Association analysis of cigarette smoking with onset of primary open-angle glaucoma and glaucoma-related biometric parameters

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Abstract

Background: To date, studies on the role played by cigarette smoking in primary open-angle glaucoma (POAG) remains controversial. The current study evaluated cigarette smoking as a risk factor of POAG and its relationships with vertical cup-to-disc ratio (VCDR), central corneal thickness (CCT) and intraocular pressure (IOP) in a Chinese cohort.

Methods: In a total of 248 unrelated individuals including 30 juvenile-onset POAG (JOAG), 92 adult-onset POAG (AOAG) and 126 sex-matched senile cataract controls, underwent comprehensive ophthalmic examination. Their smoking was obtained and documented by questionnaire. Association of cigarette smoking with POAG was performed using logistic regression controlled for age and sex. Effects of cigarette smoking on VCDR, IOP and CCT were analyzed with multiple linear regression.

Results: In either JOAG or AOAG, no association of cigarette smoking was found with disease onset (P = 0.692 and 0.925 respectively). In controls and JOAG, no significant effects of smoking were found on VCDR, IOP or CCT (all P > 0.05). Smoking was found to be correlated with decreased CCT in AOAG and combined POAG (JOAG + AOAG) (P = 0.009 and 0.003), but no association with VCDR or IOP was observed (P > 0.05).

Conclusions: Although cigarette smoking was not found to be risk factor for onset of POAG, it was correlated with CCT in AOAG, and thus might still play a role in the disease course, especially for AOAG.

Keywords: Primary open angle glaucoma, Cigarette smoking, Central corneal thickness, Vertical cup-to-disc ratio, Intraocular pressure

Background

Primary open-angle glaucoma (POAG) is a group of disorders characterized by loss of retinal ganglion cells associated with optic nerve degeneration and visual field loss. It’s the second leading cause of visual loss and blindness worldwide, and affected 60 million people [1]. POAG is associated with many clinical features, including vertical cup-to-disc ratio (VCDR), central corneal thickness (CCT) and intraocular pressure (IOP). According to age of disease onset, there are two categories of POAG: adult-onset POAG (AOAG, disease onset after 40 years) and juvenile-onset POAG (JOAG, disease onset between 3 and 40 years) [2]. Reported risk factors of POAG include cigarette smoking, hypertension, diabetes, and family history [3-5]. Although existing studies have reported the association between cigarette smoking and POAG [6,7], the role of cigarette smoking as a risk factor of POAG remains controversial [8,9]. And most of these studies focused on AOAG. Especially, there are limited data of these studies in the Chinese population. In this study we investigated the association of cigarette smoking with POAG, and its relationship with VCDR, CCT and IOP in a Southern Chinese cohort.

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Methods
Patient recruitment and clinical information
The study subjects were unrelated, and included 122 POAG patients and 126 controls recruited at the Joint Shantou International Eye Center in Shantou, China from March, 2008 to November, 2011 (Table 1). Both POAG patients and controls received comprehensive ophthalmic examination. Their highest IOP of both eyes before medication, maximum VCDR of both eyes, and mean CCT were documented when they were first presented to the clinic. The highest IOP was measured using Goldman Ocular tonometry. VCDR and CCT were measured using a standard protocol. Before measuring, a single drop of proparacaine 1% (Alcaine, Alcon Laboratories, Ft. Worth TX) was placed in the eye. VCDR was measured by an experienced glaucoma specialist, and then confirmed by another experienced glaucoma specialist. IOP was measured by an experienced glaucoma specialist using Goldmann applanation tonometry, and recorded as the mean of three measurements. CCT was measured ultrasonically (IOPac 20 Mhz Pachymeter, Heidelberg Engineering, Germany). A total of 10 measurements were made for each eye, with additional measurements obtained if the standard deviation exceeded 10 microns. Visual field function was assessed using the Glaucoma Hemifield test (Humphrey automated perimetry, Carl Zeiss Meditec, Inc., Germany). Cigarette smoking status was obtained by questionnaire (Additional file 1), and active smoking was defined as smoking at least 5 cigarettes per day for in the past one or more years [3].

The diagnosis of POAG was based on the following inclusion criteria: (1) gonioscopically open anterior chamber angle, Shaffer grade III or IV; (2) characteristic optic disc damage and/or typical visual field loss; (3) highest IOP > 21 mmHg; (4) exclusion of secondary causes, e.g., trauma, uveitis, steroid-induced or exfoliation glaucoma. Juvenile-onset POAG (JOAG) was recruited based on age of disease onset between 3 and 40 years, and adult-onset POAG (AOAG) based on disease onset after 40 years. The control subjects were recruited from senile cataract surgical inpatients aged 50 and older without family history of glaucoma. All of the controls have IOP < 21 mmHg, VCDR < 0.5, and no sign of visual field loss. Eyes met the following criteria were excluded: any history or symptom of keratopathy, Marfan's syndrome, ocular trauma, ocular surgery in prior to the recruitment, macular epiretinal membrane, macular edema, macular hemorrhage, retinal detachment, or severe cataract affecting the results of examination.

This study was approved by the Ethics Committee of Joint Shantou International Eye Center and was conducted in accordance with the Declaration of Helsinki. Written consent was obtained from each participating subject after explanation of the nature of the study.

Statistical analysis
Association and interaction analysis was performed using multiple regression implemented by the R statistical Language version 2.15.0. Association between cigarette smoking and disease was assessed in both JOAG and AOAG by logistic regression controlled age and sex. Multiple linear regression was used to analyze effects of cigarette smoking on VCDR, IOP and CCT. Two-factor interaction between smoking and age/sex was evaluated in both logistic and linear regression.

Results
Patients and clinical data
Their clinical features were shown in Table 1. Among POAG patients, 30 were diagnosed as juvenile-onset POAG (JOAG), 92 as adult-onset POAG (AOAG). Ocular hypertension and signs of optic disc neuropathy were found in these POAG patients, but were absent in all 126 senile cataract controls.

Table 1 Demographic features of the study subjects

|        | N | Female | Age (Year) | VCDR | IOP (mmHg) | CCT (μM) |
|--------|---|--------|------------|------|------------|---------|
|        |   |        | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Control | 126 | 29 | 69.5 | 8.9 | 0.32 | 0.06 | 13.3 | 2.6 | 541.7 | 36.1 |
| JOAG    | 30  | 6  | 25   | 6   | 0.86 | 0.17 | 34.1 | 11.4 | 542.6 | 21.9 |
| AOAG    | 92  | 14 | 59.9 | 12.1| 0.84 | 0.14 | 31.5 | 10.9 | 533.9 | 36.4 |

Table 2 Association of cigarette smoking with JOAG and AOAG in the current cohort

|        | Control | JOAG | AOAG |
|--------|---------|------|------|
|        | N (%)   | OR (95%CI) | P*  | N (%)   | OR (95%CI) | P*  |
| Non-smoker | 55 (43.7) | 4.33 (0.12-5.84 × 10^3) | 0.692 | 31 (33.7) | 1.03 (0.52-2.08) | 0.925 |
| Smoker   | 71 (56.3) | 16 (58.8) | 61 (66.3) |
VCDR, IOP or CCT (all age and sex showed significant association with many eye diseases such as cataract, age-related macular degeneration [11-13]. Existing studies on the relationship between cigarette smoking and POAG remain controversial. Findings vary among ethnic groups and study design. And most of these studies focused on AOAG. There are limited data of these studies in the Chinese population. Recently in a cohort of African-American women, Wise L. A. et al. reported that smoking might be associated with increased risk of early-onset POAG [14]. Kang, J. H. et al. also reported cigarette smoking conferring risk to POAG [15]. Similar findings were also reported in other independent studies [16-18]. But some other studies reported no association between smoking and POAG. In a prospective follow-up study from 1980 and 1986, respectively, to 1996, the results showed neither current smokers nor ex-smokers were at greater risk for POAG than those who had never smoked, and heavier smoking did not increase the risk of POAG [8]. And in a systematic review, Richard et al. also reported that there was little evidence for the association between smoking and POAG [19]. Other independent studies also reported lack of such association [9,20]. In our Chinese cohort, smoking was not found to confer risk to disease onset in either JOAG or AOAG. Our study thus did not support cigarette smoking as a risk factor of POAG onset.

Apart from disease onset, it remains to be elucidated whether cigarette smoking is related to IOP, CCT and VCDR, which are glaucoma risk factors. In 2003, Yoshida M. et al. reported that cigarette smoking had a significantly positive association with the IOP in Japanese male individuals [21]. Lee A. J. et al. also reported similar association [22]. In the current study, although no significant association with IOP was observed, we found evidence that smoking could be correlated with decreased CCT in AOAG. As reported by previous studies, in individuals with thinner cornea, their IOP tends to be lower estimated [23-25]. In AOAG smokers, their IOP could possibly be lower estimated.
due to thinner CCT. In addition, the change of CCT in POAG may affect the disease course. A previous study on corneal thickness and functional damage in patients with ocular hypertension showed that patients with ocular hypertension plus thinner corneas had a greater risk of developing functional damage over time [26].

The exact reason for decreased corneal thickness in POAG smokers remains unclear. However, cigarette smoking may exert this effect through hypoxia and collagen in the cornea. Smoking has been reported to decrease oxygen and collagen production in tissues during wound healing [27,28]. Ocular hypertension causes damage to the cornea [29]. Smoking probably deteriorates ocular hypoxia caused by ocular hypertension [27], and consequently affects the biosynthesis of collagen and extracellular matrix turnover [30], which could be an explanation to the decreased corneal thickness.

In the current study, cigarette smoking was not found to be associated with disease onset of POAG. However, the association of smoking with decreased CCT in POAG suggested that more attention should be paid on CCT in the early stage of POAG in smokers to estimate more correct target IOP in order to better reduce the early lesion of optic nerve. Current findings thus warranted further study.

Conclusions
In this study, although cigarette smoking was not found to be a risk factor for onset of POAG, it was correlated with CCT in AOAG, and thus might still play a role in the disease course, especially for AOAG.

Additional file

Additional file 1: Smoking Status Questionnaire.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
DW carried out the questionnaire, participated in statistical and drafted the manuscript. YH and CH carried out the clinical examination in patients and controls. YZ participated in study coordination. PW and JL provided support of database software. YP and YL assisted in the statistical analysis and discussion. JHC participated in the study design and statistical analysis. MZ conceived the study, participated in the study design and clinical examination, and wrote the manuscript. All authors read and approved the final manuscript.

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