A nationwide cohort study of cigarette smoking and risk of neovascular age-related macular degeneration in East Asian men

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ABSTRACT

Background Few longitudinal studies have evaluated the relationship between cigarette smoking and risk of neovascular age-related macular degeneration (AMD) among Asian populations. This study aimed to prospectively evaluate the association between cigarette smoking and risk of neovascular AMD among Korean men.

Methods Men between the ages of 45 and 79 years included in the Korea National Health Insurance Service database from 2002 through 2013. We compared hazard ratios (HR) for neovascular AMD between 64 560 past/current and 64 560 never smokers by 1:1 propensity-matched analysis and 85 267 past/current and 72 347 never smokers by unmatched cohort and propensity-adjusted analysis.

Results The risk of neovascular AMD among past/current smokers was 50% higher than that among never smokers (propensity-adjusted whole cohort analysis: HR, 1.48; 95% CI 1.22 to 1.79; propensity-matched analysis: HR, 1.50; 95% CI 1.22 to 1.84), with the risk more pronounced among current than past smokers (current vs past smokers: propensity-adjusted whole cohort analysis, HR, 1.66; 95% CI 1.35 to 2.04 vs HR, 1.15, 95% CI 0.87 to 1.52; propensity-matched analysis, HR, 1.65; 95% CI 1.32 to 2.05 vs HR, 1.21; 95% CI 0.90 to 1.63). Duration of smoking and daily cigarette consumption was associated with the incidence of neovascular AMD in a dose-dependent manner ($p<0.001$ for trend).

Conclusions Cigarette smoking is associated with a strong risk of neovascular AMD among Korean men. These data highlight the public health impact of smoking on blindness in Asia.

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. Its incidence is particularly increasing in Asia, where more than half the patients with AMD globally are estimated to reside by 2040.[1] Cigarette smoking has been consistently shown to be associated with AMD.[2–27]

However, while most previous studies have focused on the risk of early (or any) AMD,[18–21] evidence regarding the relationship between cigarette smoking and risk of neovascular 'wet' AMD is inadequate and largely based on the findings of cross-sectional[2–6] and case-control studies.[7–9] Previous longitudinal studies on cigarette smoking and AMD[10–17] have included extremely small numbers of subjects who developed neovascular AMD over time. Partly as a result of this, there are inconsistences in results among these longitudinal studies; one study, for example, could only report insignificant negative association upon evaluation of 10-year and 15-year follow-up data including a total of 47 and 63 incident AMD cases, respectively.[12 13] Therefore, large adequately powered longitudinal studies with sufficient number of patients with incident neovascular AMD are required to further understand this relationship.

Furthermore, few studies have been conducted among Asian populations,[22–24] where the prevalence of smoking is high or increasing, particularly in men.[28] Among Japanese populations, for example, the prevalence of late AMD among men (18.6%) was nearly sevenfold higher than that among women (2.6%) because of the higher prevalence of smoking among the former (36.8% vs 2.8%).[22 29] However, the risk of neovascular AMD related to cigarette smoking among Asian men has not been documented longitudinally. According to WHO, the projected prevalence of cigarette smoking in countries such as China, South Korea and Singapore in 2025 (43.3%) is higher compared with that in Western countries (16.3%).[30] Therefore, it is critical to clearly document the relationship between cigarette smoking and neovascular AMD in Asian populations, particularly among men.

The National Health Insurance Service (NHIS) database of South Korea provides a unique opportunity for evaluation of development of neovascular AMD among the general population according to smoking status. We, therefore, evaluated the association between neovascular AMD and cigarette smoking in a nationwide random sample comprising 157 614 men selected from the NHIS database of South Korea.

METHODS

Database

Participants were selected from the NHIS database, which includes approximately 510 000 randomly selected subjects between the ages of 40 years and 79 years, who were enrolled in the Korean National Health Screening Program in 2002 and 2003. These selected participants were followed up until 2013. The data include the results of medical examination, sociodemographic factors, prescription drugs and diagnostic codes for all medical care transactions from all kinds of medical facilities including private, public and hospital centres.

Study cohort

Based on a previous report regarding the presence of a large proportion of unreported smokers among

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women in Korea because of cultural and social barriers, and because of the very low proportion of female smokers in the NHIS database (see online supplementary table S1), we included only men in this study.[31] This study, therefore, included men enrolled in the National Health Screening Program between 2002 and 2003, who met the following eligibility criteria: response to questions regarding smoking status; age 45–79 years in 2002 (the lower age limit was set because the occurrence of neovascular AMD in the 40s is rare; upper limit was set based on that of the database); and data of continuous variables including body mass index, blood pressure and other parameters except age within the top and bottom 1%. Patients with any stage of AMD in 2002 and 2003 were excluded (see online supplementary figure S1). The study cohort was matched according to propensity scores based on 40 potential baseline confounders, including age, medical history and examination results, history of prescription drug use and antihypertensive medication, and utilisation of medical care (see table 1 and online supplementary table S2).

Smoking status and validation

The Korean National Health Screening Program employed a standardised questionnaire for smoking status. Participants were classified according to smoking status as never smokers or smokers (past or current smokers). Duration of smoking (≤9/10–29/≥30 years) and daily cigarette consumption (<10/10–19/≥20 cigarettes) were recorded.

To verify the smoking status of self-reported never smokers during 2008–2013, we determined the proportion of men who had reported being current or past smokers during 2002–2007. A total of 61 210 men had reported being never smokers more than once during 2008–2013, of whom, 47 178 (77.1%) had reported being never smokers more than once during 2002–2007 as well (see online supplementary table S3). Smoking status showed good agreement.

Follow-up and study end point

Participants enrolled between 2002 and 2003 were followed up from 1 August 2009 till the date of first instance of one of the following: loss to follow-up because of disqualification by the NHIS (mainly death), incidence of neovascular AMD or last visit to any medical care facility within the end of study period (31 December 2013; online supplementary figure S2). The primary end point of the study was incidence of neovascular AMD. Patients with neovascular AMD were identified by the registration code for the disease. For incidence estimates, the date of the earliest claim with the registration code and ranibizumab use was defined as the index date. Registration of 'copayment assistance policy' and ranibizumab use for treatment of newly diagnosed neovascular AMD in South Korea has been described in detail elsewhere.[32]

Statistical analysis

We developed propensity models for smokers (past/current) as well as never smokers. Individual propensities for smokers were estimated by logistic regression analysis of 40 potential confounders (table 1). Smokers and never smokers were then matched according to propensity scores in a 1:1 ratio based on 8→1 digit matching. We performed descriptive statistical analysis of the whole and propensity-matched cohorts to estimate the incidence of neovascular AMD per 10 000 person-years as well as HRs from Cox regression models. Data of the whole cohort were evaluated by propensity-adjusted analysis according to deciles of propensity scores and age. Data of the propensity-matched cohort were evaluated by age-adjusted analysis. Cumulative incidence of neovascular AMD from 1 August 2009 to 31 December 2013 was described using a Kaplan-Meier survival curve.

Dose-dependent association between smoking and neovascular AMD was evaluated from the data of the propensity-matched cohort. Cox proportional hazards analysis of duration of smoking was performed according to 1-year age strata in order to account for immortal-time bias—longer duration of smoking creates bias favouring longer life expectancy and higher risk of AMD. Association between daily cigarette consumption and neovascular AMD was evaluated by age-adjusted analysis.

Combined variables determined by univariable analysis to be associated with neovascular AMD with $p \leq 0.1$ in matched cohorts were further evaluated by multivariable Cox regression analysis. These analyses were repeated with a separate cohort selected based on history of consultation with an ophthalmologist in 2002–2003, because this variable was significantly associated with the incidence of neovascular AMD in our multivariable model.

Significance level was set at 0.05. Analyses were performed using SAS System for Windows, V.9.4 (SAS Institute, Cary, North Carolina, USA) and Stata/MP, V.14.0 (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics of the study cohort

A total of 157 614 men met the inclusion criteria, including 72 347 never smokers and 85 267 past/current smokers. Patient demographic and clinical characteristics in the whole unmatched cohort varied greatly between the two groups—never smokers were more likely to be older, and, therefore, exhibit greater instances of comorbid conditions or use of medical care than smokers. However, the incidence of neovascular AMD was similar between the two groups (both, 0.3%; p=0.181).

After 1:1 propensity matching, 129 120 participants including 64 560 each of never smokers and smokers were included in the analysis (table 1). In the propensity-matched cohort, all variables except the incidence of AMD were similar between the two groups; neovascular AMD was present in 154 never smokers and 227 smokers (p<0.001).

Incidence of neovascular AMD

The risk of neovascular AMD among smokers was significantly higher compared with that among never smokers in both whole unmatched (age-adjusted and propensity-adjusted HR, 1.48; 95% CI 1.22 to 1.79) and propensity-matched (age-adjusted HR, 1.50; 95% CI 1.22 to 1.84) cohorts (table 2). There was a clear difference in the incidence of neovascular AMD between smokers and never smokers (figure 1A) and between age subgroups (45–64 years and 65–79 years) in the propensity-matched cohort; however, the older age subgroup exhibited greater HRs than the younger age subgroup (table 2).

HRs for past smokers were greater compared with those for never smokers and lower compared with those for current smokers in both propensity-adjusted (HR: past smokers, 1.15; current smokers, 1.66) and propensity-matched analyses (HR: past smokers, 1.21; current smokers, 1.65; table 3). This trend was also reflected in the survival curve for cumulative incidence of neovascular AMD; the survival curve of past smokers was located between those of never smokers and current smokers (figure 1B).

Table 1 Baseline characteristics of the study population—smokers versus never smokers (whole and propensity score-matched cohorts)

	Unmatched whole cohort (n=157 614)			Propensity score-matched cohort (n=129 120)		
	Never smoker	Smoker (past/current)		Never smoker	Smoker (past/current)	
Characteristic	n=72 347	n=85 267	p Value	N=64 560	n=64 560	p Value
Neovascular AMD—no. (%)	192 (0.3)	257 (0.3)	0.181	154 (0.2)	227 (0.4)	<0.001
Age—years	56.3±8.2	54.1±7.6	<0.001	55.3±7.8	55.3±7.8	0.159
Body mass index—kg/m^2	24.2±2.6	23.9±2.6	<0.001	24.1±2.6	24.1±2.6	0.118
Systolic blood pressure—mm Hg	130.2±16.7	128.7±16.5	<0.001	129.6±16.6	129.6±16.6	0.642
Diastolic blood pressure—mm Hg	81.8±10.6	81.1±10.6	<0.001	81.6±10.6	81.5±10.6	0.160
Fasting glucose—mg/dL	98.5±23.3	98.6±23.8	0.525	98.4±23.3	98.6±23.6	0.226
Total cholesterol—mg/dL	198.0±33.7	199.7±34.2	<0.001	198.7±33.8	198.8±33.8	0.827
Haemoglobin—g/dL	14.7±1.1	14.8±1.1	<0.001	14.7±1.1	14.7±1.1	0.645
Urine pH	6.1±0.6	6.1±0.6	<0.001	6.1±0.6	6.1±0.6	0.982
Aspartate aminotransferase—U/L	27.3±9.4	27.4±10.0	<0.001	27.3±9.5	27.4±9.7	0.521
Alanine aminotransferase—U/L	27.2±13.4	27.5±13.9	<0.001	27.4±13.6	27.3±13.6	0.342
Charlson Comorbidity Index	0.5±1.0	0.4±0.9	<0.001	0.5±1.0	0.5±1.0	0.636
Hypertension—no. (%)	14 432 (20.0)	12 300 (14.4)	<0.001	11 006 (17.1)	11 155 (17.3)	0.271
Hyperlipidaemia—no. (%)	4540 (6.3)	4369 (5.1)	<0.001	3719 (5.8)	3708 (5.7)	0.895
Acute myocardial infarction—no. (%)	346 (0.5)	307 (0.4)	<0.001	276 (0.4)	278 (0.4)	0.932
Heart failure—no. (%)	2180 (3.0)	1771 (2.1)	<0.001	1619 (2.5)	1630 (2.5)	0.845
Peripheral vascular disease—no. (%)	938 (1.3)	922 (1.1)	<0.001	786 (1.2)	784 (1.2)	0.959
Cerebrovascular disease—no. (%)	1622 (2.2)	1335 (1.6)	<0.001	1206 (1.9)	1206 (1.9)	>0.999
Chronic pulmonary disease—no. (%)	5471 (7.6)	5863 (6.9)	<0.001	4732 (7.3)	4731 (7.3)	0.991
Liver diseases—no. (%)	5222 (7.2)	5699 (6.7)	<0.001	4563 (7.1)	4553 (7.1)	0.913
Uncomplicated diabetes—no. (%)	5348 (7.4)	5133 (6.0)	<0.001	4288 (6.6)	4339 (6.7)	0.570
Complicated diabetes—no. (%)	1645 (2.3)	1549 (1.8)	<0.001	1306 (2.0)	1331 (2.1)	0.623
Cancer—no. (%)	1259 (1.7)	988 (1.2)	<0.001	917 (1.4)	907 (1.4)	0.814
Prescription drug use in 2002–2003—no. (%)						
Antidiabetes mellitus medication						
Metformin	2594 (3.6)	2739 (3.2)	<0.001	2214 (3.4)	2199 (3.4)	0.818
Sulfonylurea	3790 (5.2)	3943 (4.6)	<0.001	3189 (4.9)	3218 (5.0)	0.710
Meglitinide	131 (0.2)	140 (0.2)	0.420	110 (0.2)	107 (0.2)	0.838
Thiazolidinedione	78 (0.1)	89 (0.1)	0.835	67 (0.1)	68 (0.1)	0.931
α-Glucosidase inhibitors	1200 (1.7)	1256 (1.5)	0.003	1003 (1.6)	1006 (1.6)	0.946
Insulin	44 (0.1)	55 (0.1)	0.771	40 (0.1)	39 (0.1)	0.910
Antihypertensives						
Angiotensin II receptor antagonist	3768 (5.2)	3326 (3.9)	<0.001	2979 (4.6)	2964 (4.6)	0.842
ACE inhibitor	7314 (10.1)	6169 (7.2)	<0.001	5551 (8.6)	5607 (8.7)	0.579
Calcium channel blocker	12 488 (17.3)	11 078 (13.0)	<0.001	9761 (15.1)	9859 (15.3)	0.447
Diuretics	7928 (11.0)	7129 (8.4)	<0.001	6259 (9.7)	6310 (9.8)	0.632
β-blocker	8113 (11.2)	7112 (8.3)	<0.001	6292 (9.8)	6374 (9.9)	0.443
Others	1092 (1.5)	1012 (1.2)	<0.001	869 (1.4)	869 (1.4)	>0.999
Statins	3559 (4.9)	3627 (4.3)	<0.001	3011 (4.7)	2963 (4.6)	0.525
Aspirin	2029 (2.8)	1744 (2.1)	<0.001	1564 (2.4)	1580 (2.5)	0.773
Exposure to medical care in 2002	62 681 (86.6)	70 211 (82.3)	<0.001	55 144 (85.4)	55 180 (85.5)	0.776
Exposure to medical care in 2003	64 533 (89.2)	72 215 (84.7)	<0.001	56 846 (88.1)	56 909 (88.2)	0.588
Exposure to ophthalmologist in 2002	15 827 (21.9)	14 826 (17.4)	<0.001	12 712 (19.7)	12 711 (19.7)	0.994
Exposure to ophthalmologist in 2003	16 862 (23.3)	15 320 (18.0)	<0.001	13 403 (20.8)	13 440 (20.8)	0.800

AMD, age-related macular degeneration.

In the 1-year age-stratified Cox model, men who had smoked for >30 years were more likely to have neovascular AMD than never smokers (HR, 1.76; 95% CI 1.40 to 2.22). Additionally, longer duration of smoking was associated with a higher risk of neovascular AMD (p<0.001 for trend; table 4). Similar dose dependency was observed in terms of daily cigarette consumption; higher cigarette consumption was associated with a higher incidence of neovascular AMD (p<0.001 for trend).

In the matched cohort, the multivariable adjusted HR for neovascular AMD for smokers was 1.50 (95% CI 1.23 to 1.85; reference HR of never smokers, 1; online supplementary tables S4 and S5). Among subjects who had visited an ophthalmologist in 2002–2003 as well as among those who had not, smokers were more likely to have neovascular AMD than never smokers (see online supplementary table S6).

DISCUSSION

The present study is the largest cohort study on the association between cigarette smoking and risk of neovascular AMD in Korean men. We have demonstrated a strong and consistent

Table 2 Incidence of neovascular AMD among smokers and non-smokers

	Propensity score-adjusted analysis (n=157 614)		Propensity score-matched analysis (n=129 120)	
Analysis	**Never smoker n=72 347**	**Smoker (past/current) n=85 267**	**Never smoker n=64 560**	**Smoker (past/current) n=64 560**
Primary analysis				
Total follow-up (PYs)	300 315	350 964	268 375	265 902
No. of neovascular AMD	192	257	154	227
Incidence (no./10 000 PYs, 95% CI)	6.4 (5.6 to 7.4)	7.3 (6.5 to 8.3)	5.7 (4.9 to 6.7)	8.5 (7.5 to 9.7)
HR (95% CI)	1 (reference)	1.48 (1.22 to 1.79)	1 (reference)	1.50 (1.22 to 1.84)
p Value		<0.001		<0.001
Subgroup analysis	p=*0.117 for interaction*		p=*0.131 for interaction*	
Age 45–64 years				
Total follow-up (PYs)	248 133	313 192	231 505	229 678
No. of neovascular AMD	124	174	109	144
Incidence (no./10 000 PYs, 95% CI)	5.0 (4.2 to 6.0)	5.6 (4.8 to 6.4)	4.7 (3.9 to 5.7)	6.3 (5.3 to 7.4)
HR (95% CI)	1 (reference)	1.33 (1.05 to 1.68)	1 (reference)	1.35 (1.05 to 1.73)
p Value		0.017		0.019
Age 65–79 years				
Total follow-up (PYs)	52 182	37 772	36 871	36 224
No. of neovascular AMD	68	83	45	83
Incidence (no./10 000 PYs, 95% CI)	13.0 (10.3 to 16.5)	22.0 (17.7 to 27.2)	12.2 (9.1 to 16.3)	22.9 (18.5 to 28.4)
HR (95% CI)	1 (reference)	1.82 (1.32 to 2.52)	1 (reference)	1.88 (1.31 to 2.71)
p Value		<0.001		0.001

AMD, age-related macular degeneration; PYs, person-years.

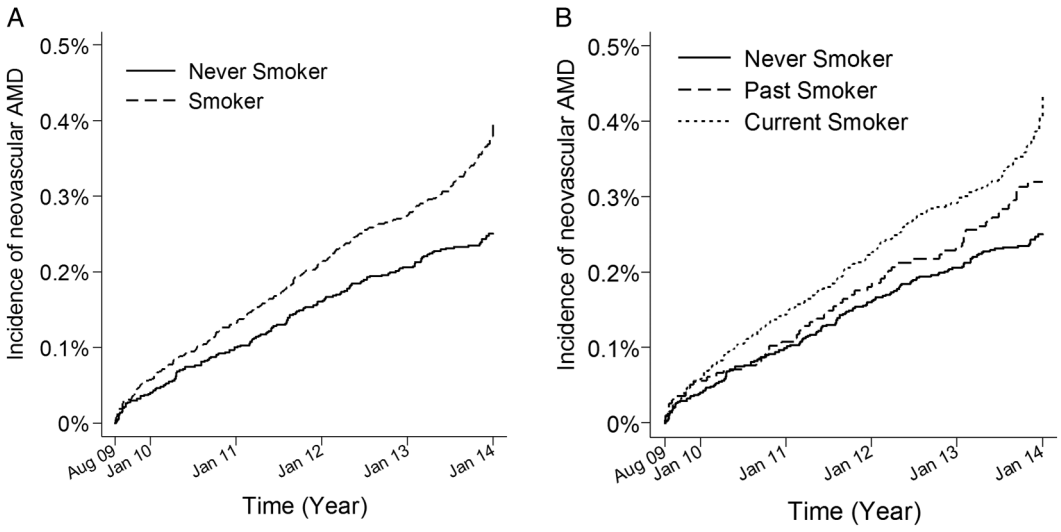

Figure 1 Cumulative incidence of neovascular age-related macular degeneration (AMD) among smokers and never smokers. For the historical cohort included in the National General Health Screening Program conducted in 2002–2003, follow-up started from the month when the National Health Insurance Service started covering ranibizumab treatment for neovascular AMD. There were differences in the cumulative incidence of neovascular AMD between smokers (current and/or past) and never smokers between 1 August 2009 and 31 December 2013.

association between cigarette smoking and an increased risk of neovascular AMD, which is more pronounced among the elderly (≥65 years of age) than among middle-aged men (45–64 years of age) and among current than past smokers. We also observed a dose-dependent increase in the risk of neovascular AMD with longer duration of smoking and greater daily cigarette consumption.

The present study is comparable with three major population-based cross-sectional studies—the Beaver Dam,[3] Rotterdam[4] and Blue Mountains[5] studies—which have previously documented the results of association between smoking and neovascular AMD. These studies included relatively small numbers of subjects with neovascular AMD (n=54, n=65 and n=47, respectively). Two large case-control studies, the Eye Disease Case-Control[7] and Age-Related Eye Disease[8] studies, reported an almost twofold increase in the risk of neovascular AMD with smoking. However, the results of previous longitudinal analyses have been somewhat different and inconsistent (see online supplementary

Table 3 Incidence of neovascular AMD among smokers and never smokers

	Propensity score-adjusted analysis (n=157 614)			Propensity score-matched analysis (n=129 120)		
	Never smoker	Smoker		Never smoker	Smoker	
Parameters	N=72 347	Past smoker n=24 801	Current smoker n=60 466	N=64 560	Past smoker n=19 688	Current smoker n=44 872
Total follow-up (PYs)	300 315	103 156	247 808	268 375	81 875	184 027
No. of neovascular AMD	192	65	192	154	60	167
Incidence (no./10 000 PYs, 95% CI)	6.4 (5.6 to 7.4)	6.3 (4.9 to 8.0)	7.7 (6.7 to 8.9)	5.7 (4.9 to 6.7)	7.3 (5.7 to 9.4)	9.1 (7.8 to 10.6)
HR (95% CI)	1 (reference)	1.15 (0.87 to 1.52)	1.66 (1.35 to 2.04)	1 (reference)	1.21 (0.90 to 1.63)	1.65 (1.32 to 2.05)
p Value		0.337	<0.001		0.217	<0.001

AMD, age-related macular degeneration; PYs, person-years.

Table 4 Association of neovascular AMD with duration of smoking and daily cigarette consumption

Smoking status	No. of cases	Crude %	HR	95% CI	p value
Duration of smoking (N=129 120)					p<*0.001 for trend*
Never smoked	154/64 560	0.24	1 (reference)		
≤9 years	17/7275	0.23	1.12	0.68 to 1.86	0.647
10–29 years	69/31 740	0.22	1.24	0.93 to 1.66	0.140
≥30 years	141/25 545	0.55	1.76	1.40 to 2.22	<0.001
Daily consumption of cigarettes (N=109 432)					p<*0.001 for trend*
Never smoked	154/64 560	0.24	1 (reference)		
<10 cigarettes	46/11 672	0.39	1.42	1.02 to 1.97	0.039
10–19 cigarettes	78/23 602	0.33	1.54	1.18 to 2.03	0.002
≥20 cigarettes	43/9598	0.45	2.33	1.66 to 3.27	<0.001

Association of neovascular AMD with duration of smoking and daily cigarette consumption were evaluated by age-stratified and age-adjusted analyses, respectively. Persons with missing data regarding daily cigarette consumption were excluded.
AMD, age-related macular degeneration.

table S7).[10–15] While the Beaver Dam cross-sectional study reported a higher risk of neovascular AMD among smokers than never smokers, the 5-year, 10-year and 15-year follow-up analyses demonstrated a non-statistically significant association between smoking and neovascular AMD because of the small numbers of subjects with incident neovascular AMD (n=0, n=47 and n=63, respectively). A pooled analysis based on the Beaver Dam, Rotterdam and Blue Mountains studies reported a relationship between current smoking and the 5-year incidence of geographical atrophy but not neovascular AMD.[16] Both the physicians' and nurses' health studies, which included the largest cohorts, found a statistically insignificant association between smoking and neovascular AMD, although a trend of a positive association was reported for current smokers, with relative risk values of 1.95 and 1.62, respectively.[10 11] Therefore, our findings are significant since they confirm a temporal relationship between cigarette smoking and subsequent development of neovascular AMD.

Of the few related studies in Asia, some have not found smoking to be a significant factor for AMD.[33–35] Although several previous findings support the positive association between smoking and AMD,[9 18 20–26] the temporal relationship between smoking and neovascular AMD has not been evaluated with adequate power. The significance of this relationship is great in Asia, where there is an increasing prevalence of smoking, particularly among men.[36] In particular, in some Asian countries, a surge in smoking has been observed among men in the 1980s and in the mid-1990s.[37] In addition, 50% of men in China are current smokers, which corresponds to about a third of the total number of smokers in the world.[38] Our findings indicating that a quarter of incident neovascular AMD cases could be related to smoking could have an enormous impact on public and eye health.

A few longitudinal studies have reported a statistically insignificant positive association between past smoking and neovascular AMD,[11 14] which corresponds with the present results of the propensity-adjusted and propensity score-matched analyses. The survival curve for the cumulative incidence of neovascular AMD among past smokers was located between those of never smokers and past smokers, which suggests that past smokers had a lower risk of neovascular AMD than current smokers and that the risk is reversible. The nurses' health study reported the dose-dependent effect of smoking on neovascular AMD by comparing subjects with different intensities of smoking in terms of pack-years,[10] which corresponds with our findings indicating an increase in the incidence of neovascular AMD with longer duration of smoking and greater daily cigarette consumption. The information that cessation or reducing the frequency of smoking might help reduce the risk of neovascular AMD in patients with early stage of the disease and in those with one affected eye could have significant clinical and public health implications.

This study has several limitations. We previously speculated on the possible scenarios of ranibizumab use during the initial period of inclusion of ranibizumab under NHIS coverage in South Korea (see online supplementary figure S3). Despite the various possibilities, prescription of ranibizumab was strictly limited to the active stage of neovascular AMD diagnosed by fluorescein angiography. Therefore, the specificity for ranibizumab-treated neovascular AMD in the present study is very high. This study might also suffer from underestimation of

self-reported smoking habits. However, this bias would only lead to the underestimation of true association between smoking and neovascular AMD. Although it is possible that the incidence of neovascular AMD and the possibility of delayed consultation were underestimated in the present study, given the acute severe visual disturbance caused by neovascular AMD and the high accessibility of medical services in South Korea, we believe that the underestimation was minimal. It is possible that the study population included in the medical claims and health screening databases might have been biased relative to general population-based controls who neither received medical care or specific diagnosis nor ever participated in the National Health Screening. The probability of this bias could be similar among smokers and never smokers. In order to minimise surveillance bias, we controlled 40 possible confounding factors, including consultation with an ophthalmologist. It is difficult to properly assess socioeconomic background and refractive error in our data set. It is known that both parameters are risk factors for AMD[34 39–42] and are possibly confounding factors for smoking (ie, people who have a lower socioeconomic status or who are hyperopic are more likely smokers). However, we believe that these confounding factors have been minimised by controlling many variables in the statistical analyses. Additionally, in order to minimise the immortal time bias, we performed 1-year age-stratified analysis to estimate the association between duration of smoking and neovascular AMD. Another limitation is the possibility of differences in disease patterns, such as those of polypoidal choroidal vasculopathy, among Asian populations.[19]

In conclusion, the present findings demonstrate a prospective link between cigarette smoking and subsequent risk of neovascular AMD among Asian men. The lower risk of neovascular AMD among past smokers compared with that among current smokers indicates the possibility of reduction of this risk by cessation of smoking. A dose-dependent relationship exists between the duration and intensity of smoking and risk of neovascular AMD. Our findings, along with those of other studies, affirm the public health impact of cigarette smoking as a major avoidable cause of blindness in Asia.

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