory pathways; it is possible, therefore, that more severe skin disease signals a higher systemic burden of inflammatory response as a result of shared susceptibility genes and/or environmental factors which may eventually result in triggering of PsA. Alternatively, the larger affected body surface area may provide a wider port of entry for the skin microbiome to interact with the immune system which may play a role in the development in PsA.

We have identified several additional novel predictors of PsA in our study. Uveitis and low level of education were associated with a higher risk of developing PsA. Uveitis is one of the characteristic extra-articular manifestations of spondyloarthritis (SpA) that affects approximately 20% of patients (25). The occurrence of uveitis is associated mostly with axial involvement and its frequency tends to be lower in patients with PsA compared to those with AS (25-27). In our study the occurrence of uveitis predicted the development of PsA, however, it should be noted that due to the small number of events the confidence intervals are wide. Two of the 3 patients with uveitis who developed PsA had predominantly axial involvement. The association between lower level of education and PsA is harder to explain. A lower level of education is a marker of lower socioeconomic status that has been associated with lifestyle habits that may increase PsA risk; some of them were measured in this study, such as smoking and alcohol consumption, while others were not. It may also be associated with blue-collar occupations that have been linked with SpA (14,28). This association will require a more comprehensive assessment of potential underlying factors.

This study has several limitations. First, generalizability of the study may be somewhat limited, as the majority of the participants were recruited from dermatology clinics leading to over-representation of moderate-severe psoriasis and possibly patients with longer duration of psoriasis. Additionally, due to the study design, patients who developed PsA prior or concurrently to psoriasis were excluded. Therefore, our incident cases of PsA may over-represent a certain subtypes of PsA such as that associated with HLA-C*06 that is linked with severe psoriasis and long duration between the onset of psoriasis and PsA (29). Another limitation may be the relatively small sample size of the study that limits its ability to draw conclusions about negative results. For example, the association between obesity and the risk of developing PsA was confirmed in two large cohort studies (12,13). In the present study the association between obesity and PsA was of borderline statistical significance, however the effect size was similar to that observed in previous studies, suggesting that limited power may explain the negative results.

In summary, in this prospective cohort study the incidence and risk factors for PsA in patients with psoriasis were assessed. Overall, it is likely that the true incidence of PsA in patients with psoriasis, particularly those attending dermatology clinics, is higher than previously reported. This highlights the role of dermatologists as key players in identifying psoriasis patients who are at higher risk of developing PsA. Several clinical markers may assist in identification of patients at risk of developing PsA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gladman

had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

STUDY CONCEPTION AND DESIGN: LE, VC, CFR, DDG, RC, KL

ACQUISITION OF DATA: LE, VC, CFR, AH, DDG

ANALYSIS AND INTERPRETATION OF DATA: LE, VC, CFR, DDG, RC, KL, AH

REFERENCES

1. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol*. 2005;**141**:1537-41.
2. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Ann Rheum Dis*. 2013;**72**:736-40.
3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;**64 Suppl 2**:ii14-7.
4. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum*. 2009;**61**:233-9.
5. Christophers E, Barker JN, Griffiths CE, Dauden E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol*. 2010;**24**:548-54.
6. Eder L, Chandran V, Shen H, Cook RJ, Shanmugarajah S, Rosen CF, et al. Incidence of arthritis in a prospective cohort of psoriasis patients. *Arthritis Care Res (Hoboken)*. 2011;**63**:619-22.
7. (UK) NCGC. Psoriasis:Assessmnet and Managment of Psoriasis. *National Institute for Health and Clinical Excellence: Guidance*. 2012.
8. Richard MA, Barnetche T, Rouzaud M, Sevrain M, Villani AP, Aractingi S, et al. Evidence-based recommendations on the role of dermatologists in the diagnosis and

management of psoriatic arthritis: systematic review and expert opinion. *J Eur Acad Dermatol Venereol*. 2014;**28 Suppl 5**:3-12.

9. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K, Augustin M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. *Br J Dermatol*. 2014;**171**:1123-8.
10. Yang Q, Qu L, Tian H, Hu Y, Peng J, Yu X, et al. Prevalence and characteristics of psoriatic arthritis in Chinese patients with psoriasis. *J Eur Acad Dermatol Venereol*. 2011;**25**:1409-14.
11. Ogdie A, Langan S, Love T, Haynes K, Shin D, Seminara N, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology (Oxford)*. 2013;**52**:568-75.
12. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann Rheum Dis*. 2012;**71**:1273-7.
13. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis*. 2012;**71**:1267-72.
14. Eder L, Law T, Chandran V, Shanmugarajah S, Shen H, Rosen CF, et al. Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis. *Arthritis Care Res (Hoboken)*. 2011;**63**:1091-7.
15. Pattison E, Harrison BJ, Griffiths CE, Silman AJ, Bruce IN. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. *Ann Rheum Dis*. 2008;**67**:672-6.
16. Olivieri I, Padula A, D'Angelo S, Scarpa R. Role of trauma in psoriatic arthritis. *J Rheumatol*. 2008;**35**:2085-7.

17. Tey HL, Ee HL, Tan AS, Theng TS, Wong SN, Khoo SW. Risk factors associated with having psoriatic arthritis in patients with cutaneous psoriasis. *J Dermatol*. 2010;**37**:426-30.

18. Gladman DD, Schentag CT, Tom BD, Chandran V, Brockbank J, Rosen C, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto Psoriatic Arthritis Screen (ToPAS). *Ann Rheum Dis*. 2009;**68**:497-501.

19. Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis*. 2009;**68**:948-53.

20. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum*. 2009;**61**:1373-8.

21. Alenius GM, Stenberg B, Stenlund H, Lundblad M, Dahlqvist SR. Inflammatory joint manifestations are prevalent in psoriasis: prevalence study of joint and axial involvement in psoriatic patients, and evaluation of a psoriatic and arthritic questionnaire. *J Rheumatol*. 2002;**29**:2577-82.

22. Mease PJ, Gladman DD, Helliwell P, Khraishi MM, Fuiman J, Bananis E, et al. Comparative performance of psoriatic arthritis screening tools in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol*. 2014.

23. McGonagle D, Tan AL, Benjamin M. The nail as a musculoskeletal appendage--implications for an improved understanding of the link between psoriasis and arthritis. *Dermatology*. 2009;**218**:97-102.

24. Love TJ, Gudjonsson JE, Valdimarsson H, Gudbjornsson B. Psoriatic arthritis and onycholysis -- results from the cross-sectional Reykjavik psoriatic arthritis study. *J Rheumatol*. 2012;**39**:1441-4.

25. Sampaio-Barros PD, Pereira IA, Hernandez-Cuevas C, Berman A, Burgos-Vargas R, Gutierrez MA, et al. An analysis of 372 patients with anterior uveitis in a large Ibero-American cohort of spondyloarthritis: the RESPONDIA Group. *Clin Exp Rheumatol*. 2013;**31**:484-9.

26. Paiva ES, Macaluso DC, Edwards A, Rosenbaum JT. Characterisation of uveitis in patients with psoriatic arthritis. *Ann Rheum Dis*. 2000;**59**:67-70.

27. Fraga NA, Oliveira Mde F, Follador I, Rocha Bde O, Rego VR. Psoriasis and uveitis: a literature review. *An Bras Dermatol*. 2012;**87**:877-83.

28. Ward MM, Reveille JD, Learch TJ, Davis JC, Jr., Weisman MH. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. *Arthritis Rheum*. 2008;**59**:822-32.

29. Haroon M, Winchester R, Giles JT, Heffernan E, FitzGerald O. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. *Ann Rheum Dis*. 2014.

Table 1 – CHARACTERISTICS OF THE STUDY POPULATION *		
	All patients (N=464)	**Incident PsA patients** (N=60)**
Age (years)	47.2±13.3	46.7±12.4
Sex: males (%)	261 (56.2%)	33 (55%)
Psoriasis duration (years)	16.4±14.4	17±15.2
Psoriasis onset prior to age 40	345 (74.4%)	45 (75%)
Family history of psoriasis	189 (40.7%)	28 (46.7%)
Family history of PsA/AS	15 (3.2%)	3 (5%)
Smoking status:		
Current smoker	104 (22.4%)	14 (23.3%)
Past smoker	155 (33.4%)	22 (36.7%)
Never	205 (44.2%)	24 (40%)
Alcohol consumption:		
Daily	59 (12.9%)	7 (12.1%)
Social	259 (56.8%)	35 (60.3%)
None	138 (30.3%)	16 (27.6%)
Level of education:		
University/College	369 (79.5%)	43 (71.7%)
High school graduate	69 (14.9%)	12 (20%)
High school incomplete	26 (5.6%)	5 (8.3%)
PASI		
<10	403 (86.9%)	47 (78.3%)
10-20	50 (10.8%)	9 (15%)
>20	11 (2.4%)	4 (6.7%)
Nail pitting	166 (36%)	33 (55.9%)
Nail onycholysis	151 (32.8%)	26 (44.1%)
Use of retinoids - Ever	44 (9.5%)	8 (13.3%)
Use of methotrexate -Ever	44 (9.5%)	9 (15%)
Use of TNF blockers - Ever	31 (6.7%)	6 (10%)
BMI:		

Obese Overweight Normal	127 (28.5%) 174 (39.1%) 144 (32.4%)	26 (43.3%) 18 (30%) 16 (26.7%)
Uveitis -Ever	5 (1%)	3 (5%)
Inflammatory bowel disease - Ever	4 (0.9%)	1 (1.7%)
Diabetes	34 (7.3%)	4 (6.7%)
Thyroid disease	38 (8.2%)	8 (13.3%)
Depression	35 (7.5%)	5 (8.3%)

AS- Ankylosing Spondylitis, BMI-Body Mass Index, PASI-Psoriasis Activity and Severity Index, PsA-Psoriatic Arthritis

*The reported variables are from the baseline visit, except when indicated "Ever", indicates the presence during the study period.

**Including (51 confirmed + 9 suspected cases of PsA)

Table 2 – CHARACTERISTICS OF THE CONFIRMED INCIDENT PsA CASES AT THE TIME OF DIAGNOSIS (N=51)	
Age at diagnosis	49.9±12.8
Pattern of joint involvement Peripheral Axial Peripheral+Axial Enthesitis alone	 33 (64.7%) 9 (17.6%) 8 (15.7%) 1 (2%)
Pattern of peripheral arthritis Polyarthritis Oligoarthritis	 10 (23.8%) 32 (76.2%)
Mean tender joint count	2.8±4.5
Mean swollen joint count	1.5±1.8
Enthesitis	10 (19.6%)
Dactylitis	3 (5.9%)
Psoriatic nail lesions	33 (64.7%)
Patients with peripheral joint erosions	9 (23%)
Patients with radiographic sacroiliitis/spondylitis	9 (21.9%)
Patients with sacroiliitis/spondylitis (by radiographs or MRI)	17 (41.4%)
Patients with peri-articular new bone formation	4 (10.2%)
HAQ	0.34±0.43
Pain score (VAS 0-10)	3.28±2.50
Patient Global Assessment of disease activity (VAS 0-10)	4.02±2.44
DLQI	6.77±6.14
HAQ- Health Assessment Questionnaire, DLQI- Dermatology Life Quality Index, VAS- Visual Analogue Scale	

Table 3 – Multivariate Cox Regression Model - Variables at Baseline (N=433, Cases=57)				
	Univariate analysis		Multivariate model	
	RR (95% CI)*	P value	RR (95% CI)*	P value
Family history psoriasis	1.42 (0.82, 2.45)	0.21		
Family history PsA/AS	1.96 (0.57, 6.71)	0.29		
Level of education				global p=0.02
HS graduate vs. HS non-graduate	0.54 (0.17, 1.66)	0.28	0.30 (0.09, 0.99)	0.049
University/College vs. HS non-graduate	0.36 (0.13, 0.95)	0.04	0.22 (0.08, 0.62)	0.005
Any psoriatic nail lesions	1.36 (0.76, 2.45)	0.31		
Nail pitting	2.21 (1.24, 3.92)	0.007		
Nail onycholysis	1.48 (0.83, 2.65)	0.18		
PASI				global p=0.02
10-20 vs. <10	1.35 (0.63, 2.91)	0.45	1.16 (0.50, 2.64)	0.73
>20 vs. <10	3.86 (1.27, 11.7)	0.02	5.39 (1.64, 17.7)	0.006
Alcohol consumption:				
Social vs. None	0.97 (0.51, 1.82)	0.92		
Daily vs. None	1.02 (0.40, 2.59)	0.97		
Smoking status				
Current vs. Never	1.36 (0.68, 2.73)	0.38		
Past vs. Never	1.05 (0.56, 1.99)	0.87		
Recent infection	1.02 (0.57,1.84)	0.94		
Recent infection req. antibiotics	1.15 (0.53, 2.49)	0.72		
BMI				
Overweight vs. Normal	1.02 (0.50, 2.10)	0.95		
Obese vs. Normal	1.76 (0.89, 3.47)	0.10		
Depression	0.92 (0.35, 2.34)	0.85		
Thyroid disease	2.03 (0.90, 4.57)	0.09		
Diabetes	0.53 (0.15, 1.84)	0.32		
Symptoms of diarrhea	3.18 (0.88, 11.4)	0.08		
Use of anti TNF agents	1.56 (0.19, 12.6)	0.68		
Use of retinoids	2.80 (1.05, 7.47)	0.04	3.42 (1.24, 9.44)	0.02
Post-menopausal state	1.19 (0.40, 3.53)	0.75		

* Controlled for age at onset of psoriasis and stratified by sex. The variables inflammatory eye disease, use of methotrexate and recent trauma were not included in this analysis due to paucity of positive responses.

HS-high school, PASI-Psoriasis Activity and Severity Index, BMI-Body Mass Index

Table 4 – MULTIVARIATE REGRESSION MODEL TIME VARYING COVARIATES (N=444, CASES=58)				
	Univariate analysis		Multivariate model	
	RR (95% CI)*	P value	RR (95% CI)*	P value
Family history psoriasis	1.26 (0.73, 2.17)	0.41		
Family history PsA/AS	2.30 (0.78, 6.82)	0.13		
Level of education HS graduate vs. HS non-graduate University/College vs. HS non-graduate	 0.81 (0.25, 2.66) 0.52 (0.18, 1.51)	 0.73 0.23		
Any psoriatic nail lesions	1.35 (0.78, 2.34)	0.29		
Nail pitting	2.20 (1.26, 3.83)	0.005	2.51 (1.37, 4.49)	0.002
Nail onycholysis	1.33 (0.76, 2.34)	0.32		
PASI 10-20 vs. <10 >20 vs. <10	 1.38 (0.61, 3.11) 4.02 (1.14, 14.2)	 0.44 0.03		
Alcohol consumption: Social vs. None Daily vs. None	 0.87 (0.49, 1.55) 0.66 (0.24, 1.82)	 0.64 0.42		
Smoking status Current vs. Never Past vs. Never	 1.10 (0.52, 2.32) 1.30 (0.71, 2.39)	 0.80 0.40		
Recent infection	0.96 (0.52,1.77)	0.89		
Recent infection req. antibiotics	0.88 (0.39, 1.98)	0.75		
Recent trauma	1.39 (0.40, 4.85)	0.61		
BMI Overweight vs. Normal Obese vs. Normal	 1.65 (0.79, 3.44) 2.02 (0.97, 4.24)	 0.18 0.06		
Uveitis - Ever	25.3 (4.93, 130.2)	0.0001	31.5 (5.06, 195.8)	0.0002
Depression	0.84 (0.37, 1.89)	0.66		
Thyroid disease	2.27 (1.04, 4.95)	0.04		
Diabetes	0.42 (0.13, 1.43)	0.17		
Symptoms of diarrhea	2.95 (0.79, 11)	0.11		
Use of methotrexate	0.60 (0.14, 2.53)	0.48		
Use of anti TNF agents	1.84 (0.67, 5.02)	0.24		
Use of retinoids	2.17 (0.88, 5.32)	0.09		
Post menopausal state (women only)	0.75 (0.23, 2.41)	0.63		

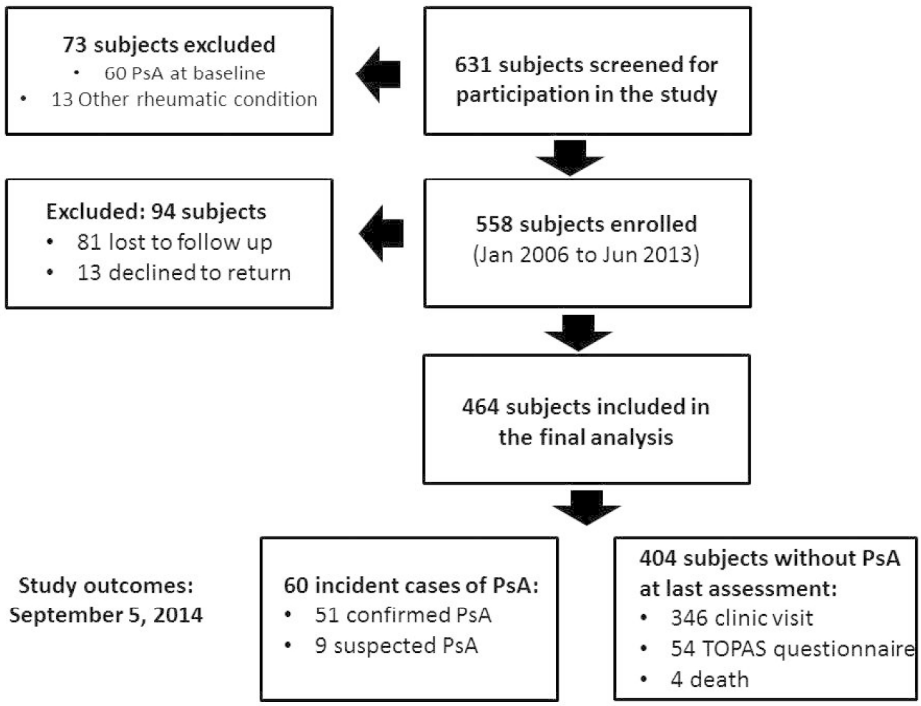
* Controlled for age at onset of psoriasis and stratified by sex. BMI-Body Mass Index, HS-high school, PASI-Psoriasis Activity and Severity Index

FIGURE LEGENDS

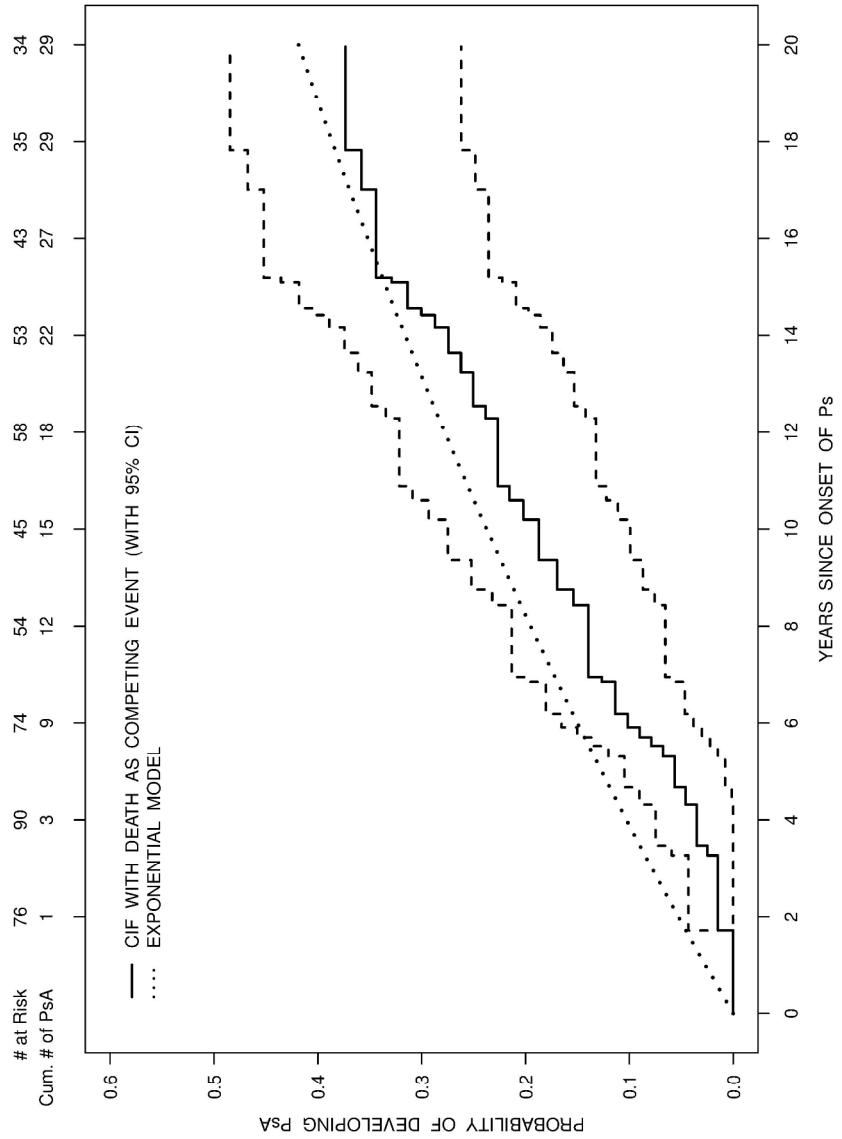
Figure 1 – Follow-up summary of the study population

Figure 2 – The probability of developing psoriatic arthritis over 20 years estimated with the cumulative incidence function (95% confidence interval) for the onset of psoriasis with death as competing events. The red dotted line denotes the estimated cumulative probability of PsA based on an exponential model

John Wiley & Sons



Follow-up summary of the study population
254x190mm (300 x 300 DPI)



The probability of developing psoriatic arthritis over 20 years estimated with the cumulative incidence function (95% confidence interval) for the onset of psoriasis with death as competing events. The red dotted line denotes the estimated cumulative probability of PsA based on an exponential model
215x279mm (300 x 300 DPI)