

Association of Smoking and Obesity on the Risk of Developing Primary Sjögren Syndrome: A Population-based Cohort Study

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ABSTRACT. Objective. To explore the role of smoking and obesity in primary Sjögren syndrome (pSS).

Methods. Olmsted County (Minnesota, USA) residents ($n = 106$) diagnosed with pSS from 2000 to 2015 were compared to 3 controls without pSS and matched for age and sex who were randomly selected from Olmsted County residents.

Results. Current smokers were less likely to be pSS cases (OR 0.34, 95% CI 0.14–0.85), while there was no association between former smoking and case/control status (OR 1.27, 95% CI 0.80–2.03) compared to never smokers. Smoking status was not associated with antinuclear antibody, anti-SSA, anti-SSB, or rheumatoid factor positivity ($p > 0.05$). OR for obesity was 0.79 (95% CI 0.48–1.30).

Conclusion. In this population-based study, current smoking was inversely associated with case/control status, while body mass index lacked any association. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.180481)

Key Indexing Terms:

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Primary Sjögren syndrome (pSS) is a multisystem autoimmune disease characterized by inflammatory infiltrate and progressive dysfunction of exocrine glands, especially the lachrymal and salivary glands^{1,2,3,4}. Smoking is considered a risk factor for the development of several rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)^{5,6}, although it has been shown to be inversely associated with ulcerative colitis and sarcoidosis^{7,8}. There are a few studies that suggest that smoking may not be related to an increased pSS risk^{9,10,11,12}.

Previous evidence showed that obesity may have a role in some autoimmune conditions and chronic systemic inflammation, including psoriasis, RA, and sarcoidosis^{8,13,14,15}. The role of body mass index (BMI) has heretofore not been investigated as a potential risk factor for pSS, to our knowledge.

To examine the relationship among smoking, BMI and pSS, we used data from a population-based incident cohort of patients with pSS with individually matched comparators from the same population.

MATERIALS AND METHODS

Case identification and ascertainment. This retrospective, population-based study used a previously identified cohort of patients with incident pSS among residents of Olmsted County, Minnesota, USA^{1,2}. All patients were included who received a definite diagnosis of pSS in the opinion of the evaluating rheumatologists between January 1, 2000, and December 31, 2015. The date of first pSS diagnosis was collected. Each of the cases was matched to 3 comparators from among Olmsted County residents of the same age and sex but without pSS and indexed to the date of pSS diagnosis.

The information was extracted using the resources of the Research Epidemiology Project, a medical records linkage system that allows ready access to complete (inpatient and outpatient) records from all healthcare

providers from the local population¹⁶. This system ensures virtually complete clinical information on all clinically recognized cases of pSS in Olmsted County residents (both cases and controls). For controls, the medical files were manually reviewed to confirm their smoking status and to verify that they did not have pSS.

In Olmsted County, smoking history is routinely obtained in the medical history questionnaire completed by patients prior to appointments. Data on smoking status were collected for patients and controls 1 year prior to index date and at index date. The medical records of cases and controls were reviewed for body weight and height to calculate BMI, closest to the index date (± 1 yr). Disease activity was retrospectively collected using European League Against Rheumatism SS Disease Activity Index outcome measures^{17,18}. The study was approved by the institutional review boards of the Mayo Clinic (16-002401) and the Olmsted Medical Center (010-OMC-16).

Statistical analyses. Data were normally distributed and descriptive statistics [means (SD), etc.] were used to summarize the data for cases and controls. Statistical procedures included chi-square test for binary variables and Student t test for continuous variables.

Conditional logistic regression models were used to calculate OR. For

the smoking analysis, OR were calculated for the 3-group comparison of the risk of pSS between current, former, and never smokers, with never smokers as the reference group. A p value of < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

Smoking and pSS. There were 106 incident cases of pSS and 318 controls. Baseline characteristics of cases and controls are described in Table 1.

The proportion of current smokers was lower and the proportion of former smokers higher in patients than in comparators, respectively, while the proportion of never smokers was the same in the 2 groups. One year prior to diagnosis, the proportions of current, former, and never smokers in cases and controls were about the same (Table 1).

The OR of pSS comparing current smokers with never smokers was 0.34 (95% CI 0.14–0.85, $p < 0.021$; Table 2).

Table 1. Epidemiological features of subjects with incident primary Sjögren syndrome (pSS) diagnosed in Olmsted County, Minnesota, USA, from 2000 to 2015, and age- and sex-matched controls without pSS.

Baseline Characteristics	Cases, n = 106	Controls, n = 318	p
Age, yrs, mean (SD)	59.7 (15.8)	59.7 (15.7)	> 0.999
Sex, female	88 (83)	264 (83)	> 0.999
Ocular symptoms	95/106 (90)	—	
Oral symptoms	89/106 (84)	—	
Antinuclear antibody positivity	77/104 (74)	—	
SSA (anti-La) positivity	78/101 (77)	—	
SSB (anti-Ro) positivity	61/100 (61)	—	
Rheumatoid factor positivity	50/90 (56)	—	
Hypergammaglobulinemia present	42/85 (49)	—	
Abnormal ocular staining [†]	10/15 (67)	—	
Schirmer's test $\leq 5/5$ min	7/9 (78)	—	
Abnormal salivary scintigraphy or parotid sialography	7/9 (78)	—	
Unstimulated salivary flow ≤ 0.1 ml/min	1/1 (100)	—	
Histopathology positivity [§]	9/14 (64)	—	
Met AECG criteria ^{††}	19 (18)	—	
Met 2012 ACR criteria ^{††}	18 (17)	—	
ESSDAI score			
Low disease activity (≤ 5)	42 (70)	—	
Moderate disease activity (5–13)	13 (22)	—	
High disease activity (≥ 14)	5 (8)	—	
Smoking status at index date*			0.012
Never smoker	49 (46)	140 (45)	
Former smoker	51 (48)	117 (38)	
Current smoker	6 (6)	51 (17)	
Smoking status 1 year prior to index date*			0.005
Never smoker	48 (46)	138 (45)	
Former smoker	52 (50)	116 (38)	
Current smoker	5 (5)	51 (17)	
BMI at index date, kg/m ² **, mean (SD)	27.9 (7.2)	29.2 (7.4)	0.062
Obesity (BMI ≥ 30 kg/m ²) at index date**	33 (32)	113 (37)	0.318

Values are the number/total number (%) unless otherwise indicated. [†] Van Bijsterveld score ≥ 4 or Rose Bengal test. [§] According to the report of the revising pathologist. ^{††} A minority of the patients fulfilled AECG (18%) and ACR (17%) classification criteria because the requisite tests were not performed, not because they were negative. * Among cases, smoking status at date of diagnosis and 1 year prior to diagnosis date was available in all (100%) and in 105 (99%) of subjects, respectively, and among controls in 308 (97%) and 305 (96%) of subjects, respectively. ** BMI within 1 year before to 1 year after date of diagnosis was available for 104 cases (98%) and 304 controls (96%). AECG: American-European Consensus Group; ACR: American College of Rheumatology; ESSDAI: European League Against Rheumatism SS Disease Activity Index; BMI: body mass index.

Table 2. OR for smoking, BMI, and obesity, and risk of primary Sjögren syndrome.

Variables	OR	95% CI	p
Smoking status at index date			
Current smoker (vs never smoker)	0.34	0.14–0.85	0.021
Former smoker (vs never smoker)	1.27	0.80–2.03	0.320
BMI at index date, kg/m ²	0.97	0.94–1.01	0.090
Obesity (BMI ≥ 30 kg/m ²) at index date	0.79	0.48–1.30	0.350

The reported OR are calculated by conditional logistic regression stratified by age- and sex-matched pair. BMI: body mass index.

The OR of pSS was not significantly different between former and never smokers (OR 1.27; 95% CI 0.80–2.03).

Among patients, 65% of ever smokers (current and former smokers combined) were antinuclear antibody (ANA)–positive compared with 83% of never smokers ($p = 0.06$), 72% of ever smokers were SSA-positive compared with 83% of never smokers ($p = 0.16$), 62% of ever smokers were SSB-positive compared with 60% of never smokers ($p = 0.78$), and 56% of ever smokers were rheumatoid factor (RF)–positive compared with 55% of never smokers ($p = 0.92$).

Obesity, BMI, and pSS. Mean BMI and proportion of obesity in patients and comparators were not statistically different between patients and comparators (Table 1). The OR of pSS comparing obese with nonobese subjects was 0.79 (95% CI 0.48–1.30; Table 2). The OR of pSS for BMI analyzed as a continuous variable approached statistical significance (OR 0.97; 95% CI 0.94–1.01).

DISCUSSION

In this population-based incident cohort of Olmsted County (USA) residents, an inverse association was observed between current smoking status and pSS. The results are consistent with previous preliminary referral-based cohort studies of smoking in pSS^{9,10,11,12}. In addition, this is the first study analyzing the relationship between BMI, obesity, and pSS in a population-based setting, showing that there was no association between BMI and pSS.

Although epidemiological evidence indicates smoking as a risk factor for the development of seropositive RA, and for the development of anti-dsDNA autoantibodies in SLE^{5,6}, it is still unclear why current smokers have a lower risk of pSS. In our population-based study, results regarding smoking are consistent with the previous nested case-control or mono-centric cohort observations. Two case-cohort studies showed that current smoking was associated with a reduced risk of subsequent diagnosis of pSS^{11,12}; in one of them, duration of smoking was inversely correlated with pSS¹². In the other, to be a former smoker was associated with an increased risk of pSS¹¹. Indeed, pSS is a slowly evolving disease, and patients could quit smoking when they experience the first early symptoms of pSS, such as dry mouth or dry cough, years before the diagnosis is made. Hence, as for other retro-

spective studies, the potential for reverse causality between current smoking and onset of symptoms may not be completely excluded.

A debatable effect of smoking on antibody production has been reported in pSS. A previous cross-sectional, case-control study showed an association between ANA positivity and smoking in patients with pSS¹⁰. Further, 2 studies demonstrated that anti-SSA and anti-SSB are negatively associated with smoking^{9,12}. In contrast, our findings did not demonstrate an association between previous or current smoking status and ANA, anti-SSA, anti-SSB, and RF positivity, paralleling the results of the only other population-based pSS study on this topic¹¹. Although the selection criteria for patients with pSS were different from those of our current study (fulfillment of the American-European Consensus Group criteria vs physician-diagnosed pSS, respectively), the percentage of seropositivity of each autoantibody was similar. In the setting of a referral center dedicated to the disease, a patient with suspected pSS will usually undergo more comprehensive evaluation and diagnostic testing, including invasive procedures that aid in establishing whether the patient fulfills classification criteria — tools developed specifically for research purposes. In a community setting, physicians do not generally use classification criteria to diagnose the disease; in general, they order invasive tests, which nonetheless have important clinical value (such as gland biopsy), only if the results would change their clinical decisions. The approach of this study reflects the actual number of patients who are diagnosed with pSS in clinical practice. There is no gold standard to define a complex disease such as pSS, and the analysis of physician-diagnosed cases can be of help in quantifying the real burden of the disease in our society.

To the best of our knowledge, this is the first population-based study to explore the relationship between BMI and pSS. The mechanisms by which obesity may lead to the development of systemic rheumatic diseases are unknown, but it represents a potentially modifiable risk factor in predisposed individuals^{8,13,14,15}. In contrast to some other autoimmune diseases, no association was found between obesity or BMI and pSS. The reasons for this are speculative, possibly due to a lower level of systemic inflammation of patients with pSS compared to other systemic rheumatic diseases. The main strength of our study is that it is a population-based study of a well-defined region of the United States with complete case ascertainment and medical record availability. Moreover, our results reflect a real-life setting of patients with a physician-based diagnosis of pSS, making them relevant for routine patient care.

The limitations are those linked to the retrospective design of the study. Data were not always systematically obtained; in particular, it was not possible to perform a precise quantification of current and previous smoking status (i.e., pack/year) and to analyze the temporality between current smoking and

onset of pSS symptoms in all the subjects, precluding more detailed analysis. Nonetheless, smoking status and BMI were available for almost all cases and controls.

Current smoking status was inversely associated with pSS, meaning current smokers were less likely to have pSS. The mechanism underlying this association is unknown. Conversely, BMI and obesity lack any association with pSS.

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