AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

# 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] Nisha R. Acharya, MD, MS[1,6,7]*

***Purpose:*** 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 aged ≥18 years who were 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, 9th 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.

***Results:*** Current smokers had a 1.63 (95% confidence interval [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 with those who never smoked using the general and ophthalmology control groups, respectively. The association was even stronger with noninfectious uveitis, which yielded odds ratios 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 noninfectious 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. *Ophthalmology 2015;■:1–5 © 2015 by the American Academy of Ophthalmology.*

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 proinflammatory pathways and trigger pathologic 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]

Although uveitis and the aforementioned diseases all arise from immune dysregulation, relatively few data exist to support the association between smoking and uveitis. There has been only one prior case-control study of 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 patients with uveitis 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 more than 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 in its database. This 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



http://dx.doi.org/10.1016/j.ophtha.2015.02.034
ISSN 0161-6420/15

Table 1. Baseline Characteristics of Incident Uveitis Cases, General Controls, and Ophthalmology Controls

| Total | Incident Cases (n = 100) | General Controls (n = 522) | P Value | Ophthalmology Controls (n = 528) | P Value |
|---|---|---|---|---|---|
| Smoking history | | | 0.16* | | 0.002* |
| Current | 21 (21) | 75 (14) | | 47 (9) | |
| Past | 17 (17) | 129 (25) | | 146 (28) | |
| Passive (secondhand) | 1 (1) | 4 (1) | | 3 (1) | |
| Never | 61 (61) | 314 (60) | | 332 (63) | |
| Female sex | 48 (48) | 294 (56) | 0.15* | 287 (54) | 0.28* |
| Race | | | 0.08* | | 0.60* |
| Asian | 38 (38) | 161 (31) | | 211 (40) | |
| White | 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, yrs (SD) | 52 (17.2) | 53 (18.3) | 0.61† | 63 (17.5) | <0.001† |
| Mean median household income‡ (SD) | $55 417 ($17 907) | $55 344 ($18 438) | 0.97† | $57 202 ($17 954) | 0.38† |

SD = standard deviation.
Data are n (%) unless otherwise indicated.
*P value obtained by Fisher exact test.
†P value obtained by 2-sample t test.
‡Median household income data missing for 7 cases, 51 general controls, and 56 ophthalmology controls.

identify cases, visits between the study period of January 1, 2006, and December 31, 2007, were queried for International Classification of Diseases, 9th 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 described in detail elsewhere.[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 1 health care 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 aged at least 18 years.

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 as close as possible to the date of diagnosis. For patients without a smoking history before 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 never smoked, currently smoking, quit, or passive. Infectious uveitis was defined by an associated diagnosis of herpes simplex virus, herpes zoster virus, histoplasmosis, toxoplasmosis, human immunodeficiency virus, Bartonella, tuberculosis, syphilis, cytomegalovirus retinitis, or Lyme disease as determined by electronic ICD-9 code search and individual chart review.

Proportions were compared using the Fisher exact test. Means of continuous variables were compared using the 2-sample *t* test. Odds ratios (ORs) 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 version 13 (StataCorp LP, College Station, TX).

## 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 included only patients aged ≥18 years, 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 aged <18 years, and 12 patients were excluded for missing smoking status.

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

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

Multivariate logistic regressions comparing cases against both control groups are presented in Table 2. Although 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% confidence interval [CI], 0.88–3.00; $P = 0.12$) (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, 1.22–4.45; $P = 0.01$) (Table 2). The association between current smoking and noninfectious uveitis was even stronger, reaching statistical significance when using both the