ARTICLE

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Pack-year Smoking Associated with Poorer Functional Status, Worsened Spinal Mobility and More Radiological Damages in Axial Spondyloarthritis

Helen Hoi Lun Tsang, Ho Yin Chung*

Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

ABSTRACT

Introduction: To study the dose-response relationship between smoking and axial Spondyloarthritis (axSpA) disease outcome.

Method: One hundred and sixty participants with axSpA were recruited from a single rheumatology center. All of them fulfilled the classification criteria for axSpA by the Assessment of SpondyloArthritis International Society (ASAS). Clinical, demographic and biochemical data was collected. Participants were asked for detailed smoking histories including past and current smoking, smoking duration and quantity. Radiographs of cervical and lumbar spine were performed for modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and modified New York (MNY) criteria for radiological sacroiliitis. Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated based on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Univariate and multivariate regression models were performed to determine the associations between pack-year smoking and different disease outcomes.

Results: Among the participants, 62 (38.7%) were either current (N = 39) or former smokers (N = 23). Ex-smokers quit smoking by 18.8 ± 12.4 years. The mean pack-year for patients who had ever smoked was 19.4 ± 23.1. In univariate analyses, pack-year smoking was associated with BASFI ($p < 0.001$), modified Schober test ($p = 0.01$) and mSASSS ($p < 0.001$). Multivariate regression models showed independent dose-response associations between pack-year of smoking and BASFI (SC 0.23; 95% CI 0.01 to 0.06; $p = 0.004$), modified Schober test (SC −0.16; 95% CI −0.03 to 0.00; $p = 0.049$) and mSASSS (SC 0.22; 95% CI 0.09 to 0.47; $p = 0.01$).

Conclusion: In Chinese axSpA patients, pack-year smoking was independently associated with poorer functional status, worsened spinal mobility and more radiological damages. Smoking cessation should be encouraged in patients with axSpA.

***Keywords*:** Spondyloarthritis; Ankylosing Spondylitis; Smoking; Mobility.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a large group of inflammatory arthritis with an estimated prevalence of 0.6–1.9% [1]. This entity encompasses patients with radiographic sacroiliitis fulfilling the modified New York (MNY) criteria for ankylosing spondylitis (AS) as well as patients with features of spondyloarthritis but without definite sacroiliitis on imaging. They are characterized by inflammatory back pain (IBP), dactylitis, arthritis and extra-articular features such as uveitis and skin lesions. Ankylosing spondylitis, representing the prototype of axSpA, has a prevalence of around 0.26% in the Chinese population [2]. The development of classification criteria for axSpA by the Assessment of SpondyloArthritis International Society (ASAS) [3,4] in 2009 has led to earlier diagnoses, especially of patients in the pre-radiographic sacroiliitis stage.

Numerous studies have examined the relationship between smoking and rheumatoid arthritis (RA) [5-8] but relatively few studies have been conducted on AS and fewer still on axSpA as a whole. Smoking was demonstrated to be associated with increased disease activity [9,10], more functional impairment [9-14] and poorer quality of life [15,16] in AS patients. In addition, smoking was found to be associated with more severe radiographic damage in AS [11,17] and may predict

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*Corresponding author: Ho Yin Chung, Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Room 405B, 4/F Professorial Block, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong, Email: jameschunghoyin@gmail.com

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radiographic spinal progression in early axial SpA [18]. An international study on patients with early axSpA showed that smoking was independently associated with earlier onset of IBP, higher disease activity, increased structural damage and axial inflammation, poorer functional status and lower quality of life [19].

There are very few studies that have looked specifically into the dose-response relationship between smoking and AS, and even then, the results have been conflicting. Reed et al. [10] found that current but not former smoking was associated with worse outcomes but there was no relationship between cumulative exposure and disease activity scores. On the contrary, Mattey et al. [16] reported that smoking has a dose-dependent relationship with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), pain numeric rating scale and is associated with a poorer quality of life, which are all independent of age, sex, deprivation level and disease duration.

There is limited data on the association and dose-response relationship between smoking and disease activity, functional status and radiographic damage in Chinese patients with axSpA. Since smoking is a potentially modifiable risk factor, it would be worthwhile to study the impact of smoking on Chinese axSpA patients and to ascertain whether the association is equivalent to those reported in the Western counterparts. This study was carried out on Chinese patients with axSpA in a single center in Hong Kong. The aim of the study was to determine the effect of smoking and its cumulative exposure on disease activity, functional status and radiographic damage in Chinese axSpA patients. Participants were recruited to evaluate their disease activities by BASDAI, functional impairment by BASFI and radiographic damage by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [20].

METHODS

Study design

This is a cross-sectional study of a consecutive sample of participants of axSpA aged over 18 years from the rheumatology outpatient clinic in Queen Mary Hospital, Hong Kong. All participants were recruited between February 2012 and October 2015. The data has been used in our previous publications [21,22]. The aim of this study was to evaluate the influence of smoking on the outcome measures of axSpA as described below.

Sample size

The sample size of the study was calculated based on the prevalence of smokers in Hong Kong and the expected margin of error. Based on 12% of smokers in Hong Kong [23] and the aim to achieve a 95% confidence interval with a 5% margin of error, the sample size was estimated to be around 160.

Inclusion and exclusion criteria

We included Chinese participants who were aged over 18 years with axSpA fulfilling the ASAS classification criteria [3,4]. Pregnant ladies were excluded from the study. Informed consent was obtained and participants were assessed by rheumatologists for study eligibility. Once recruited, they underwent a series of assessment for axSpA related variables, blood testing, as well as radiological tests.

Clinical, demographic data, and physical examination

Participants were interviewed by rheumatologists in the outpatient clinic to collect clinical and demographic data. These included: age, sex, smoking history including past and current smoking, smoking duration and quantity, duration of back pain, duration of peripheral arthritis, nature of back pain, extra-spinal, and extra-articular manifestations and other comorbidities.

Physical examination was performed for modified Schober test to assess for spinal mobility. We also recorded the past and current treatment received including the use of disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), steroids and biologics agents. Disease activity was assessed by patient self-reported disease outcome measures including BASDAI [24], BASFI [25] and Bath Ankylosing Spondylitis Global Index (BASGI) [26].

Laboratory tests

Blood tests were carried out. These included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Ankylosing Spondylitis Disease Activity Score (ASDAS) [27] was calculated based on CRP or ESR.

Radiological and magnetic resonance imaging assessment

Radiographs of the cervical (lateral view) and lumbar spine (anteroposterior and lateral views) were performed and graded by a trained rheumatologists (HHLT). Grading of sacroiliitis was based on the

MNY criteria for AS [28]. Spinal radiographs were scored according to the mSASSS in which the anterior vertebral edges of the cervical and lumbar spine are scored: 0, normal; 1, erosion, sclerosis or squaring; 2, syndesmophyte; 3, bridging syndesmophyte, adding up to a maximum of 72 points [20]. Missing values of up to 3 were allowed and were substituted by the average of the remaining scored vertebral corners. Magnetic resonance imaging (MRI) of the SI joints was performed and read by a trained rheumatologist (HYC) if participants did not fulfill the MNY criteria for defined radiological sacroiliitis to ensure fulfillment of ASAS classification criteria for axSpA. All readers were blinded to clinical data.

Statistical analyses

Normally distributed data were expressed as mean +/− standard deviation (SD) and data not normally distributed were represented by the mean and interquartile range (IQR). The Chi-square test and Student's t test were used to compare categorical and continuous variables between smokers and non-smokers. Univariate linear regression and logistic regression models were used to identify variables (those with a p-value of less than 0.1 in Chi-square and Student's t test) that were associated with the disease outcomes. Variables with a p-value of less than 0.1 were included in multivariate models for analyses. Results were reported as odds ratio (OR) and standardized coefficients (β) in logistic and linear regression models respectively. The 95% confidence intervals (CI) were calculated and p values <0.05 were considered statistically significant. Interactions were checked. All statistic calculation was performed using the commercial software Statistical Package for Social Sciences (SPSS) version 25.

Ethical approval

This study was approved by the Research and Ethics Committee of Queen Mary Hospital and all patients were provided with written informed consent forms according to the Helsinki Declaration.

RESULTS

One hundred and sixty participants were recruited and 113 (70.6%) were male patients. The mean age of participants was 46.2 ± 12.7 years and the duration of IBP was 14.7 ± 11.3 years. One hundred and forty-four (90%) fulfilled the MNY criteria for AS. The remaining 16 participants were classified as undifferentiated axSpA. The mean BASDAI was 3.9 ± 1.9 and the mean ASDAS-CRP and mean ASDAS-ESR were 1.6 ± 0.8 and 1.7 ± 1.0 respectively. The mean BASFI was 2.5 ± 2.5. Smoking data were available for all 160 participants and sixty-two participants (38.7%) were either current (N = 39) or former smokers (N = 23). On average, ex-smokers quit smoking by 18.8 ± 12.4 years. The mean pack-year for patients who had ever smoked was 19.4 ± 23.1. Radiographs were missing or inadequate in 27 out of 160 participants, resulting in 133 participants involved in the mSASSS analyses. Our cohort was characterized by long disease duration, high disease activity and moderate function impairment.

Table 1 shows the baseline characteristics of participants according to their smoking status. The "smoker" group included participants who were either current or former smokers. The scores for BASFI, ASDAS-CRP and mSASSS were higher in the "smoker" group compared to participants who had never smoked and they all showed statistical significance (p values of 0.001, 0.02 and 0.01 respectively). The modified Schober test values indicative of spinal mobility were lower in smokers compared to non-smokers with a p value of 0.02. The BASDAI score was also higher in participants who had ever smoked compared.

Univariate regression analyses were carried out in order to gauge the quantitative relationship between smoking and disease outcome measures. Those with a p value of less than 0.1 were recruited as independent variables. These included BASDAI (p = 0.07), BASFI (p = 0.001), ASDAS-CRP (p = 0.02), modified Schober test (p = 0.02) and mSASSS (p = 0.01). ASDAS-ESR (p = 0.4). Results of the univariate regression analyses are shown in Table 2.

Outcome variables that were found to be significantly associated with pack-year of smoking in the univariate analyses were BASFI, modified Schober test and mSASSS with p values of <0.001, 0.01 and <0.001 respectively. They were further analyzed in multivariate regression with adjustment for age, sex and duration of IBP. The results for multivariate regression are summarized in Tables 3, 4 and 5. After adjustment for age, sex and duration of IBP, the dose-response associations between pack-year of smoking and BASFI, modified Schober test and mSASSS persisted and remained statistically significant (p values of 0.004, 0.049 and 0.01 respectively). There was no interaction between smoking and male gender for the above studied outcome variables.

Table 1. Baseline characteristics of the study population, stratified according to their smoking history.

	Smoker	Non-smoker	p-value
Age (years)	47.5 ± 11.9	45.4 ± 13.2	0.31
Duration of IBP (years)	15.8 ± 11.7	13.9 ± 11.1	0.32
Duration of peripheral arthritis (years)	11.8 ± 11.7	12.7 ± 10.3	0.67
ESR (mm/hr)	27.9 ± 21.0	33.5 ± 26.1	0.18
CRP (mg/dL)	1.0 ± 1.8	0.8 ± 1.3	0.50
BASDAI	4.3 ± 2.0	3.7 ± 1.7	0.07
BASFI	3.3 ± 2.6	2.0 ± 2.3	0.001
ASDAS-CRP	1.8 ± 0.8	1.5 ± 0.8	0.02
ASDAS-ESR	2.8 ± 0.9	2.7 ± 1.0	0.40
Modified Schober test (cm)	2.2 ± 1.9	3.0 ± 1.8	0.02
mSASSS	39.1 ± 21.8	29.0 ± 19.0	0.01
Male sex (N = 160)	53 (85.5%)	60 (61.2%)	0.001
MNY criteria (N = 144)	45 (86.5%)	76 (82.6%)	0.54
History of enthesitis (N = 160)	34 (54.8%)	66 (67.3%)	0.11
History of uveitis (N = 159)	30 (49.2%)	35 (35.7%)	0.09
History of psoriasis (N = 159)	7 (11.5%)	16 (16.3%)	0.40
History of inflammatory bowel disease (N = 160)	3 (4.9%)	3 (3.1%)	0.55
NSAID user (N = 160)	52 (83.9%)	86 (87.7%)	0.50
DMARD user (N = 160)	30 (48.4%)	48 (49.0%)	0.94
Steroid user (N = 159)	6 (9.8%)	10 (10.2%)	0.94
Ever used biologics (N = 159)	1 (1.6%)	8 (8.2%)	0.08

ASDAS-CRP, ankylosing spondylitis disease activity score, C-reactive protein based; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; CRP, C-reactive protein; DMARD, disease modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; IBP, inflammatory back pain; MNY, modified New York; mSASSS, modified Stoke ankylosing spondylitis spine score; NSAID, non-steroidal anti-inflammatory drug.

Table 2. Univariate linear regression analyses between pack-year of smoking and outcome measures.

	Standardized coefficient (Beta)	Unstandardized coefficient (Beta)	95% confidence interval	P-value
BASDAI (N = 156)	0.09	0.01	−0.01; 0.03	0.29
ASDAS-CRP (N = 152)	0.11	0.01	0.00; 0.01	0.17
ASDAS-ESR (N = 151)	0.09	0.01	0.00; 0.02	0.26
BASFI (N = 160)	0.30	0.04	0.02; 0.07	<0.001
Modified Schober test (N = 158)	−0.22	−0.02	−0.04; −0.01	0.01
mSASSS (N = 133)	0.34	0.44	0.23; 0.66	<0.001

ASDAS-CRP, ankylosing spondylitis disease activity score, C-reactive protein based; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; mSASSS, modified Stoke ankylosing spondylitis spine score.

Table 3. Multivariate linear regression analyses of BASFI with adjustment for age, sex and duration of IBP.

	Standardized coefficient (Beta)	Unstandardized coefficient (Beta)	95% confidence interval	P-value
Pack-year smoking	0.23	0.03	0.01; 0.06	0.004
Age	0.24	0.05	0.02; 0.08	0.004
Male sex	0.02	0.10	−0.72; 0.93	0.810
Duration of IBP	0.14	0.03	−0.01; 0.07	0.090

BASFI, Bath ankylosing spondylitis functional index; IBP, inflammatory back pain.

Table 4. Multivariate linear regression analyses of modified Schober test with adjustment for age, sex and duration of IBP.

	Standardized coefficient (Beta)	Unstandardized coefficient (Beta)	95% confidence interval	P-value
Pack-year smoking	−0.16	−0.02	−0.03; 0.00	0.049
Age	−0.26	−0.04	−0.06; −0.01	0.002
Male sex	0.02	0.06	−0.55; 0.68	0.20
Duration of IBP	−0.27	−0.05	−0.07; −0.02	0.001

IBP, inflammatory back pain.

Table 5. Multivariate linear regression analyses of mSASSS with adjustment for age, sex and duration of IBP.

	Standardized coefficient (Beta)	Unstandardized coefficient (Beta)	95% confidence interval	P-value
Pack-year smoking	0.22	0.28	0.09; 0.47	0.01
Age	0.33	0.58	0.31; 0.85	<0.001
Male sex	0.17	8.17	1.42; 14.93	0.02
Duration of IBP	0.31	0.62	0.32; 0.91	<0.001

IBP, inflammatory back pain; mSASSS, modified Stoke ankylosing spondylitis spine score.

DISCUSSION

The negative impact of smoking on AS and axSpA outcome parameters has been reported in previous studies. We report similar findings on Chinese patients with axSpA. Apart from the negative impact of smoking on the functional status and radiographic damage in Chinese patients with axSpA, we also demonstrated a dose-dependent relationship between smoking and outcome measures, which was independent of age, sex and duration of IBP.

Previous studies have suggested that the negative impact of smoking on functional status may just be a surrogate of another lifestyle factor or health-related behavior [9,12,14] but Mattey and colleagues found

that the correlation exists even after adjustment for socioeconomic status [16]. Other postulated mechanisms include direct toxic effects of smoking and their interference with response to treatment. Cigarette smoke is known to be pro-inflammatory and proposed mechanisms include: increased release of pro-inflammatory markers such as tumor necrosis factor (TNF) alpha, CRP, interleukin 6 (IL-6), soluble intercellular adhesion molecule type 1 and E-selectin [29,30]; higher titres of free radicals which cause DNA damage [31]; and increased expression of nuclear factor kappaB-associated genes which further promotes pro-inflammatory cytokine gene expression [32,33]. Furthermore, smokers were found to have increased circulating T lymphocytes and polymorphonuclear cells especially granulocytes [34,35].

Various studies involving patients with RA have suggested that smokers may respond less well to anti-TNF therapies [36-39] and methotrexate [39,40]. One study also found that smokers with RA have a greater need for DMARDs and feel worse, without having more radiographic damage when compared to non-smokers [41]. Although the exact mechanism of how smoking affects patient's response to therapy is unknown, this may reflect the more general negative effect of smoking on the potency of anti-rheumatic drugs.

In our study, we found that smokers (past and current) have more functional impairment when compared to non-smokers and this finding is consistent with previous studies [9-14]. We also demonstrated that there is a dose-dependent effect of smoking which was reported in an international study [16]. This may reflect the cumulative effect of smoking, leading to heightened levels of inflammation and more structural damage.

There are numerous mechanisms by which smoking may lead to decreased physical function. Firstly, smoking causes worsening of lung function and this may lead to reduction in physical capacity. Indeed, smokers with AS have been found to have a lower forced vital capacity when compared to non-smokers [9]. Secondly, a sedentary lifestyle secondary to a poor pulmonary function may lead to increased medical comorbidities. Thirdly, smoking may lead to decreased joint mobility by causing inflammation as reflected by worse results in the metrology indices, such as modified Schober test, occiput-to-wall distance and finger-to-floor distance, in other studies [9,11].

Apart from using patient self-reported outcome measures, we also assessed the structural damage using mSASSS, which showed a significant dose-dependent association with pack-year of smoking. In fact, a correlation between spinal structural damage, as measured by mSASSS, with spinal mobility and physical function has been shown in AS patients with disease duration longer than 3 years [20,42] and also in early axial SpA patients [19]. Although the limitation in spinal mobility may be contributed by both irreversible spinal damage and reversible spinal inflammation, Poddubnyy and colleagues [18] previously reported that AS patients with symptom duration of <5 years have a slower mean mSASSS progression compared to those with symptoms for 5 to 10 years. This may imply a 'window of opportunity' which may potentially allow for intervention in preventing irreversible structural damage.

We found that smoking was not associated with BASDAI in the regression models. Indeed, the results for this correlation had been conflicting with some studies showing a positive correlation [9,10,18], while others did not [16]. However, BASDAI has been shown to correlate poorly with axial joint activity [22,43,44]. A more accurate method to assess the disease activity would be essential to demonstrate the true relationship.

The study has several limitations. Some of our participants did not perform radiographs or had other missing values resulting in only 133 patients in the mSASSS calculation. Despite a smaller analyzed population size, we still managed to find a significant correlation between pack-year of smoking and higher BASFI, lower modified Schober test and more radiographic damage on mSASSS. The use of mSASSS to assess spinal damage in axSpA can also lead to both overestimation (degenerative changes in spine which may be mistaken for AS-associated lesions) and underestimation (exclusion of the thoracic spine in mSASSS where inflammation and damage can also take place). Last but not least, the use of pack-years as a quantitative measure of smoking may result in inaccuracy due to recall bias and the inability to account for changes in the number of cigarettes smoked over time. There may also be potential under-reporting of smoking in physician interview-acquired smoking status but Jeemon and colleagues previously validated the use of history taking on tobacco smoking as an accurate method of obtaining smoking history [45].

In conclusion, our study found that in Chinese axSpA patients, smoking was independently associated

with poorer functional status and more structural damage. We also demonstrated a dose-dependent relationship between cumulative smoking exposure and greater functional impairment and radiographic damage. Given that smoking is a potentially modifiable lifestyle factor, we strongly support smoking cessation in patients with axSpA, or at the very least reduction in the number of cigarettes they smoke. This may be achieved by referral to specialist smoking cessation clinics as well as frequent education of patients about the negative impact of smoking.

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