# Smoking Is a Risk Factor for Pahcychoroid-related Disorders in Asian Patients: a Case Control Study

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# Abstract

## Background

Cigarette smoking has been reported as a risk factor for the development of neovascular age-related macular degeneration (nAMD). However, the associations between cigarette smoking and subtypes of drusen and nAMD were incomplete, as it lacked consideration of pachydrusen or no significant drusen. Therefore, this study intended to reveal the associations between cigarette smoking and subtypes of drusen and nAMD.

## Purpose

To evaluate the associations between cigarette smoking and subtypes of drusen and nAMD in an Asian population.

## Methods

This retrospective case-control study included 189 eyes in 189 patients with treatment-naïve nAMD, including typical AMD, polypoidal choroidal vasculopathy (PCV), and type 3 neovascularization. The patients were stratified into never-, former-, and current-smoker groups, and drusen subtypes, including no significant drusen, soft drusen, subretinal drusenoid deposits (SDDs), and pachydrusen, were analyzed in each group.

## Results

The proportions of no significant drusen and pachydrusen in the fellow eyes were significantly higher in the former- and current-smoker groups ($P = 0.016$ and $P < 0.001$), respectively. There was a significantly higher proportion of PCV in the affected eyes in the current-smoker group ($P = 0.041$). The proportions of SDDs in the fellow eyes and type 3 neovascularization in the affected eyes were significantly higher in the never-smoker group ($P < 0.001$ and $P = 0.037$), respectively.

## Conclusion

Ever smokers (former and current smokers) had significantly higher proportions of pachychoroid-related disorders, including no significant drusen, pachydrusen, and PCV, than nonsmokers. Thus, cigarette smoking could be a risk factor for the development of pachychoroid-dependent abnormalities.


# Background

Neovascular age-related macular degeneration (nAMD) is a leading cause of blindness in elderly populations in developed countries and is categorized into typical AMD, polypoidal choroidal vasculopathy (PCV), and type 3 neovascularization [1–3]. Although there are no racial differences in the prevalence of nAMD [4], the frequency of nAMD subtypes varies between racial groups [3]. The

prevalence of PCV and type 3 neovascularization is higher and lower in Asians than in Caucasians, respectively [5, 6]. These subtypes have different clinical characteristics, and identifying the risk factors for each subtype could reduce the development of nAMD.

Drusen, which are accumulations of extracellular matrix components between the retinal pigment epithelium (RPE) and Bruch's membrane [7], have been described as retinal precursors of AMD [8, 9]. Recently, pachydrusen was reported to be thicker choroid-associated drusen [10], and drusen are classified into soft drusen, subretinal drusenoid deposits (SDDs), and pachydrusen. This particular type of drusen has been found to be associated with the development of a specific subtype of nAMD [11–13]. Eyes with SDDs have a higher risk of developing type 3 neovascularization. Spaide constructed a novel AMD classification system based on three drusen subtypes for the prediction of a more precise prognosis in AMD patients [14].

Of the many risk factors for nAMD, cigarette smoking is consistently associated with the development of nAMD [15–21]. A population-based cohort study [22] reported that cigarette smoking increased the risk of large soft drusen. However, the drusen classification used in previous studies on the association between nAMD and smoking was incomplete, as it lacked consideration of pachydrusen. In addition, those with PCV, a major subtype of nAMD in Asian people, have a comparatively low incidence of drusen [3]. Even among Caucasians, who have a high prevalence of drusen, the incidence of drusen is lower (16.7%) in those with PCV[23]. Therefore, the effect of cigarette smoking on nAMD, especially in Asians, requires the evaluation of the eye without drusen.

To assess the associations between drusen subtypes and cigarette smoking in nAMD patients, we examined the prevalence of no significant drusen, soft drusen, SDDs, and pachydrusen in the fellow eyes of newly diagnosed nAMD patients stratified by smoking history. Moreover, we investigated the 5-year incidence of nAMD in the fellow eyes and the 1-year outcome of anti-vascular endothelial growth factor (VEGF) therapy in the affected eyes in each smoking history group.

# Methods

2.1. Study Design and Participants

We retrospectively evaluated Japanese patients aged 50 years or older with newly diagnosed nAMD, including typical AMD, PCV, and type 3 neovascularization at Kawasaki Medical School between May 2016 and January 2021. The study was complied with the principles of the Declaration of Helsinki. The study was performed with the approval of the Institutional Review Board of Kawasaki Medical School Ethics Committee (2543-1) and is registered in the UMIN Clinical Trials Registry (UMIN000023676). The inclusion criteria were the presence of nAMD diagnosed by funduscopic, swept-source optical coherence tomographic (OCT) (DRI OCT-1 Atlantis; Topcon Corporation, Tokyo, Japan), and angiographic findings (HRA-2; Heidelberg Engineering GmbH, Dossenheim, Germany), and a best-corrected visual acuity (BCVA) of 20/400 or better at baseline. Data on cigarette smoking were obtained from hospital records and

patient recall. The patients were divided into never-, former-, and current-smoker groups. Former and current smokers were those who smoked at least 1 cigarette per day for more than 1 year in their lifetime. Former smokers were those who did not smoke at baseline and had quit smoking for at least 1 year. The patients were treated with aflibercept (Bayer AG, Leverkusen, Germany) for at least one year. Patients who had received or were receiving other anti-VEGF agents (bevacizumab, pegaptanib, ranibizumab) or had undergone laser photocoagulation, verteporfin photodynamic therapy, or submacular surgery were excluded, as were those with choroidal neovascularization (CNV) as a result of high myopia, angioid streaks, or uveitis. Patients with eye diseases that could potentially influence the clinical features of the studied eyes, such as glaucoma, diabetic retinopathy, or rhegmatogenous retinal detachment, were also excluded.

### 2.2. Group Classification

We classified drusen subtypes into four groups depending on the condition of the fellow eye as follows: no significant drusen, soft drusen, SDDs, or pachydrusen. The type of drusen was determined using fundus color photographs and swept-source OCT according to the criteria presented in a previous study[10]. The no significant drusen group included eyes without drusen or eyes with small drusen (size: <63 μm) or few intermediate drusen (number: <20 lesions, size: <125 μm). The soft drusen group included eyes with numerous intermediate drusen (number: ≥20 lesions, size: ≥63 μm and < 125 μm) or one large drusen (size: ≥125 μm) according to the Age-Related Eye Disease Study (AREDS). Eyes with pachydrusen and soft drusen or SDDs were classified into the soft drusen or SDDs group, respectively. Eyes with soft drusen and SDDs were classified into the SDDs group. The subtype of neovascular AMD (typical AMD, PCV, or type 3 neovascularization) was comprehensively diagnosed on the basis of the findings of fundoscopy, angiography, OCT, fluorescein angiography (FA), and indocyanine green angiography (ICGA). The diagnosis of PCV was based on ICGA findings, including polypoidal structures at the borders of the branching choroidal vascular networks. The diagnosis of type 3 neovascularization was based on the characteristic findings of retinal pigment epithelial detachment with overlying cystic retinal edema on OCT images, intraretinal hemorrhage, and intraretinal vascular anastomoses. Typical nAMD was characterized by the presence of exudative changes due to CNV on FA and ICGA.

### 2.3. Treatment and Assessments

Treatment-naïve nAMD patients received intravitreal aflibercept at Kawasaki Medical School between May 2016 and January 2021. All patients received 3 monthly injections of the anti-VEGF agent initially on a pro re nata basis. If recurrence, including new macular hemorrhage, intraretinal fluid, and subretinal fluid, was observed, anti-VEGF therapy based on a pro re nata or treat-and-extend regimen was resumed. All the included patients were followed for 12 months or longer after the initial intravitreal administration of aflibercept and provided written informed consent for treatment with an anti-VEGF agent and participation in the study. The patients underwent a comprehensive ophthalmological examination, including BCVA measurement, slit-lamp biomicroscopy, indirect fundoscopy, fundus color photography, and swept-source OCT. The treatment outcome measures were the change in BCVA and retinal thickness

at baseline and 1 year after the start of anti-VEGF therapy, respectively, as well as the number of injections received, the rate of dry macula after the loading dose, and the retreatment-free period after the loading dose. The BCVA was recorded as decimal values, followed by conversion to the logarithm of the minimal angle of resolution (logMAR) units for statistical analysis. Central retinal thickness (CRT) was defined as the mean retinal thickness measured at the fovea as previously described [24].

### 2.4. Statistical Analysis

The results are presented as means and standard deviations. One-way ANOVA followed by Sidak's test was performed to compare age, BCVA, retinal thickness at the fovea, and the number of injections received among the nAMD-stratified smoking history groups. The chi-square test followed by residual analysis concerning cross-tabulation was used to compare the proportions of sex, drusen subtype, nAMD subtype, and rate of dry macula after the loading dose among the nAMD-stratified smoking history groups. Kaplan-Meier analysis was performed to estimate the incidence of nAMD in the fellow eye and the retreatment-free period after the loading dose. Statistical analyses were performed using Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd, Tokyo, Japan). P-values < 0.05 were considered statistically significant in all analyses. * Chi-square test.

## Results

In total, 189 eyes in 189 patients with nAMD were included (Table 1). The mean patient age was 74.2 ± 8.5 (range, 50–94) years, and there were 58 females and 131 males. All the patients were Japanese. The characteristics of the patients with nAMD in the smoking history groups are shown in Table 1. The analysis included 66, 97, and 26 patients in the never-, former-, and current-smoker groups, respectively. The three study groups were comparable regarding age ($P = 0.15$); however, there was a significantly higher proportion of males in the former- and current-smoker groups than in the never-smoker group ($P < 0.001$). The proportions of drusen subtypes in the fellow eyes were significantly different ($P < 0.001$). The proportions of no significant drusen and pachydrusen in the fellow eyes were significantly higher in the former- and current-smoker groups ($P = 0.016$ and 0.001), respectively. There were significantly higher and lower proportions of SDDs in the fellow eyes in the never- and former-smoker groups ($P < 0.001$ and $< 0.001$), respectively. Similarly, the proportions of nAMD subtypes in the affected eyes were significantly different ($P = 0.022$). The proportions of typical AMD and PCV in the affected eyes were significantly lower and higher in the current-smoker group ($P = 0.005$ and 0.041), respectively. There was a significantly higher proportion of type 3 neovascularization in the affected eyes in the never-smoker group ($P = 0.037$).

After a follow-up period of 5 years, 16 of 65 (24.6%) fellow eyes developed nAMD. The numbers of eyes that developed nAMD in the fellow eye were 31.3%, 38.5%, and 5.0% in the never-, former-, and current-smoker groups, respectively. The Kaplan-Meier curve showed that the incidence of nAMD development in the fellow eye was not significantly different among smoking history groups ($P = 0.051$, Fig. 1). However, nAMD development in the fellow eye was significantly associated with the drusen subtype in the fellow eye. The numbers of eyes that developed nAMD in the fellow eye were 21.9%, 16.7%, 83.3%, and 0% in the

no significant drusen, soft drusen, SDDs, and pachydrusen groups, respectively ($P$ = 0.0028, Fig. 2). The incidence of nAMD development in the fellow eye was significantly higher in the SDDs group. Therefore, we evaluated the relationship between smoking history and the development of nAMD in the fellow eye according to each drusen subtype. The SDDs and pachydrusen groups were excluded due to their small sample sizes ($n$ = 6 and 3, respectively); the numbers of patients who developed nAMD in the fellow eye were 7 of 32 in the no significant drusen group and 4 of 24 in the soft drusen group. The incidence of nAMD development was not significantly different among smoking history groups in either group (no significant drusen group: $P$ = 0.97, soft drusen group: $P$ = 0.82, Fig. 3).

To evaluate the effect of smoking on anti-VEGF therapy, we analyzed the data of nAMD patients treated with aflibercept who completed 12 months of follow-up. A total of 147 eyes were eligible for analysis. The outcome of anti-VEGF therapy in patients with nAMD is shown in Table 2 (55, 72, and 20 eyes in the never-, former-, and current-smoker groups, respectively). The association between age and smoking history was not statistically significant ($P$ = 0.11). The mean BCVA and CRT in the overall sample improved from 0.29 and 320.0 μm to 0.13 and 232.2 μm over 12 months, respectively; there were no significant differences among smoking history groups. Additionally, we evaluated the injection number, the presence of residual intraretinal or subretinal fluid after the 3-month loading dose, and the retreatment-free period after the loading dose to investigate the treatment frequency. The mean number of injections, rate of dry macula after the loading dose, and retreatment-free period after the loading dose in the overall sample were 6.5, 81.0%, and 3.3 months, respectively; there were no significant differences among smoking history groups. Similarly, the Kaplan-Meier curves for the retreatment-free periods after the loading dose were not significantly different among smoking history groups ($P$ = 0.30, Fig. 4).

# Discussion

In our study, ever smokers (former- and current-smokers) had significantly higher proportions of fellow eyes with no significant drusen or pachydrusen and affected eyes with PCV than never-smokers, suggesting that cigarette smoking was associated with pachychoroid-related abnormalities. “Pachychoroid” is a term to define macular diseases characterized by a thick choroid, choroidal vascular hyperpermeability, and dilatation of the choroidal vessels in Haller’s layer with attenuation of inner choroidal vessels, including choriocapillaris and Sattler’s layer [25]. Although it is ambiguous whether the attenuation of inner choroidal vessels is a primary pathologic change or a secondary morphological change, inner choroidal attenuation could cause ischemic damage to the RPE [26, 27], followed by CNV, including pachychoroid neovasculopathy (PNV) [28] and PCV [29]. Miyake et al. evaluated differences in genetic backgrounds and clinical features between PNV and non-PNV of Japanese patients with nAMD and demonstrated that PNV patients were significantly younger and had lower genetic risk scores than non-PNV patients [30]. In additon, the frequency of genes associated with nAMD (CFH rs800292) in PNV patients was comparable to that in normal Japanese subjects. They suggested that the risk factors for pachychoroid-dependent CNV may differ from those for drusen-dependent nAMD. However, the risk factors for the development of pachychoroid-dependent CNV have not been clarified. Cigarette smoking is a known risk factor for traditional nAMD. Cigarette smoke contains more than 4000 chemicals [31] that

cause oxidative damage and ischemia in almost all organs in the body and induce many chronic diseases, such as cerebral stroke, myocardial infarction, and chronic obstructive pulmonary disease. The mechanism of CNV induced by smoking has not been fully elucidated; however, one pathway by which smoking accelerates the development of CNV is impairment of the RPE and Bruch's membrane through the accumulation of reactive oxygen species induced by components of cigarettes and ischemia due to reduced blood flow in the choriocapillaris. Thus, our results strongly indicate that smoking, which causes ischemic damage to the RPE, plays an essential role in the development of pachychoroid-related abnormalities.

The proportions of fellow eyes with SDDs and affected eyes with type 3 neovascularization were higher in the never-smoker group. Type 3 neovascularization [32], also known as retinal angiomatous proliferation, is characterized by macular neovascularization originating from the retinal vessels, unlike PCV and typical AMD. Yannuzzi et al. reported that type 3 neovascularization tended to affect a higher proportion of females than males, with a sex ratio of more than 2:1 [33]. Even though Asian nAMD patients are predominantly male, Asian patients with type 3 neovascularization are predominantly female [3]. Several epidemiologic studies performed in Asia documented a higher prevalence of late AMD in males than in females, which is attributed to the substantially higher prevalence of smoking in males than in females in Asian countries [34–36]. These results suggest that the effect of cigarette smoking on the development of type 3 neovascularization is less than expected. More than 90% of eyes with type 3 neovascularization have SDDs [37], and SDDs are important in the pathophysiology of type 3 neovascularization. The mechanism of SDD formation is considered to be associated with choroidal circulatory disturbances [38–40], lipid transport abnormalities [41–43], or retinoid cycle disorers [44, 45]. In contrast with the finding of choroidal circulatory disorders as a cause of SDDs, Curcio et al. reported no difference in the proportion of ghost vessels of the choriocapillaris between locations with and without SDDs [46]. Additionally, Vongkulsiri et al. demonstrated no concordance between subretinal drusenoid deposits and large choroidal vessels or the stroma [47]. In the SDD group in our study, the proportion of never-smokers was 72.2%, which is comparable to the rate in the healthy elderly population (70.0% [112/160], data not shown), and our results supported the lack of association between SDDs and choroidal vessels. Although further research on the association between cigarette smoking and the development of SDDs or type 3 neovascularization is required, the effects of cigarette smoking on each drusen subtype likely differ.

The 5-year incidence of nAMD in the fellow eyes was 24.6% in this study. A recent study in Asia that investigated the 5-year progression rate of nAMD in the fellow eye reported a rate of 20.9% [48]. They classified nAMD patients using the new drusen classification and showed that eyes with soft drusen and/or SDDs had a significantly higher risk of nAMD in the fellow eye at 5 years than eyes with pachydrusen or no significant drusen. Another study also demonstrated that the pachydrusen group had a significantly lower frequency of nAMD development in the fellow eye than the soft drusen and SDD groups [49]. In this study, the rate of development of nAMD in the fellow eye did not differ among smoking history groups; however, there was a significant difference among drusen subtypes, similar to

previous studies. These results suggest that the new drusen classification could play an important role in predicting the prognosis of patients.

The limitations of this study include its retrospective study, single-center design and relatively small number of nAMD patients. All participants in this study were Japanese. Since the frequency of nAMD subtypes varies among racial groups, the results may not be generalizable to other racial and ethnic groups. We showed that cigarette smoking did not affect the 1-year outcomes of anti-VEGF therapy, but we did not confirm long-term outcomes. The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) showed that cigarette smoking did not influence on visual prognosis at 1 year after initial treatment in 1,105 nAMD patients who were treated with ranibizumab or bevacizumab [50]. However, the five-year outcomes in the CATT study reported that cigarette smoking was associated with an increased risk of poor visual prognosis (20/200 or worse) [51]. In a prospective study examining 987 eyes, nonsmokers had higher visual acuity improvements than former and current smokers [52]. In contrast, McKibbin et al. demonstrated that the visual outcome associated with anti-VEGF therapy for nAMD was not significantly different among never smokers, former smokers, and current smokers [53]. This inconsistency may be due to differences in follow-up periods, agents, treatment methods, race, nAMD subtype ratios, and smoking history classification. It should be noted that the patients in this study were treated with aflibercept monotherapy, and the study did not include patients treated with other anti-VEGF agents or photodynamic therapy.

In conclusion, ever smokers had a significantly higher proportion of pachychoroid-related abnormalities (no significant drusen or pachydrusen in the fellow eyes and PCV in the affected eyes) that nonsmokers, suggesting that cigarette smoking could promote the development of pahychoroid diseases due to ischemic damage in the RPE. Never smokers had a significantly higher frequency of SDDs in fellow eyes and type 3 neovascularization in affected eyes. Therefore, circulatory insufficiency may not be strongly associated with the development of SDDs or type 3 neovascularization. Cigarette smoking is a well-known modifiable risk factor for nAMD development, and the new drusen classification allowed us to clear differences in the contribution of cigarette smoking for nAMD development. Our present findings should heighten awareness of the risks of cigarette smoking in both the general population and health professionals.

# Abbreviations

BCVA: Best-corrected visual acuity; CNV: Choroidal neovascularization; CRT: Central retinal thickness; FA: Fluorescein angiography; ICGA: Indocyanine green angiography; nAMD; neovascular age-related macular degeneration; OCT: Optical coherence tomographic; PCV Polypoidal choroidal vasculopathy; PNV: Pachychoroid neovasculopathy; RPE: Retinal pigment epithelium; SDDs: Subretinal drusenoid deposits; VEGF: Vascular endothelial growth factor

# Declarations

### Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Kawasaki Medical School Ethics Committee (2543-1). The committee waived the need for written informed consent due to the retrospective design. Research information was disclosed to the patients on our website, and the freedom to refuse research use was guaranteed.

### Consent for publication

Not applicable.

### Availability of data and materials

Data will be made available upon reasonable request.

### Competing interests

The authors declare that they have no competing interests.


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This study received no funding support.


### Authors' contributions

Conceptualization: HK; Methodology: HK; Formal analysis and investigation: SA, KG, and KM; Writing-original draft preparation: HK; Supervision: KM, AM, and JK. All authors have read and approved the manuscript.


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# Tables

Due to technical limitations, table 1 and 2 tif are only available as a download in the Supplemental Files section.

# Figures

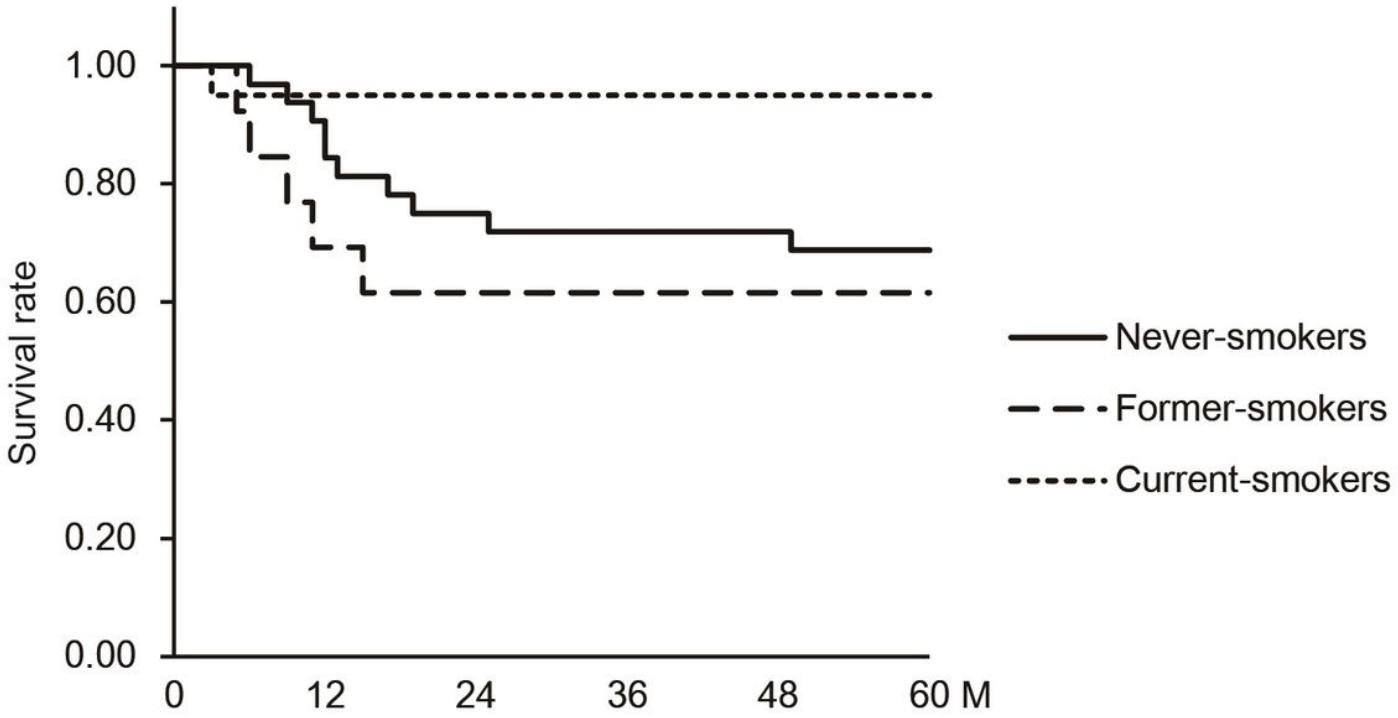
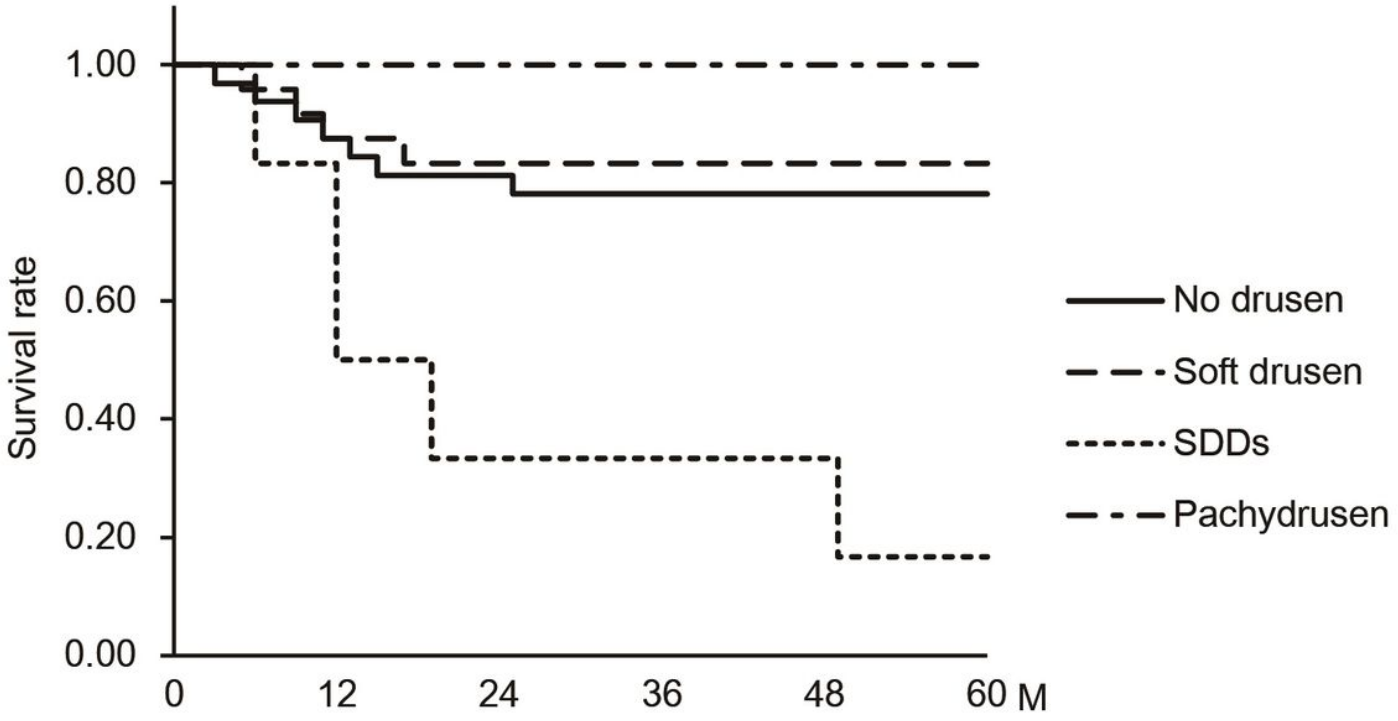



**Figure 1**

Five-year incidence of nAMD in the fellow eyes stratified by smoking history. The numbers of patients who developed nAMD in the fellow eye were 31.3%, 38.5%, and 5.0% in the never-, former-, and current-smoker groups, respectively. The Kaplan-Meier curve demonstrated that the incidence of nAMD development in the fellow eye was not significantly different among the three groups (P = 0.051).




## Figure 2

Five-year incidence of nAMD in the fellow eyes classified drusen subtype. The numbers of patients who developed nAMD in the fellow eye were 21.9%, 16.7%, 83.3%, and 0% in the no significant drusen, soft drusen, SDDs, and pachydrusen groups, respectively. The incidence nAMD development in the fellow eye was significantly associated with the drusen subtype in the fellow eye (P = 0.0028)

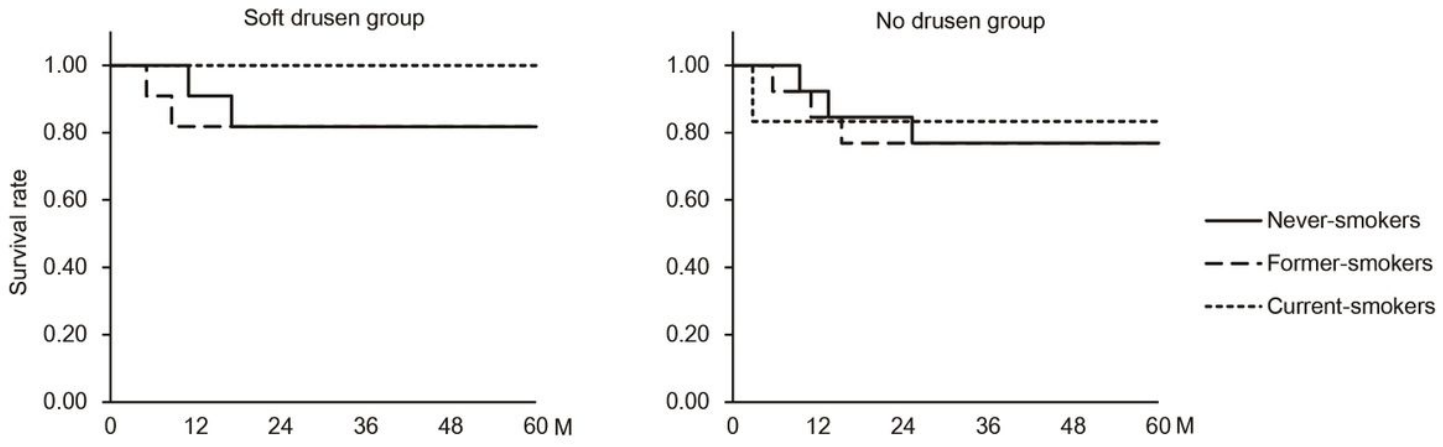


**Figure 3**

Five-year incidence of nAMD in the fellow eyes stratified by smoking history in soft drusen and no significant drusen groups. The incidence of nAMD development was not significantly different among smoking history groups in either group (no significant drusen group: P = 0.97, soft drusen group: P = 0.82).

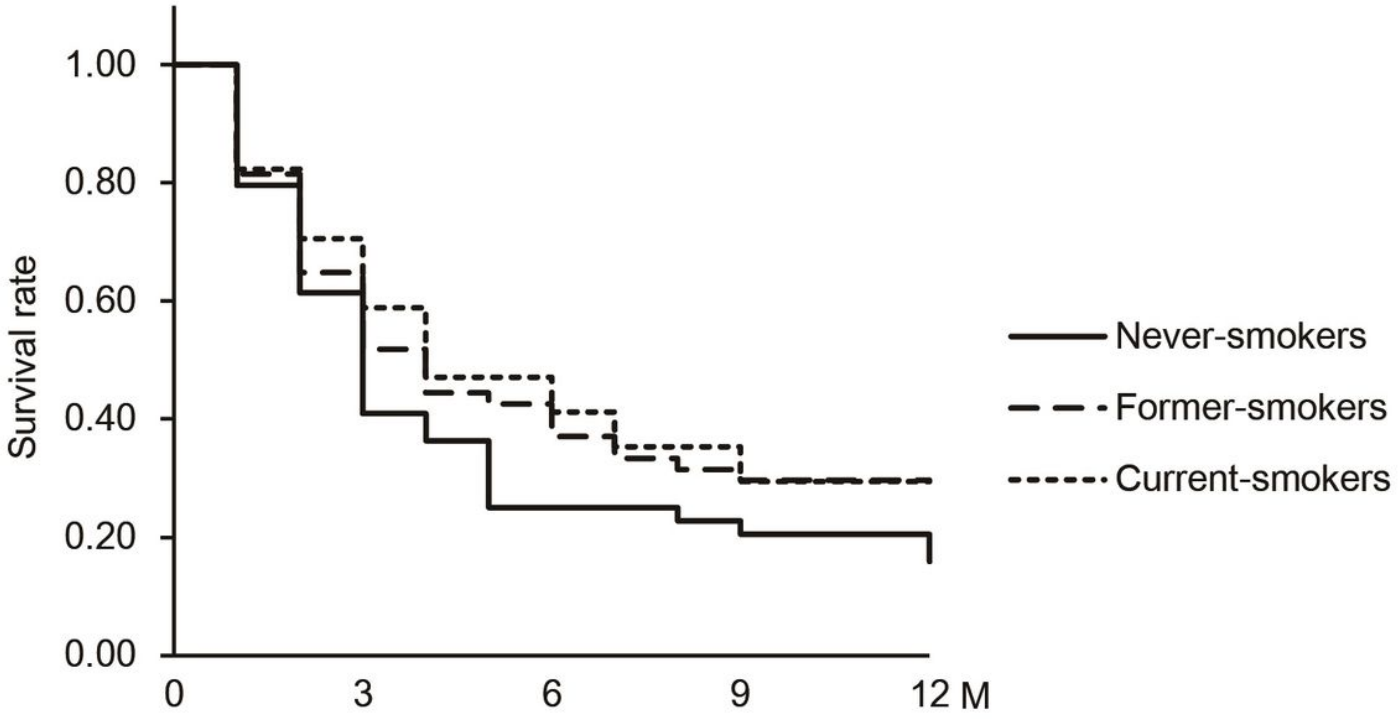



**Figure 4**

Retreatment-free periods after the loading dose. The Kaplan-Meier curves for the retreatment-free periods after the loading dose were not significantly different among smoking history groups (P = 0.30).

# Supplementary Files

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- Authorshipform.tif
- Table1.tif
- Table2.tif