Purpose. We conducted a meta-analysis to evaluate the relationship between smoking and age-related cataract (ARC).

Methods. Eligible studies were identified via computer searches and reviewing the reference lists of the key articles. The summary relative risk ratio (RR) or odds ratio (OR) and 95% confidence interval (CI) were calculated. Study-specific risk estimates were pooled using a random-effects model. Meta-regression to assess heterogeneity by several covariates and subgroup analysis on ARC types were performed.

Results. A total of 13 prospective cohort and eight case-control studies met our inclusion criteria. Ever smoking was statistically significantly associated with increased risk of ARC among cohort studies (OR 1.41, 95% CI 1.23–1.62) and case-control studies (OR 1.57, 95% CI 1.20–2.07). In subgroup analysis, ever smoking exhibited a positive relationship with nuclear cataract (NC; OR 1.66, 95% CI 1.46–1.89) and a marginally significant relationship with posterior subcapsular cataract (OR 1.43, 95% CI 0.99–2.07) in cohort studies. Similar results were found in case-control studies (NC OR 1.86, 95% CI 1.47–2.36; posterior subcapsular cataract OR 1.60, 95% CI 0.97–2.65). Current smokers were at higher risk of ARC than past smokers. No association between smoking and cortical cataract was observed.

Conclusions. The overall current literature suggests that smoking was associated with increased risk of ARC, especially NC. Further efforts should be made to confirm these findings and clarify the underlying biological mechanisms. (Invest Ophthalmol Vis Sci. 2012;53:3885–3895) DOI:10.1167/iovs.12-9820

Age-related cataract (ARC) remains the leading cause of blindness in the world.1,2 According to the World Health Organization’s (WHO) latest assessment, ARC is responsible for 51% of world blindness, which represents about 20 million people.2 Although cataracts can be removed surgically and replaced by an artificial intraocular lens to restore sight, many people remain blind from cataracts due to inadequate surgical services and high surgery expenses.3 Furthermore, with the rapidly aging population, cataract-induced visual dysfunction and blindness are on the increase.4 These diseases are becoming a significant social problem all over the world.5 Therefore, preventing cataracts or delaying the progression to visual disability carries the potential for significant benefits, and the financial as well as clinical burden of the disease could be abridged. Thus, identifying modifiable risk factors for cataract is important and may help to establish preventive measures. A cluster of epidemiologic studies in populations from around the world already has evaluated and identified several factors associated with an increased risk of ARC,6–8 but quantitative evidence to certify this association still is lacking. Therefore, our meta-analysis was performed to address this gap in the evidence, providing robust evidence for the association.

We updated and assessed quantitatively the effects of ever smoking, current smoking, and past smoking on the risk of ARC from the cohort and case-control studies. We also investigated whether the association between smoking and ARC risk differed by types of ARC.

Methods

Search Strategy

We identified relevant publications in the MEDLINE database using PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://apps.webofknowledge.com/WOS), and the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html) up to August 2011. Search terms included “smoking,” “tobacco,” “cigarette,” or “lifestyle” combined with “cataract” or “lens opacities.” The titles and abstracts were scanned to exclude any clearly irrelevant studies. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. Furthermore, references in the retrieved publications, as well as those in previous reviews,21–24 were checked for any other pertinent studies.

Study Selection (Fig. 1)

For the purpose of meta-analysis, eligible studies had to fulfill all of the following inclusion criteria: (1) case-control or cohort study published as an original article, (2) papers reported in English between 1980 and
August 2011, (3) estimation of the relationship between active smoking and the risk of ARC expressed as odds ratio (OR) or relative risk (RR) with their corresponding 95% confidence intervals (CIs), and (4) adjustment made for potential risks, at least age, or sufficient information allowing us to compute them. We also excluded studies that were limited to non-generalizable patients, including two studies of ARC in diabetic patients. In studies with overlapping patients or controls, only the latest or the most complete were included. Any study with inconsistent or erroneous data was excluded. Meeting abstracts with insufficient data or unpublished reports were not considered.

Data Extraction

Information from the included studies was extracted independently by two researchers (JH and CW). Conflicting evaluations were resolved by discussion. If a consensus still could not be reached, the senior investigator (JY) made the final decision. We extracted the name of the first author, year of publication, country in which the study was conducted, sample size, mean age, outcomes definitions and grading, smoking exposure status, mean follow-up time for prospective cohort studies, and covariates included in the final adjusted models. Our primary analysis compared the risk of ARC in ever smokers to never smokers. Several studies did not report an overall RR or OR for ever smoking, but separate adjusted odds ratios of several smoking consumption strata. For these studies, we abstracted the adjusted odds ratio comparing the highest category of smoking consumption with the lowest category (reference group). In addition, summary estimates also were calculated according to smoking status (past and current smoking) and ARC subtypes (NC, cortical cataract, and posterior subcapsular cataract). If a study provided several risk estimates, the most completely adjusted estimate was extracted.

Statistical Analysis

The OR was used as a measure of the relative risk for all studies, and the RR estimates were log-transformed. The data from individual studies were pooled by use of the random-effect model with the DerSimonian-Laird method, which considers within-study and between-study variation. We performed subgroup analyses based on smoking status (past and current smoking) and ARC subtypes (NC, cortical cataract, and posterior subcapsular cataract). Sensitivity analyses were performed, excluding the two studies where the outcome was assessed by self-report and chart review. The Q-statistic and $I^2$ score were used to assess the between-study heterogeneity of results. Meta-regression analysis was used to assess the heterogeneity in publication year, length of follow-up, and sample size, age, and geographical region. Publication bias assessment was done using the Egger regression asymmetry test and the Begg adjusted rank correlation test. The statistical software used was Stata/SE 11.0 (Stata Corporation, College Station, TX), and the significance level was set to $P < 0.05$.

RESULTS

The search revealed 376 articles, 318 of which were excluded after first-pass review of titles and/or abstract because they were not relevant to the subject of ARC and smoking. Upon closer examination, 37 studies were excluded for the following reasons: 24 articles were cross-sectional studies, five studies did not provide sufficient information to estimate a summary OR and its 95% CIs or a summary OR adjusted at least for age, three studies provided hazard ratios instead of OR or RR, two studies estimated the incidence of ARC among diabetic patients, two studies were updated by Klein et al. and Hankinson et al., and one study identified cataract subtypes as waterclefts and retrodots.

Finally, 13 cohorts and eight case-control studies were evaluated further in this analysis. Two of the cohort articles were analyses at different time points from the same study, but the 13.6-year follow-up study did not report the relationship between smoking and subtype of ARC; therefore, both articles were included as one study.

Tables 1 and 2 provide summaries of the study designs and participant characteristics. Not all studies reported every subtype of ARC. Age-related cataract assessments and definitions varied among the studies. Standardized criteria for diagnosis of cataract were used in some studies, while in others cases were diagnosed medically by ophthalmologist or medical record review to identify the case. Likewise, the outcome measure of cataract was not consistent. Many studies used the prevalence or incidence of cataract, but some studies used cataract extraction as the measure of outcome, and found an association between smoking and cataract extraction.

Prospective Cohort Study

Table 1 shows that 12 cohort studies were included in the analysis of the association between ever smoking and ARC risk. Of the studies seven were conducted from North America, two from Europe, two from Australia, and one from Asia. There were 11 population-based and one clinic-based study. The mean time to follow-up ranged from 3–16 years.

We found that ever smoking (OR 1.41, 95% CI 1.23–1.62) was statistically significantly associated with increased risk of ARC. There was significant heterogeneity ($I^2 = 67.8, P = 0.000$) among ever smokers (Fig. 2). Further scrutiny found that the heterogeneity among ever smokers shifted from $P = 0.000$ to $P = 0.074$ by $Q$ test when two studies with patients with self-reported ARC were excluded (OR 1.32, 95% CI 1.15–1.51, see Supplementary Fig. S1, http://www.iovs.orglookup/suppl/doi:10.1167/iovs.12-9820/-/DCSupplemental). We used meta-regression analysis to explore the influence of publication year, sample size, and study conducted area. However, none was identified as a possible source of heterogeneity among all the included studies (data not shown). Egger's test suggested no statistically significant asymmetry of the funnel plot ($P = 0.437$), indicating no evidence of substantial publication bias.

Eight studies were included in the analysis of the association between past smoking and ARC risk, and 10 between current smoking and ARC risk. The associ-
### TABLE 1. Prospective Cohort Studies Evaluating the Association between Smoking and Cataract

<table>
<thead>
<tr>
<th>Source (Publication Yr., Country)</th>
<th>Mean Follow-up Time (yrs.)</th>
<th>Study Period</th>
<th>Population (Sample Size)</th>
<th>Mean Age (yrs.)</th>
<th>ARC Outcome</th>
<th>ARC Definition and Grading</th>
<th>Smoking Exposure Status</th>
<th>Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christen et al. 60 (1992 USA)</td>
<td>5</td>
<td>1982–1987</td>
<td>Volunteer health professionals (N = 17,824 male only)</td>
<td>40–84</td>
<td>Nuclear PSC Any type</td>
<td>Self-report confirmed by medical record review</td>
<td>Past Current (≥20 cigarettes/day)</td>
<td>Age, aspirin, β-carotene treatment assignment, history of diabetes, hypertension, high cholesterol levels, obesity, alcohol use, physical activity, parental history of myocardial infarction, age, diabetes, hypertension, BMI, alcohol use, current smoking, past smoking, smoking status adjusted for age, sex, aspirin and β-carotene treatment assignment, physical activity, parental history of myocardial infarction, current multivitamin use, and number of cigarettes smoked.</td>
</tr>
<tr>
<td>Christen et al. 28 (2000 USA)</td>
<td>13.6</td>
<td>1982–1997</td>
<td>Volunteer health professionals (N = 20,907 male only)</td>
<td>40–84</td>
<td>Any type Extraction</td>
<td>Self-report confirmed by medical record review</td>
<td>Past Current</td>
<td>Age, sex, smoking status adjusted for age, sex, aspirin and β-carotene treatment assignment, physical activity, parental history of myocardial infarction, current multivitamin use, and number of cigarettes smoked.</td>
</tr>
<tr>
<td>Leske et al. 64 (1998 USA)</td>
<td>4.6</td>
<td>1989–1993</td>
<td>Clinic-based (N = 764)</td>
<td>≥40</td>
<td>Nuclear Opalescence increased</td>
<td>LOCS III</td>
<td>Current others</td>
<td>Age, education</td>
</tr>
<tr>
<td>Weintraub et al. 29 (2002 USA)</td>
<td>16 (female) 10 (male)</td>
<td>1980–1996</td>
<td>Volunteer health professionals (N = 124,690)</td>
<td>≥45</td>
<td>Extraction</td>
<td>Self-report confirmed by ophthalmologists or nurses</td>
<td>Current</td>
<td>Age, diabetes mellitus, BMI, dietary intake of lutein/zeaxanthin, state of residence at baseline, and 2-year time period.</td>
</tr>
<tr>
<td>Mares et al. 69 (2010 USA)</td>
<td>6</td>
<td>1994–2004</td>
<td>Population-based (N = 1808 female only)</td>
<td>50–79</td>
<td>Nuclear or extraction</td>
<td>AREDS-SCC</td>
<td>Ever (pack-years ≥7)</td>
<td>Age, iris pigmentation, HEI-1995 score, BMI, pulse pressure, dietary variables, energy</td>
</tr>
<tr>
<td>Delcourt et al. 65 (2003 France)</td>
<td>3</td>
<td>1998–2000</td>
<td>Population-based (N = 17,360)</td>
<td>≥60</td>
<td>Nuclear Cortical PSC Extraction</td>
<td>LOCS III</td>
<td>Current Past Ever (pack-years ≥40)</td>
<td>Age, gender and CO, NOx, P0 for cataract surgery, and NOx, P0 for cortical cataract, and CO, P0 for nuclear cataract, and CO, NOx for posterior subcapsular cataract.</td>
</tr>
</tbody>
</table>
## Table 1.

<table>
<thead>
<tr>
<th>Study Source</th>
<th>Follow-Up Period (yrs.)</th>
<th>Study Population (Sample Size)</th>
<th>ARC Definition and Grading</th>
<th>Smoker Exposure Status</th>
<th>Smoker Adjustment Variables</th>
<th>Smoking Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Taylor and West Cohort Study (1997 USA)</td>
<td>20</td>
<td>Surviving members of the Framingham Heart Study (N = 660)</td>
<td>The Taylor and West grading system</td>
<td>Past</td>
<td>Age, sex, education, diabetes, smoking status</td>
<td>OR 1.19 (95% CI 1.10–2.00)</td>
</tr>
<tr>
<td>West et al. (1995 USA)</td>
<td>40</td>
<td>Study population (N = 3251)</td>
<td>Modified AREDS-SCC</td>
<td>Current</td>
<td>Age, gender, education, income, BMI, refractive error, alcohol consumption</td>
<td>OR 0.93 (95% CI 0.76–1.14)</td>
</tr>
<tr>
<td>Zhang et al. (2011 China)</td>
<td>5</td>
<td>Population-based (N = 3251)</td>
<td>Modified AREDS-SCC</td>
<td>Ever</td>
<td>Age, sex, education, diabetes, smoking status</td>
<td>OR 2.10 (95% CI 1.02–4.29)</td>
</tr>
</tbody>
</table>

### Case-Control Studies

Table 2 shows that eight case-control studies were included in the analysis of the association between smoking and ARC risk. Two studies were conducted from North America, three from Europe, one from Asia, and two from Africa. Six of the studies were hospital-based, while the other two were population-based. We found that ever smoking was associated strongly with increased risk of ARC (OR 1.57, 95% CI 1.20–2.07). As well as the two different statuses of smoking (past smoking OR 1.60, 95% CI 1.02–2.49; current smoking OR 1.35, 95% CI 1.02–1.80).
There was statistically significant heterogeneity among ever smokers ($I^2 = 66.1$, $P = 0.004$) and current smokers ($I^2 = 72.6$, $P = 0.003$). We used meta-regression analysis to explore the influence of publication year, sample size, and study conducted area. However, none was identified as a possible source of heterogeneity among all the included studies. No publication bias was found among all studies ($P = 0.322$ by Egger’s test).

Because only one case-control study evaluated separate relation between past smoking and each cataract subtype, we pooled estimates for only current smoking in the subgroup analysis. Three studies were included in the analysis of the association between current smoking and NC risk. The summary risk was $1.89$ (95% CI 1.45–2.45) without being statistically significantly heterogeneous ($P = 0.861$). Two studies were included in the analysis of the association between current smoking and PSC risk. These same studies also were included in the analysis between current smoking and cortical cataract risk. In this pooled subgroup analysis (see Supplementary Fig. S4, http://www.iovs.org/lookup/suppl doi:10.1167/iovs.12-9820/-/DCSupplemental), smoking was not associated significantly with the likelihood of cortical cataract (OR 1.09, 95% CI 0.73–1.63, $P = 0.939$), while the summary risk estimate of PSC was strong (OR 1.89, 95% CI 1.17–3.03, $P = 0.512$). The findings were homogeneous across the studies.

### DISCUSSION

Our meta-analysis showed that smoking was associated with an increased risk of ARC in cohort and case-control studies. The positive association also was found in the stratified analyses by NC and PSC. The association was stronger among current smokers than past smokers. However, no association between any smoking status and cortical cataract was observed in the cohort and case-control studies.

<table>
<thead>
<tr>
<th>Source (Published Year, Country)</th>
<th>Designed</th>
<th>Case/Control (Mean Age, yrs.)</th>
<th>Cataract Type</th>
<th>Case Definition</th>
<th>Smoking Exposure Status</th>
<th>Adj usted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harding et al.71 (1988 UK)</td>
<td>Hospital-based Case-control</td>
<td>124/266 (50–79)</td>
<td>Extraction</td>
<td>Admitted to the Oxford Eye Hospital for cataract extraction</td>
<td>Heavy smokers (with cigarette-year score &gt;1500)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>AREDS Research group77 (2001 USA)</td>
<td>Population-based Case-control</td>
<td>NS/4757 (60–80)</td>
<td>Moderate Nuclear Opacity</td>
<td>AREDS-SCC</td>
<td>Current</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Theodoropoulou et al.79 (2011 Greece)</td>
<td>Population-based Case-control</td>
<td>314/314 (45–85)</td>
<td>Cortical Nuclear PSC All types</td>
<td>Medically diagnosed and classified in the Ophthalmology Department of the &quot;Attikon&quot; Hospital in Athens, Greece</td>
<td>Current Ex-smoker</td>
<td>Age, sex, education, BMI</td>
</tr>
<tr>
<td>Leske et al.72 (1991 USA)</td>
<td>Hospital-based Case-control</td>
<td>945/435 (40–79)</td>
<td>Cortical Nuclear PSC Mixed</td>
<td>LOCS III</td>
<td>Current smoking</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Phillips et al.74 (1996 UK)</td>
<td>Hospital-based Case-control</td>
<td>990/858 (NS)</td>
<td>Any type</td>
<td>On the waiting lists of surgeons at Princess Alexandra Eye Pavilion</td>
<td>Smoking</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Katoh et al.75 (1993 Japan)</td>
<td>Hospital-based Case-control</td>
<td>212/212 (≥40)</td>
<td>Senile cataract</td>
<td>The criteria of the Japanese Co-operative Cataract Epidemiology Group</td>
<td>Current smoker Ex-smoker</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Ughade et al.76 (1998 India)</td>
<td>Hospital-based Group-matched Case-control</td>
<td>262/262 (51–70)</td>
<td>Any type</td>
<td>Sufficiently advanced lens opacity that impaired vision</td>
<td>History of heavy smoking (smoked ≥10 cigarettes/bidis daily for ≥2 yrs.)</td>
<td>Age, low socioeconomic status, sex, illiteracy, history of diabetes, history of diarrhoea, glaucoma, myopia, hypertension, cheap cooking fuel</td>
</tr>
<tr>
<td>Ojofeitimi et al.76 (1999 Nigeria)</td>
<td>Hospital-based Case-control</td>
<td>31/31 (60–69)</td>
<td>Any type cataract</td>
<td>Medically diagnosed in the Ophthalmology clinic at Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife</td>
<td>Past history of smoking</td>
<td>Age, sex</td>
</tr>
</tbody>
</table>

NS, not stated.
The mechanistic actions of smoking on ARC are not fully understood, but several possible biologic mechanisms have been suggested for the association of smoking with ARC. Firstly, oxidative damage appears to have a major role in cataract formation. Smoking causes an additional oxidative challenge through invoking free radical activity, and promoting oxidation and lipid peroxidation. On the other hand, smoking may impose indirectly the oxidative stress on the lens through depletion of endogenous antioxidant pools, such as vitamin C, vitamin E, and β-carotene. Secondly, by-products of tobacco contain heavy metals, such as cadmium, lead, and copper, which accumulate in the lens and cause direct toxicity. Thirdly, cyanide and aldehyde levels rise in the blood of smokers, and then aldehydes and isocyanate, which are formed from cyanide, can modify lens proteins, causing lens opacification in vitro. These changes are similar to those seen in human cataracts.

The weaker association with cortical cataract may be a result of different pathophysiologic processes in these situations, suggesting that risk factors may differ for the different cataract types. Meanwhile, because the human lens grows throughout life, the lens core is exposed for a longer
period to such influences caused by smoking. Another explanation for this relative lack of protection of the lens nucleus from oxidative attack has been provided by Sweeney and Truscott.\textsuperscript{89} Their studies demonstrated the appearance of a barrier to the inward diffusion of glutathione (GSH), which is the most important antioxidant molecule of the lens.\textsuperscript{90} The relatively low ratio of GSH to protein-SH in the adult nucleus of the lens, combined with low activity of the GSH redox cycle, makes the nucleus especially vulnerable to oxidative stress. On the contrary, the superficial cortex is supplied better with scavenger molecules to combat oxidative effects. More recently, Mathias et al.\textsuperscript{91} and Donaldson et al.\textsuperscript{92} hypothesized that micronutrients sift to the center of the lens via a process called electro-osmosis, which may be the cellular and molecular mechanism responsible for lens transparency. Cumulative oxidative damage to any dissipation of the Na\textsuperscript{+} gradient in the core of the lens will reduce nutrients and antioxidants (e.g., GSH) uptake in this region, leading to cataract formation. This may explain why cigarette smoke affects nuclear and posterior cortical opacity more than cortical opacity.

Our meta-analysis results indicated that current smokers are at higher risk of incident ARC than past smokers. Some previous epidemiological investigations found the same...
One possible reason is that current smokers may have a longer exposure time and higher total cumulative dose of smoking than past smokers. The Swedish Mammography Cohort indicated those who ceased smoking more than 20 years previously had no excess risk of ARC.\textsuperscript{66,67} Weintraub et al. pooled results from the Nurses’ Health Study and the Health Professionals’ Follow-up Study, and indicated that the risk among past smokers decreased with number of years since quitting, but not to the level of never smokers, even 25 or more years after cessation.\textsuperscript{29} These two studies suggest that some smoking-related damage in the lens may be reversible on smoking cessation, but the effect of cessation takes some time and may be only partial.

There was a significant amount of heterogeneity among the studies, likely reflecting differences among study populations, model selection, analytic methodology, exposure assessment, and operational definitions of ARC and its subtypes. We conducted a meta-regression analysis to assess the effect of publication year, study conducted area, study design, primary outcome, and sample size on the heterogeneity. However, none of the confounding factors could explain heterogeneity between the individual studies. We also performed sensitivity analyses excluding the two studies where the outcome was assessed by self-report and chart review. The results showed that the pooled estimates were robust among ever smokers and current smokers. Nonetheless, we failed to find the major source of study heterogeneity in this sensitivity analysis. The presence of heterogeneity indicates the need for consensus definitions for ARC and its subtypes in future studies.

To interpret our study results properly, it is necessary to understand several limitations. First, only English-language articles that had been published were included. We did not attempt to uncover unpublished observations and did not include studies with insufficient information to estimate an
adjusted OR, which could bring publication bias, even though no significant evidence of publication bias was observed in Egger’s and Begg’s test. Second, we also excluded the cross-sectional studies that did not provide information regarding the temporal relation between ARC and smoking. Third, the assessment of ARC or its subtype varied between studies (Tables 1, 2). Some studies used cataract extraction as the measure of outcome, and found an association between smoking and cataract extraction. However, cataract extraction rates depend on health care provision and access, which if different between smokers and nonsmokers would create bias. In addition, all studies used qualitative and/or quantitative criteria for ARC diagnosis. Qualitative measures, such as levels of lens opacity, introduce the potential of interobserver variation. Fourth, smoking status misclassification is another potential source of bias. The smoking data were self-reported in all included studies. Patients may underestimate or under report their smoking habits, resulting in misclassification of exposure status and inducing bias in estimates of association. Moreover, many prospective cohort studies assess smoking status only at baseline. Smoking status may change during follow-up. Of the 13 cohort studies, seven reassessed smoking status. Finally, the smoking consumption levels in the lowest and highest categories, and the range of smoking consumption varied across studies. These differences may have contributed to the heterogeneity among studies in the analysis of the highest versus lowest categories.

CONCLUSIONS

Our meta-analysis of cohort and case-control studies summarized the risk estimates of smoking and ARC, and provided robust evidence for the association. It helped resolve some of the inconsistencies with smoking and ARC risk, but some do remain. Future research is needed to confirm these findings and resolve the remaining problems. These findings also provide an opportunity for the public health and eye health communities to work actively to educate the public about the impacts of smoking on eye health. Such education will improve quit rates and help to discourage people from starting to smoke.

References


