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Authors

Mahmoudinezhad, Golnoush
Nishida, Takashi
Weinreb, Robert N
et al.

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Impact of Smoking on Visual Field Progression in a Long-term Clinical Follow-up

Golnoush Mahmoudinezhad, MD, MPH[1], **Takashi Nishida, MD, PhD**[1], **Robert N. Weinreb, MD**[1], **Sally Baxter, MD, MSc, MD**[1,2], **Medi Eslani, MD**[1], **Eleonora Michelleti, MD**[1], **Jeffrey M. Liebmann, MD**[3], **Massimo A Fazio, PhD**[4], **Christopher A. Girkin, MD, MSPH**[4], **Linda M. Zangwill, PhD**[1], **Sasan Moghimi, MD**[1]

[1]Hamilton Glaucoma Center, Shiley Eye Institute, Viterbi Family Department of Ophthalmology, University of California San Diego, La Jolla, CA, United States.

[2]Department of Biomedical Informatics, University of California San Diego, La Jolla, CA, United States.

[3]Bernard and Shirlee Brown Glaucoma Research Laboratory, Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Medical Center, New York, NY, United States.

[4]Bernard School of Medicine, University of Alabama-Birmingham, Birmingham, AL, United States.

Abstract

Purpose: To investigate the effect of smoking on the rates of progressive visual field damage over time in glaucoma.

Design: Retrospective cohort study.

Participants: A total of 511 eyes of 354 patients with glaucoma followed from multicenter glaucoma registries.

Corresponding author: Sasan Moghimi, Shiley Eye Institute, University of California, San Diego, 9500 Campus Point Drive, La Jolla, CA, 92093-0946, sasanimii@yahoo.com.

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Methods: In this longitudinal study, 354 primary open-angle glaucoma (POAG) patients with a minimum of 3 years follow-up and 5 visual field (VF) tests were enrolled from the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES). Univariable and multivariable linear mixed models were used to investigate the effects of smoking on the rates of 24–2 VF mean deviation loss. VF progression was defined using pointwise linear and significant negative VF MD loss. Logistic regression was used to identify baseline factors and whether different levels of smoking intensity were associated with VF progression. Kaplan-Meier survival analysis and the log-rank test were used to compare the cumulative risk ratio of progression between smoker and never smoker groups.

Main Outcome Measures: VF progression

Results: A total of 511 eyes of 354 patients were included over the median follow-up of 12.5 years. Median baseline age was 64.8 years. Of the 354 patients, 124 (35%) were African ethnicity, and 168 (59.8%) and 149 (42.1%) had reported a history of smoking or alcohol consumption, respectively. In a multivariable model, higher smoking intensity was associated with faster VF loss (coefficient −0.05 (−0.08, −0.01)dB/year per 10 pack-years, P=0.010). Developing VF progression in eyes of heavy smokers (≥20 pack-years) was 2.2 times greater than in eyes of patients without smoking history (OR=2.21; 95% CI: 1.02,4.76; P=0.044). Statistically significant differences were found between heavy smokers (≥20 packs-year) and never smokers by Kaplan-Meier analysis (log-rank test, P=0.011).

Conclusions: Heavy smokers are more likely to have VF loss in eyes with glaucoma. The prospective longitudinal design of this study supports the hypothesis that levels of smoking may be a significant predictor for glaucoma progression. Additionally, this information can be used for clinically relevant tobacco prevention and intervention messages.

Keywords

glaucoma; progression; smoking; visual field

Introduction

Glaucoma is a progressive optic neuropathy and a leading cause of irreversible blindness worldwide, characterized by retinal ganglion cell (RGC) degeneration and associated visual field (VF) damage.[1] The chronic, progressive, and irreversible nature of damage in glaucoma makes the timely detection of disease progression and its potential risk factors highly important.[2] Knowing patients' risk factors, especially modifiable risk factors for glaucoma development and progression, allows clinicians to identify high-risk individuals who can be targeted for closer monitoring or more aggressive treatment. Risk factors can also provide insight into disease mechanisms and may help identify other potential treatment approaches, potentially reducing the economic burden of glaucoma.[3–5]

A myriad of factors, including older age[6], abnormal systemic blood pressure,[7] elevated intraocular pressure (IOP)[6], and disc hemorrhage (DH)[8] are known to contribute to the disease. However, IOP remains the only proven modifiable risk factor for both the development and progression of glaucoma.[9, 10] Nevertheless, many patients with glaucoma still develop progressive functional loss despite relatively low IOP levels.[11] Vascular factors

affecting ocular blood supply have been suspected to have a role in the glaucomatous process. Understanding these modifiable factors may improve glaucoma management.

Smoking is a major global public health concern that has been associated with many chronic diseases. Tobacco exposure contributes to vascular disease by occluding arterial lumina with atherosclerotic plaques and intimal thickening. Smoking can also increase inflammation, thrombosis, and oxidative stress as a potential mechanism for initiating vascular disfunction.[12] Smoking has been known to contribute to ocular diseases such as cataracts, age-related macular degeneration (AMD), and anterior ischemic optic neuropathy through ischemic and oxidative mechanisms.[13, 14] Previous studies reported controversial results about associations between smoking and glaucoma.[15–18] A compromised blood flow in the optic nerve head has been suggested to contribute to the pathogenesis of glaucoma.[19] Moreover, the high oxidative stress with the production of free radicals has been known to damage trabecular meshwork cells (TMC) and RGCs in glaucoma.[20] Smoking has been suggested to influence the microcirculation with endothelial-dependent vasorelaxation by abnormal nitric oxide activity, platelet aggregation, and endothelial cell dysfunction, resulting in vascular blood flow changes in vivo and vitro[21] and may worsen glaucoma. Consequently, there is a theoretical basis suggesting that smoking has a role in the development of POAG and its progression. However, until now, clinical studies have not been able to determine the effect of smoking levels on glaucoma progression since they have primarily included cross-sectional investigations, a limited duration of follow-up, small sample sizes, or did not consider the level of smoking in their analysis.[9, 15–18] For example, in a longitudinal study by United Kingdom Glaucoma Treatment Study (UKGTS), they found a protective association between smoking and VF progression based on the history of smoking over 2 years of follow-up.

In the present study, a large cohort of glaucoma patients from a multicenter study was used to investigate the hypothesis that the level of smoking (e.g., heavy smoking) increases the rate of VF deterioration in glaucoma. We also investigated the cumulative probability of glaucoma progression over a long-term follow-up between heavy smokers and never smokers.

Methods

This was a retrospective cohort study of POAG patients enrolled in Diagnostic Innovations in Glaucoma Study (DIGS) and African Descent and Glaucoma Evaluation Study (ADAGES)[22] which are conducted at the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), and ADAGES is a multicenter study conducted at UCSD, the University of Alabama at Birmingham, and the Columbia University (previously at the New York Eye and Ear Infirmary). The protocols of the two studies are identical, and the methodological details have been described. [22] Informed consent was obtained from all study participants. The studies received Institutional Review Board approval at each of the three sites. The methodology adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. Informed consent was obtained from all participants.

All participants underwent annual comprehensive ophthalmologic evaluation, including best-corrected visual acuity, slit-lamp biomicroscopy, dilated fundus examination, and stereoscopic optic disc photography in both eyes. Semi-annual evaluations included Goldmann applanation tonometry measurement and Standard Automated Perimetry testing using the Swedish Interactive Thresholding Algorithm (SITA) Standard 24–2 strategy. Self-reported history of smoking, smoking intensity (including duration and packs per day), alcohol consumption, and Body Mass Index (BMI) were also collected.

Participant Selection

POAG eyes having a minimum follow-up time of 3 years and a minimum of 5 VFs were included in this study. Eyes were classified as glaucomatous if they had repeatable (at least 2 consecutive) abnormal VF test results with evidence of glaucomatous optic neuropathy – defined as excavation, the presence of focal thinning, notching of neuroretinal rim, or localized or diffuse atrophy of the retinal nerve fiber layer (RNFL) based on the grading of optic disc photographs. An abnormal VF test was defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits. Glaucoma disease severity was classified as early (24–2 VF mean deviation (MD) >−6 dB), or moderate (−12 dB≤ 24–2 VF MD<−6 dB).[23] All VF tests were performed on the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA), with the results being considered unreliable and excluded from the analyses if they had >33% fixation losses or false-negative errors or >33% false-positive errors. In order to avoid the risk of truncation (floor effect), we also removed eyes with VF baseline MD less than −12 dB.[24]

Inclusion criteria also included (1) older than 18 years of age, (2) open angles on gonioscopy, and (3) best-corrected visual acuity of 20/40 or better at study entry. Exclusion criteria included (1) history of trauma or intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), (2) coexisting retinal disease, uveitis, or non-glaucomatous optic neuropathy, (3) other systemic or ocular diseases known to affect VF such as pituitary lesions or demyelinating diseases, (4) significant cognitive impairment, Parkinson's disease, Alzheimer's disease, dementia, or a history of stroke or (5) axial length of 27 mm or more. Questionnaire about smoking and alcohol consumption were provided in Supplementary Table 1.

Statistical analysis

Patient and eye characteristics data were presented as median (Interquartile range (IQR)), for continuous variables and count (%) for categorical variables. The smoking intensity was calculated as the pack-year index at the baseline VF. The time between filling out the questionnaire and the baseline VF was also reported. Two methods were used for evaluating the progression:

1. **Trend-based analysis:** Linear mixed models estimate the average rate of change in an outcome variable using a linear function of time, and subject- and eye-specific deviations from this average rate are introduced by random slopes.[25, 26] Univariable models were first used to evaluate the effect of smoking intensity as well as baseline demographics and clinical characteristics on the rates of VF

MD loss over the entire follow-up time (i.e., at the end of the patients' VF series). To allow for the interpretation of the effect of smoking intensity, we built multivariable models for smoking intensity that included additional adjustment for mean IOP, central corneal thickness (CCT), and baseline MD, and any other variable in which the P-value was <0.10 in univariable analysis.

2. **Pointwise linear regression (PLR):** Ordinary least squares of the raw threshold sensitivities in VF were performed for each of the 52 VF locations over time. A rate of change of at least −1.0 dB/y and 2-sided P < .01 defined a single location as progressing. The entire eye was labeled as progressing if at least 3 locations met the above criteria over the entire follow-up over the course of the patients' VF series, consistent with prior descriptions of using PLR analysis for longitudinal evaluation of VFs.[27–29] Univariable and multivariable logistic regression was used to evaluate the effect of different level of smoking and other variables on the frequency of VF progressors. Multivariable model was adjusted for baseline age, baseline MD, mean IOP, BMI, and alcohol consumption.

VF progression was also assessed using a survival analysis method, where an eye was considered to have progressed (i.e., reached an endpoint) if at least 2 consecutive visits during the follow-up had a p-value less than 0.05 and rates of change below 0. Kaplan-Meier survival analysis and the log-rank test were used to compare the cumulative risk ratio of progression between two groups stratified by the heavy smokers (≥20 pack-years at baseline) and never smokers. An inter-eye correlation was also considered. Cox proportional hazard regression analysis with random effect on eyes was used to determine predictive factors for progression. In addition to smoking intensity, smoking history, alcohol consumption status, and BMI were also introduced into the separate multivariable model to explore the effect of these covariates on VF progression. In addition, Cox Proportional Hazards regression was used to estimate hazard ratios for the risk of VF progression across our cohorts of different levels of smoking intensity in pack-years. The variable of smoking intensity was modeled using splines to allow for a nonlinear association with the log hazard of VF progression. Statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX). P values of less than 0.05 were considered statistically significant for all analyses.

Results

A total of 511 eyes of 354 POAG patients were enrolled in this study. Median age (IQR), was 64.8 (55.5, 70.5) years. Median baseline VF MD was −2.5 (−5.2, −0.9) dB. The median number of 17 (13.0, 22.0) VFs was observed over the 12.5 (9.4, 15.4) years follow-up period. A total of 149 (42.1%) patients had reported ever smoking and 39 (11.0%) were heavy smokers at baseline. Among smokers, the median smoking intensity was 7.8 (3.0, 19.0) pack-years. Current alcohol consumption was reported in 168 (59.8%) patients, and median BMI was 26.1 (23.0, 30.1) kg/m^2. Demographics and baseline clinical characteristics of the subjects are presented in Table 1.

Table 2 summarizes the factors contributing to the rate of VF worsening over time by univariable analysis. Current alcohol consumption (P=0.63) was not associated with VF worsening, while smoking intensity (coefficient (95% CI) −0.05 (−0.08, −0.02) μm/year

per 10 pack-years higher; P=0.001) and lower BMI (coefficient (95% CI) 0.06 (0.01, 0.12) per 10 kg/m^2; P=0.018) was significantly associated with the faster rates of VF worsening over time. Older age was also found to be significantly associated with faster rates of VF worsening over time (coefficient (95% CI) −0.07 (−0.10, −0.04) per 10 years; P<0.001). History of ever smoking tended to be associated with VF worsening (coefficient (95% CI) −0.06 (−0.13, 0.00); P=0.061).

Table 3 summarizes the multivariable linear mixed models examining the rate of VF worsening over time for smoking history and smoking intensity (with and without adjustment with current alcohol consumption, and BMI), separately. After adjustment for confounding factors, history of ever smoking was not significantly associated with the rates of VF worsening over time (P=0.288). Smoking intensity was associated with rates of VF worsening over time (coefficient (95% CI) −0.05 (−0.08, −0.01) dB/year per 10 pack-years higher; P=0.010) even after adjustment for current alcohol consumption and BMI in POAG patients. Supplementary Table 2 shows the results of multivariable linear mixed models examining the effect of current alcohol consumption and BMI on the rate of VF worsening over time, separately. Alcohol consumption was not associated with fast VF progression (P=0.592). Lower BMI tended to be associated with the faster rates of VF worsening over time (coefficient (95% CI) 0.05 (−0.01, 0.10) dB/year per 10 Kg/m^2 lower; P=0.089).

In a three-way interaction between smoking intensity, age, and time; higher smoking intensity was associated with faster VF loss (coefficient (95% CI) −0.06 (−0.09, −0.02) dB per each 10 pack-years higher and 10 years older at baseline, P=0.002). Additionally, the three-way interaction between different categories of smoking intensity, age, and time showed that aging increased the risk of the effect of heavy smoking on VF progression (coefficient (95% CI) −0.20 (−0.30, −0.05) dB/year per each 10 years older at baseline, P=0.009).

The distribution of the proportion of VF progressor group (according to PLR) in each smoking intensity category (0 pack-year smoking, between 0–20 pack-years, and ≥ 20 pack-years smoking) was shown in Figure 1. A total of 38.5% of eyes progressed among patients with ≥20 pack-years smoking, while 26% of eyes progressed among never smokers. Table 4 shows the result of univariable and multivariable analysis for progressors vs. non-progressor eyes according to PLR criteria. Multivariable analysis showed that smoking ≥20 pack-years (OR, 2.21 [95% CI, 1.02, 4.76] per 10 pack-years higher; P=0.044) was associated with a statistically significant increase in the odds of VF progression after adjustment for alcohol consumption and BMI. Lower BMI tended to be associated with VF worsening (OR, 0.68 [95% CI, 0.46, 1.00] per 10 kg/m^2 higher; P=0.054). In progressors, while in the heavy smokers, median (IQR) VF MD worsened to −14.5 (−18.4, −7.8) dB from a baseline VF MD of −3.7 (−1.4, −10.0) dB; in never smokers, the final VF MD was −10.0 (−13.3, −8.0) dB from a baseline MD of −3.2 (−5.7, −1.1)) dB. In mild/moderate smokers, baseline and final MD among progressors were −2.9 (−0.9, −5.9) dB and −11.8 (−8.3, −14.3) dB, respectively. Similar results were found using Cox proportional hazard regression analysis, examining the hazard ratio of VF worsening over time among POAG patients. In multivariable analysis, heavy smoking was significantly predictive of VF progression (adjusted HR, 1.74 95% CI (1.03, 2.93); P= 0.037), while mild/moderate smoking was not

associated with VF progression (adjusted HR, 0.78 95% CI (0.62,1.24); P=0.443). The risk of VF progression across increasing smoking intensity is shown in the Supplementary Figure 1.

Similarly, Kaplan–Meier survival analysis also showed that the heavy smoker group had significantly shorter survival periods than the never smoker group (P= 0.011, log-rank test), Figure 2.

Discussion

This longitudinal study demonstrated that at the time of their baseline VF, heavy smokers (≥20 pack-years) were more likely to experience VF progression than never smokers over 12 years of follow-up. The risk of developing progression for heavy smokers was approximately 2.2 times the risk for never smokers. Additionally, the risk of developing POAG progression increases as the intensity of smoking increases. Our results suggest a cumulative effect of long-term high-intensity smoking, especially ≥20 pack-years, can result in optic nerve damage in glaucoma. This factor could potentially be used in patient selection for identifying high-risk patients for more intensive therapy. To our knowledge, this is the first study to demonstrate that heavy smoking is an independent and significant prognostic factor for progression in VF worsening.

The dynamic and diverse nature of POAG poses challenges for physicians. Current treatment regimens are based on reducing IOP mainly through medical or surgical procedures.[11] Moreover, patients with the same IOP level may have remarkably distinct treatment responses and clinical outcomes.[30] Therefore, it remains an unsolved critical issue to identify patients at high risk for progression to receive more aggressive therapy. Smoking is thought to be a risk factor for increased IOP, which normally ranges between 10 and 21 mmHg.[31] In the present study, we found a relationship between smoking and VF progression; each 10 pack-years higher smoking was independently associated with a 0.05 dB/year faster VF progression over time in POAG patients. Moreover, the risk of developing progression was higher in the heavy smokers. This is possibly due to different levels of nicotine absorption or difference in end-organ response to the combination of chemicals in tobacco smoke in different duration and severity of smoking's use.[32] The effect of smoking intensity with ≥20 pack-years on vascular and neural tissue may be extended in smokers and attribute to faster glaucoma progression later in the life.

Some cross-sectional studies have investigated the cumulative effect of smoking on VF damage. A follow-up study showed that smokers with greater pack-years were significantly more likely to have a peripheral VF than paracentral VF defect in POAG.[33] Akarsu et al.,[34] showed that moderate cigarette smoking (10–20 cigarettes per day for at least the past 5 years) is associated with both diffuse and localized reductions in retinal sensitivity using white on white perimetry. In healthy chronic heavy smokers, retinal sensitivity was found to be decreased, although the central vision was not affected, possibly due to a cumulative effect of chronic smoking onto the retinal and/or optic nerve functions without clinically evident optic neuropathy.[35]

A consistent longitudinal relationship between smoking and VF progression previously has not been reported. A few studies reported that cigarette smoking might have a protective effect against glaucoma in a lower dose.[18] In the UKGTS, a history of smoking was negatively associated with VF worsening over 2 years.[18] It is postulated that high levels of nitric oxide can induce beneficial vasodilation that leads to increased optic nerve blood flow, while nitric oxide can also induce hyperperfusion damage and reactions that form peroxynitrites, free radicals that induce retinal ganglionic cell death.[36] An advantage of UKGTS was that treatments were standardized and were controlled for in the analysis. Additionally, UKGTS could evaluate several potential factors which affect VF deterioration. These various factors may also have an association with smoking history. For example, they evaluated the effect of sleep apnea, migraine, Reynaud's phenomenon, heart attack, cardiovascular disease, angina, and claudication. Evaluating and adjusting the model for these risk factors in UKGTS is important as there might be some pathophysiological links between glaucoma and other systemic diseases. For example, smoking may lead to cardiovascular disease, which may then lead to glaucoma, or it may also be an independent risk factor for glaucoma. However, investigators in this study only collected information based on history of smoking for 2 years of follow-up. Therefore, heavy smoking over a longer time period may eliminate such protective effects.[37] The cumulative effect of tobacco through chronic nicotine toxicity can have a direct neurotoxic effect on the optic nerve, as demonstrated in our cohort by those patients with more than 12 years of follow-up. Also, nicotine or other harmful substances can diminish the blood velocity in vessels of the optic nerve head and chorioretina and aggravate nerve function.[38]

In current study, patients with heavy smoking intensity were more than twice as likely to progress as compared to those who had never smoked. In contrast to the many current known risk factors for POAG, tobacco smoking is a modifiable risk factor. 10% of the current study population were heavy smokers, and the difference in progression incidence with the Kaplan Meier plot is about 17% (75% heavy vs. 57.7% never smokers). In addition, the final baseline MD in heavy smokers was −14.5 (−18.4, −7.8) vs. −10.0 (−13.3, −8.0) in never smokers. Additionally, aging increased the effect of smoking intensity on VF progression in a three-way interaction. Therefore, this synergistic effect could be due to cumulative exposure of tobacco and its products that leads to a snowball effect in glaucomatous progression as the patients get older. Therefore, even a small effect may be important in public health considering the fact that smoking is a modifiable risk factor. This is also important in terms of public health considerations and the economic burden of glaucoma management because better understanding of the role and effect of smoking can provide an opportunity for enhanced glaucoma management through modifying lifestyle habits.

Controversy exists regarding the effects of pack-years on retinal thickness in glaucoma patients in several cross-sectional studies.[39–41] Chronic smokers for more than 25 years showed thinner ganglion cell complex thicknesses than control subjects.[40] Kumar et al. evaluated the effects of moderate to heavy smoking on RNFL thickness. They showed significantly thinner RNFL in smokers compared to never smokers only in the nasal quadrant.[39] However, Duman et al., did not find any difference in RNFL thickness between smokers (average of 22 pack-years) and never smokers, possibly due to small sample size.[42]

Other studies did not find any association between smoking status and RNFL thickness.[43, 44] This observation could shed light on the fact that the cumulative effect of smoking may need a longer time to impact retinal thickness in glaucoma patients.[32, 44]

Tobacco smoke contains many toxic compounds which harm the ocular tissues, triggering ischemic or oxidative mechanisms.[45] Inflammation and apoptosis marker levels increase with smoking in the aqueous humor and plasma samples with POAG.[46] Increased oxidant stress was shown in the anterior segment, such as in trabecular meshwork as well as in the posterior pole of a glaucoma patient.[47] Other detrimental effects of smoking on the eye were also proposed, including compromised arterial blood flow to the optic nerve head,[19, 48] generation of free radicals, oxidative effect in the blood circulation, aqueous humor, and ocular tissue[13], increasing blood viscosity, and inducing vasospasms.[49, 50] Therefore, according to previous evidence, it seems that the damage caused by smoking may be similar to a putative pathophysiological mechanism of POAG, which contributes to vascular damage through compromised blood flow and decreasing the outflow of the aqueous humor through TMC and RGC damage by high oxidative stress.[20, 51] Moreover, the mechanism associated with vasoconstriction of the episcleral veins can reduce the aqueous outflow.[45] Consequently, smoking seems to be involved in the pathogenesis of POAG progression, along with other risk factors.

We also did not find an association between baseline IOP and mean IOP during follow-up and VF worsening, suggesting that smoking may not be related to IOP but is involved in neuronal death. A previous study showed that smoking was associated with IOP, probably due to reduced aqueous outflow resulting from vasoconstriction of episcleral veins and inhibition of aqueous outflow from the trabecular meshwork.[45] However, Dikopf et al. did not find any association between the smoking and mean, peak, or variability of IOP in non-glaucoma patients. [52]Additionally, patients in the current study were under aggressive therapy. This also may be another reason for lack of association between mean IOP and VF worsening in our study.

In addition, it is possible that smoking may be associated with another unmeasured factor (nicotine replacement therapy), which affects rates of VF progression. Smokers may be less adherent to medication or have other poor health behaviors. Additionally, poor diet and health may interact with some of the variables evaluated in the current study as confounding factors, especially among heavy smokers. Therefore, this may make the measurement of the dose-dependent effect of smoking difficult and imprecise. However, we tried to evaluate the effect of possible factors related to health conditions and exist in our dataset on VF progression. For example, we tried to evaluate the effect of diabetes, hypertension, BMI, and alcohol consumption on VF progression. Moreover, smoking, alcohol consumption, and BMI may be surrogates for general health and nutritional status in the current study.

A convergence might be observed at the end of the follow-up period in the survival plot. This convergence happened more prominently between heavy and mild/moderate smokers. Various reasons might be considered for this observation. First, since the patients included in this study were under treatment, treatment changes or intensification by clinicians might affect the behavior of progression over time. The other reasons might be that IOP-related

metrics and clinical characteristics are important for glaucoma progression in the long term. Second, the current study included patients who were former smokers, and smoking cessation may change the effect of smoking on VF progression over time. This is an interesting hypothesis whether smoking cessation could reduce rates of VF progression after long-time smoking, especially in heavy smokers, and should be evaluated in future studies.

The current study showed lower BMI tended to be associated with faster VF worsening over time. Several studies found that lower BMI is protective for developing POAG.[17, 53] There are some possible mechanisms for the protective effect of BMI against glaucoma progression. First, leptin receptors were found on axons of RGCs. Leptin in adipose tissue can act as a neuroprotective agent for retinal ganglion cells.[54] Second, estrogen, which is increased in both men and women in the obese population[55], has a neuroprotective effect through estrogen receptors in RGCs as well as increasing ocular blood flow.[56] In addition, increased neuropeptide Y release, which is known to be associated with obesity, has been reported to inhibit the decrease in the number of ganglion cells.[57] Future studies with larger sample sizes are needed to explore the association of BMI and VF progression.

Of note, in some countries, there is a decline in the frequency and prevalence of smoking over time, with younger people in the community less inclined to smoke as heavily or frequently as people from older generations. For example, in US, current smoking has declined from 20% in 2005 to 13% in 2020.[58, 59] This is the achievement of a consistent and coordinated effort by the public health community and many other partners. However, cigarettes have still remained the most commonly used tobacco product among adults.[59] Moreover, psychosocial risk factors associated with smoking also have to be considered when asking patients about cigarette smoking or encouraging them to quit smoking. These include intrapersonal distress, substance use, family relationships, negative life events, financial stressors, perceptions that tobacco use is normative, and use of tobacco by family and peers (among other measures).[60, 61] Different ethnic groups may be differentially impacted by psychosocial factors. For example, a previous study suggested that the influence of psychosocial factors on using tobacco product use was stronger among non-Hispanic whites than among Hispanics.[62] Therefore, encouraging smoking cessation needs multidisciplinary approaches. Clinicians in ophthalmology clinical practice need to be aware that they need to address this issue through several domains of an individual’s life while assessing smoking use.

This study has several limitations. First, we excluded glaucoma patients with MD less than −12 dB. Therefore, caution should be exercised when extrapolating the results to severe stages of glaucoma. Second, the questionnaire only reflected baseline conditions. Further study is needed to examine lifestyle changes and glaucoma progression over time. Although a long follow-up period could be considered one of the strengths of the current study, a potential difficulty of the study is the challenge of accurately determining smoking exposure, both before study enrolment and during the long follow-up period. This might be considered because the average follow-up of the study was long, and smoking exposure may have differed during the entire follow-up. Our study did not consider the effect of environmental tobacco smoking (passive smoking) on glaucoma. POAG patients with a no smoking history might include passive smokers in our study. It will be necessary for

future studies of glaucoma progression to include comprehensive exposure questionnaires to account for various routes of inhaled nicotine, tobacco, and marijuana exposure. Although the questionnaire for the current study included alcohol consumption, many patients did not have the amount of alcohol consumption despite having a history of alcohol consumption. Therefore, we only included the history of alcohol consumption in the analysis. Although a correlation between smoking and VF progression exists, a linear model may not be the best demonstration of the effect of smoking on ocular tissue. In addition, it is possible that patients in the current study received different treatments during follow-up due to their risk factors (e.g., smoking) that might influence their rates of VF progression. IOP during follow-up was included in the multivariable model, which would have captured some treatment effects. However, it is possible that not all treatment effects were captured by IOP. For example, it is possible that smokers were less likely to receive beta-blockers due to their effects on the respiratory system, which could potentially lead to a poorer outcome and faster VF progression. Finally, the effect of smoking cessation was not evaluated in the current study. Future studies are required to assess the reversal of risk in glaucoma progression after quitting smoking.

This study demonstrated that heavy smoking significantly increases the risk and incidence of progression in POAG, and smoking intensity may be an independent prognostic factor of POAG progression. This has important health care implications, as modifying smoking behavior may reduce the risk of developing severe glaucoma and eventual blindness. In this case, providing smoking cessation advice for smokers and support to at-risk patients would be an important preventive intervention. Screening for smoking in the clinic may help decrease glaucoma progression, especially in the high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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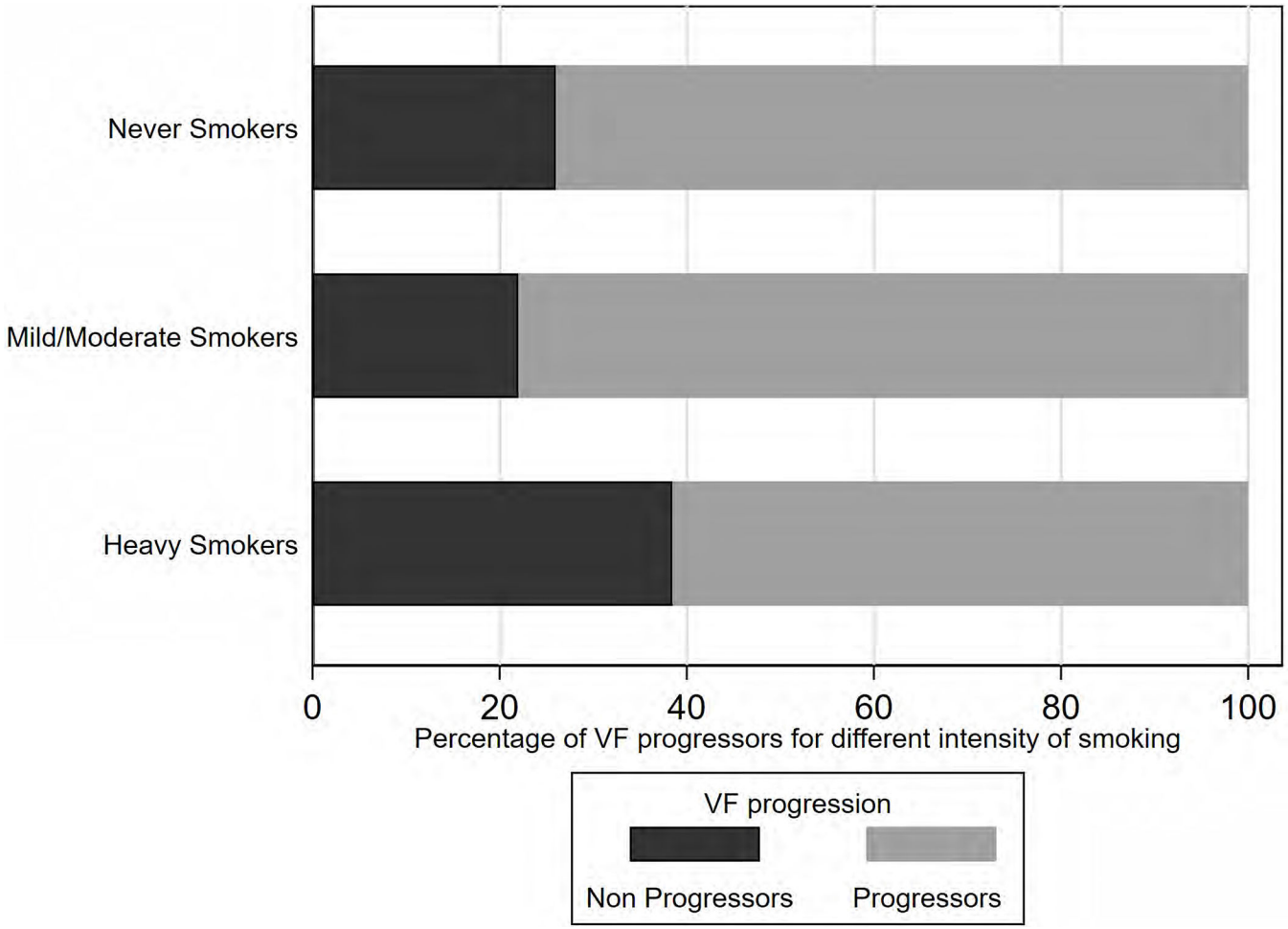

Figure1.

Graph illustrating the proportion of VF progressors for different smoking intensity categories (Never smokers (n=205), Mild/Moderate Smokers (n=110), and Heavy Smokers (n=39)). The proportion of VF progressors was higher in heavy smokers with more than 20 pack-years smoking (39%) as compared to never smokers (26 %) (P=0.044) at the time of their baseline VF. Never smokers:0 pack-year, Mild/Moderate Smokers:<0 and <20 pack-years, and Heavy Smokers: ≥20 pack-years.

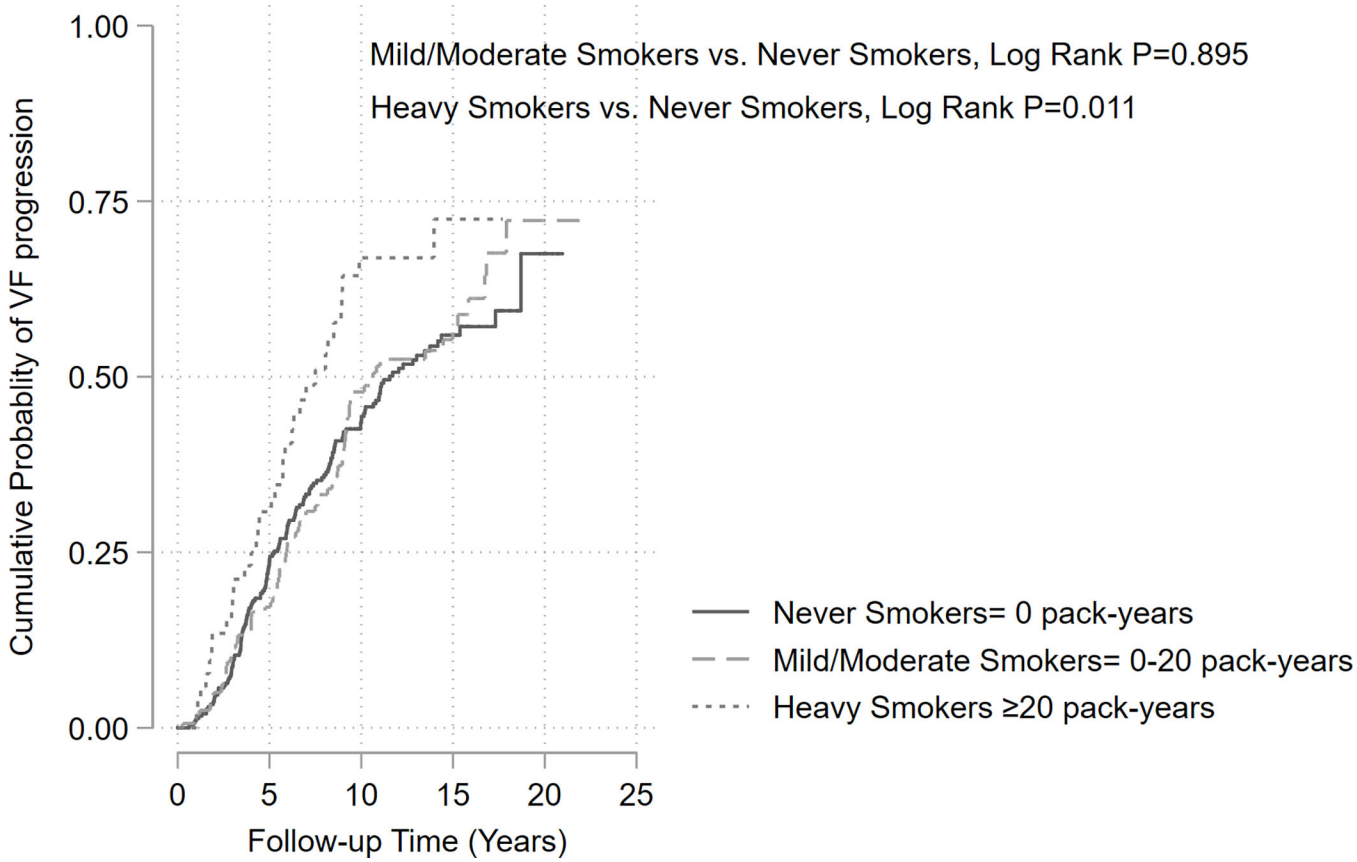

Figure2.

Kaplan-Meier analysis of the probability to detect visual field progression in glaucoma eyes. After 10 years, 75% of eyes in group with more than 20 pack-years smoking history developed progression, while 58 % of eyes in group with no smoking history developed progression after a similar period. Log-rank tests comparing eyes in heavy smoker group (≥20 pack-years) vs. eyes in group with no smoking history showed statistically significant differences (P= 0.011, log-rank test).

Table 1.

Demographics and Baseline Characteristics of included eyes.

Characteristic	n=511 eyes of 354 patients
Baseline age (years)	64.8 (55.5,70.5)
Gender (Female/Male), n (%)	188 (53.1%)/166 (46.9%)
Ethnicity (African American/Non-African American), n (%)	124 (35%)/230 (65%)
Ever reported smoking, n (%)	149 (42.1%)
Smoking at baseline VF, n (%)	
0 pack-years	205 (57.9%)
0–10 pack-years	83(23.5%)
10–20 pack-years	27(7.6%)
20–30 pack-years	24 (6.8%)
≥30	15(4.2%)
Smoking intensity among smokers (n=149) at baseline VF, pack-year	7.8 (3.0, 19.0)
Alcohol consumption, n (%)	168 (59.8%)
BMI (kg/m^2)	26.1 (23.0, 30.1)
Self-reported hypertension, n (%)	229 (64.7)
Self-reported diabetes, n (%)	80 (22.6)
Axial length (mm)	24.0 (23.4, 24.7)
CCT (μm)	540.0 (515.3, 568.7)
Baseline IOP (mmHg)	17.0 (14.0, 21.0)
Mean IOP during follow-up (mmHg)	15.0 (13.1, 17.5)
Disease Severity by baseline 24–2 VF MD	
Early glaucoma, Eye No. (%)	414 (81.0%)
Moderate glaucoma, Eye No. (%)	97 (19.0%)
Baseline VF MD (dB)	−2.5 (−5.2, −0.9)
VF follow-up visits (n)	17 (13.0, 22.0)
Follow-up (years)	12.5 (9.4, 15.4)
Time between Smoking Questionnaire and baseline VF (years)	10.3 (6.3,14.1)

BMI = Body Mass Index; CCT = Central Corneal Thickness; IOP = Intraocular Pressure; MD = Mean Deviation; OCT = Optical Coherence Tomography; VF = Visual Field; n = number. Values are shown in median (Interquartile range (IQR)), unless otherwise indicated.

Table 2.

Factors contributing to the rate of visual field loss over time by univariable linear mixed model analysis

Variables	Coefficient, 95% CI	P value
Ever reported smoking yes	−0.06 (−0.13, 0.00)	0.061
Smoking intensity, per 10 pack-year higher	−0.05 (−0.08, −0.02)	**0.001**
Alcohol consumption, yes	−0.02 (−0.09, 0.06)	0.630
BMI, per 10 kg/m^2 higher	0.06 (0.01, 0.12)	**0.018**
Baseline age (year) per 10 years older	−0.07(−0.10, −0.04)	**<0.001**
Gender: female	0.02 (−0.05, 0.08)	0.580
Ethnicity: African descent	0.05 (−0.01, 0.12)	0.114
Self-reported hypertension	0.01 (−0.06, 0.08)	0.830
Self-reported diabetes	0.04 (−0.04, 0.11)	0.305
Axial length, per 1 mm longer	0.02 (−0.01, 0.05)	0.273
CCT, per 100 μm thinner	0.07 (−0.01, 0.15)	0.099
Baseline IOP, per 1 mmHg higher	−0.01 (−0.03, 0.00)	0.145
Mean IOP, per 1 mmHg higher	−0.00 (−0.01, 0.00)	0.306
Baseline 24–2 VF MD, per 1 dB worse	0.01(−0.002, 0.018)	0.125

BMI = Body Mass Index; CCT = Central Corneal Thickness; IOP = Intraocular Pressure; MD = Mean Deviation; OCT = Optical Coherence Tomography; VF = Visual Field. Values are shown in mean (95% confidence interval). Bold text indicates a statistically significant difference with a p-value less than 0.05.

Table 3.

Multivariable Linear Mixed Models Assessing the Rate of Visual Field Loss Over Time (Visual Field MD) in POAG Patients

Variables	Multivariable Model 1 History of ever smoking		Multivariable Model 2 Smoking intensity		Multivariable Model 3 (Smoking intensity adjusted for alcohol consumption and BMI)	
	Coefficient, 95% CI	P value	Coefficient, 95% CI	P value	Coefficient, 95% CI	P value
Ever reported smoking yes	−0.04 (−0.10, 0.03)	0.288				
Smoking intensity, per 10 pack-years higher			−0.04 (−0.07, −0.01)	**0.023**	−0.05 (−0.08,−0.01)	**0.010**
Alcohol consumption, yes					0.01 (−0.06,0.09)	0.707
BMI, per 10 kg/m^2 higher					0.06 (−.003,0.12)	0.061
Baseline age (year) per 10 years	−0.06 (−0.1, −0.03)	**<0.001**	−0.06 (−0.09, −0.03)	**<0.001**	−0.05 (−0.09,−0.02)	**0.004**
CCT, per 100 μm thinner	0.07 (−0,01,0.26)	0.094	0.07 (−0.02, 0.15)	0.114	0.04 (−0.05,0.13)	0.378
Mean IOP during follow-up (mmHg) per 1 mmHg higher	−0.01 (−0.02, −0.00)	**0.010**	−0.01 (−0.02,−0.00)	**0.007**	− 0.02 (−0.03,−0.01)	**0.003**
Baseline 24–2 VF MD (dB) per 1 dB worse	0.01 (−0.00,0.02)	0.166	0.01 (−0.00,0.02)	0.161	0.007 (−.005,0.02)	0.254

BMI = Body Mass Index; IOP = Intraocular Pressure; MD = Mean Deviation; VF = Visual Field. Values are shown in mean (95% confidence interval), unless otherwise indicated. Model 1 included smoking history while adjusting other covariates. Model 2 included smoking intensity while adjusting other covariates. Model 3 included smoking intensity while adjusting for alcohol consumption, BMI, and other covariates. Bold text indicates a statistically significant difference with a p-value less than 0.05.

Table 4.

Univariable and Multivariable Logistic Regression Assessing Risk Factors Associated With Visual Field Progression Defined Using the Pointwise Linear Regression (PLR) Method

Variables	Univariable Model		Multivariable Model	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Smoking intensity (reference:never smokers)				
0–20 pack-year	0.80(0.50,1.30)	0.373	0.78(0.44,1.39)	0.402
≥20 pack-year	1.78(0.91,3.49)	0.094	2.21(1.02,4.76)	**0.044**
Alcohol consumption, yes	0.64(0.45,1.22)	0.241	0.64 (0.37,1.11)	0.113
BMI, per 10 kg/m^2 higher	0.78(0.56,1.08)	0.133	0.68 (0.46,1.00)	**0.054**
Baseline age (year) per 10 years	1.18(0.93,1.48)	0.170		
Gender: female	0.88(0.57,1.37)	0.575		
Ethnicity: African Descent	0.84(0.53,1.34)	0.462		
Self-reported hypertension	0.90(0.57,1.43)	0.666		
Self-reported Diabetes	0.93(0.55,1.57)	0.789		
Axial length, per 1mm longer	1.05(0.84,1.33)	0.659		
CCT, per 100 μm thinner	1.00(0.99, 1.002)	0.218		
Baseline IOP during follow-up (mmHg) per 1 mmHg higher	1.02(0.98,1.05)	0.341		
Mean IOP during follow-up (mmHg) per 1 mmHg higher	0.99(0.93, 1.04)	0.603	1.01(0.94,1.07)	0.865
Baseline 24–2 VF MD (dB) per 1 dB worse	0.94(0.88,1.00)	0.049	0.94 (0.88,1.02)	0.140

BMI = Body Mass Index; IOP = Intraocular Pressure; MD = Mean Deviation; VF = Visual Field, POAG=Primary Open Angle Glaucoma. Values are shown in mean (95% confidence interval), unless otherwise indicated. The multivariable model was adjusted for baseline age, mean IOP during follow-up, baseline VF MD, current alcohol consumption, and BMI. Bold text indicates a statistically significant difference with a p-value less than 0.05.