**Current smoking is increased in axial psoriatic arthritis and radiographic sacroiliitis**

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**Abstract**

**Objective:** The effect of smoking in psoriatic arthritis (PsA) is controversial. Our aim was to test if smoking is increased in axial PsA (axPsA).

**Methods:** 1535 patients from *PsArt-ID (PsA-International Database)* were included in the analysis. The effect of smoking on axPsA (compared to other PsA phenotypes) and radiographic sacroiliitis were investigated.

**Results:** Current smoking was more common in axPsA (28.6% vs 18.9%, p<0.001). It also was found as an independent predictor of axPsA [Odds ratio (OR)=1.4] and radiographic sacroiliitis (OR=6.6).

**Conclusion:** Current smoking is significantly associated with both axPsA and radiographic sacroiliitis in patients with PsA.

**Key words:** Axial Psoriatic arthritis, smoking, sacroiliitis

## Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease, with diverse disease manifestations (1). Several genetic and environmental factors have been implicated as the mechanism underlying PsA, one of the latter being smoking. Although smoking has long been recognized as a risk factor in multiple immune-mediated diseases, there is inconsistent data in the literature regarding its role in PsA. Studies on the general population had demonstrated that smoking increases the risk of PsA (2, 3). However, looking at the risk of developing PsA in patients with psoriasis, 2 studies had shown that smoking does not have any effects on the risk of PsA whereas 2 others demonstrated a decreased risk (3-6).

Smoking has well been recognized as a prognostic marker in axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS), with poorer outcomes, more severe disease and radiographic damage (7,8). A population-based study demonstrated that incident AS was associated with current smoking, but not with ex-smoking (8). To date, there is no information on the effect of smoking as a risk factor for axial PsA (axPsA).

We hypothesize that smoking is increased in axPsA, similar to AS. Therefore in this study we aimed to understand a) the frequency of smoking in axPsA in comparison to non-axPsA, b) to investigate risk factors on axPsA, with a focus on smoking.

## Method

### *Patient selection and data collection*

*PsArt-ID (Psoriatic Arthritis- International Database)* is a prospective, multicenter registry in PsA, which was initially developed in Turkey in 2014, with participation of Canada since 2015 and Italy since 2018 (9). Ethics approval was obtained from the local ethics committees [Hacettepe University Ethics Board, Ankara (GO 14/578); Ottawa Health Science Network Research Ethics Board, Ottawa (20160436-01H); Sacro-Cuore Don Calabria Hospital, Italy (F8MRG)] and all patients gave informed consent prior to data collection. Patients were consecutively registered to the registry with the aim of investigating real-life data using a web based system (www.trials-network.org) and the details of the registry has been published before (9). In addition, smoking

status was categorized as never, current smoker or ex-smoker at enrollment with duration and intensity to calculate smoking packs-year. AxPsA definition was clinicians' decision of axPsA, based on the inflammatory back pain according to the physician and the clinician's final judgment but not mandating any imaging. However whenever possible, radiographs of the sacroiliac joints (SIJs) were read and scored centrally by an experienced rheumatologist (SZA) blinded to the clinical data and further analysis were made based on the imaging findings also. Those readings were done according to the definitions used in the modified New York (mNY) classification criteria (10) and radiographic sacroiliitis defined as ≥ grade II both sides or ≥ grade III unilaterally.

### *Statistical analysis*

Two group comparisons were made by Fisher's exact, chi-square, student's t-test or Mann Whitney-u tests, as appropriate. ANOVA or Kruskall Wallis test was used in multiple groups' comparisons with Bonferroni correction. Risk factors for axial disease based on the literature and clinically relevant factors including age, sex, BMI, disease duration, disease subtypes, disease activity scores, function and CRP were tested in univariable analyses and factors with a significance level below $p<0.05$ were carried to multivariable analysis. An intraobserver agreement analysis was done on 28 SIJ radiographs by reading the same images 3 months apart, which revealed good intraobserver agreement (kappa= 0.79) (11). Statistical Package for Social Sciences software (SPSS version 22.0, IBM® corp., Armonk, NY, USA) was used to conduct all statistical analyses.

## Results

### *Baseline characteristics*

For this study, 1535 patients who had smoking data were included. Among these patients, 562 (36.6%) were male and the mean age was 46.9 (13.4) years. For smoking, 334 patients (21.8%) were current smokers, 324 patients (21.1%) had quit smoking and 877 patients (57.1%) had never smoked (Table-1 and supp.Table-1).

***The effect of smoking on disease outcomes***

Current and ex-smokers were more frequently males (Supp.Table-2). Ever-smoking was also more frequent in axPsA (48.2% vs 40.6%, p:0.006). Current smokers were significantly younger than ex-smokers and non-smokers, also had had more frequent nail disease (Supp.Table-2). BMI was slightly lower in current smokers than ex-smokers and non-smokers (adjusted p-value: current vs non-smoker=0.04, current vs ex-smoker=0.05). Current smokers had axPsA more often than ex and non-smokers (Supp.Table-2).

***Disease characteristics in patients with and without axPsA***

According to the rheumatologist, 454 (29.6%) had axial involvement. Only 7.1% (109/1535) of patients with PsA have axial disease only, without peripheral arthritis. AxPsA patients were more frequently males and younger compared to patients without axPsA (non-axPsA). Within axPsA patients, there were more current smokers in axPsA then non-axPsA, compared to ex-smokers and non-smokers. Smoking pack-years were found similar between groups. AxPsA patients also had more frequent nail disease (Table-1, Supp.Table-1).

***Multivariable analyses for prediction of axial disease***

Multivariable analysis to predict axPsA showed that younger age, male, current smoking and nail disease were significant predictors for axPsA whereas as the presence of polyarticular peripheral arthritis and distal interphalangeal joint involvement were protective (Table-2). Ex-smoking did not have any impact on axPsA, similar to non-smokers.

The multivariable analysis was also repeated by excluding patients that do not fulfil the CASPAR criteria which revealed similar results (data not given).

***The effect of smoking on radiographic sacroiliitis***

187 (41.2%) patients with axPsA had available sacroiliac joint x-ray for central reading and 137 (73.2%) of them had radiographic sacroiliitis according to the mNY criteria. Current smoking was more frequent in patients with sacroiliitis (sacroiliitis vs no sacroiliitis: current smoking: 39% vs 20%; ex-smoking: 15.3% vs 20%, non-smoking: 45.3% vs 60%, p=0.05). Smoking pack-years were

higher in patients with sacroiliitis [16.7 (13.5) vs 10.9 (11.5), p=0.030]. Patients with sacroiliitis had significantly higher health assessment questionnaire (HAQ) score and less BMI whereas age, gender, disease characteristics and activity scores were similar (Supp.Table-3).

In the multivariable model, current smoking status and higher HAQ scores had increased risk for radiographic sacroiliitis (Table-3).

**Discussion**

Smoking has been shown to be a risk factor in many immune mediated diseases (12). There is a clear link between smoking and new bone formation, as demonstrated in AS and AxSpA however the underlying mechanism has not been clearly understood (13,14). Previous studies suggest that smoking has effects on both cellular and humoral components of the immune system which include leukocytosis, decreased leukocyte function and increasing some of the cytokines and soluble receptors (IL-15, IL-1Ra, IL-6, sIL-6R and VEGFR3) as well as generation of reactive oxygen species. Smoking may be triggering the tissue hypoxia and increasing danger signals, similar to the effect of mechanical stress (15,16). We hypothesize a similar relationship between smoking and structural damage may also be underlying in patients with PsA. Herein we demonstrated that smoking is more linked a specific phenotype in PsA, to patients with axial disease. In addition, current smoking also increased the risk of sacroiliitis with an OR of 6.6. These observations are in parallel to what's been observed in AS. The differences across PsA studies can be due to the heterogeneity of the PsA population and representation of different subtypes with different frequencies.

The axPsA does not have a definition that is universally agreed upon. Some studies have only used the clinicians' diagnosis (17), whereas others have mandated the presence of sacroiliitis (18). The definition of imaging findings were initially developed in AS. Since differences in imaging findings have been demonstrated in AS and AxPsA whether the same set of imaging criteria can be used in AxPsA requires further testing. In addition, the IBP criteria were also developed for AS and we have previously shown that those criteria lack sensitivities in AxPsA, mostly due to age at onset of symptoms. In another study, in AxSpA patients with clear imaging

findings, a subset of patients with psoriasis had the onset of back pain after the age of 45, raising a concern about the validity of the IBP criteria in AxPsA. In the absence of a widely accepted definition, we have chosen the rheumatologists' decisions for AxPsA as that would have implications on their management. The ASAS and GRAPPA groups are currently working on the definition of AxPsA criteria, which will hopefully standardize future studies and registries.

AxPsA was reported around 30% in our registry, comparable to the previous reports (19). In addition to the effect of smoking, our study found similar results with the previously demonstrated risk factors for axPsA, such as younger age, male sex and nail disease, supporting its external validation (17,19).

This study has some limitations. Genetic data or biomarkers were not systematically collected, therefore the effect of HLA-B27 could not be analyzed. The number of complete set of spinal radiographs was low and could not be further evaluated. Also due to the cross-sectional design, our results cannot support conclusions on causal relationships.

In conclusion, both axPsA and radiographic sacroiliitis are more frequent amongst current smokers, but not ex-smokers, similar to the observations in AS. The differences between current and ex-smoking are intriguing. If smoking cessation is proven to reduce to risk of axPsA in prospective studies, it can be prioritized for the prevention of axPsA among psoriasis patients.

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**Table 1.** Demographic features of axial and non-axial psoriatic arthritis

| Variables | All patients n=1535 | Axial PsA n=454 | Non-axial PsA n=1081 | P |
|---|---|---|---|---|
| Age, mean (SD) | 46.9 (13.4) | 44.7 (13.3) | 47.8 (13.3) | **<0.001** |
| Male gender, n (%) | 562 (36.6) | 201 (44.3) | 361 (33.4 ) | **<0.001** |
| Years of schooling, mean (SD) | 9.5 (4.7) | 10.5 (4.7) | 9.1 (4.7) | **<0.001** |
| Smoking status | | | | |
| Never, n (%) | 877 (57.1) | 235 (51.8) | 642 (59.4) | **<0.001** |
| Current, n (%) | 334 (21.8) | 130 (28.6) | 204 (18.9) | |
| Ex-smoker, n (%) | 324 (21.1) | 89 (19.6) | 235 (21.7) | |
| Pack-years, mean (SD) | 15.7 (13.7) | 14.8 (13.1) | 16.1 (14.0) | 0.34 |
| BMI, mean (SD) | 28.3 (5.2) | 28.1 (5.2) | 28.4 (5.3) | 0.28 |
| Psoriasis duration (years), mean (SD) | 14.8 (11.8) | 15.1 (11.5) | 14.7 (11.9) | 0.28 |
| Psoriasis type | | | | |
| Plaque, n (%) | 864/1132 (76.3) | 256/351 (72.9) | 608/781 (77.8) | 0.23 |
| Pustular, n (%) | 158/1132 (14.0) | 52/351 (14.8) | 106/781 (13.6) | |
| Plaque and pustular, n (%) | 49/1132 (4.3) | 21/351 (6.0) | 28/781 (3.6) | |
| Others, n (%) | 61/1132 (4.3) | 22/351 (6.3) | 39/781 (5.0) | |
| PsA disease duration (years), n (%) | 5.3 (7.0) | 5.7 (7.5) | 5.1 (6.8) | 0.49 |
| Psoriatic disease family history, n (%) | 534 (34.8) | 164 (36.1) | 370 (34.2) | 0.43 |
| Polyarticular disease | 744 (48.5) | 195 (43.0) | 549 (50.8) | **0.005** |
| DIP involvement, n (%) | 230 (15.0) | 49 (10.8) | 181 (16.7) | **0.004** |
| Arthritis mutilans, n (%) | 3 (0.2) | 0 | 3 (0.3) | N/A |
| Nail involvement (ever), n (%) | 738 (48.1) | 246 (54.2) | 527 (45.1) | **0.005** |
| Dactylitis (ever), n (%) | 351/1450 (24.2) | 99/435 (22.8) | 252/1015 (24.8) | 0.70 |
| Enthesitis (ever), n (%) | 364/1421 (25.6) | 107/428 (25.0) | 257/993 (25.9) | 0.94 |
| Achilles enthesitis (ever), n (%) | 275/1421 (19.4) | 87/428 (20.3) | 188/993 (18.9) | 0.50 |
| Deformity, n (%) | 248/1198 (20.7) | 68/359 (18.9) | 180/839 (21.5) | 0.33 |
| Ankylosis, n (%) | 61/1198 (5.1) | 21/359 (5.8) | 40/839 (4.8) | 0.43 |
| Sublaxation, n(%) | 49/1198 (4.1) | 15/359 (4.2) | 34/839 (4.0) | 0.91 |
| Decreased mobility, n(%) | 187/1198 (15.6) | 51/359 (14.1) | 136/839 (16.2) | 0.36 |
| Telescoping finger | 6/1198 (0.5) | 1/359 (0.3) | 5/839 (0.6) | N/A |
| Fulfillment of CASPAR criteria, n (%) | 1326 (86.4) | 397 (87.4) | 929 (85.9) | 0.76 |

BMI: Body Mass Index, CASPAR: ClASsification criteria for Psoriatic Arthritis, DIP: Distal Interphalangeal, N/A: Not applicable, PsA: Psoriatic Arthritis, SD: Standard Deviation.

**Table 2.**Univariable and multivariable analysis on factors associated with axial psoriatic arthritis

| Axial Disease present vs absent | | | | |
|---|---|---|---|---|
| | Univariable analysis | | Multivariate analysis n=1528 | |
| **Variables** | **OR** | **95%CI for OR** | **OR** | **95%CI for OR** |
| **Age** | **0.98** | **0.97-0.99** | **0.98** | **0.97-0.99** |
| **Gender (male vs female)** | **1.58** | **1.26-1.98** | **1.49** | **1.17-1.89** |
| **Smoking** | | | | |
| ***Current vs never*** | **1.7** | **1.33-2.27** | **1.42** | **1.07-1.88** |
| ***Ex-smoker vs never*** | 1.03 | 0.77-1.37 | 0.97 | 0.71-1.31 |
| **Nail involvement, ever (presence vs absence)** | **1.41** | **1.13-1.76** | **1.43** | **1.14-1.80** |
| **Polyarthritis, ever (presence vs absence)** | **0.73** | **0.58-0.91** | **0.71** | **0.56-0.89** |
| **DIP involvement, ever (presence vs absence)** | **0.60** | **0.43-0.84** | **0.56** | **0.40-0.80** |

CI: Confidence Interval, DIP: Distal Interphalangeal, OR: Odds Ratio.

**Table 3.** Univariable and multivariable analysis on factors associated with radiographic sacroiliitis

| Radiographic sacroiliitis present vs absent | | | | |
|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis n=147 | |
| **Variables** | **OR** | **95%CI for OR** | **OR** | **95%CI for OR** |
| **Smoking** | | | | |
| ***Current vs never*** | **2.61** | **1.17-5.83** | **6.6** | **2.02-21.6** |
| ***Ex-smoker vs never*** | 1.01 | 0.42-2.42 | 1.05 | 0.35-3.14 |
| **PsA Duration** | 1.07 | 1.00-1.14 | 1.05 | 0.97-1.12 |
| **Body Mass Index** | 0.93 | 0.87-0.99 | 0.93 | 0.85-1.01 |
| **Morning stiffness** | 1.01 | 1.00-1.02 | 1.00 | 0.99-1.01 |
| **HAQ** | **1.69** | **1.01-2.90** | **2.35** | **1.14-4.85** |

CRP: C - reactive protein, CI: Confidence Interval, DIP: Distal Interphalangeal, HAQ: Healthy Assessment Questionnaire, OR: Odds Ratio, PsA: Psoriatic Arthritis.