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Associations Between Smoking and Primary Sjögren Syndrome Classification Using the Sjögren's International Collaborative Clinical Alliance Cohort

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Objective. The objective of this study was to examine the association of smoking with Primary Sjögren syndrome (pSS) classification and pSS diagnostic test results. We hypothesized that past and current smokers would have lower odds of being classified as having Sjögren syndrome (SS) and lower odds of having abnormal individual SS diagnostic test results compared with nonsmokers.

Methods. Participants with suspected or established pSS were enrolled into the Sjögren's International Collaborative Clinical Alliance (SICCA) registry and had oral, ocular, and rheumatologic examinations performed; blood and saliva samples collected; and labial salivary gland biopsy examinations performed; they also completed questionnaires at baseline. Logistic regression was used to determine whether smoking status was associated with pSS classification and individual pSS diagnostic test results.

Results. A total of 3514 participants were enrolled in SICCA. A total of 1541 (52.9%) met classification criteria for pSS. Compared with never smokers, current smokers had reduced odds of being classified as having pSS, reduced odds of having a focus score ≥ 1 and serologic positivity for anti-SSA/anti-SSB antibodies, and lower odds of having abnormal signs or test results of dry eye disease. Compared with never smokers, past smokers did not have a statistically significant reduction in odds of being classified as having pSS and of having abnormal individual pSS diagnostic test results.

Conclusion. Compared with never smokers, current smokers in the SICCA cohort had lower odds of being classified as having pSS, lower odds of exhibiting abnormal signs and test results for dry eye disease, and lower odds of having a labial salivary gland biopsy supportive of pSS classification. Such negative associations, however, do not suggest that current smoking is of any benefit with respect to pSS.

INTRODUCTION

Cigarette smoking is a common yet modifiable disease risk factor that has been associated with an increased probability of being diagnosed with or exacerbating a variety of autoimmune conditions. For example, smoking is associated with an increased risk of developing rheumatoid arthritis and ankylosing spondylitis and sustaining thromboses during the course of systemic lupus erythematosus (1–4). Autoimmune ocular inflammatory diseases may be impacted by smoking as well. Current smokers have higher odds of uveitis compared with never smokers (5,6).

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SIGNIFICANCE & INNOVATIONS

- This work uses the updated 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for Sjögren syndrome.
- Current everyday smokers had lower odds of being classified as having Sjögren syndrome compared with those who were past smokers or who had never smoked.
- Current everyday smokers had lower odds of having a labial salivary gland focus score > 1 and lower odds of exhibiting focal lymphocytic sialadenitis on histopathology compared with past and never smokers.

Primary Sjögren syndrome (pSS) is a systemic autoimmune disease that classically targets the lacrimal and salivary glands, leading to the hallmark findings of dry eye disease (DED) and salivary hypofunction. The pathogenesis of pSS involves predisposition by multiple genetic polymorphisms as well as the likely contribution of epigenetic and environmental factors (7,8). Information regarding the effect of specific environmental factors on pSS is lacking. A few previous studies have examined the association of smoking and pSS, and some have identified a negative relationship (9–11). Recently, Stone and colleagues (9) showed a negative association between smoking and pSS classification using the American-European Consensus Group 2002 criteria in 596 patients recruited from four sites in the United States. We sought to verify these findings using data from the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort, which included patients with pSS from multiple international sites, and using the most updated classification criteria for pSS accepted by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (12). Registrants in this cohort were derived from multiple global sites and underwent comprehensive protocol-driven evaluations, including a minor salivary gland biopsy with central histopathologic interpretation.

As a large international multicenter study, SICCA was devoted to better characterize pSS. The SICCA cohort was instrumental in developing the definitive classification criteria for pSS, which are accepted by both the ACR and EULAR (12). The 2016 ACR/EULAR criteria represented a breakthrough in the classification of pSS because they were not only driven by consensus but also supported by analysis involving a subset of participants from the SICCA registry data and from two other large cohorts (the Oklahoma Medical Research Foundation cohort, and the Paris-Sud Kremlin Bicêtre cohort).

Our objective was to examine associations of smoking status with Sjögren syndrome (SS) classification (and individual SS classification criteria) based on 2016 ACR/EULAR criteria as well as associations between smoking and histopathologic findings from labial salivary gland biopsies.

PATIENTS AND METHODS

Study design and population. The SICCA cohort represents a cross-sectional study of participants (with a subset followed longitudinally for a second visit) enrolled from nine international research sites. Participants (≥21 years of age) met at least one of the following inclusion criteria: 1) symptoms of dry eyes or dry mouth, 2) previous suspicion or diagnosis of pSS or secondary SS, 3) abnormal serology test results (positive anti-SSA/anti-SSB antibodies, positive antinuclear antibodies [ANA], or rheumatoid factor), 4) bilateral parotid gland enlargement in a clinical setting of SS, or 5) a recent increase in dental caries. At the baseline SICCA visit, participants completed an interview and questionnaires and underwent ocular, oral, and rheumatologic examinations and biospecimen collections, including labial salivary gland biopsy specimens. The ocular examination included slit lamp examination, Schirmer I testing, tear breakup time (TBUT), and determination of the Ocular Staining Score (OSS), a previously described quantitative grading system (12–14),

For this study, we included all SICCA participants with a complete set of cross-sectional baseline data enabling them to be classified as having or not having SS by using the 2016 ACR/EULAR criteria.

Variables and measures. Smoking status was assessed by using a self-administered questionnaire that included questions on whether participants were current, past, or never smokers. If participants were current smokers, they were queried as to the number of cigarettes per day and for how many years they had been smoking; if they were past smokers, the age they stopped smoking. Past smokers were those who had ever smoked cigarettes but were not currently smoking. Potential confounders of the association between smoking and SS were adjusted in multivariable models. These variables included sex, age, country of residence, and patient-reported health, which was assessed by using a general physical health-related question ("In general, would you say your health is:") with responses being "excellent," "very good," "good," "fair," and "poor." Responses were dichotomized as healthy ("excellent," "very good," and "good") and not healthy ("fair" and "poor"). As a sensitivity analysis, we controlled for ethnicity (White or not) in our models and analyzed results for men and women separately. As an additional analysis, an interaction term between smoking and country of residence was included in multivariable models to detect any interaction that may exist between country of residence and smoking habits.

Statistical analyses. Logistic regression was performed to determine whether smoking status was associated with each of the following SS-associated outcomes: 1) SS classification, 2) labial salivary gland histopathology of focal lymphocytic

sialadenitis (FLS) with a measurable focus score (evaluated as ≥1 or not), 3) serologic positivity for anti-SSA/anti-SSB antibodies, or 4) exhibiting each of the following dry eye ocular signs/test results: a) OSS ≥5 in at least one eye, b) Schirmer I test result of ≤5 mm in 5 minutes in at least one eye, and c) TBUT <10 seconds; and having dry eye symptoms (participant-reported symptoms of eyes feeling dry, of eyes burning, of eyes feeling gritty, or of eyes experiencing light sensitivity [with responses dichotomized as "yes" and "no" depending on the presence or absence of such symptoms]).

Additionally, we assessed the effect of smoking status on specific histopathologic findings in the labial salivary gland biopsies compared to "within normal limits" using multinomial logistic regression to estimate the relative risk ratio. Histopathologic features included 1) focal lymphocytic sialadenitis, 2) focal/sclerosing lymphocytic sialadenitis, 3) nonspecific chronic inflammation, 4) sclerosing chronic sialadenitis, and 5) granulomatous inflammation. We also assessed the association between smoking status and unstimulated salivary flow rate.

Finally, for those who ever smoked, we examined the association between the age at which one stopped smoking and being classified as having pSS.

All statistical analyses were performed by using Stata/SE 15.0 software (StataCorp LLC). Methods and adjustment variables were the same for each analysis.

RESULTS

Table 1 shows demographic characteristics of the SICCA cohort based on smoking status. Among 3514 participants in the SICCA registry, 125 were excluded from analysis for missing pSS status, smoking status, or both (20 did not answer the questionnaire regarding smoking status, and 105 participants [3.3%] could not be classified using the ACR/EULAR pSS criteria because of a missing variable). Women made up 90.6% (n = 3185) of this study cohort. Fewer than half of the participants (44.0%; 1538) were classified as having pSS by using the ACR/EULAR criteria. Among those who met the ACR/EULAR pSS classification, most participants (58.6%) had never smoked, whereas 31.5% were past smokers and 9.6% were current smokers. Among past smokers, 96.2% (1045) had a gap of a year or more since they stopped smoking.

Table 2 shows results of multivariable analyses comparing past and present smokers with never smokers on pSS criteria and diagnostic tests. Compared with never smokers, current smokers had reduced odds of pSS classification (odds ratio [OR] = 0.39 [95% confidence interval (CI): 0.30-0.52], $P < 0.001$) as well as reduced odds of having an OSS ≥5 (OR = 0.61 [95% CI: 0.47-0.79], $P = 0.01$) and a Schirmer I test result of ≤5 mm per 5 minutes (OR = 0.68 [95% CI: 0.51-0.91], $P = 0.01$) (Table 2). Compared with never smokers, past smokers

TABLE 1. SICCA cohort demographics and smoking status

	Never smoker, n (%)	Past smoker, n (%)	Current smoker, n (%)
Classified as having SS (n = 1583)[a]	1022 (66.3)	439 (28.5)	77 (5)
Classified as not having SS (n = 1851)[a]	970 (52.2)	632 (34)	249 (13.4)
Sex			
Women	1916 (60.2)	974 (30.6)	295 (9.3)
Men	156 (50.5)	118 (38.2)	35 (11.3)
Race			
White	967 (47.9)	816 (40.5)	234 (11.6)
Other than White	1104 (74.9)	275 (18.7)	95 (6.4)
Age group[b]			
21-30 years	131 (66.5)	37 (18.8)	29 (14.7)
31-45 years	539 (67.1)	195 (24.3)	69 (8.6)
46-64 years	1029 (57.5)	569 (31.8)	193 (10.8)
65 years and older	372 (53.1)	291 (41.5)	38 (5.4)
Site			
Argentina	229 (52.9)	149 (34.4)	55 (12.7)
China	312 (93.7)	13 (3.9)	8 (2.4)
Denmark	220 (36.4)	245 (40.6)	139 (23.0)
India	149 (92.5)	10 (6.2)	2 (1.2)
Johns Hopkins (United States)	157 (51.5)	127 (41.6)	21 (6.9)
Japan	271 (73.6)	72 (19.6)	25 (6.8)
UCSF (United States)	406 (56.9)	277 (38.8)	31 (4.3)
United Kingdom	168 (54.0)	108 (34.7)	35 (11.3)
UPenn (United States)	160 (60.4)	91 (34.3)	14 (5.3)

Abbreviation: SICCA, Sjögren's International Collaborative Clinical Alliance; SS, Sjögren syndrome; UCSF, University of California, San Francisco; UPenn, University of Pennsylvania.
[a] One hundred twenty-five participants could not be classified by SS status, smoking status, or both.
[b] Twenty-two participants did not have age available.

TABLE 2. Multivariable analyses comparing past or present smokers with never smokers: SS criteria and ocular signs of keratoconjunctivitis sicca

Dependent variable	Independent variable (compared with never smoker)	Odds ratio	95% confidence interval	*P* value
Classified as having SS	Past smoker	0.90	0.77-1.06	0.18
	Current smoker	0.39	0.30-0.52	<0.001
Ocular staining score ≥ 5	Past smoker	0.99	0.85-1.17	0.99
	Current smoker	0.61	0.47-0.79	<0.001
Schirmer I test result of ≤5 mm/5 min	Past smoker	0.88	0.73-1.04	0.14
	Current smoker	0.68	0.51-0.91	0.01
TBUT <10 s	Past smoker	0.98	0.78-1.22	0.86
	Current smoker	0.73	0.53-1.01	0.06
Labial salivary gland focus score > 1	Past smoker	0.97	0.83-1.14	0.73
	Current smoker	0.28	0.20-0.38	<0.001
Positive anti-SSA/anti-SSB antibodies	Past smoker	0.87	0.73-1.03	0.23
	Current smoker	0.59	0.44-0.79	<0.001

Note: Covariates adjusted for sex, age, country of residence, and patient-reported health.
Abbreviations: SS, Sjögren syndrome; TBUT, tear breakup time.

did not have a statistically significant reduction in odds of pSS classification and odds of having abnormal individual pSS diagnostic test results.

We also found that compared with never smokers, those who were current smokers had reduced odds of a focus score ≥ 1 in their labial gland biopsy (OR = 0.28 [95% CI: 0.20-0.38], $P < 0.001$). Those who had a past history of smoking compared with those who never smoked did not have any statistically significant association with respect to FLS with a focus score ≥ 1 (OR = 0.97 [95% CI: 0.83-1.14], $P = 0.73$). On a more granular level, when we examined the mean focus score between the three smoking status groups, we found that current smokers had a lower mean focus score (1.42, SD 2.42, range 0.1-11.6) compared with past smokers (mean focus score 2.39, SD 2.43, range 0.1-12.4) and never smokers (mean focus score 2.53, SD 2.29, range 0.1-13.5), and this difference was significant ($P < 0.001$).

We examined associations between smoking and the labial salivary gland histopathology (Table 3) and the number of histopathologic subtypes in labial salivary gland biopsy specimens in the SICCA cohort (Supplementary Table 1). We found that compared with never smokers, current smokers had a reduced OR of having focal lymphocytic sialadenitis, focal/sclerosing lymphocytic sialadenitis, and nonspecific chronic inflammation. Additionally, past smokers, compared with never smokers, had a reduced OR of having focal lymphocytic sialadenitis (Table 3). For the association between smoking status and unstimulated salivary flow rate (≤0.1 ml/min), we found that compared with never smokers, current and past smokers did not exhibit statistically significant odds of having an unstimulated salivary flow rate of less than 0.5 (OR = 0.97 [95% CI: 0.82-1.15], $P = 0.70$). The proportion of participants with an unstimulated whole salivary flow rate of less than 0.5 were similar across smoking status.

Among those who had stopped smoking, we found that for every additional year of smoking in the past, there was a slight, but statistically nonsignificant, decrease in the odds of being classified as having pSS (OR = 0.99 [95% CI: 0.98-1.00], $P = 0.06$). We also examined how pack-year history was associated with the focus score. For each additional pack-year of smoking, there was a 1.4% decrease in the relative risk of having a focus score ≥ 1 (95% CI: 0.58%-1.7%, $P = 0.001$).

TABLE 3. Multivariable logistic regression examining labial salivary gland histopathology designation in past or current smokers compared with never smokers

Dependent variable (biopsy histopathology)	Independent variable (compared with never smoker)	Odds ratio	95% confidence interval	*P* value
Focal lymphocytic sialadenitis	Past smoker	0.59	0.38-0.93	0.02
	Current smoker	0.25	0.14-0.43	<0.001
Focal/sclerosing lymphocytic sialadenitis	Past smoker	0.70	0.42-1.15	0.16
	Current smoker	0.26	0.13-0.53	<0.001
Nonspecific chronic inflammation	Past smoker	0.66	0.41-1.07	0.09
	Current smoker	0.53	0.29-0.96	0.04
Sclerosing chronic sialadenitis	Past smoker	0.71	0.42-1.19	0.19
	Current smoker	0.87	0.46-1.67	0.68

Note: There were only four granulomatous inflammation histopathologic subtypes, so the odds ratio was not calculable.

For the relationship between smoking status and serologic positivity for anti-SSA/anti-SSB antibodies, we found that compared with those who never smoked, current smokers had lower odds of having anti-SSA/anti-SSB antibodies (OR = 0.59 [95% CI: 0.44-0.79], $P = 0.001$). Compared with never smokers, having a past history of smoking did not exhibit a statistically significant association with anti-SSA/anti-SSB antibody status (OR = 0.87 [95% CI: 0.73-1.03], $P = 0.23$).

For the sensitivity analyses, results were similar when we controlled for ethnicity. In models in which we analyzed men and women separately, results where similar when we analyzed outcomes for women only, whereas the associations between current smoker status and pSS classification, OSS ≥5, Schirmer I test result of ≤5 mm per 5 minutes, and anti-SSA/anti-SSB antibody status became nonsignificant when we analyzed men only. However, 91% of the cohort were women. Adding the interaction between smoking and country did not change the associations with pSS criteria and diagnostic tests, except for the association between current smoker status and Schirmer I test result of ≤5 mm per 5 minutes, which became nonsignificant. The interaction between smoking and country was not significant in all analyses.

DISCUSSION

In this study of the SICCA cohort, we found that current smokers had lower odds of being classified as having pSS according to the ACR/EULAR criteria and lower odds of having high ocular surface staining, focal lymphocytic sialadenitis with a focus score > 1, and anti-SSA/anti-SSB antibodies compared with never smokers. Although some of these associations have been examined in earlier studies, they have not been studied with patients classified according to the ACR/EULAR criteria for pSS (9,10,15–17). We assessed whether such associations were similar using a large multicenter international cohort of patients classified as having or not having SS and using the updated and universally accepted ACR/EULAR diagnostic criteria. Indeed, compared with no smoking history, we found no statistically significant association between past smoking history and pSS classification or abnormally high OSS.

Although smoking has been associated with an increased risk for developing particular autoimmune diseases or a having worse disease course in some cases, this does not seem to apply to all diseases associated with autoimmunity. Interestingly, smoking can be associated with less severe or less frequent disease in some instances. In the case of ulcerative colitis, for example, smoking is associated with a less severe disease course and smoking cessation is associated with disease recurrence and more requirements for systemic immunosuppression (18–21). Current or active smokers have been demonstrated to have lower risk for developing Parkinson disease compared with those who do not smoke (22–24), Extracts from cigarette smoke have been shown to suppress dendritic cell–-mediated priming of T cells, and nicotine has been associated with a decrease in inflammatory cytokines (25,26). Indeed, nicotine is used as an alternative therapy in patients with ulcerative colitis, in which inflammation characterizes the intestinal mucosa (27,28). Reduction in inflammatory mediators is suggested to mediate such a response in ulcerative colitis (29), Additionally, smoking has been associated with a decreased risk for endometriosis in women (30). Interestingly, smoking may lower endogenous estrogen levels in women, as evidenced by reduced urinary estrogen excretion (31), This is intriguing because SS has an overwhelming propensity to develop in women (32).

Current smoking has been previously described in another SS cohort (which used the American-European Consensus Group pSS classification criteria) to be associated with reduced odds of pSS classification compared with never smoking (9). Reduced odds of having a focus score ≥ 1, which is supportive of SS classification, was found in current smokers compared with those with a past (but not current) smoking history (9). Thus, it is suggested that smoking may modulate inflammation SS with respect to xerostomia and, perhaps by extension, with respect to the lacrimal gland. Given that most participants in SICCA (90%) reported having a dry mouth, smoking could cause discomfort in those with dry mouth. Therefore, although there may be biologically plausible explanations for the negative associations we found, it is also possible that the discomfort that may be exacerbated by dry mouth in pSS explains this study's findings. This would also explain current smoking's negative association with some of the individual ACR/EULAR pSS classification criteria (including an abnormal focus score and positive serologic test results for anti-SSA/anti-SSB antibodies). However, our finding that current smoking was negatively associated with having focal lymphocytic sialadenitis with a focus score ≥ 1 may suggest that smoking could decrease inflammation. This was also reported by Manthorpe et al (33), who investigated the possibility that smoking could decrease inflammation in the labial salivary glands of patients diagnosed with SS using the Copenhagen classification system. They found that smoking was negatively associated with focal lymphocytic sialadenitis (focus score > 1) in a dose-dependent manner (10). Similarly, Olsson et al (11,16) found that a history of smoking (either current or past smoking) was negatively associated with focal lymphocytic sialadenitis and risk of subsequent diagnosis with pSS. Priori et al (17) noted a mild negative association between smoking status and being classified as having pSS, as diagnosed by the American-European Consensus Group (34), and found increased odds of pSS in prior smokers. Others have found that although current everyday smoking is positively associated with ANA titers, it is not associated with extraglandular manifestations of SS and SS-associated biomarkers, including anti-SSA/anti-SSB antibodies (15). Similar to Stone et al (9) and Manthorpe et al (10), we found in our SICCA cohort a negative

association between current smoking status and anti-SSA/anti-SSB antibodies.

In our cohort, the percentage of current smokers was higher in Denmark (23%) compared with China (2.4%) and Japan (6.8%). On the basis of data on smoking rates by country, China (24.7%) and Japan (22.15%) have slightly higher smoking rates than Denmark (17%) (35). However, these trends may apply particularly to men, and SS and the SICCA cohort have a preponderance of women. Looking at women only, the trend of smoking rates is similar to what we found in our cohort (Denmark [16.4%] > Japan [10.6%] and China [1.8%]) (35).

This study has some limitations. The results found herein may not be generalizable outside of this cohort. Entry into the SICCA cohort required an established pSS diagnosis (as assessed by a referring physician) or symptom(s) compatible with pSS; thus, this study may be a good representation of the mix of SS and non-SS sicca encountered in real-life settings. Another consideration is that because current smokers had lower odds of being classified as having pSS, most current smokers would be expected to exhibit fewer signs associated with pSS (such as DED) by definition. Selection bias may be present because most participants in this cohort were female, although SS, like many other systemic rheumatologic diseases, has a female predilection. Smoking can be associated with dry mouth, and this might have led to a selection bias for smokers being referred for entrance into the cohort (36–38). However, current everyday smokers were a small proportion of the overall participants. In examining associations between smoking and SS, it is important to identify colliders, or a common effect of both smoking and SS. Such a collider could be the presence of dry mouth or dry eyes because smoking may be associated with symptoms of dry mouth and dry eyes. Additionally, SS itself causes dry eyes and dry mouth by definition. However, in our modeling, we did not control for dry mouth or dry eye symptoms (which would have created a noncausal pathway and resulted in bias). Instead, in patients with SS, a dry mouth may make someone less likely to smoke because smoking itself may cause dry mouth. Thus, in such a case, smoking would act as a mediator between smoking and SS. Immortal time bias is another limitation that is inherent to a cohort that includes patients of a variety of ages. Thus, if most people tend to stop smoking after the age of 40, those participants who are younger than 40 could not have stopped smoking because they have not reached that particular age. Moreover, there may be bias introduced because of secular trends, in which those who are younger in the SICCA cohort are less likely to smoke because of changing secular ideas and turning away from smoking. Alternatively, it is possible that those who smoke may die younger and, thus, would not get referred into the SICCA cohort or be classified as having pSS. Thus, there could be a spurious effect that smoking has on SS.

Although current smoking may be associated negatively with being classified as having pSS (perhaps by its negative association with serologic testing and focus scores), smoking's well-known deleterious effects on overall health make cessation of cigarette smoking a worthy endeavor. However, smoking may have an impact on the inflammatory mediators that drive lymphocytic sialadenitis. Future studies that identify such inflammatory mediators may inform future therapeutic directives.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gonzales had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gebreegziabher, Oldenburg, Shiboski, Baer, Jordan, Rose-Nussbaumer, Bunya, Akpek, Criswell, Shiboski, Lietman, Gonzales.

Acquisition of data. Jordan, Criswell, Shiboski, Lietman, Baer, Akpek.

Analysis and interpretation of data. Gebreegziabher, Oldenburg, Shiboski, Jordan, Criswell, Shiboski, Lietman, Gonzales, Baer, Akpek, Rose-Nussbaumer, Bunya.

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