Smoking and Age-related Macular Degeneration

The POLA Study

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Objective: To assess the associations between age-related macular degeneration (ARMD) and smoking.

Methods: The POLA study is a population-based study taking place in the town of Sète, located on the French Mediterranean Sea border. The presence of early and late ARMD was assessed in 2196 participants on the basis of 50° color fundus photographs using an international classification system.

Results: After adjustment for age and sex, current and former smokers showed an increased prevalence of late ARMD (odds ratio [OR] = 3.6, 95% confidence interval [CI] = 1.1-12.4; OR = 3.2, 95% CI = 1.3-7.7, respectively). An increased risk was present in participants who smoked more than 20 pack-years (OR = 3.0, 95% CI = 0.9-9.5 for 20-39 pack-years; OR = 5.2, 95% CI = 2.0-13.6 for 40 pack-years and more). In addition, the risk of late ARMD remained increased until 20 years after cessation of smoking (OR = 9.0, 95% CI = 3.0-27.0 for 1-9 years; OR = 4.0, 95% CI = 1.3-12.0 for 10-19 years; OR = 1.3, 95% CI = 0.4-4.3 for 20 years and more). Smoking was not significantly associated with early signs of ARMD.

Conclusions: This study further confirms the adverse effect of tobacco on late ARMD. Former smokers seem to remain at high risk for ARMD.


A ge-related macular degeneration (ARMD) is the leading cause of blindness among older people in the Western countries.1 With the aging of the population, the burden of ARMD is expected to increase dramatically. Currently, the only available treatment is laser photocoagulation, which has been proven useful in only a small percentage of patients, with limited benefit.2 It is, therefore, urgent to determine factors that may lead to prevention of this condition.

The pathogenesis of this disease is poorly understood. In addition to genetic factors,3,4 oxidative stress or low levels of antioxidants may play a role,5 although data are still scarce and inconsistent.5 Age-related macular degeneration also may be associated with atherosclerosis.6 Tobacco smoking is related both to oxidative stress and atherosclerosis because it lowers plasma antioxidant levels8,9 and increases the risk of atherosclerosis.10 Initial reports of ARMD and smoking had shown inconsistent results: smoking was associated with ARMD in some studies,11,12 but not in others13; smoking was even shown to be protective in one study.14 However, in the past 5 years, results of 5 cross-sectional or case-control studies15-19 and 2 prospective studies20,21 have consistently shown an adverse effect of smoking on ARMD. Smoking is one of the rare modifiable risk factors identified. However, results of these studies show that not only current smokers but also past smokers are at high risk for ARMD. Results of 2 studies have suggested that the adverse effect of smoking lasts as long as 20 years after cessation.18,20

We present the relationship of ARMD with smoking, number of pack-years, and time since cessation of smoking in the POLA (Pathologies Oculaires Liées à l’Age) study, an epidemiological study taking place in the south of France.

RESULTS

As shown in Table 1, by comparison with data from the 1990 census of Sète, our sample underrepresents persons 80 years and older (10.2% vs 19.8%). Sex distribution was similar in our sample and in the eligible population. Concerning the professional category, among men, our sample
PARTICIPANTS AND METHODS

STUDY POPULATION

The POLA study is a prospective study taking place in Sète, a town of 40,000 inhabitants located on the French Mediterranean Sea border. Its principal economic activities are harbor and fishing, oyster farming, tourism, and industry. This town, located near our research center, was chosen because of the diversity of the exposures in this population (fishermen and oyster farmers with high life-exposure to sunlight, people coming from other countries in Southern Europe, French people who were born in Northern Africa, people from the north of France coming to retire, etc.).

Our objective was to study age-related ocular diseases (cataracts and ARMD) and their risk factors. Inclusion criteria were (1) being a resident of the town of Sète and (2) being aged 60 years or older on the day of the baseline examination. According to the 1990 population census, there were almost 12,000 eligible residents. Our objective was to recruit 3000 participants among them. The population was informed of the study through the local media (television, radio, and newspapers). We also contacted 4543 residents individually by mail and telephone using the electoral roll. Between June 1995 and July 1997, we recruited 2584 participants of both sexes.

The baseline examinations took place in a mobile unit equipped with ophthalmologic devices (a projector of Snellen chart, a decimal scale [model I28 IR, Lunecu, Chartres, France], an autorefractometer [model RM-A7000, Topcon, Tokyo, Japan], a slitlamp [model SL7F, Topcon], and a retinal camera [model TRC 50 XF, Topcon]). The mobile unit moved from one area to another to be in the close neighborhood of the contacted participants.

Participants underwent an ophthalmologic examination, a limited physical examination, and a standardized questionnaire on medical antecedents, sunlight exposure, and lifestyle habits, including smoking.

Participants gave written consent for participation in the study. The design of this study was approved by the Ethical Committee of the University Hospital of Montpellier, Montpellier, France.

OPHTALMOLOGIC EXAMINATION

Four ophthalmologists performed the ophthalmologic examination. This examination included, in particular, a recording of the ophthalmologic history (in particular of retinal diseases) and a measure of best-corrected far visual acuity in the right and left eyes; after pupil dilation, one 50° color photograph (Kodacolor Gold 100 ASA, Eastman Kodak Company, Rochester, NY) centered on the macular area was taken in each eye.

PHOTOGRAPHIC GRADING

After film processing, photographs were scanned and digitized. They were then recorded on compact discs (Kodak procedure). Finally, for interpretation, photographs were examined on a 17-in (43-cm) computer screen. Total magnification was approximately ×31.5. Processed in this way, photographs do not change with time. Moreover, this procedure allows zooming in on lesions and the use of color filters.

For the grading of photographs, we used the definitions and grids of an international classification system.22 We also used the standard photographs of the Wisconsin Age-Related Maculopathy Grading System23 to train the ophthalmologist (J.-L.D.) and the technician who did the interpretation. Two levels of grading were carried out on the fundus photographs. After the main grid was superimposed on the photograph, a preliminary grading was performed by an ophthalmologist (J.-L.D.). The ophthalmologist recorded qualitative information for all lesions associated with ARMD (coded as absent/questionable/present, inside and outside the grid) and other abnormalities involving the retina and the optic nerve head.

Second, for all participants for which soft distinct or indistinct drusen or hypopigmentation or hyperpigmentation was coded as present anywhere on the photograph by the ophthalmologist, detailed grading was performed by a specially trained technician using the international classification system.22

All lesions that were classified as geographic atrophy or neovascular macular degeneration by the ophthalmologist interpreting photographs were discussed and adjudicated by 2 of us (J.-L.D. and C.D.). In some cases, we also asked the ophthalmologist in charge of the patient for some additive information about the history of the lesion.

Fundus photographs were not taken in 81 cases (3.1%): in 42 cases because of technical failure, in 9 cases because of refusal, in 5 cases because of contraindication of dilation, in 17 cases because of poor dilation or severe opacities of the lens or cornea, and in 8 cases because of poor cooperation. In addition, for 307 participants, photographs were ungradable in both eyes because of technical failure or the presence of opacities. Thus,gradable photographs were available in at least 1 eye of 2196 participants (85%).

DEFINITIONS OF ARMD

Late ARMD and early signs of ARMD were defined according to the international classification system.22 Late ARMD was defined by the presence of neovascular ARMD or geographic atrophy within the grid (3000 µm from the fovea). Neovascular ARMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, subretinal or sub–retinal pigment epithelium hemorrhages, and fibrous scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation, 175 µm or larger, characterized by a sharp border and the presence of visible choroidal vessels.

Soft distinct and indistinct drusen were defined as large drusen (>125 µm) with uniform density and sharp edges or decreasing density from center outward and fuzzy edges, respectively. Areas of hyperpigmentation and hypopigmentation (without visibility of choroidal vessels) were also noted.

MEASUREMENT OF SMOKING

Smoking history was ascertained using an interviewer-administered questionnaire. Former and current smokers were asked about their total number of years of smoking, the average number of cigarettes smoked per day, and, for former smokers, year of smoking cessation. Pack-years were calculated by multiplying the number of years smoked by the number of cigarettes smoked per day, divided by 20.

STATISTICAL ANALYSIS

The relationship between smoking characteristics and ARMD was analyzed using multiple logistic regression analysis. Odds ratios and their 95% confidence intervals were calculated using ARMD as the dependent variable and smoking characteristics, age, and sex as the independent variables. Potentially confounding variables were added to the model to obtain multivariate odds ratios.
overrepresents the middle and upper social classes (21.8% vs 10.4% for the intermediate professions; 20.5% vs 9.8% for managers and executives) and underrepresents the lower social classes (9.9% vs 26.4% for office workers; 34.1% vs 40.4% for laborers). Among women, unemployed housewives are underrepresented (26.5% vs 42.1%).

Among 2196 participants, we identified 41 persons with late ARMD, 280 with soft distinct drusen, 49 with indistinct drusen, 200 with hyperpigmentation, and 126 with hypopigmentation. As shown in Table 2, the prevalence of late ARMD was similar in men (2.0%) and women (1.8%) and increased sharply with age. The prevalence of early signs of ARMD was also similar in men and women and increased with age.

Smoking status by sex and age is presented in Table 2. In this population, nearly three fourths of the men smoked at some time during their life, regardless of their age. The frequency of current smokers decreased with age, from 17.7% in participants aged 60 to 69 years to 8.6% in participants aged 80 years and older. Frequency of ever smoking was much lower in women and decreased with age, from 16.2% in women aged 60 to 69 years to 8.4% in women aged 80 years and older. Current smokers were rare among women, representing only 4.9% of all women.

As shown in Table 3, after age and sex adjustment, current smokers had a 3.6-fold increased risk of late ARMD (95% confidence interval, 1.1-12.4; \( P = .04 \)). Similarly, former smokers had a 3.2-fold increased risk of late ARMD (95% confidence interval, 1.3-7.7; \( P < .01 \)). The risk of late ARMD regularly increased with increasing number of pack-years, with up to a 5.2-fold increase of risk among participants who smoked 40 pack-years or more, current and former smokers combined (Table 3).

### Table 1. Comparison of Demographic Variables Between POLA* Study Participants (N = 2196) and the 1990 Population Census of Sète, France (N = 11 620)

<table>
<thead>
<tr>
<th>Professional activity, %</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Shopkeeper, craftsman</td>
<td>8.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Manager, executive</td>
<td>9.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Intermediate professions†</td>
<td>10.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Office worker</td>
<td>26.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Laborer</td>
<td>40.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1.6</td>
<td>42.1</td>
</tr>
</tbody>
</table>

*POLA indicates Pathologies Oculaires Lîées à l’Age.
†Teacher, nurse, technician, foreman, policeman, etc.

### Table 2. Smoking Status and Prevalence of Age-related Macular Degeneration (ARMD) by Age and Sex in the POLA* Study (N = 2196)

<table>
<thead>
<tr>
<th></th>
<th>Men, %</th>
<th>Women, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60-69 y</td>
<td>70-79 y</td>
</tr>
<tr>
<td>Late ARMD</td>
<td>0.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Early signs ARMD†</td>
<td>9.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Soft distinct drusen</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>11.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>5.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>26.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Smoking status</td>
<td>26.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Never smoker</td>
<td>17.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Current smoker</td>
<td>55.7</td>
<td>63.9</td>
</tr>
</tbody>
</table>

*POLA indicates Pathologies Oculaires Lîées à l’Age.
†In participants free of late ARMD.

### The POLA Study Group

Coordination
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Protein cholesterol levels did not affect the results. 

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in Participants Free of Late ARMD (N = 2155)*

Table 5. Smoking Status and Early Signs of ARMD

<table>
<thead>
<tr>
<th></th>
<th>Never Smoker</th>
<th>Ever Smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft distinct drusen</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
<td>169</td>
<td>111</td>
</tr>
<tr>
<td>Absent</td>
<td>1117</td>
<td>758</td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.0</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Absent</td>
<td>1256</td>
<td>850</td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.0</td>
<td>1.3 (0.8-2.7)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
<td>111</td>
<td>89</td>
</tr>
<tr>
<td>Absent</td>
<td>1175</td>
<td>780</td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.0</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
<td>69</td>
<td>57</td>
</tr>
<tr>
<td>Absent</td>
<td>1217</td>
<td>812</td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.0</td>
<td>1.3 (0.8-2.2)</td>
</tr>
</tbody>
</table>

*Data are given as number of participants unless otherwise indicated. ARMD indicates age-related macular degeneration; OR, odds ratio; and CI, confidence interval.
†Adjusted for age and sex.

of time since cessation of smoking, the risk of ARMD in former smokers at various years since cessation was compared with that of current smokers and never smokers (Table 4). Participants who had stopped smoking less than 20 years before the study had similar risk of ARMD as current smokers. Among participants who had quit smoking more than 20 years before the study, the risk of ARMD was not significantly different than that of never smokers. As shown in Tables 3 and 4, further adjustment for diabetes, history of coronary heart disease and treated hypertension, and fasting plasma cholesterol and high-density lipoprotein cholesterol levels did not affect the results.

As shown in Table 5, we observed no significant associations of smoking habits with early signs of ARMD (soft distinct and indistinct drusen and pigmentary abnormalities). 

Results of this study confirm the strong association of smoking with late ARMD. Compared with participants who never smoked, current and former smokers had a 3.6- and 3.2-fold increased risk of late ARMD, respectively. Our data are consistent with results of recent epidemiological studies. As found in 2 other studies, there was a trend for increasing risk of late ARMD with increasing number of pack-years of smoking, a measure of lifetime exposure that reflects the duration and amount of both current and past smoking. Participants in the higher category (≥40 pack-years) had a 5.2-fold increased risk compared with never smokers. Again, consistent with these 2 studies, the increased risk of late ARMD remained increased for 20 years after cessation of smoking. Participants who stopped smoking for more than 20 years had a much shorter duration of smoking (data not shown). The absence of significant excess risk among these participants may therefore be due to a shorter duration of smoking (and to the small number of cases of late ARMD). Nevertheless, it is important for prevention purposes to note that the risk seems to remain high for at least 20 years after cessation of smoking.

By contrast, early signs of ARMD (soft distinct and indistinct drusen and pigmentary abnormalities) were not linked with smoking. Studies of the association between early ARMD and smoking are few and their results inconsistent, some finding a weak adverse effect, some a non-significant effect, and some a weak protective effect. The inconsistency between studies, and the weak effects evidenced, may be because early ARMD is ill-defined. Although large, confluent drusen, in particular soft indistinct drusen, and pigmentary abnormalities predict a higher risk of developing late ARMD, not all patients with these signs will develop late ARMD: in a prospective study, only 12% of patients with “early” ARM developed late ARMD in the next 5 years. Other prospective data are needed to better characterize early ARMD.

This study has several limitations. First, our sample underrepresents older persons and overrepresents the middle and upper social classes compared with the whole eligible population. The participants in this study thus...
may be healthier and have different lifestyle habits, in particular smoking, than the general population. This is likely to have affected the prevalence of ARMD or of smoking, but it is unlikely to have affected the association between ARMD and smoking.

In observational studies, the concern is always about confounding factors. Because atherosclerosis is linked to smoking and may also be associated with ARMD, we adjusted for several factors related to atherosclerosis: history of coronary heart disease and treated hypertension, diabetes, and fasting plasma cholesterol and high-density lipoprotein cholesterol levels. These adjustments did not change the results. We cannot completely dismiss the existence of a confounding factor responsible for the relationship we observed. However, the strength of the association, the clear dose-response relationship, and the consistency of the association across populations with different lifestyles and exposures all favor a causal relationship.

The limited number of cases of late ARMD (n = 41) in our study did not allow us to compare neovascular and atrophic ARMD. Some studies have indeed reported that smoking is associated with only neovascular ARMD or with both. The limited number of cases of late ARMD in most of these studies (<100) may explain these differences. In this regard, it is interesting to note that the only large, prospective study, including 215 newly diagnosed cases, found that smoking is related to both neovascular and atrophic ARMD.

Several mechanisms have been suggested to explain the association between smoking and ARMD. Because smoking reduces plasma antioxidant levels, it may reduce retinal antioxidant levels. The retina, and particularly the macular area, is highly susceptible to oxidative stress because of its high exposure to light and oxygen and its high content of polyunsaturated fatty acids, prone to lipid peroxidation. By reducing antioxidant levels, smoking may thus increase oxidative insults to the retina. Besides, smoking may promote atherosclerotic damage to the choroidal vessels; atherosclerosis has been shown to be linked to late ARMD.

In conclusion, the results of this study provide additional support for the adverse effect of smoking on ARMD. Because the results of this study and 2 other studies have shown that increased risk of ARMD does not decline until 20 years after cessation of smoking, this should urge younger adults to stop smoking. However, smokers, in particular former smokers, represent a significant portion of Western populations. It is therefore important to define whether other means of prevention may be efficient in smokers. Antioxidant therapy, if proven to be protective for ARMD, may be of particular importance in delaying the development of late ARMD in current and former smokers.

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REFERENCES