

Histopathologic Influences of Comorbid Smoking Status in Chronic Rhinosinusitis

American Journal of Rhinology & Allergy

2020, Vol. 34(6) 775–783

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DOI: 10.1177/1945892420929270

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Hannah N. Kuhar, MD¹ , Ashwin Ganti, BA² ,
Hannah J. Brown, BS², Paolo Gattuso, MD³, Ritu Ghai, MD³,
Mahboobeh Mahdavinia, MD, PhD⁴, Pete S. Batra, MD⁵, and
Bobby A. Tajudeen, MD⁵

Abstract

Background: Smoking status has been established as a known irritant of the upper and lower respiratory tracts, leading to inflammation throughout the respiratory system. Tobacco smoking is one comorbidity encountered among chronic rhinosinusitis (CRS) patients. The histopathologic features of CRS and comorbid smoking status have yet to be determined by structured histopathology and may have important implications on disease management.

Methods: Retrospective study of structured histopathology reports analyzing sinus tissue removed during functional endoscopic sinus surgery. Histopathology variables were compared among patients with CRS who were reported as never smokers, former smokers, or current smokers.

Results: A total of 285 CRS patients were included: 173 never smokers, 85 former smokers, and 27 current smokers. When compared with former smokers, current smokers demonstrated increased basement membrane thickening (88.9% vs 67.1%, $P < .020$). Compared with never smokers, former and current smokers collectively demonstrated increased hyperplastic changes (14.3% vs 6.9%, $P < .035$), increased squamous metaplasia (26.8% vs 17.3%, $P < .040$), and trends toward increased basement membrane thickening (72.3% vs 65.3%, $P < .124$) and increased fibrosis (47.3% vs 40.5%, $P < .154$).

Conclusion: Smoking status may influence histopathologic tissue-level changes in CRS disease. Interestingly, former and current smokers maintained few differences in histopathology. However, former and current smokers collectively demonstrated increased chronic inflammatory changes compared with never smokers. These findings suggest that the timing of smoking exposure has limited effect on the tissue level, rather exposure overall influences inflammatory change. These findings may have important implications on medical and surgical management of CRS disease and comorbid smoking status.

Keywords

chronic rhinosinusitis, smoking, histopathology, inflammation, endoscopic sinus surgery

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disease process characterized by sinonasal inflammation persisting for longer than 12 weeks.¹ Studies of structured histopathology reporting have led to the classification of CRS into phenotypes including CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Each of these phenotypes has distinct histopathologic features: CRSsNP is associated with increased neutrophilia, fibrosis, goblet cell hyperplasia, and mononuclear cell infiltration, whereas CRSwNP is associated with increased eosinophilia, edematous stroma with albumin deposition, and pseudocyst formation.²

¹Department of Otolaryngology—Head and Neck Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio

²Rush Medical College, Chicago, Illinois

³Department of Pathology, Rush University Medical Center, Chicago, Illinois

⁴Department of Immunology and Microbiology, Allergy/Immunology Section, Rush University Medical Center, Chicago, Illinois

⁵Rhinology and Skull Base Surgery, Department of Otorhinolaryngology—Head and Neck Surgery, Rush University Medical Center, Chicago, Illinois

Corresponding Author:

Bobby A. Tajudeen, Rhinology and Skull Base Surgery, Department of Otorhinolaryngology—Head and Neck Surgery, Rush University Medical Center, 1611 W. Harrison St., Suite 550 Chicago, IL 60612, USA.
Email: bobby_tajudeen@rush.edu

A common comorbidity associated with CRS is tobacco usage. Numerous prior studies have demonstrated correlations between exposure to cigarette smoke and the development of CRS: the Global Allergy and Asthma European Network (GA2 LEN) study conducted in 2011 demonstrated that an increased number of pack-years was associated with a higher odds ratio of CRS, while a study published in 2015 of over 37 000 patients in South Korea found that every year of active smoking increased CRS prevalence by 1.5%.^{3,4} In addition, a 2014 systematic review conducted by Hur et al. noted that a majority of studies reviewed identified a significant correlation between exposure to second-hand smoke and development of sinusitis.⁵

Studies have also sought to identify the pathophysiologic mechanisms by which smoking drives CRS. A study conducted in 2014 by Lee et al. demonstrated that chronic exposure to cigarette smoke promoted airway remodeling and nasal polyp formation in murine models.⁶ A more recent molecular study identified proinflammatory cytokines such as interleukin-8 (IL-8) and tumor necrosis factor- α (TNF- α) that are upregulated in the sinonasal polyps of smokers with CRSwNP.⁷

However, although studies have investigated alterations in inflammatory pathways, no study to date has analyzed the changes in structured histopathology that occur in CRS patients exposed to cigarette smoke. Thus, the purpose of this study is to compare histopathologic profiles between CRS patients who currently, formerly, and never smoked cigarettes. The findings of this study may provide insight into the mechanisms that drive disease pathogenesis in CRS patients exposed to cigarette smoke, which can in turn be utilized to tailor individualized management.⁸

Materials and Methods

A structured histopathology report consisting of 13 variables was utilized to analyze ethmoid sinus tissue removed during functional endoscopic sinus surgery (FESS; Table 1). This tissue was retrieved during the ethmoidectomy portion of the sinus surgery. Two pathologists dedicated to head and neck research, completed structured histopathology reports for a cohort of CRS patients undergoing FESS at Rush University Medical Center (RUMC) between June 2014 and January 2019. The pathologists were blinded to the purpose of the study. The study protocol was approved by the institutional review board at RUMC. Histopathologic variables assessed included the type of tissue (bone, respiratory mucosa, and mucoserous glands), degree of inflammation (mild or moderate), number of eosinophils per high power field (HPF; <5/HPF and 5+/HPF), neutrophil infiltrate (present or absent), basement

Table 1. Structured Histopathology Report.

Variables	
Tissue present	Respiratory mucosa Mucoserous glands Bone
Overall degree of inflammation	Mild Moderate
Eosinophil count per HPF	<5 5+
Neutrophil infiltrate	Presence Absence
Inflammatory predominance	Presence Absence
Basement membrane thickening	Presence Absence
Subepithelial edema	Presence Absence
Hyperplastic/papillary changes	Presence Absence
Mucosal ulceration	Presence Absence
Squamous metaplasia	Presence Absence
Fibrosis	Presence Absence
Charcot–Leyden crystals	Presence Absence
Eosinophil aggregates	Presence Absence

Abbreviation: HPF, high power field.

membrane thickening (present or absent), subepithelial edema (absent or present [focal, perivascular, or distortion of mucosal structure]), hyperplastic/papillary changes (present or absent), mucosal ulceration (present or absent), squamous metaplasia (present or absent), fibrosis (present or absent), Charcot–Leyden crystals (present or absent), and eosinophil aggregates (present or absent). The determination of presence or absence of features was made by pathologists upon examination of the biopsied tissue specimen. Papillary and hyperplastic changes are well established in head and neck pathology literature as manifestations of reactive, inflammatory processes at the tissue level.⁹ Hyperplastic changes refer to the presence of glandular hyperplasia, a histopathologic characteristic observed in the sinonasal mucosa of CRS disease. The hyperplastic changes may influence the ability of cilia of the sinonasal mucosa to effectively clear secretions.^{10,11} Hyperplastic changes can be found in other tissue sites among smokers. In Pulmonology literature, it has been posited that smoking irritants provoke hyperplastic changes involved in airway remodeling.¹² Notably, among chronic obstructive pulmonary disease patients, significant hyperplastic changes specifically of goblet cells takes place over long-

term exposure to cigarette smoke.¹³ In addition, reticular basement membrane thickening has been observed in the bronchial mucosa of smoking patients.¹⁴ Basement membrane thickening has also been well established as a characteristic histopathologic change in chronic disease of the sinonasal mucosa.¹⁰

Inclusion criteria for CRSsNP patient participation in this study were patient age 18 years and older, CRS patients in need of FESS due to medically recalcitrant disease, and CRS diagnosis based on 12 weeks of continuous sinonasal symptoms and positive findings for sinusitis on endoscopy and sinus computed tomography scan based on clinical guidelines.¹⁵ Two dedicated fellowship-trained rhinologists performed the surgeries at RUMC.

A retrospective chart review was performed to collate pertinent clinical information including demographics and comorbid conditions (including tobacco smoking status—never, former, or current). We defined former smoker as any patient who smoked tobacco in the past but does not currently smoke. Student's *t* test (2-tailed) was used for comparison of parametric data. One-way analysis of variance test was used to compare means between more than 2 independent groups. Nonparametric qualitative variables were cross classified into contingency tables and compared using χ^2 testing. All statistical analyses were performed using SPSS, version 24.0.0.0 (IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, New York). A *P* value of .05 or less was considered significant for all statistical analyses.

Results

A total of 285 CRS patients were included: 173 never smokers, 85 former smokers, and 27 current smokers. Average age of the cohort was 48.82 ± 16.46 years. The cohort included 47% male and 53.0% female patients. Table 2 summarizes demographics and comorbidities by smoking status. Average 22-item Sino-Nasal Outcome Test (SNOT-22) scores for never, former, and current smokers were 42.1 ± 23.4 , 41.3 ± 21.0 , and 38.3 ± 27.8 ,

Table 2. Demographic and Comorbidity Data by Smoking Status.

Variable	Never Smokers (n = 173)	Former Smokers (n = 85)	Current Smokers (n = 27)
Average age (years)	45.9 ± 17.0	55.9 ± 13.8	45.4 ± 14.3
Male, %	36.4	60.0	74.1
Female, %	63.6	40.0	25.9
Asthma, %	37.6	35.3	25.9
AERD, %	4.6	9.4	0.0
Allergic rhinitis, %	54.9	48.2	29.6

Abbreviations: AERD, Aspirin-exacerbated respiratory disease.

respectively ($P < .738$). Preoperative antibiotics and steroids were used on patients when appropriate to treat active purulent infection and severe edema from polypoid disease. Preoperative antibiotics and steroid use could not be controlled given the retrospective nature of this study; 33.3% of patients were on antibiotics preoperatively and 63.5% of patients were on steroids preoperatively. There was no statistically significant difference in the percentage of patients on preoperative antibiotics among never smokers, former smokers, and current smokers ($P < .453$). There was no statistically significant difference in the percentage of patients on preoperative steroids among never smokers, former smokers, and current smokers ($P < .950$).

Comparison of structured histopathology by patient smoking status was obtained (Table 3). There was only one statistically significant difference in the presence or absence of histopathology measures across the 3 patient cohorts of never smokers, former smokers, or current smokers (Table 3). Compared with never and former smokers, current smokers demonstrated only increased basement membrane thickening ($P < .049$; Table 3). Structured histopathology variables were then compared between former smokers and current smokers (Table 4). Compared with former smokers, current smokers demonstrated increased basement membrane thickening ($P < .020$) and a trend toward increased polypoid disease ($P < .073$; Table 4). Next, structured histopathology variables were examined among never smokers versus “ever” smokers (inclusive of former and current smokers; Table 5). Compared with never smokers, “ever” smokers (former and current smokers) demonstrated increased hyperplastic/papillary changes ($P < .035$), increased squamous metaplasia ($P < .040$), and trends toward increased basement membrane thickening ($P < .124$) and increased fibrosis (47.3% vs 40.5%, $P < .154$; Table 5). An image of hyperplastic/papillary changes can be found in the figure attached, which is an Haematoxylin and Eosin (H&E)-stained sample showing a fragment of papillary hyperplastic mucosa ($\times 400$; Figure 1). An image of basement membrane thickening can be found in the figure attached, which is an H&E-stained sample showing a fragment of mucosa with basement membrane thickening ($\times 400$; Figure 2).

When comparing never to former smokers, former smokers had increased hyperplastic/papillary changes ($P < .031$). When comparing former to ever smokers, there were no statistically significant differences in histopathologic variables. For results stratified by polypoid or nonpolypoid disease, see Tables 6 and 7. Notably, among CRSwNP patients, current smokers demonstrate an absence of eosinophils compared with former and never smokers ($P < .006$; Table 6).

Table 3. Association of Smoking Status and Histopathology in CRS—Never, Former, Current Smoker.

Variables	Never Smoker (N = 173; %)	Former Smoker (N = 85; %)	Current Smoker (N = 27; %)	P
CRSwNP	44.5	48.2	66.7	.100
CRSsNP	55.5	51.8	33.3	
Degree of inflammation				.641
Mild inflammation	44.5	50.6	44.4	
Moderate–severe inflammation	55.5	49.4	55.6	
Number of eosinophils per HPF				.463
<5	49.7	57.6	55.6	
5+	50.3	42.4	44.4	
Neutrophil infiltrate				.441
Present	26.0	32.9	33.3	
Absent	74.0	67.1	66.7	
Basement membrane thickening				.049
Present	65.3	67.1	88.9	
Absent	34.7	32.9	11.1	
Subepithelial edema				.441
Present	61.3	52.9	59.3	
Absent	38.7	47.1	40.7	
Hyperplastic/papillary changes				.103
Present	6.9	15.3	11.1	
Absent	93.1	84.7	88.9	
Mucosal ulceration				.571
Present	3.5	2.4	0.0	
Absent	96.5	97.6	100.0	
Squamous metaplasia				.102
Present	17.3	24.7	33.3	
Absent	82.7	75.3	66.7	
Fibrosis				.449
Present	40.5	45.9	51.9	
Absent	59.5	54.1	48.1	
Fungal				.998
Present	3.5	3.5	3.7	
Absent	96.5	96.5	96.3	
Charcot–Leyden crystals				.209
Present	3.5	7.1	0.0	
Absent	96.5	92.9	100.0	
Eosinophil aggregates				.221
Present	26.6	24.7	11.1	
Absent	73.4	75.3	88.9	

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; HPF, high power field. Bold values represent statistically significant values.

Discussion

Smoking exposure causes inflammation of the sinonasal mucosa that exacerbates CRS disease. The pathophysiologic mechanisms by which smoking promotes inflammation in CRS disease have been investigated. Toxic carcinogens contained in smoke are thought to cause reactive irritation of the sinonasal mucosa in CRS disease.^{4,16} Similar to damage caused by other types of toxic exposure such as radiation, long-standing inflammation secondary to smoking exposure causes tissue-level changes.¹⁷ Specifically, squamous

metaplastic changes that occur in the context of smoking exposure likely represent transformation of the nasal mucosa provoked by toxic damage to the nasopharynx and sinonasal cavity. Toxic injury by smoking to the bronchial mucosa initiates a process of metaplastic epithelial transformation. In response to toxic smoking exposure, basal cells of the pseudostratified epithelium reenter the cell cycle as hyperproliferative cells expressing squamous phenotype markers.¹⁸ As mucosal cells of the nasopharynx and bronchial tract undergo metaplastic transformation, squamous epithelial cytokeratin and cell adhesion molecule expression increase.¹⁸ In addition,

Table 4. Association of Smoking Status and Histopathology in CRS—Former Versus Current Smoker.

Variables	Former Smoker (N = 85; %)	Current Smoker (N = 27; %)	P
CRSwNP	48.2	66.7	.073
CRSsNP	51.8	33.3	
Degree of inflammation			.369
Mild inflammation	50.6	44.4	
Moderate–severe inflammation	49.4	55.6	
Number of eosinophils per HPF			.510
<5	57.6	55.6	
5+	42.4	44.4	
Neutrophil infiltrate			.573
Present	32.9	33.3	
Absent	67.1	66.7	
Basement membrane thickening			.020
Present	67.1	88.9	
Absent	32.9	11.1	
Subepithelial edema			.364
Present	52.9	59.3	
Absent	47.1	0.7	
Hyperplastic/papillary changes			.418
Present	15.3	11.1	
Absent	84.7	88.9	
Mucosal ulceration			.574
Present	2.4	0.0	
Absent	97.6	100.0	
Squamous metaplasia			.260
Present	24.7	33.3	
Absent	75.3	66.7	
Fibrosis			.374
Present	45.9	51.9	
Absent	54.1	48.1	
Fungal			.674
Present	3.5	3.7	
Absent	96.5	96.3	
Charcot–Leyden crystals			.183
Present	7.1	0.0	
Absent	92.9	100.0	
Eosinophil aggregates			.106
Present	24.7	11.1	
Absent	75.3	88.9	

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; HPF, high power field. Bold values represent statistically significant values.

chronic toxic injury of smoking exposure has been found to promote epithelial cell metaplasia, goblet cell hyperplasia, and edematous mucus secretion.¹⁶ Such tissue-level changes are thought to be associated with cytokines IL-4, IL-13, and growth factors.¹⁶ Another recent molecular study identified specific proinflammatory cytokines such as IL-8 and TNF- α that are upregulated in the sinonasal polyps of smokers with CRSwNP.⁷

This study suggests that smoking influences histopathologic tissue-level changes in CRS disease, independent of timing of smoking exposure. Current smokers demonstrated increased basement membrane thickening

compared with never and former smokers ($P < .049$; Table 3). Notably, current smokers showed increased inflammatory changes compared with former smokers, as current smokers maintained increased basement membrane thickening ($P < .020$) and a trend toward increased polypoid disease ($P < .073$; Table 4). Interestingly, among CRSwNP patients, current smokers demonstrated the absence of eosinophils compared with former and never smokers ($P < .006$; Table 6). While CRSwNP is typically associated with increased eosinophilia,² current smokers in the present patient cohort demonstrated markedly decreased eosinophilia compared with their smoking

Table 5. Association of Smoking Status and Histopathology in CRS—Never Versus Ever Smoker.

Variables	Never Smoker (N = 173; %)	Ever Smoker (N = 112; %)	P
CRSwNP	44.5	52.7	.110
CRSSNP	55.5	47.3	
Degree of inflammation			.261
Mild inflammation	44.5	49.1	
Moderate–severe inflammation	55.5	50.9	
Number of eosinophils per HPF			.134
<5	49.7	57.1	
5+	50.3	42.9	
Neutrophil infiltrate			.126
Present	26.0	33.0	
Absent	74.0	67.0	
Basement membrane thickening			.124
Present	65.3	72.3	
Absent	34.7	27.7	
Subepithelial edema			.155
Present	61.3	54.5	
Absent	38.7	45.5	
Hyperplastic/papillary changes			.035
Present	6.9	14.3	
Absent	93.1	85.7	
Mucosal ulceration			.327
Present	3.5	1.8	
Absent	96.5	98.2	
Squamous metaplasia			.040
Present	17.3	26.8	
Absent	82.7	73.2	
Fibrosis			.154
Present	40.5	47.3	
Absent	59.5	52.7	
Fungal			.602
Present	3.5	3.6	
Absent	96.5	96.4	
Charcot–Leyden crystals			.313
Present	3.5	5.4	
Absent	96.5	94.6	
Eosinophil aggregates			.199
Present	26.6	21.4	
Absent	73.4	78.6	

Abbreviations: CRS, chronic rhinosinusitis; CRSSNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; HPF, high power field. Bold values represent statistically significant values.

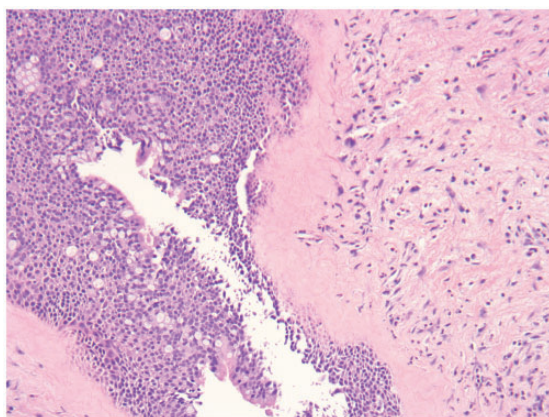


Figure 1. H&E-stained sample showing a fragment of papillary hyperplastic mucosa ($\times 400$).

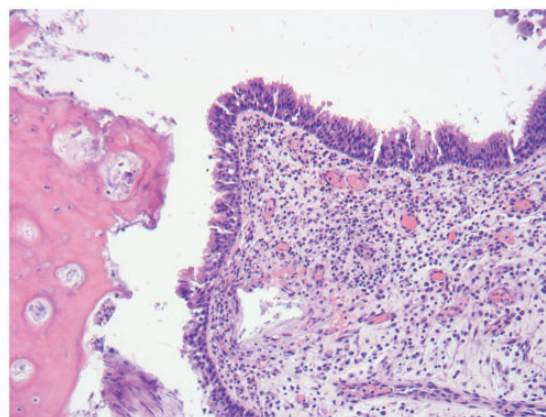


Figure 2. H&E-stained sample showing a fragment of mucosa with basement membrane thickening ($\times 400$).

Table 6. Association of Smoking Status and Histopathology in CRS—Never, Former, Current Smoker Among CRSwNP Patients.

Variables	Never Smoker (N = 77; %)	Former Smoker (N = 41; %)	Current Smoker (N = 18; %)	P
Degree of inflammation				.318
Mild inflammation	31.2	34.1	50.0	
Moderate–severe inflammation	68.8	65.9	50.0	
Number of eosinophils per HPF				.036
<5	24.7	29.3	55.6	
5+	75.3	70.7	44.4	
Neutrophil infiltrate				.175
Present	29.9	43.9	22.2	
Absent	70.1	56.1	77.8	
Basement membrane thickening				.403
Present	74.0	75.6	88.9	
Absent	26.0	24.4	11.1	
Subepithelial edema				.140
Present	70.1	75.6	50.0	
Absent	29.9	24.4	50.0	
Hyperplastic/papillary changes				.054
Present	10.4	26.8	11.1	
Absent	89.6	73.2	88.9	
Mucosal ulceration				.618
Present	5.2	4.9	0.0	
Absent	94.8	95.1	100.0	
Squamous metaplasia				.162
Present	19.5	34.1	33.3	
Absent	80.5	65.9	66.7	
Fibrosis				.845
Present	49.4	53.7	55.6	
Absent	50.6	46.3	44.4	
Fungal				.661
Present	3.9	2.4	0.0	
Absent	96.1	97.6	100.0	
Charcot–Leyden crystals				.168
Present	7.8	14.6	0.0	
Absent	92.2	85.4	100.0	
Eosinophil aggregates				.006
Present	44.2	46.3	5.6	
Absent	55.8	53.7	94.4	

Abbreviations: CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; HPF, high power field.

Bold values represent statistically significant values.

status counterparts. This finding suggests that chronic toxic injury of smoking exposure may cause tissue-level changes that influence the inflammatory milieu within established phenotypes of CRS disease.

Importantly, “ever” smokers (inclusive of former and current smokers) demonstrated the signs of chronic inflammatory responses through increased hyperplastic/papillary changes ($P < .035$), increased squamous metaplasia ($P < .040$), and trends toward increased basement membrane thickening (72.3% vs 65.3%, $P < .124$) and increased fibrosis (47.3% vs 40.5%, $P < .154$; Table 5). These findings suggest that tissue-level changes of the sinonasal mucosa occur secondary to smoking

independent of chronicity of smoking exposure. Although current smokers fare worse than former smokers, tissue-level changes persist among former smokers even after ending smoking exposure.

Several limitations to this study exist. As a retrospective study, we were unable to control for systemic steroids or inhaled corticosteroids. Steroids have been well established as an anti-inflammation treatment regimen for CRS.^{19–21} The established cutoff value for sinus tissue eosinophilia of “5/HPF” is a potential limitation of this study as studies have utilized different approaches to define eosinophilia in sinus tissue.^{8,22,23} Specific histopathologic characteristics of CRS disease, namely, the presence of eosinophil aggregates,

Table 7. Association of Smoking Status and Histopathology in CRS—Never, Former, Current Smoker Among CRSsNP Patients.

Variables	Never Smoker (N = 96; %)	Former Smoker (N = 44; %)	Current Smoker (N = 9; %)	P
Degree of inflammation				.165
Mild inflammation	55.2	65.9	33.3	
Moderate–severe inflammation	44.8	34.1	66.7	
Number of eosinophils per HPF				.098
<5	69.8	84.1	55.6	
5+	30.2	15.9	44.4	
Neutrophil infiltrate				.089
Present	22.9	22.7	55.6	
Absent	77.1	77.3	44.4	
Basement membrane thickening				.196
Present	58.3	59.1	88.9	
Absent	41.7	40.9	11.1	
Subepithelial edema				.010
Present	54.2	31.8	77.8	
Absent	45.8	68.2	22.2	
Hyperplastic/papillary changes				.641
Present	4.2	4.5	11.1	
Absent	95.8	95.5	88.9	
Mucosal ulceration				.571
Present	2.1	0.0	0.0	
Absent	97.9	97.6	100.0	
Squamous metaplasia				.390
Present	15.6	15.9	33.3	
Absent	84.4	84.1	66.7	
Fibrosis				.705
Present	33.3	38.6	44.4	
Absent	66.7	61.4	55.6	
Fungal				.496
Present	3.1	4.5	11.1	
Absent	96.9	95.5	88.9	
Charcot–Leyden crystals				N/A
Present	0.0	0.0	0.0	
Absent	100.0	100.0	100.0	
Eosinophil aggregates				.191
Present	12.5	4.5	22.2	
Absent	87.5	95.5	77.8	

Abbreviations: CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; HPF, high power field; N/A, not applicable. Bold values represent statistically significant values.

has been associated with increased steroid requirements for disease control.²⁴ Oral and topical steroids have been shown to modulate nasal polyp mucosa remodeling, through promotion of epithelial repair, tissue remodeling regulation, increasing collagen content, and reducing eosinophil infiltration.²⁵ Topical steroids have also been shown to affect the microbiome of the nasal sinuses.²⁶

Conclusion

Smoking status may influence histopathologic tissue-level changes in CRS disease. Interestingly, former and current smokers maintained few differences in histopathology. However, “ever” smokers (former and current

smokers collectively) demonstrated increased chronic inflammatory changes compared with never smokers. This study suggests that the timing of smoking exposure has limited effect on longstanding tissue-level changes. Instead, exposure overall influences inflammatory change. These findings may have important implications for medical and surgical management of CRS disease and for counseling CRS patients in the context of comorbid smoking status.

Authors' Note

This study has been presented as an oral presentation at the 2019 *Rhinoworld Meeting*, Chicago Illinois, June 9, 2019.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P. S. B. Medtronic (research grant), Optinose, Sanofi Regeneron (Advisory Board), Springer (royalties). All the other authors have nothing to disclose.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: H. J. B. was supported by a grant from Rush University (Cohn Scholarship Program).

ORCID iDs

Hannah N. Kuhar  <https://orcid.org/0000-0003-4276-1193>

Ashwin Ganti  <https://orcid.org/0000-0002-4576-2557>

References

1. Bachert C, Akdis CA. Phenotypes and emerging endotypes of chronic rhinosinusitis pathogenesis of chronic rhinosinusitis: inflammation Structured histopathology profiling of chronic rhinosinusitis in routine practice. *J Allergy Clin Immunol Pract.* 2016;4(4):621–628.
2. Van Crombruggen K, Zhang N, Gevaert P, et al. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol.* 2011;128(4):728–732.
3. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2) LEN study. *Allergy.* 2011;66(9):1216–1223.
4. Lee WH, Hong SN, Kim HJ, et al. Effects of cigarette smoking on rhinologic diseases: Korean National Health and Nutrition Examination Survey 2008–2011. *Int Forum Allergy Rhinol.* 2015;5(10):937–943.
5. Hur K, Liang J, Lin SY. The role of secondhand smoke in sinusitis: a systematic review. *Int Forum Allergy Rhinol.* 2014;4(1):22–28.
6. Lee K-I, Kim DW, Kim EH. Cigarette smoke promotes eosinophilic inflammation, airway remodeling, and nasal polyps in a murine polyp model. *Am J Rhinol Allergy.* 2014;28(3):208–214.
7. Xie L, Liu AG, Peng LY, et al. Expression of E-prostanoid receptors in nasal polyp tissues of smoking and nonsmoking patients with chronic rhinosinusitis. *PLoS One.* 2018;13(7):e0200989.
8. Snidvongs K, Lam M, Sacks R. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol.* 2012;2(5):376–385.
9. Muller S. Update from the 4th Edition of the World Health Organization of head and neck tumours: tumours of the oral cavity and mobile tongue. *Head Neck Pathol.* 2017;11:33–40.
10. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol.* 2017;12:331–357.
11. Li YY, Li CW, Chao SS. Impairment of cilia architecture and ciliogenesis in hyperplastic nasal epithelium from nasal polyps. *J Allergy Clin Immunol.* 2014;134(6):1282–1292.
12. Michaeloudes C, Kuo C-H, Haji G. Metabolic re-patterning in COPD airway smooth muscle cells. *Eur Respir J.* 2017;50(5):1700202.
13. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013;187(3):228–237.
14. Liesker JJ, T, Hacken NH, Zeinstra-Smith M, et al. Reticular basement membrane in asthma and COPD: similar thickness, yet different composition. *Int J Chron Obstruct Pulmon Dis.* 2009;4:127–135.
15. Fokkens WJ, Lund VJ, Mullol J. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology.* 2012;50(1):1–12.
16. Hadar T, Yaniv E, Shvili Y, et al. Histopathological changes of the nasal mucosa induced by smoking. *Inhal Toxicol.* 2009;21(13):1119–1122.
17. Kuhar HN, Tajudeen BA, Heilingoetter A. Distinct histopathologic features of radiation-induced chronic sinusitis. *Int Forum Allergy Rhinol.* 2017;7(10):990–998.
18. Rigden HM, Alias A, Havelock T. Squamous metaplasia is increased in the bronchial epithelium of smokers with chronic obstructive pulmonary disease. *PLoS One.* 2016;11(5):e0156009.
19. Howard BE, Lal D. Oral steroid therapy in chronic rhinosinusitis with and without nasal polyposis. *Curr Allergy Asthma Rep.* 2013;13(2):236–243.
20. Head K, Chong LY, Hopkins C, et al. Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016;4:CD011992.
21. Liu YF, Richardson CM, Bernard SH, et al. Antibiotics, steroids, and combination therapy in chronic rhinosinusitis without nasal polyps in adults. *Ear Nose Throat J.* 2018;97(6):167–172.
22. Tokunaga T, Sakashita M, Haruna T. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy.* 2015;70(8):995–1003.
23. Bhattacharyya N, Vyas DK, Fechner FP, et al. Tissue eosinophilia in chronic sinusitis: quantification techniques. *Arch Otolaryngol Head Neck Surg.* 2001;127(9):1102–1105.
24. Tajudeen BA, Ganti A, Kuhar HN. The presence of eosinophil aggregates correlates with increased postoperative prednisone requirement. *Laryngoscope.* 2019;129(4):794–799.
25. de Borja Callejas F, Martínez-Antón A, Picado C. Corticosteroid treatment regulates mucosal remodeling in chronic rhinosinusitis with nasal polyps. *Laryngoscope.* 2015;125(5):E158–167.
26. Liu CM, Kohanski MA, Mendiola M. Impact of saline irrigation and topical corticosteroids on the postsurgical sinonasal microbiota. *Int Forum Allergy Rhinol.* 2015;5(3):185–190.