

Does Cigarette Smoking Alter the Risk of Pterygium? A Systematic Review and Meta-Analysis

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PURPOSE. To determine the association of cigarette smoking with pterygium.

METHODS. Potentially eligible studies published from the year 1946 to December 28, 2013 were identified from MEDLINE, EMBASE, and Cochrane Library databases, and reference lists. All studies that evaluated smoking as an independent factor for pterygium were identified. Study-specific odds ratios (ORs) were combined using the random-effects model when $P < 0.1$ in the test for heterogeneity, or otherwise the fixed-effects model was used. Meta-regression, sensitivity analysis, and evaluation of potential biases were undertaken. The ORs with 95% confidence intervals (CIs) of smoking as an associated factor for pterygium were analyzed.

RESULTS. We included 24 articles incorporating 95,279 participants from 20 cross-sectional studies, 2 hospital-based case-control studies, and 2 population-based cohort studies. The combined OR of cigarette smoking (current or ever smoked) for risk of pterygium was 0.82 (95% CI, 0.69–0.97; $P = 0.025$). The results remained consistent among current smokers (OR, 0.68; 95% CI, 0.61–0.76; $P = 4.57 \times 10^{-12}$), but not in ex-smokers (OR, 1.05; 95% CI, 0.87–1.27; $P = 0.59$). The impact of ultraviolet light (UV) exposure ($P = 0.082$) and sex ($P = 0.553$) on the effect of smoking was insignificant in meta-regression. Sensitivity analysis confirmed the protective effect and nonrelevance of these two study-level variables. Begg's funnel plots and Egger's test showed minimal publication bias.

CONCLUSIONS. The results of this meta-analysis show that cigarette smoking was associated with a reduced risk of pterygium, especially in current smokers. This effect may be independent of UV exposure and sex. Investigations are needed to unveil its molecular basis serving therapeutic purposes.

Keywords: smoking, cigarette smoking, pterygium, pterygia, risk factor, protective factor

Pterygium is an inflammatory fibrovascular mass that extends from the interpalpebral conjunctiva over the adjacent peripheral cornea.¹ Its corneal ingrowth can lead to ocular irritation and visual impairment by induction of astigmatism, blockade of visual axis, or loss of corneal transparency.² The prevalence of pterygium varies in different populations, ranging from 2.83% in Australians³ to 39.0% among the Chinese Bai.⁴

Despite its poorly understood pathogenesis, several risk factors had been confirmed in the occurrence of pterygium, namely old age, male sex, and ultraviolet light (UV) exposure (i.e., lower latitude and outdoor work).^{3–24} Cigarette smoking, a modifiable factor and an important public health problem, has been studied as a risk factor for pterygium.^{5,8,9,14,17,19,20,22–25} However, so far the role of smoking in pterygium development remains unclear and evidences are contradictory. Furthermore, smoking has been reported repeatedly as a protective factor against pterygium after adjusting for multiple risk factors.^{11,14,19,22,23,25} This observation has been attributed variously to small study sample size, imbalance of factors distributed in cases and controls, or unclear definition of

smoking status. We conducted this systematic review and meta-analysis to determine the association between smoking and pterygium based on the available evidence.

METHODS

Eligibility Criteria

We included studies that fulfilled the following criteria: (1) a cross-sectional, prospective cohort, or case-control study; (2) diagnosis of pterygium was based on slit-lamp examination by ophthalmologists; (3) smoking status was recorded and tested as an independent factor; (4) adjusted odds ratio (OR) and 95% confidence interval (95% CI) were estimated with multiple logistic regression; or the occurrence of pterygium in subjects with and without current/past smoking history were reported or can be resolved. Animal studies, case reports, reviews, abstracts, conference proceedings, editorials, non-English articles, and studies that did not analyze smoking as a factor were excluded.

Search Strategies

Literature search was performed via Ovid platform in MEDLINE (available in the public domain at <http://www.nlm.nih.gov/bsd/licensee/medpmmenu.html>), EMBASE (available in the public domain at <http://www.embase.com/info/helpfiles/>), and the Cochrane Library (available in the public domain at <http://www.thecochranelibrary.com/view/0/index.html>) databases from the year 1946 up to December 28, 2013. We used Boolean logic and search terms with controlled vocabularies (i.e., Medical Subject Heading terms), including “pterygium,” “pterygia,” “epidemiology,” “prevalence,” “incidence,” “occurrence,” and “risk or protective factor” (Supplementary Table S1). To supplement the online search, we manually scanned the reference lists of identified articles, reviews, and meta-analysis for all potentially relevant articles. No language filters were applied during literature search.

Study Selection

Duplicated records in retrieved citations were removed. Two reviewers (SSR and YP) independently sifted through the titles and abstracts. Consensus on inclusion and exclusion of studies was reached.

Data Extraction and Risk of Bias Assessment

The following information was collected: (1) study information, including the year of publication, study design, study country/region/city, ethnicity of participants, age range, and sample size; (2) outcome measures, namely, definition of smoking status, occurrence of pterygium in subjects with and without smoking exposure, reported unadjusted and adjusted ORs, and 95% CI (or SE), and adjusted co-variables; and (3) study design features, including the proportion of male sex, smokers, and subjects with researcher-defined high and low level of UV exposures in patients and nonpatients.

Referring to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines²⁶ and the Cochrane Handbook for Systematic Reviews of Interventions,²⁷ we modified the Estabrooks' Quality Assessment and Validity Tool for Cross-Sectional Studies (Supplementary Methods). The modified Estabrooks' tool contains 14 items covering three core domains: (1) sample (probabilistic sample used, representative, sample size appropriate for power, sample drawn from multiple sites, cluster/stratified design, multiple adjusted, response rate >50%), (2) measurement (detective variable [primary outcome] directly measured/administrative, reliability, validity), and (3) statistical analysis (appropriate tests used, *P* values reported, CI reported, missing data managed appropriately). We separated the 14 items into two groups based on relative importance in assessing the risk of bias. Group one included six items: probabilistic sample used, sample size appropriate for power, response rate exceeding 50%, validity, appropriate tests used, and CI reported. Group two included the remaining 8 items. Study was considered to be of high risk when one item in group one was marked as “No” or two items marked as “N/A,” or any two items from group two marked as “No” or three items marked as “N/A.”

The Newcastle Ottawa Scale (NOS, available in the public domain at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was adopted to evaluate case-control and cohort studies (Supplementary Methods).²⁸⁻³⁰ Stars were given to study that meets requirements in NOS from three dimensions. Studies with six or less stars were considered high risk and were excluded from sensitivity analysis.

Two reviewers (SSR and YP) extracted data and assessed risk of bias separately. Data were recorded on a customized data form. Disagreements in data extraction and assessment of risk of bias were resolved with consensus.

Data Synthesis and Analysis

We assessed the association between smoking status and pterygium by combining OR from case-control, cross-sectional, and cohort studies. We classified smoking status into three groups: never smoked, ex-smokers who had smoked in a predefined period of time in the past, and current smokers who have been smoking for a certain period of time and exceeded a predefined cumulative amount. In the eligible studies for meta-analysis, 7 studies used “ever smoked” as the definition for smokers.^{5,7,9,11,22,31,32} However, only Rezvan et al.⁵ reported a detailed definition for subjects who “ever smoked” which was the person who smoked at least once a week for at least 6 months at some time in their lives. Another study used “lifetime smoker” (defined as current smokers and have smoked at least 100 cigarettes in their lifetime) that grouped current smokers and subjects who ever smoked together.²³ Studies without explicit definition of smoking status were grouped into current smoker and “ever smoked” groups. In our analysis, adjusted ORs and 95% CI were used assuming that they were more accurate estimates of the true associations. If adjusted OR and 95% CI were not available, unadjusted OR with 95% CI was estimated using nonsmoker as reference and was meta-analyzed. Heterogeneity between studies was ascertained by *Q*-statistic and was assessed by *I*².³³ The *Q*-statistic was considered significant when *P* < 0.1. Higher values of *I*² denoted greater degree of heterogeneity, with <24%, 25% to 49%, 50% to 74%, and ≥75% denoting none, low, moderate, and high heterogeneity, respectively.^{33,34} If *P* for *Q* < 0.1 or *I*² ≥ 50%, a random-effects model (DerSimonian and Laird method) was used,³⁵ otherwise we used a fixed-effects model (Mantel-Haenszel method).³⁶ Funnel plot and Egger's test for asymmetry were performed routinely to detect the presence of potential biases, that is, publication bias.^{27,37,38} Subgroup analysis was conducted by smoking status (current smoker, ex-smoker, and subjects current smoker or “ever smoked”), study design (i.e., case-control and cross-sectional study), availability of adjusted OR, and race group.

We performed meta-regression to assess the impact of UV exposure and sex on the effect of smoking. We extracted the number of subjects who have high or low UV exposure, which was defined by individual studies as number of hours out in the sun/outdoor activity, outdoor job/main occupation, outdoor job history, lifetime ocular sun exposure (estimated using the Melbourne visual impairment project model),^{3,39} and wearing of protective gear (i.e., sunglasses/spectacles and hat/umbrella) in the pterygium and pterygium-free groups, respectively. The number of males and females from the pterygium group and pterygium-free group also was extracted. The difference between disease and disease-free groups was calculated as the extra proportion of subjects with high UV exposure (or males) in patients than that in nonpatients. The differences then were transformed by multiplying by 100. The natural logarithm of OR was the outcome (dependent) variable, whereas, the UV exposure and sex differences were explanatory (potential effect modifier) variables. Random-effects meta-regression was used. The study was weighted by precisions (1/[within-study variance + residual between-study variance]). The residual between-study variance was estimated using restricted maximum likelihood method.^{40,41}

Furthermore, we conducted sensitivity analysis to confirm the association by removing studies with higher risk of

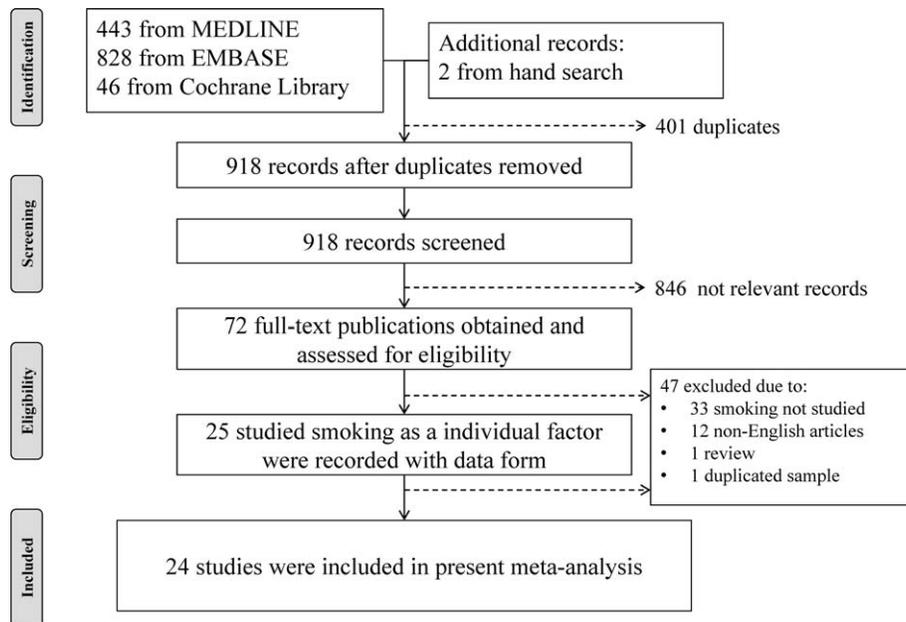


FIGURE 1. Flow chart showing method of literature search and results of literature review.

introducing bias and to assess the contribution of each study to the heterogeneity by sequentially omitting one study and recalculating the combined ORs.

Meta-analyses were performed with R software for statistical computing (v3.0.0, available in the public domain at <http://cran.r-project.org/>). Meta-regression was conducted in STATA version 12.1 (StataCorp LP, College Station, TX, USA). Alpha was set to 0.05 for a 2-sided test.

RESULTS

Overall, 1319 citations were identified from online search and manual screening of reference lists. We selected 24 studies published between 2000 and 2013 for meta-analysis.^{3-5,7-11,14,17-25,31,32,42-45} Figure 1 summarizes the workflow of selection process and results. Included studies consisted of 20 cross-sectional, 2 hospital-based case-control, and 2 population-based cohort studies (Table 1). We included 24 studies, incorporating 95,279 subjects, mainly from six ethnic groups or races, namely, Chinese,^{4,20,21,25,32} Caucasians,^{3,18,19} Indians,^{8,22,45} Arabs,^{5,43,44} Barbadians,^{14,31} Japanese,^{17,24} and others (Bamar,¹⁰ Korean,²³ Malay,⁹ and mixed^{7,42,46}). All included studies defined the pterygium cases as having involvement of either or both eyes, and 17 studies adopted a clear definition for smoking status^{5,7-9,11,14,18-20,22,23,25,31,32,42,45}. Sample size ranged from 186 to 14,920, and the majority of study populations exceeded 1000 (Table 1). Duplicated study populations were identified in two studies,^{42,46} and one of these two studies⁴² was used in the analysis. In all, 14 studies provided adjusted OR and SE. The other studies reported either unadjusted OR or the number of smokers in patients and nonpatients that enabled calculations (Table 2).

Meta-Analysis

We found that smoking reduced the risk of pterygium in meta-analysis of unadjusted and adjusted ORs. This finding was consistent in the analyses for participants who had ever smoked and the current smokers (Table 3). Based on 13 studies that included current smokers or subjects who had

ever smoked, meta-analysis using adjusted ORs showed a risk modifying effect of smoking (Fig. 2A; OR, 0.82; 95% CI, 0.69–0.97; $P = 0.025$). Analysis using studies of each type of study design did not show statistical significance ($P > 0.138$, Table 3). In further analysis of 8 studies that included current smokers, the pooled OR showed protective effects of smoking (OR, 0.70; 95% CI, 0.51–0.96; $P = 0.026$) on pterygium. This observation was confirmed (OR, 0.68; 95% CI, 0.61–0.76; $P = 4.57 \times 10^{-12}$) by combining adjusted ORs of 6 studies from the same category (Fig. 2B; Table 3). Although the meta-analyzed OR from 7 cross-sectional studies fell at borderline significance (OR, 0.75; 95% CI, 0.56–1.01; $P = 0.05$), smoking reduced risk of pterygium in current smokers. In the analysis of two cross-sectional studies on ex-smokers we did not find a significant effect of smoking ($P = 0.590$). In subgroup analysis by ethnicity, we found that this association was maintained in the Asian population (OR, 0.8; 95% CI, 0.65–1.00; $P = 0.048$) and in current smokers of Asian (OR, 0.66; 95% CI, 0.58–0.76; $P = 1.69 \times 10^{-9}$) or Caucasian (OR, 0.77; 95% CI, 0.62–0.97; $P = 0.024$; Supplementary Table S2) ancestry.

Risk of Bias Assessments and Sensitivity Analysis

In our evaluation, most studies had a robust design and, therefore, had low risk for introduction of bias (Supplementary Tables S3–S5). However, we identified one cross-sectional study²¹ that may introduce bias to the result (Supplementary Table S3). Subsequently, a sensitivity analysis was performed.

We performed the analyses by sequentially omitting one study at a time (in descending order for risk of bias) to confirm the associations. We found that the effects became significant in the analysis using all smokers from cross-sectional and case-control studies ($P = 0.036$), and in analysis only used cross-sectional studies ($P = 0.045$, Table 3). The heterogeneity was reduced when the study of Li and Cui²¹ was excluded. All of the other results remain unchanged.

No indication of any obvious asymmetry was observed according to the shapes of funnel plots and Egger's test as detailed in Table 3.

TABLE 1. Characteristics of Included Studies in Meta-Analysis

	First Author	Study Title	Year of Publication	Study Design	Country (Ethnicity)	Age Range	Sample Size	Studied Smoking Status
1	McCarty CA ³	-	2000	CS	Australia (Caucasian)	40+	5,044	Smokers (not specified)/nonsmokers
2	Saw SM ⁴²	-	2000	CC	Singapore (mixed)	30+	186	Current smokers/nonsmokers
3	Wong TY ²⁰	TPS	2000	CS	Singapore (Chinese)	40-79	2,000	Current smokers/nonsmokers
4	Luthra R ¹⁴	Barbados ES	2001	CS	Barbado (Barbadian)	40-84	2,617	Current smokers/nonsmokers
5	Gazzard G ¹¹	-	2002	CS	Indonesia (Indonesian)	21+	1,210	Smokers (defined as ever)/nonsmokers
6	Al-Bdour M ⁴³	-	2004	CC	Jordan (Arab)	22-72	288	Smokers (not specified)/nonsmokers
7	Durkin SR ¹⁰	MES	2007	CS	Myanmar (Bamar)	40+	2,076	Smokers (not specified)/nonsmokers
8	Nemesure B ³¹	Barbados ES	2008	PC	Barbado (Barbadian)	40-84	1,888	Smokers (defined as ever)/nonsmokers
9	Fotouhi A ⁴⁴	TES	2009	CS	Iran (Persian)	1+	4,564	Smokers (not specified)/nonsmokers
10	Shiroma H ¹⁷	KS	2009	CS	Japan (Japanese)	40+	3,747	Smokers (not specified)/nonsmokers
11	West S ¹⁹	PVER	2009	CS	USA (Caucasian)	40+	3,788	Current smokers/ex-smokers/nonsmokers
12	Cajucum-Uy H ⁹	SMES	2010	CS	Singapore (Malay)	40-79	3,257	Smokers (defined as ever)/nonsmokers
13	Viso E ¹⁸	-	2011	CS	Spain (Caucasian)	40+	619	Current smokers/ex-smokers/nonsmokers
14	Asokan R ⁸	CGS	2012	CS	India (Indian)	40+	7,774	Current smokers (mild/moderate/heavy)
15	Li Z ²¹	SHES	2012	CS	China (Chinese)	50+	5,057	Smokers (not specified)/nonsmokers
16	Marcus A ⁷	-	2012	CS	Singapore (mixed)	40+	8,906	Smokers (defined as ever)/nonsmokers
17	Rezvan F ⁵	SECS	2012	CS	Iran (Iranian)	40-64	5,190	Smokers (defined as ever)/nonsmokers
18	Zhong H ⁴	YMES	2012	CS	China (Chinese)	50+	2,133	Smokers (not specified)/nonsmokers
19	Lanping S ²⁵	HES	2013	CS	China (Chinese)	40+	6,599	Current smokers/ex-smokers/nonsmokers
20	Marmamula S ²²	APEDS	2013	CS	India (Indian)	30+	5,586	Smokers (defined as ever)/nonsmokers
21	Nangia V ⁴⁵	CIEMS	2013	CS	India (Indian)	30+	4,711	Smokers (package-y)
22	Rim THT ²³	KNHNES	2013	CS	South Korea (Korean)	30+	14,920	Current smokers/nonsmokers
23	Tano T ²⁴	LSHOACS	2013	CS	Japan (Japanese)	40-74	2,312	Smokers (not specified)/nonsmokers
24	Zhao L ³²	Beijing ES	2013	PC	China (Chinese)	40+	2,695	Smokers (defined as ever)/nonsmokers

CC, hospital-based case-control study; CS, population-based cross-sectional study; PC, population-based cohort; TPS, the Tanjong Pagar Survey; Barbados ES, Barbados Eye Study; MES, Meiktila Eye Study; TES, The Tehran Eye Study; KS, Kumejima Study; PVER, Proyecto VER; SMES, Singapore Malay Eye Study; CGS, the Chennai Glaucoma Study; SHES, the Southern Harbin Eye Study; SECS, Shahroud Eye Cohort Study; YMES, Yunnan Minority Eye Study; HES, Handan Eye Study; APEDS, the Andhra Pradesh Eye Disease Study; CIEMS, The Central India Eye and Medical Study; KNHNES, The Korean National Health and Nutrition Examination Survey 2008-2010; LSHOACS, The Locomotive Syndrome and Health Outcome in Aizu Cohort Study; Beijing ES, The Beijing Eye Study.

Meta-Regression

To investigate the impact of UV exposure and sex on estimated OR for smoking, we performed random-effects meta-regression analysis. The regression used data from 12 and 21 studies for UV exposure and sex, respectively. Initially, the difference of UV exposure and sex, as defined in the Methods section, was put in the regression model separately. We did not obtain any statistically significant association for UV exposure (coefficient, -0.012; SE, 0.006; $P = 0.082$) and sex (coefficient, 0.004; SE, 0.006; $P = 0.553$). In multiple regression analysis of both factors, we did not detect significant contribution of these two factors to the effects of smoking. In subsequent sensitivity

analysis, we restricted the regressions to studies of cross-sectional design, reporting unadjusted ORs, adjusted ORs, and by adopting the different definitions for UV exposure in two studies.^{11,43} The results remained unchanged.

DISCUSSION

Cigarette smoking is a public health problem. Its negative impact has been confirmed in ocular conditions; that is, age-related macular degeneration⁴⁷ and thyroid eye disease.^{48,49} Its contribution to the development of pterygium has been controversial in a number of population-based studies. Obvious

TABLE 2. Reported ORs and Adjusted Factors From Individual Study

First Author (Year of Publication)	Reported or Estimated OR, 95% CI				Adjusted Factors
	Current Smoker	Ex-Smoker	Ever Smoked	Not Specified	
1 McCarty CA (2000) ³	-	-	0.82 (0.51-1.31)	-	-
2 Saw SM (2000) ⁴²	0.27 (0.12-0.62)	-	-	-	-
3 Wong TY (2000) ²⁰	-	-	-	1.70 (1.1-2.7)	-
4 Luthra R (2001) ¹⁴	0.62 (0.41-0.94)	-	-	-	-
	0.50 (0.32-0.77)*	-	-	-	-
5 Gazzard G (2002) ¹¹	-	-	0.96 (0.57-1.60)	-	Age, sex, income, occupation, outdoor activity
	-	-	0.46 (0.24-0.90)*	-	-
6 Al-Bdour M (2004) ⁴⁵	-	-	-	0.75 (0.46-1.22)	-
7 Durkin SR (2007) ¹⁰	-	-	-	1.04 (0.79-1.35)	Not specified: "various risk factors"
	-	-	-	0.97 (0.74-1.27)*	-
8 Nemesure B (2008) ³¹	-	-	0.82 (0.48-1.39)*	-	Age, sex
9 Fotouhi A (2009) ⁴⁴	-	-	-	2.70 (0.93-7.60)	Age, sex, ethnicity
10 Shiroma H (2009) ¹⁷	-	-	-	0.92 (0.80-1.06)	-
11 West S (2009) ¹⁹	1.03 (0.83-1.26)	1.51 (1.27-1.80)	-	-	Sex, education, income
	0.75 (0.59-0.94)*	1.04 (0.86-1.26)*	-	-	-
12 Cajucom-Uy H (2010) ⁹	1.20 (0.9-1.5)	-	-	-	Age, sex, total cholesterol, education, occupation
	1.20 (0.90-1.50)*	-	-	-	-
13 Viso E (2011) ¹⁸	-	1.46 (0.55-3.89)*	1.68 (0.56-5.01)*	-	Age, sex
14 Asokan R (2011) ⁸	-	-	-	-	Age, sex, population, and nature of work
Moderate vs. mild	0.69 (0.37-1.28)*	-	-	-	-
Heavy vs. mild	0.69 (0.37-1.33)*	-	-	-	-
15 Li Z (2012) ²¹	-	-	-	1.90 (1.51-2.35)	-
16 Marcus A (2012) ⁷	-	-	1.00 (0.90-1.20)*	-	Age, sex, race, education, diastolic BP, dry eye
17 Rezvan F (2012) ⁵	-	-	0.81 (0.62-1.06)	-	-
18 Zhong H (2012) ⁴	-	-	1.06 (0.81-1.38)	-	-
19 Lanping S (2013) ²⁵	-	-	0.50 (0.40-0.70)*	-	Age, sex, occupation, income, alcohol drinking and use of sunglasses or other protective measures
20 Marmamula S (2013) ²²	-	-	1.11 (0.94-1.32)	-	Age, sex, education, area of residence (urban/rural), occupation (outdoor work/no outdoor), alcohol use, spectacles use, hypertension, diabetes mellitus
	-	-	0.60 (0.40-0.70)*	-	-
21 Nangia V (2013) ⁴⁵	-	-	-	1.01 (1.00-1.02)	-
22 Rim THT (2013) ²³	-	-	0.70 (0.60-0.90)*	-	Age, sex, education, area of residence, occupation, and sun exposure
23 Tano T (2013) ²⁴	-	-	-	1.14 (0.60-2.18)*	Age, sex, outdoor job history
24 Zhao L (2013) ³²	-	-	1.15 (0.79-1.70)	-	-

* Adjusted OR and 95% CI.

disagreements between studies illustrate the necessity of conducting an exhaustive review and quantitative analysis on all available evidences to determine the association between smoking and occurrence of pterygium. In the current systematic review and meta-analysis, we examined 1319 published reports and analyzed data of 95,279 participants from 24 original articles. We found that smoking reduced the risks of pterygium, and this effect is unlikely to be affected by UV exposure and sex. To our knowledge, this is the first comprehensive summary and meta-analysis to address this issue. Although the definition of smoking status varied between studies, and in some studies the details were not provided, the results of our meta-analysis showed that regardless of the definitions used, smoking shows protective effects especially in current smokers. Past smoking did not alter the risks of pterygium that was revealed by two studies using explicit definition for an ex-smoker.^{18,19} Despite the large variations of genetic factors and lifestyles, we found no obvious

ethnic divergence regarding the association between smoking habit and risk of pterygium.

We noticed that the adjusted ORs pointed toward protective effects. In three studies published by Gazzard et al.,¹¹ West and Munoz,¹⁹ and Marmamula et al.²² The ORs became protective in multiple regressions when adjusted for age, sex, and outdoor activity. Although the adjusted ORs from Durkin et al.,¹⁰ West and Munoz,¹⁹ and Cajucom-Uy et al.⁹ remained insignificant, two of the ORs pointed toward protective direction (Durkin et al.,¹⁰ from 1.04-0.97; West and Munoz,¹⁹ from 1.51-1.04).

In this meta-analysis, we included two publications from the Barbados Eye Study. One cross-sectional study was reported in 2001 by Luthra et al.,¹⁴ while the other follow-up observation was published in 2008 by Nemesure et al.³¹ The fact that the adjusted OR in year 2008 was insignificant (OR, 0.82; 95% CI, 0.48-1.39) could be explained by the change in definition of smoking status from "current smoker" to subjects who "ever

TABLE 3. Meta-Analysis of Smoking as a Risk-Modifying Factor for Pterygium

	No. of Studies	Sample Size	Overall Effect			Heterogeneity		Egger's Test (P)	References
			OR, 95% CI	Z Score	P Value	I ² , %	Q (P)		
Current smoker or subjects ever smoked									
CS+CC	22	92,584	0.91 (0.79-1.05)	-1.267	0.205	90.9	<0.001	0.970	3,5,7-11,14,17-25,41,42,44,45,47
CS+CC*	21	87,527	0.84 (0.74-0.97)	-2.379	0.017	88.2	<0.001	0.889	3,5,7-11,14,17-20,22-25,41,42,44,45,47
CS+CC†	13	63,160	0.82 (0.69-0.97)	-2.246	0.025	79.7	<0.001	0.235	7-11,14,18,19,22-25,44
CS	20	92,110	0.91 (0.78-1.07)	-1.135	0.257	92.3	<0.001	0.479	3,5,7-11,14,17-25,44,45,47
CS*	19	87,053	0.87 (0.76-1.00)	-2.003	0.045	88.0	<0.001	0.374	3,5,7-11,14,17-20,22-25,44,45,47
CC	2	474	0.48 (0.18-1.27)	-1.483	0.138	76.3	0.040	-	41,42
PC	2	4,583	1.02 (0.75-1.40)	0.156	0.876‡	5.0	0.305	-	43,46
Current smoker									
CS+CC	8	38,503	0.70 (0.51-0.96)	-2.234	0.026	82.3	<0.001	0.823	8,14,18-20,23,25,41
CS+CC†	6	35,798	0.68 (0.61-0.76)	-6.918	<0.001‡	21.5	0.195	0.545	8,14,18,19,23,25
CS	7	38,317	0.75 (0.56-1.01)	-1.903	0.050	79.9	0.002	0.292	8,14,18-20,23,25
CC	1	186	0.28 (0.12-0.62)	-3.098	0.002	-	-	-	41
Ex-smoker									
CS†	2	4,407	1.05 (0.87-1.27)	0.539	0.590‡	0	0.505	-	18,19

* One study of higher risks in introducing bias was excluded (detailed in result section).

† Only adjusted ORs were meta-analyzed.

‡ Fixed-effects model was used when low heterogeneity was affirmed.

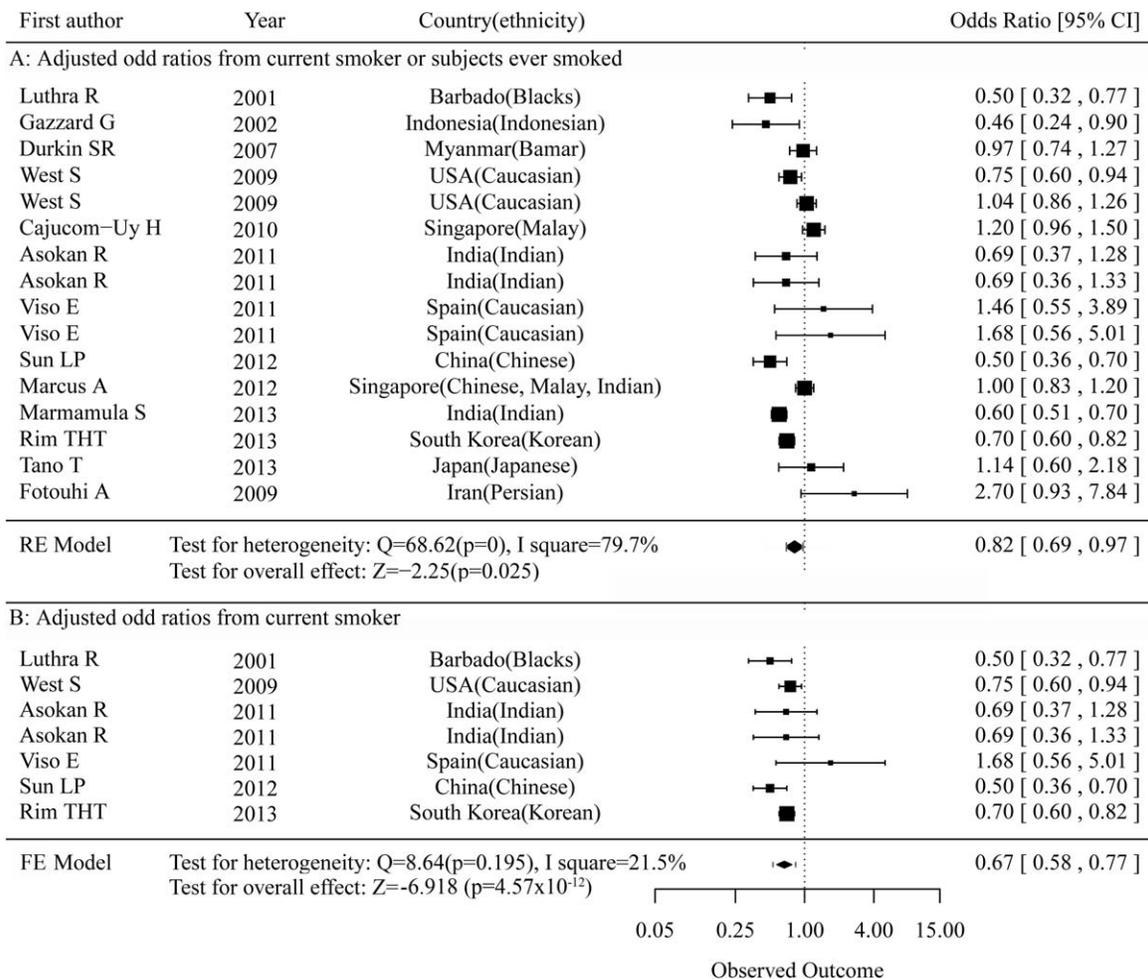


FIGURE 2. Forest plots for the meta-analysis of smoking as a risk factor for pterygium using adjusted OR. (A) Based on 13 studies that included current smokers or subjects who had ever smoked, meta-analysis using adjusted ORs showed a protective effect of smoking. (B) Based on 8 studies that included only current smokers, the combined adjusted OR showed protective effects of smoking. FE, fixed-effects model; RE, random-effects model.

smoked.” On the other hand, this finding underlines the necessity to conduct more prospective cohorts to further affirm the long-term effects of smoking on pterygium.

In the meta-regression analysis, we did not detect any effects of UV exposure and sex on the risk-modifying effects of smoking on pterygium. It is important to note that none of the studies measured the actual UV exposure, instead alternative measurements were used, that is, occupation as outdoor workers, outdoor working hours, and habit of wearing sunglasses. We based our analysis on 12 and 21 studies for UV exposure and sex, respectively. On the other hand, we limited the number of independent variables to two. Thus, we lowered the possibility in obtaining false-positive findings. Moreover, the negative results remained unchanged in the sensitivity analysis.

It has been reported that smoking can cause a wide spectrum of diseases, and subsequently lead to morbidity and mortality. Despite the reduced risks that smoking may contribute toward the occurrence of pterygium, the advantages gained are unlikely to outweigh the compromised general health after all. This precludes smoking from being a feasible therapy for the protection against pterygium. Nonetheless, our meta-analysis shows that smoking reduces the risks of pterygium with the lowest OR of 0.68. This finding may help place a high value on uncovering the molecular basis underlying the protective effects and isolate the therapeutic agents from aggressive ones.

The exact mechanism for the protective effect of smoking on pterygium is not known. The number of substances in cigarette smoke is well over 5000.⁵⁰ Various biological functions of each substance and the heterogeneous responses from the individuals with a divergent smoking history, contributes to the complexity of effects of smoking. In general, cigarette smoke increases the production of proinflammatory cytokines (i.e., TNF- α , IL-1, IL-6, and IL-8) and inflammatory markers (i.e., C-reactive protein [CRP]).⁵⁰⁻⁵² It also is the major source of free radicals involving reactive oxygen species and reactive nitrogen species, and can directly promote oxidative stress.^{50,53} However, smoking may induce protective effects via vasoconstriction or suppression of cytokines induced by nicotine under certain conditions, such as ulcerative colitis and chronic periodontal diseases.^{50,53-55} For pterygium, the factors that modify risks of disease include ultraviolet radiation-related molecular and cellular injuries, viral infection, or other ocular surface dysfunctions.⁵⁶ Inflammatory cytokines and growth factors were altered, such as IL-1, IL-6, IL-8, and TNF- α .⁵⁷ The protective effects of current smoking against pterygium could be explained by the following observations. First, suppression of the expression of inflammatory mediators may inhibit the growth of pterygium.⁵³ The vasoconstrictive effect of nicotine and cigarette smoke through stimulation of α 1-adrenergic receptors followed by adrenaline and noradrenaline secretion was proposed as an explanation for reduced inflammatory response.⁵⁰ Second, smoking may alter the component of tear film, such as secreted antibodies. This might exert protective effects against ocular surface stimulation. However, to our knowledge the altered components and relevant functional changes have not been studied.

In this study, we used risk of bias assessment tools for observational studies referring to MOOSE guidelines and the Cochrane Handbook for Systematic Reviews. We eliminated duplicated study populations, adopted adjusted ORs and ethnic grouping in subgroup analysis, and further performed sensitivity analysis to confirm the association. Nevertheless, our study entailed some limitations. First, multiple risk factors have been reported for pterygium. However, some studies did not adjust for any of them. Therefore, we performed analysis using only adjusted ORs and sensitivity analysis to minimize the

risk of bias. Second, smoking is a potential confounder for individuals who are active and use the outdoors. However, in the present collection of the eligible studies for the meta-analysis, we could not find the data in which types of outdoor activity were categorized as outdoor sports activity and/or nonsports outdoor activity (such as occupations). Thus, we were not able to dissect the interactive effect between smoking habits and types of outdoor activity on the risk of pterygium. Third, the number of longitudinal cohort studies was limited. Fourth, the severity and course of pterygium, and the amount of tobacco consumption could be potentially interesting and important factors. However, few studies provided this information and details about other clinical parameters. Moreover, none of the studies provided details regarding the type of cigarettes (filtered or unfiltered).

In conclusion, this meta-analysis showed that cigarette smoking reduces risk of pterygium, especially in current smokers. This effect may be independent of UV exposure and sex. No clear association between past smoking and pterygium was found. More epidemiological investigations, especially cohort studies and biological studies involving the inflammatory networks, are needed to confirm the association and isolate agents serving potential therapeutic purpose.

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