Published in final edited form as:

Ophthalmology. 2010 March ; 117(3): 585–590. doi:10.1016/j.ophtha.2009.08.011.

Cigarette smoking as a risk factor for uveitis

Phoebe Lin, MD, PhD^{1,2}, Allison R. Loh, BA¹, Todd P. Margolis, MD, PhD^{1,2}, and Nisha R. Acharya, MD, MS^{1,2}

¹F.I. Proctor Foundation, University of California, San Francisco, California, USA

²Department of Ophthalmology, University of California, San Francisco, California, USA

Abstract

Purpose—To determine the association between tobacco smoking history and uveitis.

Design—Retrospective, case-control study.

Participants—564 ocular inflammation patients seen in the Proctor Foundation uveitis clinic between 2002–2009, and 564 randomly selected comprehensive eye clinic patients within the same time period.

Methods—A retrospective medical record review of all cases and controls.

Main Outcome Measures—A logistic regression analysis was conducted with ocular inflammation as the main outcome variable and smoking as the main predictor variable while adjusting for age, gender, race, and median income.

Results—The odds of a smoker having ocular inflammation were 2.2 fold that of a patient who had never smoked (95% confidence interval [CI] 1.7–3.0, $p < 0.001$). All anatomical subtypes of uveitis were associated with a positive smoking history, with odds ratios (OR) of 1.7 (95% CI 1.2–2.4, $p = 0.002$) for anterior uveitis, 2.7 (95% CI 1.4–5.6, $p = 0.005$) for intermediate uveitis, 3.2 (95% CI 1.3–7.9, $p = 0.014$) for posterior uveitis, and 3.9 (95% CI 2.4–6.1, $p < 0.001$) for panuveitis. In patients with panuveitis and cystoid macular edema (CME), the OR was 8.0 (95% CI 3.3–19.5, $p < 0.001$) compared to 3.1 (95% CI 1.8–5.2, $p < 0.001$) for those patients without CME. Patients with intermediate uveitis and CME also had a higher OR (OR 8.4, 95% CI, 2.5–28.8, $p = 0.001$) compared to patients without CME (OR 1.5, 95% CI 0.6–3.8, $p = 0.342$). Patients with a smoking history were at much greater odds of having infectious uveitis (OR 4.5, 95% CI 2.3–9.0, $p < 0.001$) than non-infectious uveitis (OR 2.1, 95% CI 1.6–2.8, $p < 0.001$), although both were associated with smoking.

Conclusions—A history of smoking is significantly associated with all anatomical subtypes of uveitis and infectious uveitis. The association was greater in intermediate and panuveitis patients with CME as compared to those without CME. In view of the known risks of smoking, these findings, if replicated, would give an additional reason to recommend smoking cessation in uveitis patients.

© 2009 American Academy of Ophthalmology, Inc. Published by Elsevier Inc. All rights reserved.

Address for reprints: Nisha Acharya, MD, MS, F.I. Proctor Foundation, University of California San Francisco, 95 Kirkham St, San Francisco, CA 94143-0944. Tel: 415 476 8131; Fax: 415 476 0527. nisha.acharya@ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Meeting presentation: This study was presented at the Association for Research in Vision and Ophthalmology meeting at Fort Lauderdale, Florida, May, 2009

Introduction

Cigarette smoking is the primary preventable cause of disease, disability, and premature death in the United States, largely due to the 4,000 known active compounds found in tobacco smoke, 40 of which are known chemical carcinogens.^{1, 2} Compounds found in the water soluble portion of cigarette smoke include oxygen free radicals which can induce vascular inflammation and have been implicated in a number of systemic disease processes.³ Several observational studies have determined that smoking is a strong risk factor for the development of neovascular age-related macular degeneration, cataract, and thyroid eye disease.^{2, 4–7} The pathogenesis of some of these conditions is thought to be partially the result of a complex inflammatory process mediated by oxidative stress through the proinflammatory components of cigarette smoke.^{3, 8–10}

Given that uveitis is a result of immune dysregulation, it is plausible that smoking may contribute to the pathogenesis of uveitis. Despite the many studies that have investigated the relationship between smoking and macular degeneration or thyroid eye disease there have been few studies investigating the association between smoking and uveitis. Although one study reported smoking as a significant risk factor for the development of cystoid macular edema among intermediate uveitis patients,¹¹ there have been no case-control studies demonstrating an association between uveitis and a history of smoking. The objective of our study was to investigate the relationship of cigarette smoking to all types of uveitis.

Methods

After obtaining institutional review board approval, we retrospectively reviewed the charts of uveitis patients seen at the F.I. Proctor Foundation at the University of California, San Francisco between 2002 and 2009. As standard practice, new patients seen in all eye clinics complete a standard questionnaire which includes a section on smoking history with check boxes for past, current, or no history of smoking. Only patients who completed the smoking section of their intake questionnaire were included in the study. Patients with all types of ocular inflammation were included, except for patients with post-surgical inflammation and endophthalmitis. Any patient who was examined and found to not have ocular inflammation was excluded from the case group. The anatomical location of inflammation was noted for all patients, and included scleritis, episcleritis, anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis, according to the Standardized Uveitis Nomenclature classification system.¹² Etiology of inflammation was also recorded, if known, including both infectious and non-infectious associations. Finally, we recorded information regarding complications associated with ocular inflammation, including cystoid macular edema (CME), cataract, and glaucoma. We randomly selected controls at a ratio of 1:1 from patients seen in the comprehensive eye clinic within the same time period. Patients who were seen in the comprehensive eye clinic who had a past or current history of ocular inflammation (including uveitis, scleritis, or episcleritis) were excluded from the control group. Demographic information collected for both cases and controls included age, gender, self-reported race, and zip code. To approximate socioeconomic status, we utilized the patient's zip code and U.S. census bureau data (<http://factfinder.census.gov/>, accessed March 29, 2009) to determine the median household income for the area in which each patient lived.¹³ For all cases and controls, smoking history (current, past, or never) was recorded from the questionnaire. Smoking exposure was our predictor of interest given our *a priori* hypothesis that smoking may be a risk factor for uveitis. We did not examine any other potential risk factors for uveitis in this study. For the primary analysis, current and past smoking were evaluated as separate predictors, although for the subgroup analyses, we grouped current and past smoking history into the same category (ever smokers).

Statistical analysis

Univariate analyses were conducted using a Fisher's exact test for categorical comparisons including race, gender, and smoking history. Continuous variables such as age and median household income were compared using a t-test. We performed multivariate analyses with a logistic regression model with ocular inflammation as the main outcome variable, and smoking history as the main predictor variable, while adjusting for age, gender, race, and median household income. A P -value < 0.05 was considered statistically significant. In addition, we conducted the following subgroup analyses: sub-analysis by race, sub-analysis excluding patients younger than age 21 given that patients under that age may be less likely to smoke, sub-analysis by anatomic location of ocular inflammation with and without CME, and sub-analysis by infectious/noninfectious etiology of inflammation. All statistical analyses were performed using Stata 10 software (Stata Corp, College Station, TX).

Results

Baseline characteristics of cases and controls

Among the 755 patients seen in the Proctor Medical Group between 2002–2009, 564 patients were found to have completed the questionnaire form (75% completion) and met our inclusion criteria. For the control group, 610 randomly selected patient charts from the comprehensive eye clinic had to be reviewed in order to obtain an equivalent number of patients (564) with completion of smoking information (92% completion). The anatomical and diagnostic classifications of ocular inflammation in the study patients (or cases) are listed in Table 1 and Table 2, respectively. Two hundred and ninety-three patients (51.9%) had no known cause for their ocular inflammation and were recorded as idiopathic ocular inflammation (Table 2). Two hundred twenty-two (39.4%) study patients had known non-infectious causes, and 49 (8.5%) had a known infectious cause. The most common non-infectious type of uveitis was HLA-B27-associated (65, 11.5%). Other non-infectious and infectious associations are listed in Table 2.

The baseline characteristics of the cases and controls are shown in Table 3. In the univariate analysis, the variables that were significantly different between the two groups included a history of past or current smoking, age, and race. The smoking prevalence (including both past and current smokers) in the ocular inflammation group was 35.5% as compared to a 23.6% prevalence in the comprehensive eye clinic controls. By univariate analysis this resulted in an odds ratio (OR) of 1.8 (95% confidence interval [CI] 1.4–2.3, $P < 0.001$) (Table 3). By univariate analysis, similar odds ratios were found in current smokers (OR 1.7, 95% CI 1.2–2.5, $P = 0.006$) and past smokers (OR 1.7, 95% CI 1.2–2.3, $P = 0.002$) compared to never smokers. There were no statistically significant differences between groups in regards to gender and median income (based on median household income for the patient's zip code).

Smoking and ocular inflammation

A multivariate logistic regression model adjusting for differences in age, race, sex, and median income was used to determine whether or not there was a significant association between smoking and ocular inflammation (Table 4). As compared with individuals that never smoked, current smokers had an odds ratio of 2.0 (95% CI 1.3–2.9, $P = 0.001$) while past smokers had an odds ratio of 2.4 (95% CI 1.7–3.4, $P < 0.001$) (Table 4) for having ocular inflammation. The combined result for past and current smokers yielded an odds ratio of 2.2 for having ocular inflammation compared with patients who had never smoked (95% CI 1.7–3.0, $P < 0.001$). Other significant associations with ocular inflammation were younger age and Hispanic or Indian race.

Subgroup analyses

Subgroup analyses were conducted to determine the robustness of the association between smoking and ocular inflammation across various sub-populations. These analyses included studying the association within each racial group and excluding patients younger than age 21 ($n=39$ in controls, $n=92$ in cases). Subgroup analysis stratifying by race showed a significant association between smoking and ocular inflammation in Caucasian, Hispanic, Asian/Pacific Islander, and Indian patients, but not in African-Americans, Middle Easterners, or Native Americans. With the exception of the latter three racial groups, the association between smoking and ocular inflammation persisted (OR 2–3, all with P values < 0.05).

Additional subgroup analyses were conducted to study the association between smoking and inflammation across anatomical subtypes of uveitis. The entire control group was utilized as a comparison, using a logistic regression model while adjusting for differences in age, sex, race, and median income. All anatomical subtypes of uveitis were associated with a positive smoking history, with an odds ratios of 1.7 (95% CI 1.2–2.4, $P=0.002$) for anterior uveitis, 2.7 (95% CI 1.4–5.6, $P=0.005$) for intermediate uveitis, 3.2 (95% CI 1.3–7.9, $P=0.014$) for posterior uveitis, and 3.9 (95% CI 2.4–6.1, $P<0.001$) for panuveitis (Table 5). Subgroup analyses for the anterior uveitis group excluded any patients with concurrent intermediate or posterior uveitis. No significant relationship between smoking and scleritis (OR 1.7, 95% CI 0.8–3.8, $P=0.166$) or episcleritis (OR 0.9, 95% CI 0.2–4.5, $P=0.877$) was observed.

The association between smoking and ocular inflammation remained significant in intermediate uveitis and panuveitis patients with CME, but not in patients with anterior uveitis or posterior uveitis who had CME (Table 5). In panuveitis patients, the relationship to smoking was established in patients with and without CME, with an increase in odds ratio to 8.0 (95% CI 3.3–19.5, $P<0.001$) in patients with CME, as compared to an odds ratio of 3.1 (95% CI 1.8–5.2, $P<0.001$) for those patients without CME. Patients with intermediate uveitis and CME had an odds ratio of 8.4 (95% CI, 2.5–28.8, $P=0.001$) as compared with intermediate uveitis patients without CME (OR 1.5, 95% CI 0.6–3.8, $P=0.342$).

The association between smoking and inflammation was stronger with infectious (OR 4.5, 95% CI 2.3–9.0, $P<0.001$) compared to non-infectious ocular inflammation (OR 2.1, 95% CI 1.6–2.8, $P<0.001$, Table 6), although both had a significant association with smoking. Uveitis patients with an infectious etiology and CME had an odds ratio of 32.3 (95% CI 2.5–411.1, $P=0.007$), which was significantly higher than the odds ratio for infectious uveitis patients without CME (OR 3.8, 95% CI 1.8–7.8, $P<0.001$). Finally, smoking was not significantly associated with HLA-B27-associated uveitis either with or without CME (Table 6).

Discussion

We report a case-control study demonstrating a strong association between cigarette smoking and uveitis. After adjusting for differences in age, race, gender, and median income, we demonstrated that smoking was significantly associated with an increased odds of having any anatomical subtype of uveitis, with an overall odds ratio of 2.2 for smokers (either past or current) compared with those who had never smoked. This is comparable to the odds ratios seen in multiple retrospective case-control studies that demonstrated an association between smoking and macular degeneration, including the Eye Disease Case-Control Study and the Beaver Dam Eye Study, which reported odds ratios of 2.2 and 2.5, respectively, for developing neovascular macular degeneration in smokers.^{4, 14} Other inflammatory conditions of the eye as well as certain systemic autoimmune conditions have also been linked to smoking.² A recent meta-analysis summarized studies that investigated the association between smoking and rheumatoid arthritis.¹⁵ The consensus was that there was a strong correlation between smoking and rheumatoid factor positive rheumatoid arthritis.¹⁵ Another meta-analysis reported a causal

relationship between thyroid eye disease and smoking. It established that there was a positive association, with a reduced risk of thyroid eye disease in ex-smokers.⁷ In contrast to the latter two conditions, very little has been published regarding an association with smoking and uveitis. In a retrospective cohort study looking at the characteristics of patients with intermediate uveitis in Olmstead County, Minnesota, Donaldson et al reported that 52% of intermediate uveitis patients were smokers compared to a 16% rate of smoking in the general population (the national smoking rate is 23%).¹⁶ In a small study (37 study patients) presented at a 1970 meeting of the American Medical Association, David Knox reported a smoking prevalence of 87% among men and 54% among women with pars planitis compared with respective smoking prevalences of 27% and 14% in the general population at the time.¹⁷ In our case-control study, we find that the rate of smoking (past or current) was higher in both controls and cases compared to the smoking rate in San Francisco county (18.9%, <http://www.sonoma-county.org/health/prev/pdf/regional.pdf>, accessed on May 5, 2009). This demonstrates the importance of a case-control study design.

Our data also suggest an especially strong association between smoking and infectious uveitis (OR 4.5, $P < 0.001$). There are complex host, pathogen, and environmental factors that result in an infectious agent reaching intraocular tissues without direct inoculation. These mechanisms are not yet completely understood. We can speculate that the pro-inflammatory components of tobacco smoke which are known to cause vascular inflammation may promote not only access of organisms to intraocular tissue, but also perhaps enhance the response of inflammatory cells to the microorganism, although this would have to be tested in the appropriate models. This may partially explain why highly prevalent infections, such as herpes simplex virus-1 and toxoplasmosis, cause intraocular inflammation in only a small subset of infected individuals.

Subgroup analyses were robust for certain subgroups, but small sample size limited our ability to draw conclusions in other cases. In contrast to the strong association between smoking and uveitis, a strong association between smoking and scleritis could not be established in our study. This may be due to different pathophysiologic mechanisms underlying the development of scleritis as compared to uveitis. No conclusions could be drawn about the association between episcleritis and smoking. However, this could have been due to the small number of cases with a diagnosis of episcleritis. The relationship between smoking and uveitis was evident in both current smokers and past smokers alike, as well as in various analyses used to test the robustness of the association. This included patients over 21 and patients stratified by racial group. In certain racial groups, however, such as African Americans, the association between uveitis and smoking did not hold. Conclusions cannot be drawn in regards to our Native American and Middle Eastern patients as these subgroups had small sample sizes.

There is a biologically plausible mechanism which may explain the association between cigarette smoke exposure and uveitis. Although nicotine itself may have antiinflammatory properties, cigarette smoke has a pro-inflammatory effect primarily through the promotion of vascular inflammation related to the release of reactive oxygen species.^{3, 9} It has been reported that exposure to cigarette smoke extract increases vascular H_2O_2 production, activates NF- κB , and results in the up-regulation of the proinflammatory cytokines, IL-1 β , IL-6, and TNF- α .³ The mechanism of smoking in the development of macular degeneration and thyroid eye disease is thought to be related to the production of reactive oxygen species.^{18, 19} Although we have found that there is a strong correlation between smoking and uveitis in patients seen at the Proctor Foundation, we have not proven that smoking causes uveitis, nor can we determine that smoking exacerbates uveitis, although both scenarios are biologically plausible.

In addition to the association between smoking and all anatomical subtypes of uveitis, we also found a correlation of smoking with CME in intermediate and panuveitis patients, but not in

anterior or posterior uveitis. Among the latter two types of uveitis, anterior uveitis patients had low rates of CME, and we had small numbers of posterior uveitis patients compared with the other types of uveitis. The notion of smoking increasing the risk of CME in intermediate uveitis is not novel. In a cross sectional study Thorne et al demonstrated that smoking was a risk factor in the development of CME in intermediate uveitis patients.¹¹ This result corroborated unpublished data reported by Cunningham and colleagues (Invest Ophthalmol Vis Sci 2001 [Suppl]:708). Here we show that smoking was associated with CME in patients with both panuveitis and intermediate uveitis. We hypothesize that smoking not only plays a role in the development of uveitis, but also contributes to the severity of inflammation resulting in the development of a sight-threatening complication such as CME. An issue that deserves discussion is whether smoking causes CME, regardless of its etiology, or if it exacerbates inflammation resulting in a complication such as CME. We propose that it is the latter, given that in our study, we have shown that smoking is associated with uveitis, even in the absence of CME. Furthermore, studies looking at other causes of CME, such as diabetic retinopathy, have shown that there is no relationship between smoking and the incidence or progression of diabetic macular edema.^{20–24} This implies that the primary mechanism of uveitic CME may be different than that of diabetic CME, although there is likely some overlap.

There are many strengths of our study, including the large size and the case-control design. However, the results should be interpreted conservatively given its retrospective nature. We did not have information on the timing of onset of smoking in relation to the onset of uveitis, nor did we have information regarding the dosage in pack-years of smoking, given that patients did not routinely self-report (nor did we routinely collect) this particular type of information. Relying on patient self-report may also introduce underestimation of the smoking prevalence in our study although this would be expected to have an effect on both the study and control groups.²⁵ We also did not have specific information on the type of smoke exposure (cigar, cigarette, filtered, non-filtered, environmental cigarette smoke, etc.). Despite these limitations, both current and past smoking had a significant association with uveitis, although we cannot do anymore than conjecture why past smoking had a slightly higher odds ratio than current smoking. One possibility is that ex-smokers have a particularly high rate of misclassification of current smoking status according to serum biomarker measurements, as one study suggests.²⁶ Another possibility is that non-incident cases of uveitis seen in our clinic that classify themselves as ex-smokers may have been smoking prior to the onset of their uveitis but quit smoking for a variety of unknown reasons before they were seen in our clinic.

Although we adjusted for many significant confounders including age, gender, race, and median income, there remains the possibility of other unknown factors (e.g., systemic cardiovascular disease) that may inherently differ between our cases and controls. We chose to adjust for median household income by zip code as a surrogate for socioeconomic status, but this method has its limitations. In choosing our controls, we used comprehensive eye clinic patients rather than retina or other subspecialty patients given that common retinal diseases have been associated with smoking. In regards to the relationship between CME and smoking, careful prospective studies looking at complication rates and severity of inflammation in relation to smoking would need to be conducted to test the hypothesis that smoking increases the severity of inflammation in uveitis, although even then, causality would not necessarily be established.

Our data suggest that smoking is a significant risk factor for all anatomic types of uveitis as well as infectious uveitis. We also show a particularly strong relationship with smoking in inflammatory CME in intermediate and panuveitis patients. Whether or not this information is applied broadly towards a change in counseling uveitis patients will depend on results borne out over multiple independent studies. However, we do feel that the strength of the association is substantial and warrants further investigation.

Acknowledgments

Financial support: This research was supported by a National Eye Institute K23EY017897 grant and a Research to Prevent Blindness Career Development Award to Dr. Acharya. Dr. Lin is supported by an institutional Clinical and Translational Science Institute resident research grant. The sponsor or funding organization had no role in the design or conduct of this research.

References

1. Pryor WA, Prier DG, Church DF. Electron-spin resonance study of mainstream and sidestream cigarette smoke: nature of the free radicals in gas-phase smoke and in cigarette tar. *Environ Health Perspect* 1983;47:345–355. [PubMed: 6297881]
2. Solberg Y, Rosner M, Belkin M. The association between cigarette smoking and ocular diseases. *Surv Ophthalmol* 1998;42:535–547. [PubMed: 9635902]
3. Orosz Z, Csiszar A, Labinskyy N, et al. Cigarette smoke-induced proinflammatory alterations in the endothelial phenotype: role of NAD(P)H oxidase activation. *Am J Physiol Heart Circ Physiol* 2007;292:H130–H139. [PubMed: 17213480]
4. Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol* 1992;110:1701–1708. [PubMed: 1281403]
5. Christen WG, Glynn RJ, Manson JE, et al. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA* 1996;276:1147–1151. [PubMed: 8827967]
6. Blumenkranz MS, Russell SR, Robey MG, et al. Risk factors in age-related maculopathy complicated by choroidal neovascularization. *Ophthalmology* 1986;93:552–558. [PubMed: 2425325]
7. Thornton J, Kelly SP, Harrison RA, Edwards R. Cigarette smoking and thyroid eye disease: a systematic review. *Eye* 2007;21:1135–1145. [PubMed: 16980921]
8. Satriano JA, Shuldiner M, Hora K, et al. Oxygen radicals as second messengers for expression of the monocyte chemoattractant protein, JE/MCP-1, and the monocyte colony-stimulating factor, CSF-1, in response to tumor necrosis factor-alpha and immunoglobulin G: evidence for involvement of reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase. *J Clin Invest* 1993;92:1564–1571. [PubMed: 8397228]
9. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004;43:1731–1737. [PubMed: 15145091]
10. Cawood TJ, Moriarty P, O'Farrelly C, O'Shea D. Smoking and thyroid-associated ophthalmopathy: a novel explanation of the biological link. *J Clin Endocrinol Metab* 2007;92:59–64. [PubMed: 17047020]
11. Thorne JE, Daniel E, Jabs DA, et al. Smoking as a risk factor for cystoid macular edema complicating intermediate uveitis. *Am J Ophthalmol* 2008;145:841–846. [PubMed: 18321467]
12. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. *Am J Ophthalmol* 2005;140:509–516. [PubMed: 16196117]
13. Krupski TL, Kwan L, Litwin MS. Sociodemographic factors associated with postprostatectomy radiotherapy. *Prostate Cancer Prostatic Dis* 2005;8:184–188. [PubMed: 15809671]
14. Klein R, Klein BE, Linton KL, DeMets DL. The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *Am J Epidemiol* 1993;137:190–200. [PubMed: 8452123]
15. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis*. In press.
16. Donaldson MJ, Pulido JS, Herman DC, et al. Pars planitis: a 20-year study of incidence, clinical features, and outcomes. *Am J Ophthalmol* 2007;144:812–817. [PubMed: 18036872]
17. Knox DL. Pars planitis: a 20-year study of incidence, clinical features, and outcomes [letter]. *Am J Ophthalmol* 2008;146:479. author reply 479. [PubMed: 18724984]
18. Dong A, Xie B, Shen J, et al. Oxidative stress promotes ocular neovascularization. *J Cell Physiol* 2009;219:544–552. [PubMed: 19142872]
19. Tsai CC, Cheng CY, Liu CY, et al. Oxidative stress in patients with Graves' ophthalmopathy: relationship between oxidative DNA damage and clinical evolution. *Eye*. In press.

20. Klein R, Klein BE, Davis MD. Is cigarette smoking associated with diabetic retinopathy? *Am J Epidemiol* 1983;118:228–238. [PubMed: 6881128]
21. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116:497–503. [PubMed: 19167079]
22. Moss SE, Klein R, Klein BE. Association of cigarette smoking with diabetic retinopathy. *Diabetes Care* 1991;14:119–126. [PubMed: 2060413]
23. Moss SE, Klein R, Klein BE. Cigarette smoking and ten-year progression of diabetic retinopathy. *Ophthalmology* 1996;103:1438–1442. [PubMed: 8841303]
24. Romero P, Baget M, Mendez I, et al. Diabetic macular edema and its relationship to renal microangiopathy: a sample of Type I diabetes mellitus patients in a 15-year follow-up study. *J Diabetes Complications* 2007;21:172–180. [PubMed: 17493551]
25. Gorber SC, Schofield-Hurwitz S, Hardt J, et al. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine Tob Res* 2009;11:12–24. [PubMed: 19246437]
26. Lewis SJ, Cherry NM, McI Niven R, et al. Cotinine levels and self-reported smoking status in patients attending a bronchoscopy clinic. *Biomarkers* 2003;8:218–228. [PubMed: 12944174]

Table 1

Anatomical classification of ocular inflammation

Location of ocular inflammation*	Number out of 564 (%)
Anterior	331 (58.7%)
Intermediate	57 (10.1%)
Posterior	25 (4.4%)
Panuveitis	133 (23.6%)
Scleritis	39 (6.9%)
Episcleritis	10 (1.8%)

* 31 patients had more than one anatomical location

Table 2

Diagnostic categories of ocular inflammation

Diagnosis	Number out of 564 (%)
Non-Infectious*	222 (39.4%)
HLA-B27 associated	65 (11.5%)
Sarcoidosis	27 (4.8%)
Ankylosing spondylitis	23 (4.1%)
Juvenile idiopathic arthritis	23 (4.1%)
Vogt-Koyanagi-Harada	19 (3.4%)
Rheumatoid arthritis	16 (2.8%)
Multifocal choroiditis	8 (1.4%)
Multiple sclerosis	7 (1.2%)
Inflammatory bowel disease	6 (1.1%)
Birdshot chorioretinopathy	5 (0.9%)
Behcet's	5 (0.9%)
Fuchs' heterochromic iridocyclitis	4 (0.7%)
Reactive arthritis	4 (0.7%)
Systemic lupus erythematosus	4 (0.7%)
Tubulointerstitial nephritis uveitis	3 (0.5%)
Wegener's granulomatosis	2 (0.4%)
Sympathetic ophthalmia	2 (0.4%)
Posner-Schlossman	1 (0.2%)
Serpiginous choroidopathy	3 (0.5%)
Relapsing polychondritis	3 (0.5%)
Infectious	49 (8.5%)
Herpetic (simplex or zoster)	22 (3.9%)
Toxoplasmosis	9 (1.6%)
Tuberculosis	7 (1.2%)
Syphilis	5 (0.9%)
<i>Bartonella hensalae</i>	2 (0.4%)
Lyme disease	2 (0.4%)
Cytomegalovirus	2 (0.4%)
Idiopathic	293 (51.9%)

* 8 patients had more than one known etiology

Table 3

Baseline characteristics, univariate analysis

Characteristics	Control Group number (%)	Uveitis Group number (%)	P-value
Smoking History			
Ever smoker (past or current)	133 (23.6%)	200 (35.5%)	<0.001
Current smoker	54 (9.6%)	79 (14.0%)	0.006
Past smoker	82 (14.5%)	117 (20.7%)	0.002
Gender			
Female	340 (60.3%)	349 (61.2%)	0.625
Race			
Caucasian	292 (51.8%)	283 (50.2%)	0.171
Asian/Pacific Islander	117 (20.7%)	82 (14.5%)	0.001
Black	72 (12.8%)	74 (13.1%)	0.929
Hispanic	59 (10.5%)	88 (15.6%)	0.020
Middle Eastern	21 (3.7%)	15 (2.7%)	0.397
Indian subcontinent	3 (0.5%)	14 (2.5%)	0.012
Native American	0 (0%)	8 (1.4%)	0.008
Mean age in years (SD)	54 (18.7)	45 (18.5)	<0.001
Mean median income (SD)	\$60,397 (\$17,076)	\$58,504 (\$21,131)	0.106

*
SD: standard deviation

Table 4

Multivariate logistic regression model predicting ocular inflammation

Covariate	Odds Ratio (95% CI)	P-value
Current smoker vs never	2.0 (1.3–2.9)	0.001
Past smoker vs never	2.4 (1.7–3.4)	<0.001
Current age (by decade)	0.8 (0.7–0.8)	<0.001
Female	1.2 (0.9–1.6)	0.130
Median Income (by \$10,000)	0.9 (0.9–1.1)	0.603
Race (reference = Caucasian)		
Asian/Pacific Islander	0.7 (0.5–1.0)	0.083
Black	0.8 (0.5–1.2)	0.274
Hispanic	1.6 (1.0–2.3)	0.028
Middle Eastern	0.7 (0.4–1.6)	0.490
Indian subcontinent	5.5 (1.5–19.9)	0.010

CI: confidence interval

Table 5

Multivariate analysis by anatomical classification for ever smokers

Anatomical location	Odds Ratio (95% CI)	P-value
Anterior uveitis*		
all, n=315	1.7 (1.2–2.4)	0.002
without CME, n=294	1.7 (1.2–2.4)	0.003
With CME, n=21	1.4 (0.5–4.1)	0.501
Intermediate uveitis		
all, n=57	2.7 (1.4–5.6)	0.005
without CME, n=39	1.5 (0.6–3.8)	0.342
With CME, n=18	8.4 (2.5–28.8)	0.001
Posterior uveitis		
all, n=25	3.2 (1.3–7.9)	0.014
without CME, n=18	3.3 (1.1–9.7)	0.032
With CME, n=7	2.1 (0.4–9.5)	0.358
Panuveitis		
all, n=133	3.9 (2.4–6.1)	<0.001
without CME, n=102	3.1 (1.8–5.2)	<0.001
With CME, n=31	8.0 (3.3–19.5)	<0.001
Scleritis** n=39	1.7 (0.8–3.8)	0.166
Episcleritis** n=10	0.9 (0.2–4.5)	0.877

* Excludes patients with concurrent intermediate and anterior uveitis

** No patients with scleritis or episcleritis had CME

CI: confidence interval

CME: cystoid macular edema

Table 6

Multivariate analysis for infectious etiology and HLA-B27 associated uveitis in ever smokers

Type of uveitis	Odds Ratio (95% CI)	P-value
Infectious		
all, n=49	4.5 (2.3–9.0)	<0.001
without CME, n=43	3.8 (1.8–7.8)	<0.001
with CME, n=6	32.3 (2.5–411.1)	0.007
Noninfectious*		
all, n=515	2.1 (1.6–2.8)	<0.001
without CME, n=444	1.8 (1.3–2.5)	<0.001
with CME, n=71	3.4 (2.0–5.7)	<0.001
HLA-B27 associated uveitis		
all, n=65	1.6 (0.9–3.0)	0.144
without CME, n=61	1.7 (0.9–3.3)	0.117
with CME, n=4	0.83 (0.8–8.8)	0.874

* Includes known non-infectious etiologies and idiopathic

CI: confidence interval

CME: cystoid macular edema