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Original Article

The role of smoking in the development and progression of structural damage in axial SpA patients: A systematic review and meta-analysis

Servet Akar[1], Yusuf Cem Kaplan[2], Sertaç Ecemiş[3], Elif Keskin-Arslan[2], Önay Gercik[1], Sercan Gücenmez[1], Dilek Solmaz[1]

Abstract

Objective: The objective of this study was to determine whether smoking was associated with the cumulative radiographic spinal damage and radiographic progression in patients with ankylosing spondylitis (AS). Thus, we conducted a systematic review and meta-analysis of the available studies to date.
Methods: An electronic search was conducted from inception to June 21, 2016, in EMBASE, the MEDLINE/PubMed Cochrane Central Register of Controlled Trials databases. Cross-sectional and longitudinal cohort studies investigating the association between smoking and cumulative spinal structural damage or radiographic progression were included. The outcome of interest was the presence of syndesmophytes in cross-sectional studies and radiographic progression in longitudinal studies. The quality assessment was done using the Agency for Healthcare Research and Quality checklist. The authors of potentially relevant studies were contacted regarding the unpublished data. Data from eligible cross-sectional studies were extracted and arranged in a 2x2 table. The odds ratios (ORs) and 95% confidence intervals (CIs) for the dichotomous outcome of interest were computed.
Results: The combined data of eight eligible cross-sectional studies for the assessment of association between smoking and cumulative spinal structural damage suggested a significant association (OR, 2.02; 95% CI, 1.51–2.70). No significant heterogeneity was detected between studies (I^2=23.0%, p=0.25). The heterogeneity of the longitudinal study data did not permit us to undertake a meta-analysis. Hence, a qualitative review was performed.
Conclusion: The results of our meta-analysis show that smoking is associated with increased cumulative spinal structural damage in patients with AS. Therefore, rheumatologists should encourage patients with AS to quit smoking.
Keywords: Ankylosing spondylitis, syndesmophyte, smoking, meta-analysis

ORCID IDs of the authors:
S.A. 0000-0002-3734-1242;
Y.C.K. 0000-0003-0369-7934;
E.K.A. 0000-0001-9538-4817;
Ö.G. 0000-0002-0994-8899;
D.S. 0000-0002-9035-689X.

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[1] Division of Rheumatology, Department of Internal Medicine, İzmir Katip Çelebi University School of Medicine, İzmir, Turkey
[2] Department of Pharmacology, İzmir Katip Çelebi University School of Medicine, İzmir, Turkey
[3] Department of Internal Medicine, İzmir Katip Çelebi University School of Medicine, İzmir, Turkey

Address for Correspondence: Servet Akar; Division of Rheumatology, Department of Internal Medicine, İzmir Katip Çelebi University School of Medicine, İzmir, Turkey

E-mail: servet.akar@gmail.com

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by the involvement of axial skeleton. The disease may also affect peripheral joints and entheses. In patients with AS, erosive damage of sacroiliac joints and vertebrae is of limited value. However, new bone formation, which may lead to progressive spinal ankylosis, is the most important long-term outcome of the disease (1). Inflammation and new bone formation almost always start from sacroiliac joints, and approximately 1 in 3 of AS patients have spinal radiographic damage at baseline, whereas more than 10% of patients may develop new syndesmophytes in 2 years of follow-up (2). This progressive spinal ankylosis may lead not only to disease-related signs and symptoms, but also to functional loss and (1, 3, 4).

Molecular mechanisms underlying the new bone formation in patients with AS are not well understood yet. There is some evidence supporting the thesis on the activation of bone morphogenetic protein signal (5) and a decrease in Dickkopf-related protein 1 and sclerostin levels, which are natural inhibitors of the Wnt pathway (6-8). Disease activity may be longitudinally associated with radiographic damage evaluated by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (2, 9).

Beyond the very well-known association between smoking and cardiovascular diseases, smoking may also have unfavorable effects on inflammatory rheumatic diseases. Smoking is one of the major known environmental risk factors for rheumatoid arthritis (RA), and it increases not only the risk of having RA, but it

also may trigger RA-specific immune reactions to citrullinated proteins in the context of the HLA–DR shared epitope genes (10). Fewer studies evaluated the impact of smoking on AS and axial spondyloarthritis as a whole. A recent study showed that smokers were younger at the onset of inflammatory back pain (11). Smoking was also found to be associated with high disease activity, worse physical functioning, and poor quality of life in patients with AS (11-18). We and some other groups showed that smoking may be also related to the presence of syndesmophytes and spinal radiographic progression (2, 19, 20). Therefore, the aim of this study was to evaluate the relationship between smoking and the cumulative radiographic spinal structural damage, namely the presence of syndesmophytes in cross-sectional studies and their progression in longitudinal studies in patients with AS by using the advantage of the meta-analysis methodology.

Methods

Search strategy

Searches were conducted in PubMed, MEDLINE, Epub & Medline in Process, EMBASE, and Cochrane Central Register of Controlled Trials databases from inception to June 20, 2016, by a professional librarian. Studies published in either English or Turkish were targeted. A manual search was also conducted through the reference list of the previous systematic reviews, and it included studies to identify other possible eligible studies. A detailed presentation of the search process can be found in Appendix 1.

The flow chart was prepared in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (21) and is presented in Figure 1. We adhered to the Meta-Analysis of Observational Studies in Epidemiology guidelines (22) to report our findings.

Inclusion and exclusion criteria

Cross-sectional and longitudinal cohort studies investigating the association between smoking and cumulative spinal structural damage or radiographic progression were included. A study was considered eligible if it met the following criteria: (a) included patients aged >16 years diagnosed with AS according to the modified New York criteria (23); (b) assessed/reported basal radiographic findings and/or radiographic progression or relevant prognostic criteria; (c) reported a minimum of 1-year radiographic follow-up; (d) either events or estimates of risk (odds ratio [OR]) were reported; (e) the data reported were not overlapping with another study (if an overlap between two studies was detected, the most recent one was included, ensuring the methodological quality of the studies were comparable); and (f) the study sample size was >10. The exclusion criteria were case reports and series, animal studies, editorials, and reviews.

Quality assessment

For the quality assessment of the study methodologies. The Agency for Healthcare Research and Quality (ARHQ) checklist (24) was used for cross-sectional studies.

Outcome measures

The outcomes of interest were the presence of syndesmophytes in cross-sectional studies and radiographic progression in longitudinal studies.

Data extraction

Four authors (S.E., S.A., E.K-A., and Y.C.K) independently reviewed the studies. The data were extracted by using a standardized data extraction form and presented in Tables 1 and 2. Any disagreements were resolved by discussion among the authors. We contacted the corresponding authors of potential studies through e-mail regarding additional information.

Meta-analytic methods

The ORs and 95% confidence intervals (CIs) for the dichotomous outcome of interest were computed. The random-effects method was used to combine the outcome data in Comprehensive Meta-analysis Software Version 3.3.070 and RevMan (Review Manager Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was assessed utilizing the Q- and I-square statistic. An I-square value between 25% and 50% signified low heterogeneity, between 50% and 75% moderate, and >75% high heterogeneity (25). A funnel plot was not utilized to assess the publication bias since it was suggested to have low power for detecting asymmetry with good accuracy if the number of included studies was <10 (26), which was the case with our meta-analysis.

Main Points

- Smoking is related with the cumulative structural damage determined by the presence of syndesmophytes.
- Smoking may also cause an increase in the structural progression.
- Rheumatologists should encourage all AS patients about quitting smoking.

Results

Cross-sectional studies

Our search strategy retrieved 910 relevant results (Figure 1), and 8 cross-sectional studies provided data necessary for the evaluation of effects of smoking on the presence of syndesmophytes (Table 1). Two of the studies were in the abstract form (19, 27). We contacted the authors of relevant studies through e-mail regarding our questions and unpublished data which were provided by 6 authors. The smoking status was analyzed as ever and never smoked. The results of the quality assessment performed by the ARHQ checklist are summarized in Table 1.

In total, 1199 patients from a wide geographical area were included in the analysis. In all the studies, cumulative radiographic damage was reported to be numerically higher in "ever-smoking"' patients with AS than patients who never smoked before. The combined data from 8 eligible cross-sectional studies for the assessment of the association between smoking and cumulative spinal structural damage, in other words, the presence of syndesmophytes, suggested a significant association (OR, 2.02; 95% CI, 1.51–2.70). No significant heterogeneity was detected between studies (I^2=23.0%, p=0.25) (Figure 2). However, studies included in the meta-analysis may have some differences such as sex and disease duration, which might have an effect on the development of syndesmophytes.

Longitudinal studies

We were unable to perform a meta-analysis for the association between smoking and the progression of radiographic damage in longitudinal studies due to (a) different handling of smoking history in different studies (qualitative vs quantitative data); (b) not presenting or providing the necessary data for the inclusion of meta-analysis; (c) different evaluation procedures in the assessment of radiographic damage (different time intervals or different scoring methods). Therefore, we decided to summarize the results of our systematic literature review.

Haroon et al. (28, 29) published a study evaluating the impact of anti-tumor necrosis factor therapy on radiographic damage in two separate papers. One of these reports is in abstract form, so we summarized the findings of the full article (28). In this multicenter study, authors scored radiographic damage according to the mSASSS in only patients who had two paired radiographs at a minimum 1.5 years interval, and their smoking status assessed a

Table 1. Characteristics of cross-sectional studies.

Author and year	Country	ARHQ checklist Score	Patients and Comparison	Exposure	Outcome	Resuts & notes
Solmaz et al., 2011 (19)	Turkey	6/10	114 patients fulfilling the modified New York criteria for AS.	Smoking status was obtained from medical records	Vertebral and lateral heel radiographs were evaluated by two independent eviewers for the presence of syndesmophytes and enthesophytes at the insertion of the achilles tendon or plantar fascia. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever /never) were obtain from unpublished data.	Smoking, male sex, age and BASMI scores are independently associated with structural damage in AS.
Tuylu et al., 2014 (54)	Turkey	7/9	49 AS patients without syndesmophytes and 45 AS patients with syndesmophytes were included. The Modified New York criteria were fulfilled for AS.	Smoking status (defined as ever/ never smoker) was collected as cardiovascular risk factor.	Syndesmophytes on lateral plain radiographs of the cervical and lumbar spine and the anterior sites of the lower and upper portion of each vertebra were randomly and blindly assessed by two rheumatologists. Any disagreements were resolved by both readers together.	Fetunin-A was found as an independent, significant predictor of syndesmophytes. No correlation was detected between presence of syndesmophytes and smoking status.
Poddubnyy et al., 2013 (20)	Germany	7/9	210 patients with axSpA (115 with AS and 95 with non-radiographic axSpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were included. The authors were contacted regarding the data from only the 115 patients with AS.	The patients were assessed with regard to their smoking status and smoking intensity (non-smoker, 10 cigarettes a day and less, 11–20 cigarettes, and more than 20 cigarettes a day) every 6 months during 2 years of follow-up.	The authors used an extended syndesmophytes count including the lateral views of the cervical and lumbar spine, and also antero-posterior views of the lumbar spine. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever/ never) were obtain from unpublished data.	The effect of smoking on radiographic spinal progression in axSpA is dependent on smoking intensity and seems to be mediated by increased systemic inflammation in smokers.
Joo et al., 2014 (5)	Republic of Korea	6/9	After exclusion, 365 patients with AS (modified New York criteria) who referred to the Hanyang University Hospital for Rheumatic Disease were included. Patients were classified as severe	Smoking status was obtained from clinical data.	The anterior radiographic changes of the lumbar spine and cervical spine in lateral radiographic view were independently scored according to the mSASSS by two radiologists. Any disagreements were resolved by both	Two SNPs in BMP6 were significantly associated with radiologic severity in patients with AS.

Table 1. Characteristics of cross-sectional studies (Continued).

Author and year	Country	ARHQ checklist Score	Patients and Comparison	Exposure	Outcome	Resuts & notes
			AS (defined by three or more syndesmophytes and/or fusion) or mild AS (defined by absence of syndesmophytes).		readers together. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status were extracted from Table 1 of study.	
Klingberg et al., 2014 (55)	Sweden	5/9	204 patients fulfilling the modified New York criteria for AS were included. All patients registered the departments of rheumatology at the Sahlgrenska University Hospital and Hospitals of Alingsås and Borås.	The information regard to current and previous smoking, age at onset and disruption of smoking, and average daily cigarette consumption were obtained from patients. Smoking pack-years were subsequently calculated.	Lateral radiographs of the cervical and lumbar spine were scored for chronic AS-related changes using the mSASSS by radiologist. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever /never) were obtain from unpublished data.	A positive correlation was found between smoking pack-years and mSASSS, BASMI, and age. The mSASSS and BASMI scores and age in ever smokers were significantly higher than never smokers.
Sakellariou et al., 2015 (56)	Greece	9/9	TNF treatment naive 106 patients with AS in accordance with modified New York criteria. All patients consulted the outpatient clinics of the Rheumatology Department of 424 General Military Hospital between June 2010 and January 2015.	Smoking status was obtained and quantitative measure of cigarette exposure was determined from measurement of smoking pack years (1 pack year = 20 cigarettes/ day for 1 year).	The severity of radiographic damages on plane radiographs of the pelvis, and lumbar and cervical spine lateral views were scored using the mSASSS at least 3 months apart by a single rheumatologist. All radiographs were also scored by a radiologist to test the agreement between two readers. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever /never) were obtain from unpublished data.	BASDAI score in current smoker, BASFI in ever smokers were found significantly high. A positive correlation was found between smoking pack-years and mSASSS, BASFI and duration of inflammatory back pain. Current smoking and increasing pack years were independently associated with a higher BASDAI score and mSASSS, respectively. The authors identified that current smoking in patient with AS was strongly and independently associated with higher disease activity, and cumulative smoking exposure with more radiographic spinal damage.
Rueda-Gotor et al., 2015 (57)	Spain	8/9	115 patients fulfilling the modified New York criteria for AS. All patients referred to the Hospital Universitario Marqués de Valdecilla	Smoking status (Non-smokers, current smokers, ex-smokers) was obtained as a part of cardiovascular risk factors.	The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever /never) were obtain from unpublished	Carotid plaques were significantly frequent in patients with ax-SpA. Plaques were significantly frequent in patients with hip involvement,

Table 1. Characteristics of cross-sectional studies (Continued).

Author and year	Country	ARHQ checklist Score	Patients and Comparison	Exposure	Outcome	Resuts & notes
			and Hospital de Laredo (Cantabria, Spain) during one year period and had definite radiographic sacroiliitis on plain radiographs.		data.	syndesmophytes, higher functional limitation and mobility index measured by BASFI and BASMI. Patients with plaques had longer duration of the disease than those without plaques.
Betancur et al., 2015 (27)	Argentina	6/9	187 patients fulfilling the modified New York criteria and/or ASAS criteria for AxSpA. All patients were ≥ 18 years and were extracted from ESPAXIA cohort.	Smoking status was collected as a part of cardiovascular risk factors.	Radiographs of cervical spine, lumbar spine and sacroiliac joints were scored using mSASSS by a blinded observer. The numbers of syndesmophyte + and syndesmophyte - patients with regard to their smoking status (current/ever /never) were obtain from unpublished data.	After adjustment, patients with metabolic syndrome had significantly increased radiological damage.

ARHQ: The Agency for Healthcare Research and Quality; AS: Ankylosing Spondylitis; BASMI: The Bath Ankylosing Spondylitis Metrology Index; axSpA: axial spondyloarthritis; GESPIC: German Spondyloarthritis Inception Cohort; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index; BASFI: The Bath Ankylosing Spondylitis Functional Index; ASAS: Assessment of Spondyloarthritis International Society; ESPAXIA: Estudio de Espondiloartritis Axial IREP Argentina.

continuous variable as number of pack–years. In univariate analysis, smoking was significantly associated with radiographic progression, as defined by a change of ≥1 mSASSS unit/year with an OR of 1.06 (95% CI, 1.02–1.09; p=0.002). Smoking was also a significant predictor for radiographic damage in this study with an OR of 1.09 (95% CI, 1.02–1.17; p=0.01) in the propensity score matching along with baseline mSASSS and anti-TNF usage. The same group had also reported their own experience in 288 patients with AS who had had pairs of radiographs at a minimum interval of 2 years (30) according to the abstract. In this work, authors found that the baseline radiologic damage (OR 22.8) and smoking (OR 2.8) were independent predictors of radiographic progression defined as a ≥2 mSASSS change between two time points. However, from the text, it was not clear how smoking was evaluated and analyzed.

Interestingly, another abstract (31), which also included patients' data of Haroon et al, reported factors associated with the radiographic progression in 368 patients with AS with two sets of radiographs at least 1.5 years apart from the United States, Canada, and Australia. In this study, smoking was not found to be predictive of radiographic progression defined as more than two mSASSS units in 2 years.

There are several papers (2, 32-36) reporting spinal radiographic damage predictors in the German Spondyloarthropathy Inception Cohort. Among the whole group of axial spondyloarthritis (including both patients with AS and non-radiographic axial spondyloarthritis [nr-axSpA]) patients (2), the authors found in univariate analysis that (a) the presence of syndesmophytes at baseline (OR, 6.29; 95% CI, 2.77–14.26), presence of definite radiographic sacroiliitis (OR, 3.14; 95% CI, 1.28–7.69), elevated C-reactive protein (CRP) level (OR, 2.47; 95% CI, 1.12–5.44), elevated erythrocyte sedimentation rate (ESR) (OR, 4.04; 95% CI, 1.82–8.97), and current smoking (OR, 2.75; 95% CI, 1.25–6.05) were associated with spinal radiographic progression defined as ≥2 mSASSS units after 2 years. The authors also stated that when they analyzed separately all the above-mentioned variables, they still found a significant association in the AS subgroup; however, in nr-axSpA, only the baseline presence of syndesmophytes was significantly associated with spinal radiographic progression. And in the multivariate logistic regression analysis, the authors reported that the baseline radiographic damage, current smoking, elevated ESR, and time-averaged CRP were independent predictors of spinal radiographic damage among the whole

Table 2. The data regarding smoking status and syndesmophyte which were extracted from cross-sectional studies.

	Country of origin	Age, years (mean±SD)	Male (%)	B27 + (%)	Disease duration, years (mean±SD)	Smokers[a] (%)	Syndesmophyte in ever smokersa (%)	Syndesmophyte in never smokersa (%)
Solmaz et al. (19), 2011 (n=114)	Turkish	40.7±11.4	67.5	NA	6.7±7.9	71.7	61	39.1
Poddubnyy et al. (20), 2013 (n=115)	German	37.1±10.6	51	79	4.2±2.7	38	52.2	35.2
Tuylu et al. (54), 2014 (n=94)	Turkish	NA	69.1	NA	NA	75.5	50.7	39.1
Joo et al. (5), 2014 (n=365)	Korean	37.0±8.6	93.2	97.1	14.1±6.8	55	56.7	49.3
Klingberg et al. (55), 2014 (n=197)	Swedish	49(17-78)*	57	87	12(1-47)*	46	63.3	31.7
Sakellariou et al. (56), 2015 (n=106)	Greek	41.5±12.7	94.3	65.8	15.6±11.2	79.2	76.1	63.6
Rueda-Gotor et al. (57), 2015 (n=115)	Spanish	46.2±11.9	59	72.4	NA	52.3	50.7	32
Betancur et al. (27) 2015 (n=93)	Argentinean	45*	74.2	NA	18.5*	53.7	62	48.8
Total (n=1199)							59	42.3

NA: Not available.
*These data were presented as median and range values.
[a]The percentages of smokers, syndesmophyte in ever smokers, syndesmophyte in never smokers were extracted from published and unpublished data.

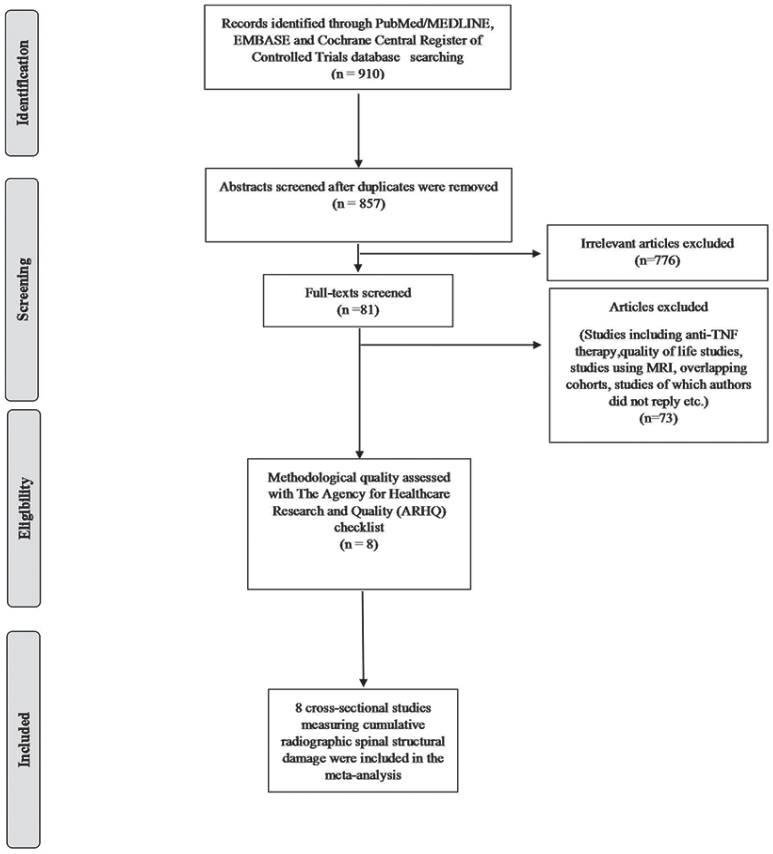

Figure 1. PRISMA flow diagram of cross-sectional studies.

group of axSpA patients. The same group also reported the separate analysis of the relationship between smoking and spinal radiographic progression in AS and nr-axSpA subgroups (36). However, this time, smoking was analyzed in three categories: (a) non-smokers, (b) ≤10 cigarettes a day, (c) ≥11 cigarettes a day. Radiographic progression had been defined as (1) worsening of the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) by ≥2 units after 2 years and (2) development of a new syndesmophyte or progression of existing syndesmophytes after 2 years. In this analysis, the mSASSS was statistically significantly worse and associated with the intensity of smoking in the AS group (3.12±5.54 in heavy smokers, 0.57±1.70 in moderate smokers, and 0.58±1.78 in non-smokers, p=0.002 for group comparison). Both definitions of spinal radiographic progression in AS were significantly associated with heavy smoking (>10 cigarettes/day). Worsening of the mSASSS score by ≥2 units over 2 years was 12.7% in non-smokers, 25.9% in moderate smokers, and 41.2% in heavy smokers (p<0.05 for heavy smokers vs non-smokers). Likewise, new syndesmophytes or syndesmophyte progression over 2 years was observed at a rate of 14.1% in non-smokers, 14.8% in moderate smokers, and 35.3% in heavy smokers (p<0.05 for heavy smokers vs non-smokers).

Our systematic literature search also revealed several reports regarding the association between smoking and structural progression in AS in the Outcome in AS International Study cohort (37, 38). In total, 184 patients with AS from the Netherlands, Belgium, and France were followed up until 12 years were included in this analysis (38). The authors scored radiographs using the mSASSS and evaluated progression longitudinally in 2-year intervals up to 12 years. According to the smoking status the patients were labeled as smokers and non-smokers. In one report, the authors investigated a direct effect of job type on radiographic progression and indirect effect of job type on the relationship between ASDAS and radiographic progression. In the direct model, researchers did not find any association between smoking and radiographic progression (p=0.22). However, smoking (n=49) lead to a 1.94 (95% CI, 1.00–2.87) unit increase in the 2-year mSASSS score in per one ASDAS unit increase. This relationship was only significant for the whole AS group and men, but not for women, and it was replicated in their sensitivity analysis.

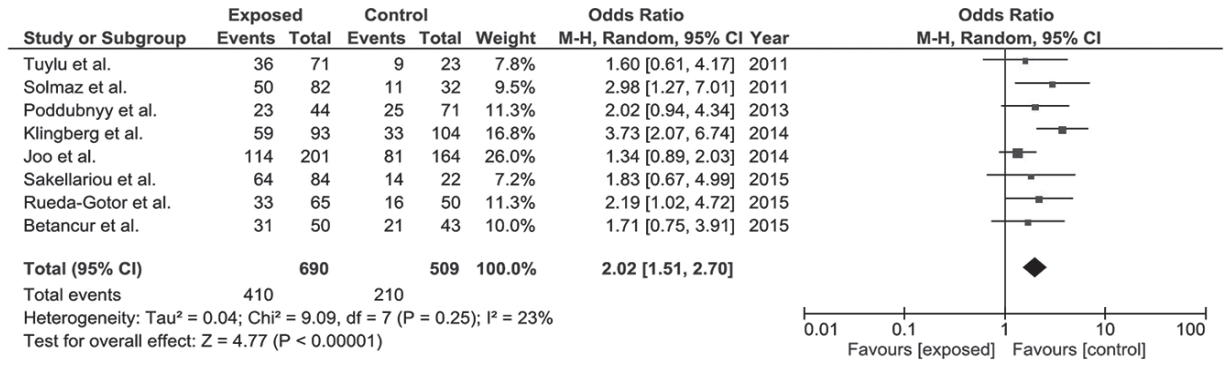

Figure 2. Forest plot of the association between ever-smoking and cumulative spinal structural damage in patients.

Another cohort (Groningen Leeuwarden AS [GLAS] cohort) from the Netherlands included consecutive 176 patients with AS who were started on anti-TNF therapy (39), and 50 had reached 6 years of follow-up. Radiographs were scored by using mSASSS, and spinal radiographic progression was analyzed longitudinally by the generalized estimating equations analytic technic. Interestingly, the smoking status was included in the analysis as the duration of smoking. Although it was found to be associated with the presence of syndesmophytes at baseline (p=0.02), during the follow-up, there was no relationship between the radiographic progression and smoking among patients with AS treated with anti-TNF (p=0.117).

Another study from Alberta, Canada, that evaluated the effects of anti-TNF therapy on radiographic progression in 384 patients with AS (40) used mSASSS for the analysis. In this work, the authors reported that smoking was not associated with radiographic progression. However, it is not clear how they handled the smoking status.

Discussion

The results of the present meta-analysis revealed that smoking was related to cumulative structural damage in AS because we showed that the patients who ever smoked had significantly more syndesmophytes than those who had never smoked. In addition, smoking might be one of the risk factors for spinal structural progression in patients with AS. The underlying mechanism behind the association of smoking and new bone formation has not been clearly understood yet. Previous studies suggested that smoking might have some effects on both cellular and humoral components of the immune system: (a) smoking may cause a change in the generation of reactive oxygen species (10, 41); (b) leukocytosis and decreased leukocyte function was found in chronic smoke exposure (41-44); (c) CRP serum levels, (C-C motif) ligand CCL 17/thymus, activation regulated chemokine (CCL17/TARC), and CCL11/EOTAXIN were found to be increased, and some of the cytokines and soluble receptors (IL-15, IL-1Ra, IL-1β, IL-16, SCF, sIL-6R and sVEGFR3) were reported to be decreased in current smokers in comparison to individuals who have never smoked before (45). In addition, there were similar levels of CRP, chemokines (CCL17/TARC, CCL11/EOTAXIN), and some of the cytokines (IL-15, IL-1β, IL-1RA) found in former smokers and individuals who have never smoked before. These findings might indicate various deviations in the immune/inflammation response, such as chemotaxis of T-cells, eosinophils, and other cells; pro- and anti-inflammatory processes; as well as markers involved in cell development/differentiation, cell growth and activation, angiogenesis, and hematopoiesis (45).

The main limitation of this systematic review was that we were not able to perform a meta-analysis by using longitudinal data regarding the impact of smoking on the structural progression in patients with AS. In addition to a different handling of smoking history in available studies, the way of quantification of structural progression has restricted us in this regard. However, it may not be possible to fully extract the effect of smoking on structural damage from other confounding factors in cross-sectional studies. Conventional X-rays of the spine are still considered the gold standard for the assessment of the presence and the progression of structural changes (46-48). However, the scoring of radiographs in AS is somehow difficult (49). The mSASSS has been considered to be the best scoring method for the evaluation of structural changes in the spine of patients with AS (50), because it was reported that mSASSS was sensitive to change in determination and quantification of radiographic progression over a 2-year interval (46, 51). Since radiographic progression is a slow process, detection of real progression might be jeopardized by the measurement error in the sequential scoring in intervals shorter than 2 years. However, the assessment of progression in the conditions such as (a) paired reading of films in random order and (b) cutoff based on smallest detectable differences (SDD) for inter-observer data might also decrease the reliability of method for the determination of progression in some patients with AS (49, 52)0-36 each. Therefore, simultaneously paired reading of graphs and smallest detectable change instead of SDD was recommended (52).

In our study, we used the presence of syndesmophytes as a surrogate marker of cumulative structural damage in cross-sectional evaluation of patients with AS. Previously, we revealed that the kappa agreement among readers for the presence of syndesmophytes were markedly better than the squaring, erosion, and sclerosis and highest for ankylosis (53). It was also suggested that the calculation of proportion of patients with AS with definite radiographic progression defined as the presence of syndesmophytes or ankylosis might be regarded as the gold standard in the evaluation of radiographic change in AS, since the presence of definite radiographic damage was shown to be more predictive of radiographic progression (46).

In conclusion, considering a very high frequency of smoking among patients with AS and the available evidence about the negative impact of smoking on the structural damage, it is clear that we should strongly encourage our patients with AS to quit smoking.

You can reach the appendix of this article at eurjrheumatol.org.

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Appendix 1. Detailed presentation of the search process

1. PubMed Search

Database: PubMed
Date searched: June 21, 2016
Topic: Is smoking associated with radiographic damage in axial spondylorthritis?

Search #1 39096

((((((spondylarth* OR spondyloarth* OR spondyl-arth* OR spondylo-arth*))) OR (((anky* AND (spondy* OR spin* OR verteb* OR axial* OR sacro* OR lumbar* OR pelvi*)))) OR ((((spondy* AND (spondy* OR spin* OR verteb* OR axial* OR sacro* OR lumbar* OR pelvi*))))) OR (((rheumatoid AND spondy*)))) OR ((bechterew* OR marie-strumpell* OR axial SpA OR AxSpA OR ASAS OR ASDAS OR SASSS OR mSASSS OR m-SASSS OR BASRI OR BASDAI OR BASFI OR BASMI OR BAS-G OR ASQoL))

Search #2 313850

(tobacco* OR smoking OR smoker OR smokers OR cigar* OR nicotine*)

Search #3 2873900

(publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)

Search #4

#1 AND #2 AND #3 55

Results of database searches are subject to limitations of the database(s) searched. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the search results. While the staff of HealthSearch makes every effort to ensure that the information gathered is accurate and up-to-date, HealthSearch disclaims any warranties of any kind, expressed, implied, or statutory regarding the accuracy or completeness of the information or its fitness for a particular purpose. HealthSearch provides information from public sources both in electronic and print formats and does not guarantee its accuracy, completeness or reliability. The information provided is only for the use of the Client and no liability is accepted by HealthSearch to third parties.

2. Embase Search

Database: Embase 1974 to 2016 June 20
Date searched: June 21, 2016
Topic: Is smoking associated with radiographic damage in axial spondylorthritis?

Embase 1974 to 2016 June 20

#	Searches	Results	Type
1	spondylarthritis/	3920	Advanced
2	spondylarthritis/	3920	Advanced
3	spondyloarthropathy/	4476	Advanced
4	bath ankylosing spondylitis disease activity index/	1936	Advanced
5	bath ankylosing spondylitis functional index/	1127	Advanced
6	bath ankylosing spondylitis metrology index/	96	Advanced
7	spondyl?arth*.mp,kw.	12561	Advanced
8	spondyl?-arth*.mp,kw.	131	Advanced
9	(anky* adj2 spondy*).mp,kw.	26014	Advanced
10	(anky* adj2 spin*).mp,kw.	627	Advanced
11	(anky* adj2 verteb*).mp,kw.	161	Advanced
12	(anky* adj2 axial*).mp,kw.	77	Advanced
13	(anky* adj2 sacro*).mp,kw.	144	Advanced
14	(anky* adj2 lumbar*).mp,kw.	15	Advanced
15	(anky* adj2 pelvi*).mp,kw.	19	Advanced
16	(spondy* adj2 spin*).mp,kw.	1046	Advanced
17	(spondy* adj2 verteb*).mp,kw.	357	Advanced
18	(spondy* adj2 axial*).mp,kw.	1590	Advanced
19	(spondy* adj2 sacro*).mp,kw.	278	Advanced
20	(spondy* adj2 lumbar*).mp,kw.	1568	Advanced
21	(spondy* adj2 pelvi*).mp,kw.	57	Advanced
22	(rheumatoid adj2 spondy*).mp,kw.	644	Advanced
23	bechterew*.mp,kw.	846	Advanced
24	marie-strumpell*.mp,kw.	39	Advanced
25	axial SpA.mp,kw.	790	Advanced
26	AxSpA.mp,kw.	673	Advanced
27	ASAS.mp,kw.	1792	Advanced
28	ASDAS.mp,kw.	704	Advanced
29	SASSS.mp,kw.	46	Advanced
30	mSASSS.mp,kw.	390	Advanced
31	m-SASSS.mp,kw.	13	Advanced
32	BASRI.mp,kw.	201	Advanced
33	BASDAI.mp,kw.	2592	Advanced
34	BASFI.mp,kw.	1604	Advanced
35	BASMI.mp,kw.	626	Advanced
36	BAS-G.mp,kw.	115	Advanced
37	ASQoL.mp,kw.	286	Advanced
38	or/1-37	35962	Advanced
39	exp "smoking and smoking related phenomena"/	264558	Advanced
40	exp "tobacco use"/	253119	Advanced
41	tobacco consumption/	946	Advanced
42	exp smoking/	250395	Advanced
43	cigarette smoke/	9828	Advanced
44	tobacco smoke/	10963	Advanced
45	tobacco dependence/	15827	Advanced
46	smoking cessation/	44790	Advanced
47	tobacco/	39069	Advanced
48	nicotine/	40537	Advanced
49	tobacco*.mp,kw.	119174	Advanced
50	smoking.mp,kw.	359480	Advanced
51	smoke??.mp,kw.	148847	Advanced
52	cigar*.mp,kw.	98380	Advanced
53	nicotine*.mp,kw.	56621	Advanced
54	or/39-53	465845	Advanced
55	38 and 54	737	Advanced
56	(exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)	5933265	Advanced
57	55 not 56	736	Advanced
58	limit 57 to (english or turkish)	708	Advanced

3. Epub and Medline Search

Database: Epub Ahead of Print and In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) June 20, 2016
Date searched: June 21, 2016
Topic: Is smoking associated with radiographic damage in axial spondylorthritis?

Epub Ahead of Print and In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) June 20, 2016

#	Searches	Results	Type
1	spondyl?arth*.mp,kw.	638	Advanced
2	spondyl?-arth*.mp,kw.	5	Advanced
3	(anky* adj2 spondy*).mp,kw.	1034	Advanced
4	(anky* adj2 spin*).mp,kw.	55	Advanced
5	(anky* adj2 verteb*).mp,kw.	10	Advanced
6	(anky* adj2 axial*).mp,kw.	17	Advanced
7	(anky* adj2 sacro*).mp,kw.	13	Advanced
8	(anky* adj2 lumbar*).mp,kw.	3	Advanced
9	(anky* adj2 pelvi*).mp,kw.	2	Advanced
10	(spondy* adj2 spin*).mp,kw.	176	Advanced
11	(spondy* adj2 verteb*).mp,kw.	44	Advanced
12	(spondy* adj2 axial*).mp,kw.	153	Advanced
13	(spondy* adj2 sacro*).mp,kw.	28	Advanced
14	(spondy* adj2 lumbar*).mp,kw.	206	Advanced
15	(spondy* adj2 pelvi*).mp,kw.	3	Advanced
16	(rheumatoid adj2 spondy*).mp,kw.	35	Advanced
17	bechterew*.mp,kw.	6	Advanced
18	marie-strumpell*.mp,kw.	1	Advanced
19	axial SpA.mp,kw.	41	Advanced
20	AxSpA.mp,kw.	62	Advanced
21	ASAS.mp,kw.	104	Advanced
22	ASDAS.mp,kw.	35	Advanced
23	SASSS.mp,kw.	3	Advanced
24	mSASSS.mp,kw.	20	Advanced
25	m-SASSS.mp,kw.	0	Advanced
26	BASRI.mp,kw.	8	Advanced
27	BASDAI.mp,kw.	117	Advanced
28	BASFI.mp,kw.	73	Advanced
29	BASMI.mp,kw.	28	Advanced
30	BAS-G.mp,kw.	7	Advanced
31	ASQoL.mp,kw.	18	Advanced
32	or/1-31	1827	Advanced
33	smoking.mp,kw.	17509	Advanced
34	smoke??.mp,kw.	10131	Advanced
35	cigar*.mp,kw.	5190	Advanced
36	nicotine*.mp,kw.	2876	Advanced
37	tobacco*.mp,kw.	9966	Advanced
38	or/33-37	29215	Advanced
39	32 and 38	35	Advanced