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Association of smoking and obesity on the risk of developing primary Sjögren's Syndrome: A population-based cohort study

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Abstract

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

Methods: One-hundred-six Olmsted-County residents diagnosed with pSS during 2000–2015 were compared to 3 age-/sex-matched controls without pSS randomly selected from Olmsted-County residents.

Results: Current smokers were less likely to be pSS cases (OR0.34;95%CI:0.14,0.85), while there was no association between former smoking and case/control status (OR1.27;95%CI: 0.80,2.03) compared to never smokers. Smoking status was not associated with ANA, anti-SSA, anti-SSB or RF 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 BMI lacked any association.

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Keywords

Sjögren syndrome; obesity; smoking; epidemiology

INTRODUCTION

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

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

To examine the relationship between 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.

METHODS

Case Identification and Ascertainment

This retrospective, population-based study utilized a previously identified cohort of patients with incident pSS among Olmsted County, Minnesota residents (1, 2). All patients who received a definite diagnosis of pSS in the opinion of the evaluating rheumatologists, between January 1, 2000, and December 31, 2015, were included. The date of first pSS diagnosis was collected. Each of the cases was matched to 3 comparators from Olmsted County residents of the same age and sex 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 heath care providers from the local population (16). 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 of controls 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 body

mass index (BMI), closest to the index date (±1 year). Disease activity was retrospectively collected using European League Against Rheumatism (EULAR) SS outcome measures-the Disease Activity Index (ESSDAI) (17, 18). The study was approved by the institutional review boards of Mayo Clinic (16–002401) and 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-squared test for binary variables and Student T test for continuous variables.

Conditional logistic regression models were used to calculate odds ratios (OR). For the smoking analysis, ORs 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 less than 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Smoking and pSS

One-hundred-six incident cases of pSS and 318 controls were identified. Baseline characteristics of cases and controls are described in Table 1.

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

The OR of pSS comparing current smokers with never smokers was 0.34 (95% confidence interval (CI):0.14,0.85;p<0.05) (Table 2). The odds 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 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 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). OR of pSS comparing obese with nonobese subjects was 0.79 (95%CI:0.48,1.30) (Table 2). OR of pSS for BMI analyzed as a continuous variable approached statistical significance (OR0.97; 95%CI:0.94,1.01).

DISCUSSION

In this population-based incident cohort of Olmsted County (U.S.), an inverse association between current smoking status and pSS was observed. The results are consistent with previous preliminary referral-based cohort studies of smoking in pSS (9–12). 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 epidemiologic evidence indicate smoking as a risk factor for the development of seropositive rheumatoid arthritis, and for the development anti-double strand-DNA autoantibodies lupus (5, 6), it still is 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 monocentric cohort observations. Two case-cohort studies showed 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 pSS (12), in the other to be a former smoker associated with an increased risk of pSS (11). Indeed, pSS is a slow 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 retrospective studies, the potential for reverse causality between current smoking and onset of symptoms may not be completely excluded

A controversial effect of smoking on the antibody production has been reported in pSS. A previous cross-sectional, case-control study showed an association between ANA positivity and smoking in pSS patients (10). Furthermore, two studies demonstrated that anti-SSA and anti-SSB are negatively associated with smoking (9) (12). In contrast, our findings from 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 topic (11). Although the selection criteria for pSS patients was different from those of the current study (fulfillment of the AECG criteria *versus* 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 which aid for instance in establishing if 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, and in general order invasive tests, which have nonetheless important clinical value, such as gland biopsy, only if their 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 we believe that the analysis of physician-diagnosed cases can be of help to quantify 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, 13–15). 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 pSS patients compared to other systemic rheumatic diseases. The main strength of this study is that it is a population-based study of a well-defined region of the US 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, which are relevant for routine patient care.

The limitations are those linked to the retrospective nature 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 almost all both cases and controls.

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

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Table 1.

Epidemiological Features of subjects with incident primary Sjögren's Syndrome diagnosed in Olmsted County, Minnesota from 2000 to 2015, and age- and sex-matched controls without Sjögren's Syndrome

Baseline Characteristic	Cases (N=106)	Controls (N=318)	p value
Age, years, 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 ≤5/5 minutes	7/9 (78%)	-	
Abnormal salivary scintigraphy or parotid sialography	7/9 (78%)	-	
Unstimulated salivary flow ≤0.1 ml/minute	1/1 (100%)	-	
Histopathology positivity $	9/14 (64%)	-	
Met AECG criteria, no. (%) ††	19 (18%)	-	
Met 2012 ACR criteria, no. (%) ††	18 (17%)	-	
ESSDAI score, no. (%)			
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 one 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/m2) at index date **	33 (32%)	113 (37%)	0.318

Values are the number/total number (%) unless indicated otherwise.

Abbreviations: AECG=American–European Consensus Group; ACR=American College of Rheumatology; ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; BMI=Body mass index; SD=standard deviation.

$ According to the report of the revising pathologist

† Van Bijsterveld score ≥4 or Rose Bengal test.

[††] A minority of the patients fulfilled AECG (18%) and ACR (17%) classification criteria, since the requisite tests were not performed, not because they were negative.

[*] Among cases, smoking status at date of diagnosis and one year prior to diagnosis date was available in all (100%) and in 105 (99%) subjects respectively, and among controls in 308 (97%) and 305 (96%) subjects, respectively.

[**] BMI within 1 year before to 1 year after date of diagnosis was available for 104 cases (98%) and 304 controls (96%).

Table 2.

Odds ratios for smoking, body mass index and obesity and risk of primary Sjögren's Syndrome

Variables	Odds Ratio	95% Confidence of Interval	p value
Smoking status at index date			
Current smoker (*versus* never smoker)	0.34	0.14, 0.85	**0.021**
Former smoker (*versus* 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 odds ratios are calculated by conditional logistic regression stratified by age- and sex-matched pair.

Abbreviations: BMI=Body mass index.