HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Ophthalmology. 2015 June ; 122(6): 1257–1261. doi:10.1016/j.ophtha.2015.02.034.

Association between Smoking and Uveitis: Results from the Pacific Ocular Inflammation Study

Brenton G. Yuen, BA[1,2], **Vivien M. Tham, MD**[2,3,4], **Erica N Browne, MS**[1], **Rachel Weinrib, MPH**[1], **Durga S. Borkar, MD**[1], **John V. Parker, BS**[5], **Aileen Uchida, MPH**[5], **Aleli C. Vinoya, BS**[5], and **Nisha R. Acharya, MD, MS**[1,6,7]

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

[2]University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii

[3]Department of Ophthalmology, Kaiser Permanente Hawaii, Honolulu, Hawaii

[4]Pacific Vision Institute of Hawaii, Honolulu, Hawaii

[5]Center for Health Research, Kaiser Permanente Hawaii, Honolulu, Hawaii

[6]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California

[7]Department of Ophthalmology, University of California, San Francisco, San Francisco, California

Abstract

Objective—To assess whether cigarette smoking is associated with the development of uveitis in a population-based setting.

Design—Retrospective, population-based case-control study.

Participants—Patients ≥18 years of age seen at a Kaiser Permanente Hawaii clinic between January 1, 2006 and December 31, 2007. Analysis included 100 confirmed incident uveitis cases, 522 randomly selected controls from the general Kaiser Hawaii population, and 528 randomly selected controls from the Kaiser Hawaii ophthalmology clinic.

Methods—International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes were used to identify possible uveitis cases. A uveitis fellowship-trained ophthalmologist then conducted individual chart review to confirm case status. Multivariate logistic regression models were used to evaluate the association between smoking and uveitis, adjusting for age, sex, race, and socioeconomic status.

Main Outcome Measure—Development of uveitis.

Address for reprints: Nisha R. Acharya, MD, MS, Associate Professor, F.I. Proctor Foundation, Room S309, 513 Parnassus Ave, UCSF, San Francisco, CA 94143-0412. Tel: +1 415 476-8131; Fax: +1 415 476-0527. nisha.acharya@ucsf.edu.

Conflict of Interest: No conflicting relationship exists for any author.

Results—Current smokers had a 1.63 (95% CI 0.88 – 3.00, *P*=0.12) and 2.33 (95% CI 1.22 – 4.45, P=0.01) times greater odds of developing uveitis compared to never smokers using the general and ophthalmology control groups, respectively. The association was even stronger with non-infectious uveitis, which yielded ORs of 2.10 (95% CI 1.10 – 3.99 *P*=0.02) and 2.96 (95% CI 1.52 – 5.77, *P*=0.001) using the general and ophthalmology control groups, respectively.

Conclusions—Cigarette smoking is significantly associated with new onset uveitis within a population-based setting. The association was stronger for non-infectious uveitis. Given the well-established risks of smoking with regard to other inflammatory disorders, these results reaffirm the importance of encouraging patients to avoid or cease smoking.

As the leading cause of preventable morbidity and mortality in the United States, cigarette smoking remains a major public health concern.[1] The hazards of cigarette use arise from the abundance of free radicals, polycyclic aromatic hydrocarbons, and other reactive compounds present in tobacco smoke that activate pro-inflammatory pathways and trigger pathological processes.[2–3] Studies have shown associations between smoking and the onset and severity of rheumatoid arthritis, Graves' disease, multiple sclerosis, and systemic lupus erythematosus.[4–11]

While uveitis and the aforementioned diseases all arise from immune dysregulation, relatively little data exist to support the association between smoking and uveitis. There has been only one prior case-control study on the association between smoking and uveitis. This study from a tertiary eye care center reported a link between smoking and uveitis.[12] A few studies have demonstrated an increased risk of uveitic complications among uveitis patients with a history of smoking.[13–15] However, one study found that smoking does not have a negative effect on the clinical findings and prognosis of uveitis in Behçet disease.[16] To date, no population-based study has investigated the association between smoking and new onset uveitis. Such a study would afford greater certainty that cases and controls come from the same population, which is a significant issue in studies from tertiary care centers.

Kaiser Permanente Hawaii offers a comprehensive source of population-based data. Through its 18 clinics, it serves over 16% of Hawaii's racially diverse population. Unlike tertiary care centers, it typically provides its patients with all of their medical care, thus ensuring that all cases are recorded within its database. The present study aimed to investigate the relationship between smoking and uveitis within this population.

Methods

Institutional Review Boards at the University of California, San Francisco and Kaiser Permanente Hawaii approved this study. The study was compliant with the Health Insurance Portability and Accountability Act.

We conducted a population-based, case-control study using patient encounter data taken from Kaiser Permanente Hawaii electronic medical records, which were established in 2004. To identify cases, visits between the study period of January 1, 2006 and December 31, 2007 were queried for *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes suggestive of uveitis. After identification of potential cases using an

intentionally broad range of ICD-9 codes, a uveitis fellowship trained ophthalmologist conducted individual chart review to confirm case status. Classification of cases has been previously described in detail.[17]

Two control groups were created, each with patients selected randomly in a 5:1 ratio to uveitis cases. One control group consisted of patients from the general Kaiser Hawaii membership who had at least one healthcare visit during the study period. An additional control group consisted of patients who had at least one visit to the Kaiser Hawaii ophthalmology clinic during the study period and were at least 18 years of age.

Smoking status of cases was determined at their visit nearest to and before their date of diagnosis. Each control was assigned to a case such that their smoking status could be assessed nearest to the date of diagnosis. For patients without a smoking history prior to the diagnosis date, the visit at which it was recorded closest to but after the diagnosis date was used. Patients whose smoking status was not recorded in the electronic medical record were excluded from this analysis. Smoking status was categorized as either never smoked, currently smoking, quit, or passive. Infectious uveitis was defined by an associated diagnosis of herpes simplex virus, herpes zoster virus, histoplasmosis, toxoplasmosis, HIV, Bartonella, tuberculosis, syphilis, CMV retinitis, or Lyme disease as determined by electronic ICD-9 code search and individual chart review.

Proportions were compared using the Fisher's exact test. Means of continuous variables were compared using the two-sample t-test. Odds ratios for the effect of smoking on case status were calculated using multivariate logistic regression models adjusting for age, race, sex, and socioeconomic status, based on the median family income in a patient's zip code. All analyses were performed using Stata (Stata 13; StataCorp LP).

Results

A total of 224 patients had a confirmed diagnosis of uveitis, 108 of whom were incident cases during the study period. For this study, we only included cases ≥18 years of age, resulting in 105 incident cases. Five of the 105 incident cases did not have a recorded smoking status and were excluded from the study. Twelve of the 540 patients in the ophthalmology control group were excluded for missing smoking status. Six of the 540 patients in the general control group were excluded because they were <18 years of age and 12 were excluded for missing smoking status.

Demographic information was collected for uveitis cases and controls (Table 1). Compared to both control groups, cases did not differ significantly in regard to race, sex, and median household income. Uveitis patients, however, were generally younger than those in the ophthalmology control group (mean age: 52 years vs. 63 years, P<0.001).

The majority of incident cases had anterior uveitis (n=86, 86%) and were non-infectious (n=80, 80%). Intermediate and posterior/panuveitis accounted for 3 (3%) and 11 (12%) of cases, respectively. Macular edema was only noted in 2 patients.

Multivariate logistic regressions comparing cases against both control groups are presented in Table 2. While current smokers had 63% greater odds of developing uveitis relative to never smokers when using the general control group, this association did not reach statistical significance (OR 1.63, 95% CI 0.88 to 3.00, *P*=0.12, Table 2). Using the ophthalmology controls, however, revealed current smokers to have more than twice the odds of developing uveitis (OR 2.33, 95% CI 1.22 to 4.45, *P*=0.01, Table 2). The association between current smoking and non-infectious uveitis was even stronger, reaching statistical significance when using both the general control group (OR 2.10, 95% CI 1.10 – 3.99 *P*=0.02) and ophthalmology control group (OR 2.96, 95% CI 1.52 – 5.77, *P*=0.001). There was no association between infectious uveitis and current smoking using general controls (OR 0.29, 95% CI 0.03 – 2.34, *P*=0.24) or ophthalmology controls (OR 0.35, 95% CI 0.04 – 2.91, *P*=0.33).

Discussion

Results from this population-based study reveal approximately 2-fold greater odds of new onset uveitis among current smokers compared to never smokers. Multivariate logistic regressions adjusting for race, sex, age, and socioeconomic status indicate the overall odds ratios for developing uveitis to be 1.63 and 2.33 for current smokers relative to never smokers when using the general and ophthalmology control groups, respectively. Although the p-value for the odds ratio using the general control group did not reach statistical significance, the findings do not contradict the results using the ophthalmology control group. The odds ratio confidence interval using general controls includes a moderate effect in the same direction as the odds ratio using the ophthalmology control group. The association between current smoking and non-infectious uveitis was even greater. A previous study found smoking was significantly associated with infectious uveitis.[12] We were not able to show a significant association with infectious uveitis and smoking. However, the low odds ratio estimate does raise the question if there is a differential effect on the development of noninfectious versus infectious uveitis. This needs to be looked at further in future studies. Overall, these results support a potential role for cigarette smoking in the development of uveitis.

Several pathological mechanisms can explain the association between cigarette smoking and uveitis. Long term exposure to the reactive oxygen species in cigarette smoke upregulates the expression of TLR4 by human macrophages, increasing NF-κB activation and transcription of the leukocyte chemoattractant IL-8.[18,19] Nicotine exerts an analogous effect in neutrophils by generating peroxynitrite, a nitrate isomer that binds acetylcholine receptors to activate additional NF-κB-mediated IL-8 transcription.[18,20] Elevated concentrations of IL-8, as seen in the aqueous humor in uveitis, act in concert with IL-6 and TNF-α to promote the migration and activation of macrophages that attack the uvea.[21–23]

Another pathological process involves the polycyclic aromatic hydrocarbons in cigarette smoke. Many of these carcinogenic compounds induce Th17 cell expansion by binding aryl hydrocarbon receptors on memory T cells.[24, 25]The resultant rise in Th17 population leads to increased secretions of IL-17 and IL-22, which in turn promote the migration and extravasation of leukocytes into various tissues.[26] Newly emerging data have accordingly

implicated Th17 cells in the pathogenesis of not only uveitis, but also psoriasis, rheumatoid arthritis, and multiple sclerosis.[26–31] This shared pathology likely explains why smoking is associated with multiple and often concomitantly occurring autoimmune diseases.

Findings from this population-based study substantiate those reported in a previous case-control study. In 2010, Lin et al. calculated that smokers have overall 2.2-fold increased odds of developing uveitis compared to never smokers.[12] Other studies have suggested an association between smoking and increased uveitic severity. Roesel et al. recently reported that uveitis is 1.8 times more likely to have clinical activity in smokers, leading to increased incidence rates of macular edema and cataracts.[13] Galor et al. likewise observed that patients with ocular inflammation who have positive smoking histories generally have poorer visual acuity.[14] Their observations corroborated those of Thorne et al., who reported a dose-dependent association between smoking and CME among patients with intermediate uveitis.[15] Together, these studies and ours support the notion that smoking contributes not only to the severity of uveitis, but also its onset.

We acknowledge several limitations to our study. Information on the duration and quantity of exposure to cigarette smoke was not available. This precluded detection of a dose-dependent association between smoking and uveitis. Consequently, ORs for past and passive smokers should be interpreted conservatively. Compared to tertiary settings, Kaiser's patient population also generally contains less severe cases. As a result, uveitic complications such as macular edema were relatively uncommon, preventing assessment of disease severity in relation to smoking status. Risk assessment by anatomic subtype, which was done before in a tertiary setting,[12] was not done here given the relatively low number of patients with intermediate, posterior, or pan- uveitis. In addition, it is possible there was misclassification of cases as noninfectious versus infectious uveitis. Even though chart review was done to adjudicate diagnoses, it was not possible to review every laboratory investigation to insure infection was adequately ruled out. However, this does not affect our primary analysis which included all incident uveitis cases.

Even with the aforementioned limitations, this study possesses several key strengths. In addition to adjusting for confounders such as age, sex, race, and socioeconomic status, we were able to ascertain smoking status at the time of diagnosis. Given that only approximately 5% of Kaiser Hawaii patients have dual insurance plans that would allow them to receive ophthalmology care elsewhere, it is also unlikely that many cases were missed. This offers a crucial advantage that addresses a major weakness of previous studies at tertiary eye clinics, in which patients were able to access care through multiple medical systems. Despite this difference in study population, the comparability between our ORs and a previously reported one[12] suggests that our results are generalizable to other populations.

In summary, our findings implicate smoking as a risk factor for developing uveitis. From a clinical angle, these results highlight the impact of lifestyle choices on disease manifestation, emphasizing the importance of encouraging patients to modify their attitudes and behaviors with regard to smoking. Additional investigation into the pathological mechanisms that underlie the association between smoking and uveitis will be necessary in order to definitively establish causality.

Acknowledgments

Financial support: Dr. Acharya's work was supported by a University of California at San Francisco Research Evaluation and Allocation Committee Award, and she is currently supported by NEI U10EY021125. The University of California at San Francisco Department of Ophthalmology is supported by National Eye Institute grant EY06190, That Man May See Foundation, and an unrestricted grant from the Research to Prevent Blindness Foundation.

The sponsors had no role in the design or conduct of this research.

References

1. Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged ≥18 years --- United States, 2005--2010. MMWR Morb Mortal Wkly Rep. 2011; 60(35):1207–1212. [PubMed: 21900875]
2. Burchiel SW, Luster MI. Signaling by environmental polycyclic aromatic hydrocarbons in human lymphocytes. Clin Immunol. 2001; 98(1):2–10. [PubMed: 11141320]
3. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun. 2010; 34(3):J258–J265. [PubMed: 20042314]
4. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis. Ann Rheum Dis. 2003; 62(9):835–841. [PubMed: 12922955]
5. Saag KG, Cerhan JR, Kolluri S, Ohashi K, et al. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis. 1997; 56(8):463–469. [PubMed: 9306868]
6. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. JAMA. 1993; 269(4):479–482. [PubMed: 8419666]
7. 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(1):59–64. [PubMed: 17047020]
8. Hernán MA, Oleky MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. Am J Epidemiol. 2001; 154(1):69–74. [PubMed: 11427406]
9. Hernán MA, Jick SS, Logroscino G, et al. Cigarette smoking and the progression of multiple sclerosis. Brain. 2005; 128(pt 6):1461–1465. [PubMed: 15758034]
10. Costenbader KH, Kim DJ, Peerzada J, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum. 2004; 50(3):849–857. [PubMed: 15022327]
11. Ghaussy NO, Sibbitt W, Bankhurst AD, Qualls CR. Cigarette smoking and disease activity in systemic lupus erythematosus. J Rheumatol. 2003; 30(6):1215–1221. [PubMed: 12784392]
12. Lin P, Loh AR, Margolis TP, Acharya NR. Cigarette smoking as a risk factor for uveitis. Ophthalmology. 2010; 117(3):585–590. [PubMed: 20036011]
13. Roesel M, Ruttig A, Schumacher C, et al. Smoking complicates the course of non-infectious uveitis. Graefe's Arch Clin Exp Ophthalmol. 2011; 249(6):903–907. [PubMed: 21207052]
14. Galor A, Feuer W, Kempen JH, et al. Adverse effects of smoking on patients with ocular inflammation. Br J Ophthalmol. 2010; 94(7):848–853. [PubMed: 20606023]
15. 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(5):841–846. [PubMed: 18321467]
16. Bilgin AB, Turkoglu EB, Ilhan HD, et al. Is smoking a risk factor in ocular Behçet disease? Ocul Immunol Inflamm. In press.
17. Acharya NR, Tham VM, Esterberg E, et al. Incidence and prevalence of uveitis: results from the pacific ocular inflammation study. JAMA Ophthalmol. 2013; 131(11):1405–1412. [PubMed: 24008391]
18. Gonçalves RB, Coletta RD, Silvério KG, et al. Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm Res. 2011; 60(5):409–424. [PubMed: 21298317]
19. Sarir H, Mortaz E, Karimi K, et al. Cigarette smoke regulates the expression of TLR4 and IL-8 production by human macrophages. J Inflamm. 2009; 6(1):12.

20. Iho S, Tanaka Y, Takauji R, et al. Nicotine induces human neutrophils to produce IL-8 through the generation of peroxynitrite and subsequent activation of NF-κB. J Leukoc Biol. 2003; 74(5):942–951. [PubMed: 12960242]
21. Curnow SJ, Falciani F, Durrani OM, et al. Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. Invest Ophthalmol Vis Sci. 2005; 46(11):4251–4259. [PubMed: 16249505]
22. Valentincic NV, de Groot-Mijnes JD, Kraut A, et al. Intraocular and serum cytokine profiles in patients with intermediate uveitis. Mol Vis. 2011; (17):2003–2010. [PubMed: 21850175]
23. Khera TK, Copland DA, Boldison J, et al. Tumour necrosis factor - mediated macrophage activation in the target organ is critical for clinical manifestation of uveitis. Clin Exp Immunol. 2012; 168(2):165–177. [PubMed: 22471277]
24. Quintana FJ, Basso AS, Iglesias AH, et al. Control of Treg and TH17 cell differentiation by the aryl hydrocarbon receptor. Nature. 2008; 453(7191):65–71. [PubMed: 18362915]
25. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008; 453(7191):106–109. [PubMed: 18362914]
26. Torii K, Saito C, Furuhashi T, et al. Tobacco smoke is related to Th17 generation with clinical implications for psoriasis patients. Exp Dermatol. 2011; 20(4):371–373. [PubMed: 21355889]
27. Escobar T, Yu CR, Muljo SA, Egwuagu CE. STAT3 activates miR-155 in Th17 cells and acts in concert to promote experimental autoimmune uveitis. Invest Ophthalmol Vis Sci. 2013; 54(6): 4017–4025. [PubMed: 23674757]
28. Wang RX, Yu CR, Mahdi RM, Egwuagu CE. Novel IL27p28/ IL12p40 cytokine suppressed experimental autoimmune uveitis by inhibiting autoreactive Th1/Th17 cells and promoting expansion of regulatory T cells. J Biol Chem. 2012; 287(43):36012–36021. [PubMed: 22936807]
29. van Hamburg JP, Asmawidjaja PS, Davelaar N, et al. Th17 cells, but not Th1 cells, from patients with early rheumatoid arthritis are potent inducers of matrix metalloproteinases and proinflammatory cytokines upon synovial fibroblast interaction, including autocrine interleukin - 17A production. Arthritis Rheum. 2011; 63(1):73–83. [PubMed: 20954258]
30. Zhang L, Li JM, Liu XG. Elevated Th22 cells correlated with Th17 cells in patients with rheumatoid arthritis. J Clin Immunol. 2011; 31(4):606–614. [PubMed: 21556937]
31. Jadidi–Niaragh F, Mirshafiey A. Th17 cell, the new player of neuroinflammatory process in multiple sclerosis. Scand J Immunol. 2011; 74(1):1–13. [PubMed: 21338381]

Table 1

Baseline characteristics of incident uveitis cases, general controls, and ophthalmology controls

	Incident Cases	General Controls	p-value	Ophthalmology Controls	p-value
Total	**100 N (%)**	**522 N (%)**		**528 N (%)**	
Smoking History			0.16[a]		0.002[a]
Current Smoker	21 (21)	75 (14)		47 (9)	
Past Smoker	17 (17)	129 (25)		146 (28)	
Passive (Secondhand)	1 (1)	4 (1)		3 (1)	
Never	61 (61)	314 (60)		332 (63)	
Sex			0.15[a]		0.28[a]
Female	48 (48)	294 (56)		287 (54)	
Race			0.08[a]		0.60[a]
Asian	38 (38)	161 (31)		211 (40)	
Caucasian	22 (22)	133 (25)		135 (26)	
Pacific Islander	17 (17)	131 (25)		96 (18)	
African American	2 (2)	1 (<1)		6 (1)	
Alaskan/Native American	1 (1)	9 (2)		5 (1)	
Unknown	20 (20)	87 (17)		75 (14)	
Mean Age in Years (SD)	52 (17.2)	53 (18.3)	0.61[b]	63 (17.5)	<0.001[b]
Mean Median Household Income[c] (SD)	$55417 ($17907)	$55344 ($18438)	0.97[b]	$57202 ($17954)	0.38[b]

[a] P-value obtained by Fisher's exact test

[b] P-value obtained by two-sample t-test

[c] Median household income data missing for 7 cases, 51 general controls, 56 ophthalmology controls

SD= standard deviation

Table 2

Multivariate logistic regressions predicting new onset uveitis by smoking status

	Odds ratio: Cases vs General Controls (95% CI)	p-value	Odds ratio: Cases vs Ophthalmology Controls (95% CI)	p-value
Smoking Status (vs Never)				
Current Smoker	1.63 (0.88 – 3.00)	0.12	2.33 (1.22 – 4.45)	0.01
Past Smoker	0.73 (0.40 – 1.35)	0.32	0.82 (0.44 – 1.53)	0.53
Passive (Secondhand)	1.96 (0.19 – 20.06)	0.57	1.28 (0.96 – 17.19)	0.85
Age (by decade)	0.99 (0.87 – 1.14)	0.94	0.72 (0.63 – 0.83)	<0.001
Sex				
Male	1.33 (0.84 – 2.10)	0.57	1.16 (0.72 – 1.86)	0.54
Median Income (by $10,000)	0.99 (0.87 – 1.12)	0.82	0.95 (0.83 – 1.09)	0.49
Race (vs Caucasian)				
Alaskan/Native American	1.13 (0.13 – 9.99)	0.92	0.64 (0.07 – 6.32)	0.70
Asian	1.68 (0.92 – 3.10)	0.09	1.16 (0.62 – 2.15)	0.65
African American	11.80 (0.98 – 141.77)	0.05	1.52 (0.24 – 9.53)	0.65
Pacific Islander	0.91 (0.44 – 1.87)	0.80	0.79 (0.40 – 1.92)	0.55
Unknown	1.23 (0.59 – 2.58)	0.59	0.95 (0.83 – 1.09)	0.73

CI= confidence interval