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*Original article*

# Malay Glaucoma Eye Study (MaGES): cigarette smoking and primary angle-closure glaucoma

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## Abstract

*Introduction:* The detrimental effects of cigarette smoking include impairment of optic nerve head perfusion and elevation of oxidative stress levels, which are believed to be part of the pathogenesis of glaucoma. However, there is no evidence on the effect of cigarette smoking as a risk for primary angle-closure glaucoma (PACG).

*Purpose:* To determine the association between cigarette smoking and PACG in Malay patients.

*Study design:* Case control study.

*Materials and methods:* Two-hundred Malay PACG patients and 250 controls from

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three tertiary hospitals in Malaysia were involved in this study. PACG patients were diagnosed based on the World Glaucoma Association consensus. The smoking status was documented using validated questionnaire adopted from Singapore Malays Eye Study through face-to-face interview. Smoking status was divided into active smokers, ex-smokers, passive smokers, and non-smokers. The association of smoking and PACG was analysed with multiple logistic regression. Confounders such as age, gender, education status, and body mass index (BMI) were considered in the analysis.

*Results:* There was female preponderance in PACG with 3:1 ratio. Active smokers ($p = 0.656$) and ex-smokers (0.073) were not significantly associated with PACG in Malays. Passive smoking significantly increased the risk of PACG by 6.8-fold (95% CI 2.49,18.67; $p < 0.001$). Number of cigarettes/day ($p = 0.144$) and duration of smoking ($p = 0.176$) were also not significantly associated with PACG ($p = 0.144$). No formal education, primary and secondary education level increased the risk of PACG ($p < 0.001$). Each unit increment of BMI increased the risk of PACG by 1.14-fold (95% CI 1.03, 1.27; $p = 0.014$). A year increased in age increased the risk by 1.05 times (95% CI 1.00, 1.09; $p = 0.026$).

*Conclusions:* There is no significant association between active smoking and PACG. Passive smoking is a potential risk factor for PACG. The preponderance of women may contribute to this result. However, quantification of exposure to passive smoking is not possible in this study.

*Keywords:* cigarette smoking, Malay, passive smokers, primary angle-closure glaucoma (PAGC), risk factors

# Kajian Mata Glaukoma Bangsa Melayu (MaGES): merokok dan glaukoma sudut tertutup primer

## Abstrak

*Pengenalan:* Kesan kemudaratan disebabkan oleh rokok termasuklah gangguan perfusi kepala saraf optik dan peningkatan tahap tekanan oksidatif, yang dipercayai menjadi sebahagian daripada patogenesis glaukoma. Walau bagaimanapun, tidak ada bukti mengenai kesan rokok sebagai risiko untuk glaukoma sudut tertutup primer (PACG).

*Tujuan:* Untuk menentukan perkaitan antara merokok dan PACG dalam kalangan pesakit Melayu.

*Reka bentuk kajian:* Kajian kawalan kes.

*Bahan dan kaedah:* Dua ratus pesakit PACG dari bangsa Melayu dan 250 kawalan

dari tiga hospital tertier di Malaysia terlibat dalam kajian ini. Pesakit PACG didiagnos berdasarkan persetujuan am Persatuan Glaukoma Dunia. Status merokok didokumenkan menggunakan soal selidik yang telah disahkan yang diambil daripada Kajian Melayu Mata Singapura Singapura melalui temu ramah secara bersemuka. Status perokok dibahagikan kepada perokok aktif, bekas perokok, perokok pasif, dan bukan perokok. Perkaitan antara merokok dan PACG dianalisis dengan menggunakan kaedah regresi logistik berganda. Konflik dalaman seperti umur, jantina, status pendidikan, dan indeks jisim badan (BMI) dipertimbangkan dalam analisis.

*Keputusan:* Terdapat lebih ramai wanita didapati mengalami PACG dengan nisbah 3: 1. Perokok aktif (p = 0.656) dan bekas perokok (0.073) didapati tidak berkait secara ketara dengan PACG bangsa Melayu. Perokok pasif secara signifikan meningkatkan risiko PACG sebanyak 6.8 kali ganda (95% CI 2.49,18.67; p <0.001). Bilangan rokok / hari (p = 0.144) dan tempoh merokok (p = 0.176) juga tidak dikaitkan dengan PACG (p = 0.144). Tiada pendidikan formal, tahap pendidikan rendah dan menengah meningkatkan risiko PACG (p <0.001). Setiap peningkatan unit BMI meningkatkan risiko PACG sebanyak 1.14 kali ganda (95% CI 1.03, 1.27; p = 0.014). Satu tahun peningkatan umur meningkat risiko sebanyak 1.05 kali (95% CI 1.00, 1.09; p = 0.026).

*Kesimpulan:* Tidak terdapat hubungan yang signifikan antara aktiviti merokok aktif dan PACG. Aktiviti merokok pasif adalah faktor risiko yang berpotensi untuk PACG. Jumlah wanita yang lebih ramai dalam kajian ini mungkin menyumbang kepada hasil kajian ini. Walau bagaimanapun, pengiraan kuantifi pendedahan kepada merokok pasif tidak dilakukan dalam kajian ini.

*Kata kunci:* merokok, Melayu, perokok pasif, glaukoma sudut tertutup primer (PAGC), faktor risiko

## Introduction

Primary angle-closure glaucoma (PACG) is believed to cause more blindness in the Asian population than in other populations.[1] Asians constitute an heterogenous, multi-ethnic population. There are many studies on this irreversible disease among the Chinese,[2-4] Japanese,[5,6] and Indian[7-9] populations. However, there is limited knowledge of PACG in the Malay population. Based on the Singapore Malay Eye Study (SiMES), 150 (4.6%) of 3280 participants were diagnosed with glaucoma. After age and sex standardization, the prevalence of primary open-angle glaucoma (POAG) was 2.5%, PACG was 0.12%, and secondary glaucoma was 0.61% among Malays residing in Singapore.[10]

Angle closure is not uncommon in Malays.[11] A retrospective hospital-based study in two different hospitals found that Malay patients presented at more advanced

stage and progressed faster compared to Chinese patients in Malaysia.[12] However, the outcome of this study is affected by potential biases from the nature of the study and differences in the management between the two centres.[12] Understanding the clinical presentation of PACG in Malays is important to formulate a blindness prevention strategy in the Asian population.

Several risk factors for PACG have been identified. Older age, family history, female, and Chinese ethnicity are among the important non-modifiable risk factors for PACG.[13-15] Shorter axial length, shallow anterior chamber depth, increased iris thickness and anteriorly positioned lens are the ocular biometry parameters associated with PACG.[16-18] The identification of modifiable risk factors is crucial in preventive measures of blindness in glaucoma. At present, the only modifiable risk factor for glaucoma is intraocular pressure (IOP).[19,20]

Although inconclusive, cigarette smoking is found to increase the risk of POAG.[21,22] Noxious substances in cigarettes may cause elevation of oxidative stress markers[23,24] and changes in vascular integrity in the optic nerve head,[25,26] which have been postulated as part of POAG pathogenesis. Cigarette smoking may also exert similar detrimental effects in PACG patients. To the best of our knowledge, there is no study looking into cigarette smoking as a potential risk factor for PACG. The aim of this study was to evaluate the potential effects of cigarette smoking as a modifiable risk factor for PACG.

## Materials and methods

A case control study was conducted between April 2014 and May 2016 involving patients attending ophthalmology clinics of tertiary centres in Kelantan state: Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZII); and Kedah state: Hospital Sultanah Bahiyah (HSB). Malaysia is a multi-ethnic country, with Malays representing 50.1% of the population, Chinese 22.6%, indigenous people 11.8%, and Indians 6.7%.[27] Kelantan and Kedah are among the states with a majority of Malay population.[27]

This study received ethical approval from the research and ethics committee of the School of Medical Sciences, Universiti Sains Malaysia and from National Medical Research and Ethics Committee, Ministry of Health Malaysia. This study was conducted in accordance to the Declaration of Helsinki for human research.

This study is part of the Malay Glaucoma Eye Study (MaGES). MaGES is a multicentre study with the aim of identifying modifiable risk factors for glaucoma development and progression in Malays residing in Malaysia. A total of 200 PACG patients (90 from HUSM, 90 from HRPZII, and 20 from HSB) and 250 control subjects were recruited. Malay was defined based on three generations of Malay lineage. Pedigree charts were drawn to exclude potential inter-racial marriages or incomplete pedigree charts. PACG was based on the World Glaucoma Association

consensus definition.[28] Primary angle-closure suspect (PACS), primary angle-closure (PAC), and glaucoma suspect patients were excluded from the study. Patients with conditions that may affect the visual field, such as retinal diseases and neurological diseases, were excluded. Those with a history of cerebrovascular accidents and memory problems including dementia were also excluded.

Control subjects were recruited from the HUSM, HRPZII, and HSB ophthalmology clinics. They were selected based on simple random sampling among non-glaucoma patients who presented with dry eye, pterygium, and other ocular problems. A thorough ocular examination was conducted including slit lamp examination and fundus examination to rule out glaucoma. Gonioscopic examination was also conducted to rule out angle closure. Goldman applanation tonometry (Haag-Streit, Switzerland) was used to measure IOP. Those with IOP more than 20 mmHg were excluded. Humphrey visual field (HVF) 24-2 analysis was also conducted to rule out potential glaucomatous changes. Subjects who had a family history of glaucoma, history of cerebrovascular accident, and memory problems as well as glaucoma suspects were also excluded.

Weight and height of the recruited PACG patients and control subjects were obtained and body mass index (BMI) was calculated. Data on cigarette smoking was obtained using a validated questionnaire from Singapore Malay Eye Studies (SiMES) and conducted via face-to-face interview by two investigators (NLS and PS). NLS was responsible for recruitment in Kelantan state and PS was responsible for recruitment in Kedah state. The following were based on World Health Organization definitions:[29]

1. Active smoker: someone who, at the time of survey, smokes any tobacco product either daily or occasionally.
2. Ex-smoker: individual who was formerly a daily smoker, but currently does not smoke at all.
3. Passive smoker: individual who inhales cigarette smoke from the surrounding environment without directly smoking a cigarette, including smoke exhaled by active smokers (second-hand smoke); burning off the tip of the cigarette (side stream smoke); and seeping through the paper and filter of a lit cigarette (lateral stream smoke).

Subjects were required to recall cigarette smoking exposure since childhood for as long as they could remember. Pipe smoking, cigar, and rollups were converted to cigarette smoking equivalence.

Statistical analysis was performed using Statistical Analysis Software Package (SPSS) software, version 22. Simple logistic regression analysis was done for univariate analysis on predictors for PACG. Subsequently, multivariate analysis was done using multiple logistic regression method. The parameters were checked for possible interactions using enter method. A P-value of less than 0.05 was considered statistically significant.

*Table 1.* Demographic characteristics between PACG patients and control subjects

| Variables | PACG (n = 200) | Control (n = 250) | p-value |
|---|---|---|---|
| **Age (mean ± SD)** | 66.4 ± 8.80 | 60.9 ± 9.99 | < 0.001 |
| **Gender (n, %)** | | | < 0.001 |
| Male | 50 (25%) | 145 (58.0%) | |
| Female | 150 (75%) | 105 (42.0%) | |
| **Education level (n, %)** | | | < 0.001 |
| No formal education | 29 (14.5%) | 4 (1.6%) | |
| Primary level | 89 (44.5%) | 65 (26.0%) | |
| Secondary level | 70 (35.0%) | 100 (40.0%) | |
| Tertiary level | 12 (6.0%) | 81 (32.4%) | |
| **BMI (mean ± SD)** | 24.99 ± 3.85 | 23.98 ± 1.67 | < 0.001 |

#Pearson Chi-square test ($p < 0.05$ is significant)

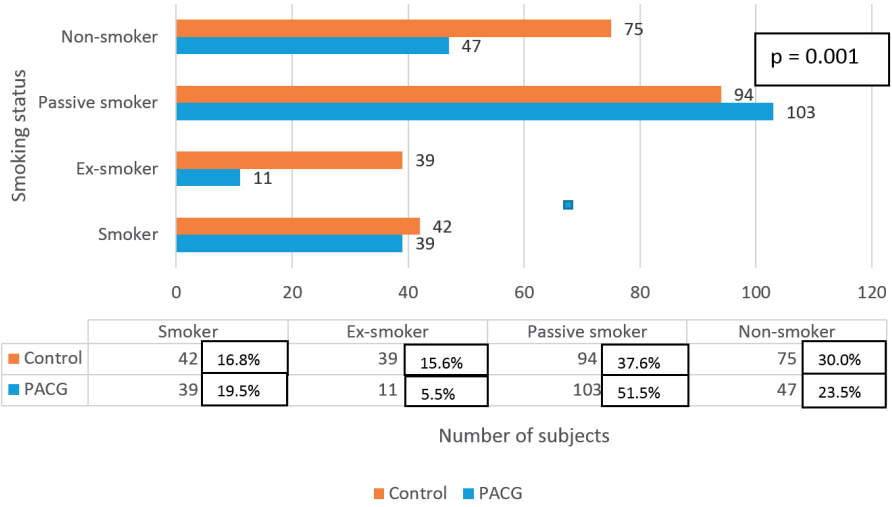


*Fig. 1.* Distribution of PACG patients and control subjects according to smoking status. Pearson Chi-square test ($p < 0.05$ is significant).

## Results

A total of 450 Malay subjects (200 PACG patients and 250 control subjects) were enrolled in this study. PACG patients were significantly older compared to control

*Table 2.* Smoking quantity of smokers and ex-smokers among PACG and control subjects

| Variable | Status | | p-value |
|---|---|---|---|
| | PACG (n = 50) | Control (n = 81) | |
| Smoking exposure | | | 0.176^ |
| Duration,mean years ± SD | 33.54 (15.38) | 36.68 (10.97) | |
| Number of cigarettes per day | | | 0.144# |
| 1 to 10 sticks | 32 (64%) | 38 (46.9%) | |
| 11 to 20 sticks | 16 (32%) | 40 (49.4%) | |
| More than 20 sticks | 2 (4%) | 3 (3.7%) | |

^Independent t-test ($p < 0.05$ is significant); #Pearson Chi-square test ($p < 0.05$ is significant)

subjects. There was significant difference in sex distribution between PACG patients and controls (Table 1), with female preponderance among PACG patients (75%). The majority of patients received at least primary education (85.5%), while 29 (14.5%) PACG patients had no formal education. PACG patients have significantly higher mean BMI compared to controls (Table 1).

A total of 103 (51.5%) PACG patients were passive smokers. Only 39 (19.5%) PACG patients were active smokers (Fig. 1). A total of 150 (75%) PACG patients were passive or non-smokers, while 169 (67.6%) were passive or non-smokers among the control subjects (Fig. 1). There was no significant difference in duration of smoking among smokers and ex-smokers between PACG and control subjects (Table 2). There was also no significant difference in the number of cigarettes smoked per day between PACG and control subjects ($p = 0.144$) (Table 2). Only 13 out of 255 female respondents were smokers or ex-smokers; all of them were PACG patients.

Based on multivariate analysis, passive smoking is significantly associated with PACG ($p < 0.001$) (Table 3). Passive smoking increased the risk of PACG by 6.8-fold (95% CI 2.49, 18.67). In this study, there was no significant association between ex-smokers and active smokers to PACG (Table 3). Lower education status increased the risk of PACG; no formal education significantly increased the risk for PACG by 48.9-fold (95% CI 14.62, 168.86; $p < 0.001$) and primary level of education increased the risk for PACG by 18.3-fold (95% CI 4.53, 73.95; $p < 0.001$). Females were at higher risk for PACG [5.3 fold (95% CI 2.37, 11.50; $p < 0.001$)]. BMI is also a significant associated factor for PACG. With each 1 unit increment of BMI, there is 1.14 times higher chance to have PACG (Table 3).

*Table 3.* Logistic regression analysis of associated factors for PACG

| Variable | Simple logistic regression | | | | Multiple logistic regression | | | |
|---|---|---|---|---|---|---|---|---|
| | b | OR[c] (95% CI) | Wald statistics | p-value* | b | OR[a] (95% CI) | Wald statistics | p-value* |
| **Smoking status** | | | | | | | | |
| Passive smoker | 0.39 | 1.48 (0.84, 2.62) | 1.84 | 0.175 | 1.92 | 6.82 (2.49, 18.67) | 13.96 | < 0.001 |
| Ex- smoker | -0.80 | 0.45 (0.21, 0.96) | 4.22 | 0.040 | -0.20 | 0.82 (0.27,2.51) | 0.12 | 0.730 |
| Active smoker | 0.56 | 1.75 (1.10, 2.77) | 5.68 | 0.017 | 0.15 | 1.16 (0.60, 2.23) | 0.19 | 0.666 |
| **No. of cigarettes per day** | | | | | | | | |
| 11 to 20 sticks | -0.74 | 0.48 (0.23, 1.00) | 3.82 | 0.475 | 0.01 | 1.01 (0.33, 3.04) | 0.00 | 0.992 |
| More than 20 | -0.23 | 0.79 (0.12, 5.04) | 0.06 | 0.805 | 1.53 | 4.59 (0.55, 38.37) | 1.98 | 0.159 |
| **Duration of smoking (years)** | -0.02 | 0.99 (0.96, 1.01) | 1.99 | 0.158 | -0.05 | 0.95 (0.90, 1.01) | 2.90 | 0.089 |
| **Age** | 0.06 | 1.06 (1.04, 1.08) | 32.05 | < 0.001 | 0.04 | 1.04 (0.10, 1.08) | 3.40 | 0.065 |
| **Gender** | | | | | | | | |
| Female | 1.42 | 4.14 (2.76, 6.22) | 46.89 | < 0.001 | 1.66 | 5.25 (2.37, 11.60) | 16.76 | < 0.001 |
| **BMI** | 0.13 | 1.14 (1.06, 1.22) | 12.80 | < 0.001 | 0.13 | 1.14 (1.02, 1.27) | 5.76 | < 0.001 |
| **Education** | | | | | | | | |
| Secondary level | 1.55 | 4.73 (2.40, 9.32) | 20.10 | < 0.001 | 2.24 | 9.40 (2.67, 33.04) | 12.20 | < 0.001 |
| Primary level | 2.22 | 9.24 (4.66, 18.34) | 40.44 | < 0.001 | 2.91 | 18.31 (4.53, 73.95) | 16.66 | < 0.001 |
| No formal education | 3.89 | 48.94 (14.62, 163.86) | 39.82 | < 0.001 | 3.87 | 48.04 (8.3, 277.99) | 18.69 | < 0.001 |

*Multiple logistic regression ($p < 0.05$ is significant); b: regression coefficient; OR[c]: crude odd ratio; OR[a]: adjusted odd ratio

## Discussion

The quest for potential modifiable risk factors for glaucoma has been a daunting task. Until now, IOP remains the only modifiable risk factor for glaucoma. Cigarette smoking has been implicated as a risk factor for ocular diseases such as age-related macular degeneration[30,31] and retinal vein occlusion.[32] It is also a known risk factor for stroke,[33] cardiovascular diseases,[34,35] and peripheral vascular diseases.[36]

Based on the present study, the ex-smoker and active smoker groups were not found to be significantly associated with PACG. There was a significant association between passive smokers and PACG. Passive smoking increased the risk of PACG by 6.8-fold (95% CI 2.49, 18.67). Higher number of passive smokers was found among PACG patients compared to controls. This is perhaps due to the sex preponderance, as women are more at risk of developing PACG.[1,37] Similarly, women were at higher risk of developing glaucoma in the present study. This is perhaps related to their ocular biometry: women tend to have a shorter axial length and shallower anterior chamber, leading to crowding of the angle and impaired aqueous outflow.[37-40] Ocular biometrical factors and crowding of the angle are established risk factors for PACG.[16-18]

In general, cigarette smoking is more prevalent among men, although currently, the prevalence among younger women is increasing.[41] Among the elderly population, only 2.9% of Malaysian women are active smokers and 3.4% are ex-smokers, in contrast to 28.1% of active smokers and 23.2% ex-smokers among men.[42] Across all ages, the prevalence of Malaysian women who smoke is about 1.7% of the Malaysian population.[43] Although there is no precise estimate of Malay smokers according to sex distribution, the prevalence of Malay smokers is 2.5 times higher compared to the Chinese population in Malaysia.[44] With higher prevalence of PACG among women, a higher percentage of passive smokers among PACG is expected.

It is believed that the detrimental effects of cigarette smoking to passive smokers are similar than those to active smokers. Numerous studies have shown that passive smoking may cause detrimental effects to vascular integrity and elevation of oxidative biomarkers similar to active smoking.[45-48] Cigarette smoking is postulated to cause impaired ocular perfusion,[49,50] increased oxidative stress markers,[23,24] and IOP elevation.[51] There is conflicting evidence on the role of cigarette smoking in POAG.[21,22,52,53] However, no studied found an association between passive smoking and POAG.

Cigarette smoking is also affected by socioeconomic status and education level.[54,55] Higher prevalence of smokers is seen among those with lower socioeconomic and educational levels in various countries.[55] PACG prevalence is higher among those living in socioeconomic deprivation.[56,57] However, we did not include household income to determine socioeconomic status in this study. A lower education level is exponentially related to lower socioeconomic status.[58] Elderly women in our present study were mainly unemployed and had lower educational

level. There was a significant association between education level and risk of PACG in the current study. A lower education level is usually associated with financial difficulties that may deter health-seeking behaviour.[59] In addition, lower education level may also cause poor awareness in asymptomatic diseases such as glaucoma, even among those with APAC.[60,61]

In the present study, the exact number of household members that smoke cigarettes at a certain point of time was not documented. Thus, the exact amount of exposure to the noxious substances from cigarette smoking (as passive smokers) cannot be quantified. Smoking among women is a social taboo and stigmatised as morally flawed in Malay culture.[62] This was reflected in the small number of women who smoked, both among PACG patients and controls. Due to this, there is also a probability that some of the subjects may not admit to smoking due to this perceived social taboo in Malay culture.

There has been limited research on the association between cigarette smoking and PACG. Based on the medical database of one hospital in China involving 662 PACG patients, the odds ratio of cigarette smoking was 0.515 (95% CI 0.293.0.906, $p < 0.05$).[63] Previous studies were mainly focused on the association between smoking and POAG.[64-66] Current studies on the effect of smoking on POAG showed inconclusive and often contradictory findings. This is probably due to the complex interaction of multiple factors, such as environmental exposure, that may be modified by genetic factors.[66]

Using questionnaires to assess cigarette smoking requires subjects to recall their cigarette smoking exposure for as long as they can remember. Although only subjects who were able to recall their cigarette smoking exposure were recruited for this study, recall bias was inevitable in view of the long recall duration required. Due to study design, the point in time at which cigarette smoking behaviour affected the optic nerve head causing glaucomatous changes could not be determined. A prospective cohort study design would be a better option to ensure that the exact quantity of cigarette and exact time point of insult can be assessed.

## Conclusion

Passive smoking is found to be significantly associated with PACG in Malay patients residing in Malaysia. Although active and ex-smokers were not found to be significantly associated with PACG in this study, smoking cessation is advised owing to the clear evidence of damage related to other ocular and systemic diseases, as well as its potential harmful effect to vascular integrity.

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