EXTENDED REPORT

Does smoking influence the type of age related macular degeneration causing visual impairment?

S S Dandekar, S A Jenkins, T Peto, A C Bird, A R Webster

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See end of article for authors' affiliations

Correspondence to: Dr Samantha S Dandekar, Professorial Unit, Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK; sam@hitbits.co.uk

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Aims: To assess the influence of smoking on the type of age related macular degeneration (AMD) lesion causing visual impairment in a large cohort of patients with AMD at a tertiary referral UK centre.
Methods: Prospective, observational, cross sectional study to analyse smoking data on 711 subjects, of western European origin, in relation to the type of AMD lesion present. Colour fundus photographs were graded according to a modified version of the international classification. Multiple logistic regression analysis was performed, adjusting for age and sex using the statistical package SPSS ver 9.0 for Windows. χ^2 tests were also used to assess pack year and ex-smoker data.
Results: 578 subjects were graded with neovascular AMD and 133 with non-neovascular AMD. There was no statistically significant association found between smoking status or increasing number of pack years and type of AMD lesion. The odds of ''current smokers'' compared to ''non-smokers'' developing neovascular rather than non-neovascular AMD when adjusted for age and sex was 1.88 (95% CI: 0.91 to 3.89; p = 0.09).
Conclusions: Smoking is known to be a risk factor for AMD and this study suggests that smokers are at no more risk of developing neovascular than atrophic lesions.

There has been increasing interest in the link between smoking and age related macular degeneration (AMD). Oxidative stress[1] and atherosclerosis[2] have been proposed as potential mechanisms to explain the causal association. It is known that tobacco smoke lowers plasma antioxidant levels[3 4] and reduces macular pigment density[1] thus allowing more oxidative damage to occur at the retina.

A recent systematic review demonstrated that 13 of 17 studies found a statistically significant association between smoking and AMD with increased risk of twofold to threefold in current smokers compared with never smokers.[5] Another paper has highlighted that approximately 28 000 cases of AMD causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking.[6]

Furthermore, it has been demonstrated that the association is stronger between smoking and late AMD (choroidal neovascularisation (CNV) or geographic atrophy (GA)) compared to early ARM (Drusen and pigment abnormalities).[7 8] Other studies have only reported an association with neovascular AMD,[2 9] others with only atrophic AMD[10] and in a study of women by Seddon and colleagues, there was an association of smoking with both types of AMD.[11] Other studies including the Blue Mountain Study, have not shown an association between smoking and particular type of late AMD.[7 11] This could be attributed to small numbers of patients in the study with late AMD. This study aimed to analyse the influence of smoking on the type of AMD lesion in a much larger cohort of patients.

METHODS

This was a prospective, observational, cross sectional study to analyse smoking data (ascertained at the time of enrolment into a large ongoing collection of clinical data of those with age related maculopathy (ARM) and AMD) on 711 subjects, in relation to the type of AMD lesion present at a tertiary referral UK centre. All patients included in the study were seen in the medical retina clinic between March 2001 and March 2003. These consisted of patients attending routine follow up appointments and all new referrals from primary care clinics, casualty, and other centres with any type of AMD to try to limit any selection bias. The ongoing collection of clinical data on ARM and AMD was well publicised within the centre to encourage more referrals to the department over the period of the study. Informed consent was obtained for all patients and the study received approval from the local ethics committee. During the collection such small numbers of ethnic minority groups were recruited with AMD (<20) and since it is known to be more prevalent in white populations, only those patients of a western European origin (n = 711) were analysed as part of the study. This allowed the group to be more homogeneous. Those patients with drusen in both eyes (ARM), those not of a western European origin and those not wishing to participate in the study were excluded from this analysis. Retinal stereo-colour fundus photographs, taken digitally using the Topcon Imagenet 2000 (UK) camera or using the Zeiss FF-series 30 degree fundus camera with 35 mm Ektachrome film which were subsequently digitised using a Nikon Coolpix 990 digital camera (Nikon, Tokyo, Japan) at a resolution of 1024×768 pixels were graded to establish the type of AMD in each eye. This latter method was validated in a previous study.[12] The images were graded according to a modified version of the international classification.[13] This version was validated before the study[14] and was essentially adapted to grade single digital images rather than stereoscopic film images and was simplified so as not to include the exact location of the AMD lesion (this information was regarded as unnecessary for the study) but graded overall presence or absence of lesions within the macula region. For the purposes of the analysis, AMD was defined as either ''neovascular'' where CNV, disciform scar, or serous detachment of the retinal pigment epithelium were present in one or both eyes or ''non-neovascular'' where there was no evidence of

Abbreviations: AMD, age related macular degeneration; ARM, age related maculopathy; CNV, choroidal neovascularisation; GA, geographic atrophy; PEDs, pigment epithelial detachments; ROIs, reactive oxygen intermediates; RPE, retinal pigment epithelium

Table 1 Age, sex, and smoking status of patients with late AMD

Age group	Current smoker	Ex-smoker	Non-smoker	Grand total
Female				
50–59	4	3	1	8
60–69	6	22	30	58
70–79	35	93	93	221
80–89	13	71	79	163
90–99	0	3	9	12
Grand total	(12.5%) 58	(41.5%) 192	(46%) 212	(65%) 462
Male				
50–59	1	5	2	8
60–69	4	17	8	29
70–79	16	62	36	114
80–89	11	60	21	92
90–99	1	3	2	6
Grand total	(13%) 33	(59%) 147	(28%) 69	(35%) 249

neovascular AMD in either eye but only GA in one or both eyes.

A full smoking history was taken, including data on number of cigarettes smoked per day, age when smoking began, and age of stopping smoking in ex-smokers. No data were collected on passive smoking exposure from spouses or occupational smoking exposure. Pack years were calculated from the total time subjects had smoked, multiplied by the usual daily cigarette intake, and divided by 20.

Data were analysed using multiple logistic regression analysis, adjusting for age and sex, which were considered to be the main confounding factors, using the statistical package SPSS ver 9.0 for windows. Pack year data were assessed using the χ^2 test for trend (Medcalc statistical software, Belgium). Odds ratios and their 95% confidence intervals were calculated for the likelihood of neovascular AMD as the dependent variable using smoking status (categorical variable: 0 = non-smoker, 1 = ex smoker, 2 = current smoker), age (continuous variable), and sex (categorical variable: F = 0, M = 1) as independent variables, as demonstrated by the model below.

$\text{Log}_e(p/1 - p) = \alpha + \beta 1$ smoking status + $\beta 2$ age + $\beta 3$ sex (p = proportion of patients with neovascular AMD; α = y intercept; $\beta 1$, $\beta 2$ etc, are the regression coefficients of the variables used in the model).

RESULTS

Of the 711 patients in the study, 578 were graded with neovascular AMD and 133 as non-neovascular. The smoking status and demographics of the participants are given in table 1. In total, 13% were current smokers (n = 91), 48% ex-smokers (n = 339), and 39% non-smokers (n = 281). Table 2 displays the smoking status according to AMD group.

It shows that 14% of the neovascular group compared to 8% of the non-neovascular group were current smokers but this difference was not significant (95% CI 0.6 to 11.4; p = 0.09). Furthermore, multiple logistic regression, adjusting for age and sex, did not show an association between smoking status or increasing number of pack years and type of AMD lesion graded (see table 3). The odds of ex-smokers compared to ''non-smokers'' developing neovascular rather than non-neovascular AMD when adjusted for age and sex was 0.86 (95% CI: 0.58 to 1.30). When data from ''current smokers'' were compared to ''non-smokers'' there was a slight bias towards more neovascular disease (OR = 1.88; 95% CI: 0.91 to 3.89) but this difference was not statistically significant. When pack year data were analysed (data available on 686 patients) using the χ^2 test for trend, again no difference was seen between the neovascular and non-neovascular groups in the number of pack years smoked (see table 4). Data were also analysed on those ex-smokers

Table 2 Smoking status according to AMD type

AMD type	Current smoker	Ex-smoker	Non-smoker	Grand total
Neovascular	81 (14%)	268 (46%)	229 (40%)	578
Non-neovascular	10 (8%)	71 (53%)	52 (39%)	133
Total with late AMD	91	339	281	711

Table 3 Multiple logistic regression table to assess the influence of smoking on the likelihood of neovascular AMD (adjusted for age and sex)

Variable	b Regression coefficient	p Value	OR for neovascular AMD	95% CI (lower)	95% CI (upper)
Age	0.0096	0.4690	1.0097	0.9837	1.0363
Sex (female, ref) Male	−0.0321	0.8753	0.9684	0.6481	1.4469
Smoking status ex-smoker cf non-smoker	−0.1467	0.4790	0.8636	0.5754	1.2961
Current smoker cf non-smoker	0.6315	0.0882	1.8805	0.9098	3.8870
Pack years of smoking (n = 686)	1.2954	0.2220	0.9996	0.9918	1.0074

Table 4 Influence of pack years of smoking on AMD lesion type

	Pack years					Pack years not known	Grand total
	0	<20	20–40	40–60	>60		
AMD type							
Neovascular	229 (81%)	154 (83%)	91 (83%)	45 (79%)	40 (77%)	19 (76%)	578
Non-neovascular	52 (19%)	32 (17%)	19 (17%)	12 (21%)	12 (23%)	6 (24%)	133
Total with late AMD	281	186	110	57	52	25	711

χ^2 test for trend = 0.465, df = 1, p = 0.5 NS.

(n = 339) who had stopped smoking more than 5 years before enrolment to assess if there was a trend towards neovascular AMD in these patients compared to those who stopped smoking within the past 5 years. This was deemed important as in the 5 year follow up of the Blue Mountain Study, ex-smokers had a similar risk of developing AMD as never smokers (see table 5). Again the results showed no difference between the groups.

DISCUSSION

This study demonstrates no statistically significant bias in the distribution of CNV and GA among smokers and non-smokers, in those of western European origin, even when pack years (which represents a measure of lifetime exposure to smoking) are considered. This was also demonstrated when analysing the ex-smoker data whereby those that had stopped smoking within the previous 5 years did not show an increase in neovascular AMD compared to those who stopped smoking more than 5 years before enrolment.

Our data showed that 13% patients were current smokers and 48% were ex-smokers. This compares well to UK statistics taken from Action on Smoking and Health (2005) (http://www.ash.org.uk/html/factsheets/html/basic01.html), whereby 15% of people aged 60 or over are reported to be smokers. Data from 2001 show that ex-smoking rates in the United Kingdom aged over 60 are 47% in men and 29% in women, which are slightly lower than in our study (Office for National Statistics (2002) General Household Survey 2001) and may reflect a bias in our sample group including the ethnicity of the group.

Further analysis of our cohort of AMD patients showed that 72% males and 54% of females had smoked at some stage in their lives. Our figure is much higher for females compared to other studies (that is, the Blue Mountain Study where 68% of the males and 39% of the females had smoked[7] and the POLA study where 74% males and 15% of females had smoked at some point.[8] This difference may represent smoking trends in the United Kingdom compared to Europe and Australia.

The lack of association between smoking status and type of AMD lesion confirms the absence of a consensus of opinion in the literature.[2 9–11]

Smoking has been proposed by some groups to promote the development and progression of subretinal new vessels and therefore CNV.[9] The exact mechanism of action is not fully understood, but nicotine administration has been shown to increase the severity of experimental CNV in a mouse model.[15] The effects of smoking are likely to be multifactorial. It is also known to promote atherosclerotic and hypoxic damage to the choroidal vasculature thus causing micro-infarctions which could increase the susceptibility to atrophic changes.[2 5 16]

Owing to its high consumption of oxygen, high proportion of polyunsaturated fatty acids, and its exposure to visible light, the retina is at risk of oxidative stress. This refers to cellular damage caused by reactive oxygen intermediates (ROIs)[1] and smoking is known to lower plasma antioxidant levels which mop up excess ROIs.[3 4]

Furthermore, lipofuscin (effectively a waste product of metabolic activity in the retina) is derived from oxidatively damaged photoreceptor outer segments and it is this compound that is believed to be responsible for GA, by affecting the viability of the retinal pigment epithelial (RPE) cells.[17 18] Findings from autofluorescence imaging in AMD has also supported this theory.[19] Increased oxidative damage from smoking may therefore cause more lipofuscin accumulation.

Macular pigments in the retina (essentially the levels of the carotenoids lutein and zeaxanthin) are thought to limit retinal oxidative damage by absorbing incoming blue light and/or quenching ROIs. Smoking is known to reduce these macular pigment levels[1] thus increasing the risk of damage to the retina including degenerative changes.

The authors acknowledge the limitations of the study, which include an inevitable selection bias in patients seen at a tertiary referral centre as they are more likely to be referred with severe disease or possibly with neovascular disease which is considered to be more treatable than atrophic disease. Additionally, the study group may be biased against those in lower socioeconomic groups, who tend to be heavier smokers and are known to have high rates of non-attendance at hospital appointments. (The prevalence of smoking in manual compared to non-manual social classes was 31% and 23%, respectively, in England in 2000, Office for National Statistics, 2001.) Patients were however referred from a number of sources to try to reduce this selection bias and rates of smokers in our group compare well to national statistics. Additionally, the study used subject reported smoking data and it is possible that subjects underestimated or overestimated the extent of their smoking. Furthermore, if the study population (especially the numbers of non-smokers) had been larger, some of the borderline differences may have reached statistical significance.

Table 5 Comparison of data in ex-smokers

	Patients with neovascular AMD	Patients with non-neovascular AMD	Total	χ^2 test
Ex-smokers stopped >5 years ago	245 (91%)	66 (93%)	311	$\chi^2 = 0.031$, df = 1, p = 0.86
Total number of ex-smokers	268	71	339	

The inclusion of serous detachment of the RPE in the neovascular AMD group may seem imprecise as some pigment epithelial detachments (PEDs) such as drusenoid PEDs are not associated with neovascularisation. This was included in the group as this is in keeping with the International Classification of ARM and AMD.[13]

Other confounding factors such as history of coronary artery disease, hypertension, lipid, or cholesterol levels could have affected the chances of finding an effect, but these factors have not been found to be important in late AMD in other studies.[9]

In conclusion, smoking is known to be a significant risk factor for AMD and there is evidence for mechanisms of retinal damage but at present this study suggests that smokers are at equal risk of developing either neovascular or atrophic lesions. Additionally, the risk of neovascular AMD does not appear to be increased with age, sex, or number of pack years smoked. This serves to emphasise that although we know that smoking is associated with visual loss and AMD, we still do not understand the mechanisms by which it acts.

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Authors' affiliations

S S Dandekar, T Peto, A C Bird, A R Webster, Moorfield's Eye Hospital, London, UK
S S Dandekar, S A Jenkins, A C Bird, A R Webster, Institute of Ophthalmology, London, UK

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