Prospective Study of Cigarette Smoking and the Risk of Primary Open-angle Glaucoma

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Objective: To examine the association between cigarette smoking and incident primary open-angle glaucoma (POAG).

Methods: Female nurses and male health professionals were prospectively followed up from 1980 and 1986, respectively, to 1996. Participants were at least 40 years old, were free of diagnosed glaucoma at baseline, and reported being examined by an ophthalmologist or optometrist during follow-up. Smoking history and other POAG risk factors were updated with biennial questionnaires. A total of 450 incident cases of POAG were identified. Both cohort-specific proportional hazards analyses and analyses pooled across cohorts were conducted.

Results: After controlling for potential risk factors of POAG, including age, hypertension, and African American heritage, neither current smokers (relative risk, 0.85; 95% confidence interval, 0.62-1.18) nor past smokers (relative risk, 0.91; 95% confidence interval, 0.63-1.32) were at greater risk for POAG than those who had never smoked. Heavier smoking did not increase the risk of POAG. A modest inverse association was observed with pack-years of smoking: those with 30 or more pack-years had a 22% reduced risk of POAG (relative risk, 0.78; 95% confidence interval, 0.55-1.11; P for linear trend, .06) than those who had never smoked.

Conclusion: Cigarette smoking is not an important risk factor for POAG.

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Glaucoma is the second leading cause of blindness worldwide.1 The most common form is primary open-angle glaucoma (POAG), but its causes are poorly understood. The established risk factors for POAG are older age, family history, African American heritage, and elevated intraocular pressure (IOP).2-4 If POAG is detected early, management of IOP can reduce the risk of further vision loss in patients with POAG.5,6 However, because vision loss in POAG usually starts from the peripheral field and produces no symptoms until advanced stages, an estimated 50% of people with POAG do not know they have the condition.7 Therefore, there is a pressing need for research into the causes and possible prevention of POAG.

Cigarette smoking is a widespread and modifiable risk factor for many eye disorders, such as cataracts and age-related macular degeneration.8 However, the relationship between cigarette smoking and POAG remains uncertain. The studies on this topic have been case-control or cross-sectional in design and have yielded inconsistent results. One case-control study with 83 cases and 237 controls showed an elevated risk of glaucoma associated with current smoking (odds ratio, 2.9; 95% confidence interval [CI], 1.3-6.6).9 However, no associations were reported in 2 large population-based, cross-sectional studies.10,11 In a study of the predictors of glaucoma in subjects with ocular hypertension, smoking status did not predict the risk of developing visual loss.12 Several other studies have reported null associations,13-16 and some even suggested inverse associations.17,18 In this study, we used data from 2 large ongoing cohorts of US men and women with at least 10 years of follow-up to evaluate prospectively the relationship between cigarette smoking and the risk of incident POAG.

Population for Current Study

The Nurses’ Health Study (NHS) started in 1976, with 121701 US female registered nurses aged 30 to 55 years who responded to a mailed questionnaire on health information, lifestyle...
behaviors, dietary habits, and medical history. The Health Professionals Follow-Up Study (HPFS) began in 1986 with the enrollment of 51,529 US male health professionals (i.e., dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists) aged 40 to 75 years who also responded to a questionnaire similar to the questionnaire of the NHS. Participants were followed up with biennial questionnaires on risk factors and newly diagnosed illnesses such as glaucoma. Participants included in this study from both the NHS and HPFS are predominantly white (NHS: 98.1% white American, 1.1% African American, or 0.8% Asian American; HPFS: 97.7% white American, 0.8% African American, or 1.3% Asian American), reflecting the demographic of the health professionals when the cohorts began. This study was approved by the human subject committees of the Brigham and Women’s Hospital and the Harvard School of Public Health, Boston, Mass.

The study period of interest was 1980 through 1996 for the NHS and 1986 through 1996 for the HPFS. Person-time accrual began from the return date of the first questionnaire completed when a participant was eligible until the earliest occurrence of glaucoma, cancer (an event unrelated to glaucoma that causes great changes in lifestyle), death, loss to follow-up, or May 31, 1996, for the NHS and December 31, 1996, for the HPFS. We included only the person-time during which a participant was aged 40 years or older (because the risk of developing glaucoma increases after age 40 years) and reported having had an eye examination to minimize possible detection bias. Person-years were accrued in approximate 2-year units and exposures were defined based on responses to the biennial questionnaires at the beginning of the interval, or if not completed, the most recent previous questionnaire.

Of the original cohort members, participants were excluded for the following reasons as of 1980 in the NHS and 1986 in the HPFS. Because this was part of a larger substudy in which examining several dietary hypotheses in relation to several age-related eye diseases was a major study objective, we excluded (1) 23,239 women who did not return the first semiquantitative food frequency questionnaire assessment in 1980; (2) 1,596 men and 5,994 women with inadequate diet information on the first food frequency questionnaire ("adequate" information for men was fewer than 70 of 131 items blank in the food frequency questionnaire, with a total caloric intake range of 800-4200 kcal/d; for women, fewer than 10 of 61 items blank and 500-3500 kcal/d; (3) 1,927 men and 3,625 women with cancers excluding nonmelanoma skin cancer; (4) 787 men and 767 women reporting a previous diagnosis of glaucoma or suspected glaucoma; (5) 1029 men and 795 women lost to follow-up after baseline; (6) 2,212 men and 1,674 women lacking smoking information; (7) 18 men and 4 women with inadequate information on age; and (8) 5,507 men and 9,868 women who never reported having had an eye examination during follow-up. After these exclusions, 38,345 men and 75,917 women remained. However, at each specific 2-year period, some of these participants were considered ineligible. For example, the number of participants who contributed person-time for the first 2 years (1986-1988 in the HPFS; 1980-1982 in the NHS) was 28,139 men and 43,680 women, respectively, as examples, the number of participants who contributed person-time were high—96.3% in the HPFS and 95.2% in the NHS. Participants who did not report having had an eye examination when examining several dietary hypotheses in relation to several age-related eye diseases were defined based on responses to the biennial questionnaires at the beginning of the interval, or if not completed, the most recent previous questionnaire.

We asked participants about having a diagnosis of glaucoma and the date of that diagnosis from 1986 onward. For all participants who reported having glaucoma, we requested their permission to review medical records and information on which ophthalmologist(s) or optometrist(s) made the diagnosis. We then asked the ophthalmologist(s) or optometrist(s) to send copies of ocular records or to complete a brief questionnaire about signs of glaucoma (maximum IOP, presence of optic disc cupping, glaucomatous visual field [VF] loss), their dates of diagnosis, and whether the glaucoma was primary or secondary. We selected the subset for whom the ophthalmologist(s) or optometrist(s) indicated POAG with glaucomatous VF loss and obtained complete ocular records, including VFs, from the original date of diagnosis to the most recent information. These records were examined independently by 2 ophthalmologists (L.R.P. and N.F.) who were masked to the participants' smoking status. Cases for analysis were those having a diagnosis that the reviewers agreed was either definite or probable POAG. The standardized criteria for these designations are described below. For the date of diagnosis, we used the earliest detected date of any of the following: optic disc cupping, VF loss, or an elevated IOP exceeding 21 mm Hg in either eye.

For defining definite POAG cases, we required that (1) gonioscopic results confirmed that angles were open and not occludable in both eyes; (2) slitlamp biomicroscopy showed no indication of secondary causes of glaucoma; and (3) VF defects were (a) present and consistent with glaucoma in the most recently available VFs (i.e., nasal step, nasal depression, para-
central scotoma, arcuate defect, blind spot enlargement, or temporal wedge), (b) reproduced on at least 1 prior set of VFs, and (c) not due to other ocular conditions or optic disc pathologic abnormality. While there was no requirement for the type of perimetry performed, static automated perimeters had to have an age-matched normal database, and VF tests had to be reliable for the affected eye(s). For static threshold or suprathreshold testing, we considered a VF result reliable if the fixation loss was 33% or less, the false-positive rate was 20% or less, and the false-negative rate was 20% or less. For kinetic VFs, we considered a VF result reliable unless the examiner noted that the VF was unreliable.

Probable POAG cases met the above criteria for slitlamp examination and VFs but did not have gonioscopy. In lieu of the gonioscopic results, the following needed to be documented: (1) an IOP difference between the 2 eyes within 5 mm Hg, (2) IOP for both eyes less than 40 mm Hg, and (3) the patient’s eyes were dilated with no adverse events.

Reviewer assessments differed for 40 (8.9%) of the 450 cases included in the analyses. The 2 main reasons for differences were errors in calculating VF test reliability parameters and omissions in reading a few VFs in the ocular records. The 2 reviewers (L.R.P. and N.F.) adjudicated their differences after an open discussion of the available information.

A total of 1275 men and 2897 women self-reported having a diagnosis of glaucoma during follow-up. Among incident reports in which diagnoses were confirmed to have occurred after baseline (1134 men and 2789 women), the participants’ personal ophthalmologist or optometrist confirmed the diagnosis in 60.6% of men and 69.6% of women as follows: 317 men and 693 women having a diagnosis of POAG with VF loss, 265 men and 730 women with at least an elevated IOP or optic disc cupping, and 116 men and 519 women with other types of glaucomas or suspected glaucomas. The remaining 39.4% of self-reports in men and 30.4% in women could not be confirmed because the participants themselves (10.7% men and 5.7% women) or their ophthalmologists or optometrists (3.5% men and 2.2% women) could not be contacted, participants did not give permission to review their medical records (10.6% men and 9.9% women), participants indicated the initial report was in error (12.9% men and 10.1% women), or participants’ ophthalmologist or optometrist disagreed the self-report (1.8% men and 2.3% women).

Of the 317 men and 693 women confirmed to have POAG with VF loss by their ophthalmologists or optometrists, 188 men (59.3%) and 321 women (46.3%) met the criteria for definite or probable cases. The remaining patients were excluded for having only 1 VF showing abnormality (8.2% men and 9.3% women), only an elevated IOP (12.3% men and 17.6% women), other glaucomas (11.0% men and 13.9% women), no glaucomatous signs (0.3% men and 3.0% women), or insufficient documentation (8.9% men and 9.9% women). After further exclusion either of those whose conditions were diagnosed after the end of follow-up or of those who did not meet our eligibility criteria (see above), 164 men and 286 women were included in the analysis.

**STATISTICAL ANALYSIS**

Cigarette smoking exposure was examined in relation to the risk of POAG in various ways. First, participants’ current smoking status (ie, current, past, or never smoker) was evaluated. Second, current smokers were divided into groups by the number of cigarettes smoked per day (1-14, 15-24, and 25+ cigarettes smoked per day); past smokers were categorized into similar groups according to the last amount reported before quitting. Third, the number of pack-years of smoking was calculated by multiplying the number of packs smoked per day (1 pack defined as 20 cigarettes) and the number of years smoked. For each smoking category, we calculated incidence rates by dividing the number of incident glaucoma cases by the person-years of follow-up. We adjusted the rates for age, using seven 5-year categories (40-44, 45-49, 50-54, 55-59, 60-64, 65-69, and 70+ years), and calculated Mantel-Haenszel age-adjusted incidence rate ratios.

We controlled for the possible confounding effects of known and potential risk factors for glaucoma by including them simultaneously in Cox proportional hazards models, using linear age as the time metameier, with stratification on linear age and on each 2-year period at risk between questionnaire cycles. This approach allowed finer control for the possible confounding by age, a strong POAG risk factor, and any time trends in POAG incidence. Variables considered for inclusion were African American heritage (yes/no), body mass index (calculated as weight in kilograms divided by the square of height in meters), alcohol intake (grams per day), and self-reported history of hypertension (yes/no) and/or diabetes mellitus (yes/no) Table 1. The categorization of variables controlled for in multivariate analysis is provided in the footnotes to Table 2. We calculated relative risks (RRs) as the measure of association and their 95% CIs, using the ratio of incidence rates of glaucoma among various smoking exposure categories. We performed tests for trend by including as a continuous variable the median value for each category in a multivariate model and evaluating the statistical significance. All P values are 2-sided, at α = .05 level.

We analyzed the data from each cohort separately and then pooled the results. Before pooling, we performed tests for heterogeneity of RRs between the cohorts and used the DerSimonian and Laird meta-analytic methods incorporating random effects for pooling results.

In secondary analyses, we explored the following hypotheses. First, as glaucoma is a slowly developing chronic disease with signs appearing after substantial damage to retinal ganglion cells has occurred, the more etiologically relevant exposure is the smoking history several years before the date of diagnosis rather than the most recent smoking status. Second, if the causes of high- and normal-tension POAG are different, then the effect of smoking may differ by case type. The distinction was made on the basis of the maximum IOP before VF loss was first detected either being 21 mm Hg or less or exceeding 21 mm Hg. Third, to explore the effect of possible detection bias, we conducted analyses that vary in strictness compared with the main analyses: (1) analysis controlling for other variables associated with eye screening practices (ie, self-reports of cataract and macular degeneration [yes/no], ophthalmologist or optometrist examination in the previous 2 years [yes/no], quartiles of levels of physical activity [metabolic equivalents per week], and number of reported eye examinations to date); (2) analysis restricted to person-time from participants who consistently report having had eye examinations at every questionnaire from 1990 onward; and (3) analysis without any eye examination requirements.

Table 1 gives the distribution of potential risk factors for glaucoma by smoking status. Increasing age and African American heritage, 2 established risk factors, did not differ materially by smoking status (Table 1). However, compared with never smokers, current smokers tended to be leaner, have a higher prevalence of diabetes mellitus or hypertension, and drink more alcohol. All of these factors were adjusted for in multivariate analyses.

During 1035227 person-years of follow-up we identified 450 cases of POAG. Table 2 gives both age-
The literature on this topic is scarce, of small scale (most studies have included <180 cases), and inconsistent. Previous studies have either been clinic-based, case-control studies with possible referral bias or cross-sectional in design with possible selective mortality owing to cigarette smoking. Nevertheless, most studies found nonsignificant weak inverse associations consistent with our findings. In addition, many studies as-
sessed smoking crudely as only current smoking status, \(^9,16,18\) current smoking dose, \(^14,15\) or having a history of ever smoking, \(^17,18\). To our knowledge, this is the first large prospective evaluation of this relationship. We were also able to examine smoking in a variety of ways—current smoking status, dosage, and pack-years. Thus, in the context of earlier studies, these prospective data provide strong evidence that smoking is not an important risk factor for POAG.

There are several limitations to our data. First, we lacked information on family history of glaucoma, which is a strong established risk factor for POAG. However, confounding by family history seems unlikely, as family history would have to be strongly associated with smoking behavior to have affected our results. Among the 3 studies of smoking in relation to POAG\(^9,13,18\) in which family history was controlled for, 2 studies\(^13,18\) found no substantial confounding by family history and no effects of smoking, independent of family history.

As repeated eye examinations are prohibitive in these large cohorts, our method of case ascertainment had low sensitivity, although the sensitivity may be higher than the general population as our participants are health professionals. Low sensitivity in the case definition does not bias RR estimates if the ascertainment method is unrelated to exposure and the case definition is highly specific (ie, low false-positive results). \(^22\) Our case definition would minimize false-positive results among identified cases because we required confirmation of the original diagnosis on at least 2 reliable VF tests by 2 independent reviewers (L.R.P. and N.F.). Also, the mean number of self-reported eye examinations did not differ materially by smoking status (in the NHS, 2.8 of 4 possible reports in never smokers vs 2.6 in longest-duration smokers; in the HPFS, 3.3 in never smokers vs 3.1 in longest-duration smokers). Finally, out of all self-reports where ocular records were available, the percentage confirmed to have either glaucoma or suspected glaucoma by the diagnosing ophthalmologist’s or optometrist’s records was similar among never smokers and smokers with more than 30 pack-years (in the NHS 73% vs 67%; in the HPFS 73% vs 75%).

Some residual detection bias issues may have occurred if the eye examinations reported by smokers were not comprehensive and were, thus, less likely to detect glaucoma, if present. The various sensitivity analyses with greater or fewer restrictions on the allowable person-

### Table 2. Cigarette Smoking Status and Dose of Smoking in Relation to Primary Open-angle Glaucoma: Age-Adjusted and Multivariate Rate Ratios

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cigarettes per Day</th>
<th>Current Smoking Dose</th>
<th>Past Smoking Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>1-14</td>
<td>15-24</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>150</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Person-time, y</td>
<td>360 348</td>
<td>49 858</td>
<td>60 022</td>
</tr>
<tr>
<td>Age-adjusted RR§</td>
<td>1.00 (Reference)</td>
<td>0.96 (0.59-1.56)</td>
<td>0.60 (0.33-1.08)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>0.96 (0.58-1.59)</td>
<td>0.66 (0.36-1.20)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>71</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Person-time, y</td>
<td>117 802</td>
<td>64 300</td>
<td>59 999</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (Reference)</td>
<td>0.77 (0.24-2.43)</td>
<td>0.82 (0.26-2.60)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>0.98 (0.29-3.26)</td>
<td>1.02 (0.31-3.38)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>0.96 (0.60-1.53)</td>
<td>0.72 (0.42-1.23)</td>
</tr>
<tr>
<td><strong>Past Smoking Dose#</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>150</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Person-time, y</td>
<td>360 348</td>
<td>139 023</td>
<td>95 744</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (Reference)</td>
<td>0.88 (0.64-1.20)</td>
<td>0.65 (0.43-0.98)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>0.84 (0.61-1.16)</td>
<td>0.62 (0.41-0.95)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>71</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Person-time, y</td>
<td>117 802</td>
<td>42 285</td>
<td>38 813</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.00 (Reference)</td>
<td>1.53 (1.06-2.22)</td>
<td>0.60 (0.35-1.01)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>1.70 (1.15-2.51)</td>
<td>0.86 (0.38-1.33)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
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<td></td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.00 (Reference)</td>
<td>1.19 (0.60-2.36)</td>
<td>0.64 (0.46-0.89)</td>
</tr>
</tbody>
</table>

*Abbreviations: NA, not applicable; RR, relative risk.

†Tests for linear trends reflect the statistical significance of the mean number of cigarettes smoked at each dose modeled continuously.

§Adjusted for age in the following seven 5-year categories: 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 70+ years.

#Past smoking dose is the dose last regularly smoked.

## Notes

- Data are given as the RR (95% confidence interval) unless otherwise indicated.
- Adjusted for age in the following seven 5-year categories: 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 70+ years.
- Tests for linear trends reflect the statistical significance of the mean number of cigarettes smoked at each dose modeled continuously.
- Adjusted for age in the following seven 5-year categories: 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 70+ years.
time did not depart materially from the primary results. As our participants are health professionals, their level of screening would likely be as high or higher than that observed in a general population sample. Thus, any such bias in this study, although possible, should be modest.

Differential follow-up because of more death, cancer, and loss to follow-up in smokers compared with never smokers is unlikely to have had a major effect on our results. The overall follow-up has been high (>95% in each cohort) and the differences by smoking status are too small to have caused the observed associations (in the NHS, the follow-up was 95.3% in never smokers and 93.9% in the longest-duration smokers; in the HPFS the percent-duration was 96.8% and 93.7%, respectively).

Random misclassification of cigarette smoking exposure may have biased our results toward the null. However, we have previously found significant positive associations between smoking and both cataract extraction and age-related macular degeneration in these cohorts, suggesting this bias is not large.

Cigarette smoke contains about 4000 substances, and there are data supporting both adverse and protective effects of cigarette smoking for POAG. Although some data show that cigarette smoking may transiently elevate IOP, this has been an inconsistent finding. It is more likely that smoking would be related to vascular changes to the optic nerve head. Vasoactive substances in smoking may compromise the vascular system by increasing blood viscosity and inducing vaso spasms, which...
could increase the risk of POAG. However, a few studies of the effect of nicotine also suggest protective mechanisms. Nicotine increases cerebral blood flow in humans, possibly by increasing brain oxygen consumption. As the optic nerve is a part of the central nervous system, nicotine may also increase its blood flow. Tamaki et al27 found that in 9 healthy habitual smokers, the acute effect of cigarette smoking compared with sham smoking was to increase optic nerve blood flow velocity, and they attributed this to nicotine. The biological mechanisms, while largely unknown, are likely to be complex. Further research into the short- and long-term ocular physiologic effects of smoking on the optic nerve would be necessary to shed light on how cigarette smoking may affect the risk of POAG. Our prospective data indicate that cigarette smoking does not materially increase one’s risk of POAG. Although smoking cessation will reduce the risk of numerous systemic and ocular disorders and remains a major public health initiative, it does not seem to offer a means for primary prevention of POAG. More efforts to find modifiable lifestyle factors are necessary to reduce the burden of POAG, a disease of considerable public health importance.

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