EXTENDED REPORT

Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation

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Background/aims: There is evidence that smoking is a risk factor for age related macular degeneration (AMD). However, not all studies have demonstrated this association and several key questions about the role of smoking in AMD have still to be determined. The aim of this study was to further investigate this relation for both choroidal neovascularisation (CNV) and geographic atrophy (GA).

Methods: To investigate the relation between smoking and the risk of developing age related macular degeneration (AMD) in white people, 435 cases with end stage AMD were compared with 280 controls. All subjects had graded stereoscopic colour fundus photography and AMD was defined as the presence of GA or CNV. Smoking history was assessed using multiple parameters in a detailed questionnaire.

Results: Comparison of current and former smokers with non-smokers was consistent with smoking being a risk factor for AMD but did not reach statistical significance. There was a strong association between AMD and pack years of cigarette smoking (p = 0.002), the odds ratio increasing with the amount smoked; for subjects with more than 40 pack years of smoking the odds ratio was 2.75 (95% CI 1.22 to 6.20) compared with non-smokers. Both types of AMD showed a similar relation; smoking more than 40 pack years of cigarettes was associated with an odds ratio of 3.43 (95% CI 1.28 to 9.20) for GA and 2.49 (95% CI 1.06 to 5.82) for CNV. Stopping smoking was associated with reduced odds of AMD and the risk in those who had not smoked for over 20 years was comparable to non-smokers. The risk profile was similar for males and females. Passive smoking exposure was associated with an increased risk of AMD (OR 1.87; 95% CI 1.03 to 3.40) in non-smokers.

Conclusions: The authors have demonstrated a strong association between the risk of both GA and CNV and pack years of cigarette smoking. This provides support for a causal relation between smoking and AMD. They also show an increased risk for AMD in non-smokers exposed to passive smoking. Stopping smoking appears to reduce the risk of developing AMD.

Age related macular degeneration (AMD) is the commonest cause of severe visual impairment in the Western world and is a significant public health problem.[1–6] Studies have attempted to define avoidable risk factors in a bid to reduce the incidence of this devastating condition and smoking has been found to be a risk factor in a number of studies.[7–15] However, this has not been a consistent finding, with other studies showing no association.[16–22] Although this is partly the result of differing definitions of AMD, several key questions about the role of smoking in AMD have still to be determined and, in particular, whether the association holds for both forms of end stage disease—namely, geographic atrophy (GA) and choroidal neovascularisation (CNV). We designed a case-control study to assess the relation between a variety of smoking behaviours and end stage AMD.

METHODS

We conducted a case-control study in the UK counties of Norfolk, Suffolk, Cambridgeshire, and Buckinghamshire from 2001 to 2003, and compared cases of choroidal neovascular membrane or geographic atrophy with spouse controls. Multicentre research ethics committee and local research ethics committee approvals were obtained for the study.

Case-control selection

Patients with AMD were ascertained from hospital ophthalmic clinics, general practices, optometrists and charitable societies for people with visual impairment. Patients with a spouse willing to act as a control were prioritised for recruitment, but cases without a spouse were also accepted. It was not the aim to match cases to their own spouse. All study subjects were examined by an ophthalmologist (JCK) and completed a detailed questionnaire on smoking history. All subjects had colour, stereoscopic fundus photography of the macular region (field 2 of the modified Airlie House classification[23]) and photographs were graded according to the International Classification of Age-related Maculopathy and Macular Degeneration.[24] In this classification the term AMD is reserved for the late stages of the disease, CNV (which also includes pigment epithelial detachment, PED) and GA. Patients were accepted as cases if they were confirmed to have AMD in one or both eyes. Spouses with early changes of age related maculopathy were accepted as controls. Spouses found to have AMD were reclassified as

Abbreviations: AMD, age related macular degeneration; CFH, complement factor H; CNV, choroidal neovascularisation; GA, geographic atrophy; PED, pigment epithelial detachment; RPE, retinal pigment epithelium

cases. All subjects were selected to be white, over 50 years old, and were excluded if they had more than 6 dioptres of myopic refractive error. If pseudophakic or aphakic they were only included if a preoperative refraction was available. Cases and controls were also excluded if they had evidence of other inflammatory or retinovascular disease such as retinal vessel occlusion, diabetic retinopathy, or chorioretinitis that could contribute to the development or confound the diagnosis of maculopathy. Fundus photographs were graded at the reading centre, Moorfields Eye Hospital, London, UK, and underwent both a preliminary and final grading process blinded to their provisional status as cases or controls. Discrepancies between preliminary and final grading were adjudicated by a senior ophthalmologist (ACB). Discrepancies between photographic grading and clinical examination were decided by reference to the medical case records and any previous colour photographs or fluorescein angiography.

Smoking history

Smoking data were collected and status was assessed in the same manner for both cases and controls using a questionnaire modified from that used for the European Prospective Investigation of Cancer (EPIC) study.[25] Smoking status was assessed as non-smoker, former, or current smoker, with smokers defined as subjects smoking at least one cigarette per day for a year. The questionnaire included an assessment of the number of cigarettes smoked per day in each decade of life, use of other tobacco products, extent to which subjects inhaled, and exposure to passive smoking (only assessed in non-smokers and defined as having lived in the same house as a smoker for at least 5 years). To calculate pack years of smoking, the average of number of cigarettes smoked per day was divided by 20 to give packs per day and multiplied by the total number of years of smoking.[26] Smoking of other tobacco products was also assessed and converted into pack years by equating 1 g of loose tobacco to one cigarette; cigars were taken as equivalent to 5 g of tobacco and cigarillos/small cigars as 2 g.

Data analysis

Data were analysed using logistic regression models and odds ratios for categorical variables are presented in relation to a reference category. Age was fitted as a continuous variable. Comparisons with controls were made for all cases of AMD, all cases with CNV (including cases also having GA), and all cases with GA (including cases also having CNV). Data were analysed using SPSS version 11.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

The study comprised 435 cases with end stage AMD and 280 spouse controls. Summary data are presented in table 1. Two hundred and sixty one cases had CNV as the only manifestation of AMD, 106 cases had GA only, and 68 had a mixed phenotype with both CNV and GA present in the

Table 1 Age, sex, disease status, and smoking data for cases and controls

	Cases (n = 435): GA only (n = 106), CNV only (n = 261), mixed GA/CNV (n = 68)	Controls (n = 280)
Mean age, years (SD)		
All subjects	80.2 (7.0)	75.6 (7.6)
GA only	81.2 (6.9)	
CNV only	79.8 (7.1)	
Sex		
Male	200 (46.0%)	116 (41.4%)
Female	235 (54.0%)	164 (58.6%)
Smoking status		
Non-smoker	159 (36.6%)	111 (39.6%)
Former	243 (55.9%)	152 (54.3%)
Current	33 (7.6%)	17 (6.1%)
Mean length of time of smoking (years) (SD)		
Former	32.5 (16.1)	26.9 (14.4)
Current	57.9 (9.8)	54.8 (10.3)
Mean pack years of cigarette smoking (SD)		
Former	23.0 (18.2)	16.0 (12.8)
Current	37.3 (14.6)	36.4 (16.7)
Categorical pack years of cigarette smoking		
0	159 (36.6%)	111 (39.6%)
0.1–20	123 (28.3%)	106 (37.9%)
20.1–40	100 (23.0%)	49 (17.5%)
>40	53 (12.2%)	14 (5.0%)
Categorical pack years of smoking other tobacco products		
0	324 (74.7%)	220 (78.9%)
0.1–20	99 (22.8%)	51 (18.3%)
20.1–40	8 (1.8%)	4 (1.4%)
>40	3 (0.7%) (1 missing data)	4 (1.4%) (1 missing data)
Inhaled (former and current smokers)		
Not at all	60 (21.8%)	37 (21.9%)
A little	134 (48.7%)	87 (51.5%)
Deeply	81 (29.5%) (1 missing data)	45 (26.6%)
Years since quitting smoking		
None (current smoker)	33 (7.6%)	17 (6.1%)
Less than 20 years	72 (16.6%)	36 (12.9%)
20 years or more	171 (39.3%)	116 (41.4%)
Non-smoker	159 (36.6%)	111 (39.6%)
Passive smoking exposure (non-smokers)		
No	44 (27.8%)	38 (34.5%)
Yes	114 (72.2%) (1 missing data)	72 (65.5%) (1 missing data)

Table 2 Comparison of cases with controls for smoking status*

Smoking status	Odds ratios (95% confidence interval)		
	All cases (n = 435) *v* controls (n = 280)	All cases with CNV (n = 329) *v* controls (n = 280)	All cases with GA (n = 174) *v* controls (n = 280)
Non-smoker†	1.00	1.00	1.00
Former smoker	1.12 (0.79 to 1.60)	1.04 (0.72 to 1.52)	1.12 (0.71 to 1.77)
Current smoker	1.89 (0.96 to 3.70)	1.97 (0.98 to 3.98)	2.15 (0.93 to 4.98)
p Value (two tailed)	0.18	0.15	0.20

*The logistic regression model described included age, sex, smoking status.
†Denotes reference category.

same subject, either in different eyes or in the same eye. The number of females in the case and control groups was 235 (54.0%) and 164 (58.6%), respectively. The mean age of cases was 80.2 (SD 7.0) years and of controls was 75.6 (SD 7.6) years. Increasing age was associated with increasing odds of AMD, OR 1.09 for each additional year (95% CI 1.07 to 1.12, $p<0.0001$) so all analyses were adjusted for age. Sex was included as a parameter in all analyses and was not found to be a risk factor for AMD.

Comparison of current and former smokers with non-smokers was consistent with smoking being a risk factor for AMD (table 2). For current smokers the data suggested an approximate doubling of risk for both CNV and GA. However, these analyses were not statistically significant.

In the logistic regression model in table 3, there was a strong association between pack years of cigarette smoking and the risk of AMD, GA, and CNV and the odds ratios increased with the amount smoked. For subjects who had smoked more than 40 pack years the odds ratio for AMD was 2.75 (95% CI 1.22 to 6.20, p = 0.01), for CNV 2.49 (95% CI 1.06 to 5.82, p = 0.04), and for GA 3.43 (95% CI 1.28 to 9.20, p = 0.01) compared to non-smokers. There was no significant association between pack years of smoking other tobacco products and risk of AMD. Whether subjects inhaled did not affect the risk of AMD. An alternative model including duration of smoking instead of pack years was investigated but did not fit the data so well.

For non-smokers, passive smoking exposure was found to increase risk for AMD, with odds ratio of 1.87 (95% CI 1.03 to 3.40), p = 0.04 (table 4). The odds were similar for CNV and GA subgroups but did not reach statistical significance.

Stopping smoking was associated with reduced odds of both GA and CNV (table 5). In comparison to non-smokers, the odds ratios for AMD, GA, and CNV were all highest in current smokers, somewhat lower in subjects who stopped smoking less than 20 years ago, and lower again in subjects who stopped smoking more than 20 years ago in whom the risk was not significantly different from non-smokers.

DISCUSSION

Of the many environmental factors investigated in relation to AMD, smoking is the one most consistently found to be associated with increased risk.[9 10 27] Several case-control and population based studies have reported odds ratios typically in the range 2–5. Other studies have failed to find any association and the parameter used to assess smoking exposure may be an important contributing factor. In common with our own findings, some studies have been unable to demonstrate a clear association between AMD and whether or not subjects have ever smoked.[11 13 17 21] This emphasises the importance of looking at a variety of smoking parameters. McCarty *et al*[11] argued that total length of time of smoking was the most significant factor for development of AMD rather than pack years or current or former smoking

Table 3 Comparison of cases with controls by other smoking variables*

	Odds ratios (95% confidence interval)		
	All cases (n = 431) *v* controls (n = 279)	All cases with CNV (n = 326) *v* controls (n = 279)	All cases with GA (n = 172) *v* controls (n = 279)
Pack years of cigarette smoking			
0†	1.00	1.00	1.00
0.1–20	0.84 (0.50 to 1.42)	0.81 (0.47 to 1.40)	0.79 (0.41 to 1.54)
20.1–40	1.62 (0.86 to 3.05)	1.51 (0.77 to 2.93)	1.65 (0.74 to 3.67)
>40	2.75 (1.22 to 6.20)	2.49 (1.06 to 5.82)	3.43 (1.28 to 9.20)
p Value (two tailed) for pack years	0.002	0.007	0.003
Pack years of smoking other tobacco products			
0†	1.00	1.00	1.00
0.1–20	1.34 (0.83 to 2.16)	(0.83 to 2.28)	1.15 (0.62 to 2.10)
20.1–40	0.82 (0.22 to 3.00)	1.05 (0.28 to 3.96)	1.21 (0.27 to 5.36)
>40	0.28 (0.06 to 1.37)	0.13 (0.01 to 1.26)	0.67 (0.14 to 3.35)
p Value (two tailed) for pack years of other tobacco smoked	0.21	0.18	0.91
Inhaled			
Not at all†	1.00	1.00	1.00
A little	1.01 (0.59 to 1.71)	0.96 (0.55 to 1.70)	1.09 (0.55 to 2.13)
Deeply	1.00 (0.55 to 1.82)	1.05 (0.56 to 1.98)	0.86 (0.39 to 1.88)
p Value (two tailed) for inhaled	1.00	0.95	0.76

*The logistic regression model included age, sex, pack years of cigarette smoking, pack years of smoking other tobacco products, and inhalation status.
†Denotes reference category.

Table 4 Comparison of non-smoking cases with non-smoking controls for passive smoking*

	Odds ratios (95% confidence interval)		
Passive smoking exposure	All non-smoking cases (n = 158) v non-smoking controls (n = 110)	Cases with CNV (n = 124) v controls (n = 110)	Cases with GA (n = 61) v controls (n = 110)
No†	1.00	1.00	1.00
Yes	1.87 (1.03 to 3.40)	1.81 (0.97 to 3.39)	1.50 (0.69 to 3.27)
p Value (two tailed)	0.04	0.06	0.30

*The logistic regression model included age and sex.
†Denotes reference category.

status. In our statistical modelling pack years of cigarettes proved to be a better fit to the data than number of years of smoking, and was the most significant risk factor for AMD. There was a dose-response relation with the odds ratio increasing with the amount smoked and the highest risk being in those smoking more than 40 pack years. We did observe a trend, although not statistically significant, with smoking status (table 2). However, it is apparent from table 1 that there are additional differences in smoking behaviour that are not captured by smoking status alone. For former smokers the mean length of time of smoking and the total amount smoked are both higher in cases than controls. The same applies to current smokers. This is why pack years of smoking is a better measure of risk for AMD. It is clear from these data that the amount smoked is more important than whether or not someone has ever smoked. Previously, the majority of positive associations have been demonstrated for CNV, which largely reflects the limited number of studies investigating the specific effect on the two types of end stage disease. Even in the large population based studies[28–30] the small numbers of cases of GA meant that in general it was not possible to show an increased risk specifically for this form of AMD. The results of this study clearly show an increased risk for GA as well as CNV.

The mean age of the control group was slightly younger than for the cases and, since age is a well established risk factor, we adjusted for this in the analyses. We found no difference in the risk profile between men and women. We found evidence that passive smoking (living with a smoker for 5 years or more) increases risk for AMD in non-smokers. Passive smoking has been suggested to increase risk for AMD in one other study,[15] which gave an odds ratio of 1.42 but did not reach statistical significance. No increased risk was demonstrated for exposure to other tobacco products. There is evidence that switching to non-cigarette tobacco products such as pipes and cigars may attenuate some of the harmful effects of cigarette smoking and this was attributed to reduced total tobacco consumption.[31] In the current study, since the majority (93%) of those using other tobacco products also smoked cigarettes, it is not possible to show a differential effect of other tobacco products. Whether or not smokers inhaled did not affect the risk of AMD but since the majority (80%) of smokers inhaled it would also be difficult to show this effect. Because of the multivariable nature of the model fitted, and the complex associations between different smoking variables, the null associations of smoking other tobacco products and inhalation with AMD cannot be reliably interpreted.

Stopping smoking was associated with reduced odds of AMD and the risk in those who had not smoked for over 20 years was comparable to non-smokers. This is another reason why smoking should be discouraged and those who do smoke should be encouraged to stop. The benefits of giving up smoking applied to both CNV and GA.

The mechanisms of smoking as a risk factor for AMD are thought to be largely related to oxidative damage. Experimental evidence suggests that smoking impairs retinal pigment epithelium (RPE) function, resulting in a build up of waste products at the RPE/retinal interface.[32] This leads to the formation of drusen and consequent damage to Bruch's membrane, allowing the in-growth of new vessels. Some of the damage may also be mediated by the direct effect of nicotine, which both potentiates PDGF mediated upregulation of endothelial smooth muscle cell proliferation[33] and activates pro-inflammatory mediators.[34] The development of GA following such oxidative damage is, similarly, thought to be related to the formation of drusen with subsequent atrophy of the adjacent RPE and photoreceptors. Complement mediated inflammation has also been proposed as an important mechanism in AMD and exciting new research has shown that a variant in the complement factor H (CFH) gene is associated with a higher risk for AMD.[35–39] Plasma levels of CFH are known to be reduced in smokers.[40]

The strength of this study lies in the fact that we have been careful to choose a highly select case group with only the late forms of AMD confirmed by clinical assessment and photographic grading. Controls were examined, questioned, and photographed in exactly the same manner as the cases

Table 5 Comparison of cases with controls by years since quitting smoking*

	Odds ratios (95% confidence interval) for AMD		
Years since quitting smoking	All cases (n = 435) v controls (n = 280)	All cases with CNV (n = 329) v controls (n = 280)	All cases with GA (n = 174) v controls (n = 280)
Non-smoker†	1.00	1.00	1.00
More than 20 years	0.91 (0.62 to 1.34)	0.85 (0.57 to 1.28)	0.92 (0.56 to 1.50)
Less than 20 years	1.74 (1.05 to 2.99)	1.70 (1.00 to 2.89)	1.83 (0.97 to 3.47)
0 years (current smoker)	2.13 (1.08 to 4.22)	2.00 (0.99 to 4.05)	2.14 (0.92 to 4.97)
p Value (two tailed) for years since quitting smoking	0.01	0.02	0.05

*The logistic regression model included age and sex.
†Denotes reference category.

and similar exclusion criteria applied. Limitations of any study of environmental risk factors include the possibility that recall bias may confound the results. Subjects were fully informed of their involvement in a study of the causes of AMD and some may have been aware of suggestions of a possible link with smoking. It is our impression, however, that participants in this study were largely unaware of smoking as a risk factor for AMD. In addition, all the questions formed part of a larger health and lifestyle questionnaire and as such it would be difficult for a subject to discern specifically which questions may be leading to a possible link with AMD. We attempted to improve the accuracy of pack year estimation by collecting data on the number of cigarettes smoked in each decade of life.[26] When analysing the results it was apparent that subjects smoked only modest amounts in their teens and during the post-war years owing to cost limitations but tended to smoke much more heavily from their 30s onwards, emphasising the importance of ascertaining information about the amount smoked throughout life.

CONCLUSIONS

We have demonstrated a clear association between the risk of AMD and pack years of cigarette smoking. This provides strong support for a causal relation between smoking and AMD. We have shown that the risk applies to both CNV and GA. We also show an increased risk for AMD in non-smokers exposed to passive smoking. Absence of an association with exposure to other types of tobacco products suggests that it is cigarettes in particular that confer increased risk. Stopping smoking appears to reduce the risk of both GA and CNV; this needs to be emphasised as a public health issue.

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