Smoking and neovascular form of age related macular degeneration in late middle aged males: findings from a case-control study in Japan

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Abstract

Aims—The risk of smoking habits for developing the neovascular form of age related macular degeneration (neovascular form of AMD) were studied by a case-control study in Japan.

Methods—56 male patients with the neovascular form of AMD and 82 healthy male controls, aged 50 to 69 years, were enrolled. A self administered questionnaire provided necessary information for the study subjects. Questions on smoking included whether the study subjects have ever smoked or not, and if smoked, depth of smoke inhalation, use of extra filter, age at starting smoking, average number of cigarettes smoked per day, and duration of smoking. When a smoker had stopped smoking, age at cessation was also recorded. Unconditional logistic analysis was adapted to calculate age adjusted odds ratios and their 95% confidence intervals (CIs) for smoking related factors.

Results—Age adjusted odds ratio of developing the neovascular form of AMD was 2.97 (95% CI 1.00–8.84) for current smokers and 2.09 (0.71–6.13) for ex smokers, compared with non-smokers. All smoking habit/smoking history related variables such as use of extra filter, smoke inhalation level, age at starting smoking, duration of smoking, and Brinkman index were found to be significantly related to an increased risk of the neovascular form of AMD.

Conclusions—Suggested is the strong possibility that cigarette smoking enhances the neovascular form of AMD risk in late middle aged males, though the magnitude of risk by smoking variables might be overestimated, in part, because of health oriented controls.

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Exudative age related macular degeneration (exudative AMD) is well known as one of the major causes of registered blindness in the elderly.¹ In a nationwide epidemiological survey in Japan, an estimated 7500 patients underwent medical care for exudative AMD, with an increasing trend in recent years.² Despite these findings, risk factors have been poorly understood for AMD, but aging is a well established risk factor.

The potential effects of cigarette smoking on the development of AMD have been controversial, though recent large studies^{3–6} support its effect. Eight epidemiological studies; two large prospective studies,^{4,6} three case control studies,^{7–9} and three population based prevalence studies^{3,5,10} incriminated smoking as a risk factor for AMD. In contrast, another population based prevalence study¹¹ found an inverse association between smoking history and AMD, and two case-control studies^{12,13} and one population based prevalence study¹⁴ failed to show an association. These 12 epidemiological studies were all undertaken in the countries other than Japan, and no epidemiological studies to disclose risk factors for AMD have been conducted in Japan, to our knowledge. This background initiated the Research Committee on Chorioretinal Degenerations to conduct a case-control study in Japan with a major aim of disclosing risk factors for the neovascular form of AMD, one type of exudative AMD. In its execution, we limited the study subjects to males only, since male patients with exudative AMD were known to account for about 69%,² and since almost 90% of females aged 50 years and more were non-smokers in Japan.¹⁵

Subjects and methods

ELIGIBILITY OF CASES AND SELECTION OF CONTROLS

A male patient with the neovascular form of AMD was defined as an eligible case, when he satisfied the following three conditions: (1) aged 50 to 69 years; (2) visited one of five university hospitals located in the Kanto district—Chiba, Nihon (Surugadai Hospital), Tokyo Ika-shika, Juntendo, and Keio—between May 1990 and May 1992; and (3) was diagnosed as having the neovascular form of AMD in the past 3 years. All cases were examined for their visual acuity and fundus photographs were taken; colour fundus photographs and fluorescein angiography were studied to detect neovascularisation in the macular area. All patients enrolled in the study were those who satisfied the classification criteria, defined by the Research Committee on Chorioretinal Degenerations (Table 1).¹⁶ Among them, the presence of macular changes due to age related subretinal neovascularisation associated with AMD was a critical criterion.

Controls were selected randomly from healthy men, aged 50 to 69 years, who visited

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Table 1 Classification of the neovascular form of AMD by the Research Committee on Chorioretinal Degenerations, the Ministry of Health and Welfare of Japan

1 Early lesion	
(1) Serous detachment of the retina	Small yellow-white lesion (neovascular membrane) surrounded by retinal detachment and/or a small amount of haemorrhage. In some instances, these lesions are surrounded by variable numbers of hard exudates.
(2) Large detachment of the retinal pigment epithelium	Large detachment of the retinal pigment epithelium associated with choroidal neovascular membrane.
2 Typical lesion	
(1) Subretinal haemorrhage	Dome-shaped haemorrhagic detachment of the sensory retina and retinal pigment epithelium in and around the macula. Vitreous haemorrhage occasionally occurs when the amount of subretinal haemorrhage is large.
(2) Disciform lesion	This lesion is the typical disciform lesion of the disease. Large yellowish-white disciform lesions in the macular area are associated by the haemorrhage, retinal detachment, and hard exudates. Extensive detachment of the retinal pigment epithelium is also occasionally observed.
3 Scar stage	
There are variations in this stage from simple atrophic lesions to formation of white or grey thickened scars.	

Table 2 Age distribution of the study subjects

Age (years)	Patients		Controls	
	N	%	N	%
50-54	2	3.6	3	3.7
55-59	4	7.1	37	45.1
60-64	27	48.2	28	34.1
65-69	23	41.1	14	17.1
Total	56	100.0	82	100.0
Mean age	66.6		60.2	
SD	3.9		4.1	

Surugadai Hospital, Nihon University (one of the hospitals where the cases were identified) for their general medical check ups between July 1991 and May 1992. Their fundi were all

Table 3 Age adjusted odds ratio (OR) of developing neovascular form of AMD according to smoking status

	Patients		Controls		OR	(95% CI)
	N	%	N	%		
Non-smokers	7	12.5	24	29.6	1.00	
Ex-smokers	24	42.9	30	37.0	2.09	(0.71-6.13)
Current smokers	25	44.6	27	33.3	2.97*	(1.00-8.84)

Information on smoking status was missing in one control.
* $p < 0.05$.

Table 4 Age adjusted odds ratios (OR) of developing neovascular form of AMD according to smoking related variables

	Patients		Controls		OR	95% CI
	N	%	N	%		
Non-smokers	7	12.5	24	29.6	1.00	
Use of extra filter:						
Regularly/sometimes	10	17.9	17	21.5	1.50	(0.43-5.26)
Never	39	69.6	38	48.1	3.07*	(1.09-8.63)
Inhalation:						
Not deeply	32	57.1	49	60.5	1.95	(0.70-5.42)
Deeply	17	30.4	8	9.9	5.41**	(1.52-19.31)
Age (years) at starting smoking:						
21~	14	25.0	27	33.8	1.49	(0.47-4.65)
~20	35	62.5	29	36.3	3.41*	(1.20-9.73)
						trend $p < 0.05$
Duration of smoking (years):						
~29	13	23.2	23	28.8	1.86	(0.59-5.84)
30-39	16	28.6	23	28.8	2.38	(0.77-7.35)
40~	20	35.7	10	12.5	3.79*	(1.13-12.70)
						trend $p < 0.05$
Brinkman index:	(numbers of cigarette per day $\times$ smoking years)					
~700	22	39.3	36	45.0	1.84	(0.64-5.33)
701~	27	48.2	20	25.0	3.66*	(1.22-10.97)
						trend $p < 0.05$

Totals may differ because of missing information.

* $p < 0.05$, ** $p < 0.01$.

examined routinely by ophthalmologists to exclude those with the neovascular form of AMD. Thus, all controls were limited to those who with no signs of macular changes or with a few hard drusen in the macular area.

DATA COLLECTION

A self administered questionnaire was used to obtain routine demographic, epidemiological, and dietary information from each study subject. Questions on smoking included whether the study subjects have ever smoked or not, and if smoked, depth of smoke inhalation, use of extra filter, age at starting smoking, average number of cigarettes smoked per day in three age periods (before 40 years old, between 40 to 54 years old, and 55 years old and over), and duration of smoking in years. When a smoker had stopped smoking, age at cessation was also recorded. The Brinkman index (BI), which is defined as numbers of cigarette smoked per day times smoking years, was calculated by summing separate BIs in three age periods. In this study, an ex smoker was defined as a man who stopped smoking 3 years or more before the date of completing a questionnaire. Smokers who stopped smoking within the past 3 years were, therefore, included as current smokers. Clinical information on eye fundus was collected by ophthalmologists.

STATISTICAL ANALYSIS

Fifty six male patients and 82 healthy controls were finally recruited in the study. Unconditional logistic analysis¹⁷ was adopted to calculate age adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for smoking related factors. Test for trend in the logistic analysis was performed, categorising the exposure variable and treating the scored variables as continuous ones.

Results

Table 2 presents the age distribution of the study subjects. Mean age was significantly higher in patients (66.6 (SD 3.9) years) than in controls (60.2 (4.1) years) indicating the necessity of age adjustment when calculating odds ratios.

Age adjusted odds ratio of developing the neovascular form of AMD was 2.97 (95% CI 1.00-8.84) for current smokers, and 2.09 (0.71-6.13) for ex smokers, compared with non-smokers (Table 3).

Table 4 lists ORs for the smoking habit/smoking history related variables. A significantly increased risk was found for ever smokers: (1) who have never used extra filter (OR 3.07, 95% CI 1.09-8.63); (2) who have inhaled cigarette smoke deeply (5.41, 1.52-19.31); (3) who started smoking before 20 years old (3.41, 1.20-9.73); (4) who have continuously smoked for more than 40 years (3.79, 1.13-12.70); and (5) who exceeded the BI of 700 (3.66, 1.22-10.97). An average BI was 773 for smokers with the neovascular form of AMD and 569 for control smokers ($p < 0.05$), and the dose-response relation by BI

Table 5 Epidemiological studies on AMD and smoking

Author(s)	Year	Place/name of study	Disease	Study design	No of study subjects	% Male of the study subjects (cases)	Age range (years)	% Smokers of study subjects (controls)	Smoking				
									Habit/history	Inhalation	No of cigarettes	Brinkman index	Passive smoking
Maltzman ¹²	1979	Jersey City	SMD	case-control	30 cases, 30 controls	33.3	52-88	76.7*	NA	—	—	—	—
Hyman ⁷	1983	Baltimore	SMD	case-control	162 cases, 175 controls	40.1	—85	50.3*	↑	—	NA	—	—
Blumenkranz ¹³	1986	South Florida	DMD	case-control	26 cases, 23 controls	35.0		52.2*	NA	—	—	NA	—
West ¹¹	1989	Maryland	AMD	cross sectional	838 watermen	100.0	30-	78.6*	↓	—	NA	—	—
The Eye Disease Case-Control Study Group ⁸	1992	Chicago, Milwaukee, Boston, New York, Baltimore	Neovascular AMD	case-control	421 cases, 615 controls	44.0	55-80	12.8†	↑				
Vinding ⁹	1992	Copenhagen City Heart Study	AMD	case-control	88 atrophic AMD, 24 exudative AMD, 661 controls	50.0 atrophic AMD, 33.3 exudative AMD	60-80	51.2*	↑	↑	—	—	—
Klein ¹⁰	1993	Beaver Dam Eye Study	ARM	cross sectional	4771 people	44.4	43-86	20.0†	↑	—	—	↑	NA
Seddon ⁴	1996	Nurses' Health Study (US)	AMD	prospective cohort	31 843 registered nurses	0.0	50-59	27.9†	↑	—	↑	↑	—
Christen ⁶	1996	Physicians' Health Study (US)	AMD	prospective cohort	21 157 physicians	100.0	40-84	10.6†	↑	—	↑	↑	—
Vingerling ⁵	1996	Rotterdam Study	AMD	cross sectional	6174 people	40.3	55-	21.0†	↑	—	—	↑	—
Smith ³	1996	Blue Mountains Eye Study	ARM	cross sectional	3654 people	43.3	49-	15.5†	↑	—	—	NA	↑
Hirvela ¹⁴	1996	Oulu, Northern Finland	ARM	cross sectional	560 people	35.8	70-	6.2†	NA	—	—	—	—
Present study		Japan	Neovascular form of AMD	case-control	56 cases, 82 controls	100.0	50-69	33.3†	↑	↑	↑	↑	—

SMD = senile macular degeneration; DMD = disciform macular degeneration; AMD = age related macular degeneration; ARM = age related maculopathy. *Current and former smokers; †current smokers. — = not available; NA = no association; ↑ = positive association; ↓ = negative association.

was statistically significant ($p < 0.01$, data not shown).

Discussion

The main methodological shortcomings of our study may be (1) the different age distribution between patients with the neovascular form of AMD and healthy controls, and (2) the possibility that our controls were more health oriented than the general population, since they were examinees of general medical check ups.

To overcome the first shortcoming, we evaluated risk modifications by age adjusted ORs which were obtained from an unconditional logistic model. According to the National Nutrition Survey in 1990 in Japan,¹⁵ current smokers, ex smokers, and non-smokers accounted for 50.1%, 20.1%, and 29.8% among males aged 50 to 59 years and 51.8%, 30.1%, and 18.1%, among those aged 60-69 years. The corresponding figures in our controls were 33.3%, 37.0%, and 29.6%, respectively; indicating less frequent smokers in our controls compared with the general population, and, therefore, possibly overestimating the risk magnitude for the neovascular form of AMD by smoking. In contrast, our case-control study might have the following advantages. Smoking information we collected might be, in general, more accurate, since our study subjects were relatively young, and since they

could readily provide such detailed information as the numbers of cigarettes smoked per day in three separate age periods.

Table 5 summarises 13 epidemiological studies, including the present one, which have assessed an association between smoking and AMD. The characteristics of our study compared with others might be the high proportion of current smokers as controls, though it is lower than the general population in Japan as mentioned above, and the male: female ratio of the study subjects—all were men. Eight studies³⁻¹⁰ found an elevated risk by smoking for AMD. For men, the risk of ever smokers was 2.6 times,⁷ and the risk of current smokers was 3.29,¹⁰ 3.2,³ and 2.1⁶ times. The sex adjusted odds ratio of 2.8 and 3.6 for current smokers, compared with never smokers was also found in a case-control study⁸ and a cross sectional study,⁵ respectively. In our study, the risk of the neovascular form of AMD for men was higher by 2.97 times in current smokers than in never smokers. Our magnitude of risk by smoking was comparable with that in other studies.^{3,7,8,10} On the other hand, for women who were current smokers, 2.50¹⁰, 4.1³ and 1.7⁴ fold risk was reported compared with non-smokers, but Hyman *et al* failed to find an elevated risk.⁷ The reported magnitude of risk to develop AMD by smoking seems to be slightly lower in women compared with men, though we could not confirm this point in our

study. Deep smoke inhalers and smokers who did not use an extra filter were found to be at an increased risk of 5.41 and 3.07, respectively, in our study. Only one study,⁹ which had assessed an association with smoke inhalation, showed an elevated risk of 2.4 in smoke inhalers. For exudative macular degeneration, Klein and coworkers¹⁰ reported an increased risk (1.16 per 10 pack years smoked) for females, but not for males, and no risk elevation was found in other types of AMD. Two cohort studies, one for women⁴ and another for men,⁶ both found a significantly increasing risk for AMD with an increasing number of cigarette pack years. Four studies^{3, 7, 11, 13} failed to find a statistically significant association with the numbers of cigarette consumed a day or cigarette pack years. In our study, however, the greater the numbers of cigarettes smoked, the longer the smoking duration, and the younger the age at starting smoking, the higher the risk of the neovascular form of AMD.

The retina is highly susceptible to oxidative stress as a result of the close proximity of visible radiation and free radical producing lipid components.¹⁸ In one review of the literature,¹⁹ it was concluded that basic research studies showed that antioxidants could protect against the cumulative effects of oxidative stress in animal models of macular degeneration. Recent epidemiological studies have reported a protective effect of some antioxidants on the development of AMD,^{18, 20, 21} with the understanding that smoking might reduce the serum level of antioxidants²² and increase oxidative stress and lipid peroxidation.²¹ Therefore, the effect of cigarette smoking on the neovascular form of AMD might possibly be ascribable to the decreased level of antioxidants in the retina, which was evoked by depressed serum antioxidants, though the interrelation of antioxidant concentration in the retina with that in plasma has not yet been clearly shown.

In short, our case-control study clearly suggested the strong possibility that cigarette smoking enhances the risk for the neovascular form of AMD, though the magnitude of risk is likely to be overestimated because of health oriented controls. To substantiate the risk modification of the neovascular form of AMD by smoking habit, a much larger epidemiological study is warranted.

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