Light Exposure and the Risk of Age-Related Macular Degeneration

The Pathologies Oculaires Liées à l’Age (POLA) Study

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Background: The role of light exposure in the development of age-related macular degeneration (ARMD) has been questioned. We present the relationship between lifetime light exposure and ARMD as examined in the Pathologies Oculaires Liées à l’Age (POLA) study.

Methods: The POLA study is a population-based study on cataract and ARMD and their risk factors. It included 2584 residents of the town of Sète, located in the South of France. The presence of early and late ARMD was assessed on the basis of 50° color fundus photographs using an international classification system. A questionnaire about light exposure was administered.

Results: Late ARMD (n=38) was not significantly associated with any light exposure variable. Subjects exposed to high ambient solar radiation and those with frequent leisure exposure to sunlight had a decreased risk of pigmentary abnormalities (odds ratio [OR]=0.61; 95% confidence interval [CI], 0.39-0.93, and OR=0.70; 95% CI, 0.52-0.95, respectively) and of early signs of ARMD (OR=0.73; 95% CI, 0.54-0.98, and OR=0.80; 95% CI, 0.64-1.00, respectively). Subjects who had used sunglasses regularly had a decreased risk of soft drusen (OR=0.81; 95% CI, 0.66-1.00). These relationships were not modified by further adjustments for potential confounders.

Conclusion: Our study does not support a deleterious effect of sunlight exposure in ARMD.

Arch Ophthalmol. 2001;119:1463-1468

AGE-RELATED macular degeneration (ARMD) is the leading cause of blindness among older people in Western countries. With the aging of the population, the burden of ARMD is expected to increase dramatically. A tremendous effort has been made in the last decade to develop treatments for choroidal neovascularization, the type of late ARMD that is the most frequent cause of severe visual loss. In particular, photodynamic therapy has recently proved beneficial for patients with classic choroidal neovascularization. Unfortunately, many patients remain ineligible for these treatments. In addition, although they are effective, such treatments do not completely stop the course of the disease; severe visual loss still occurs in many of the patients. To have a major effect on the extent of severe vision loss in patients with ARMD, we must attack the disease much earlier in its course. Therefore, it is urgent to determine factors that may lead to the prevention of this disorder.

The pathogenesis of ARMD is poorly understood. It is probably multifactorial, involving genetic factors, adverse effects caused by tobacco smoking, and a possible association with atherosclerosis. In addition, exposure to sunlight has long been suggested to play a role in its etiology. However, previous epidemiological studies have yielded inconsistent results: whereas most studies found no association between sunlight exposure and ARMD, others found either a positive association with some exposure variables or a negative association.

The Pathologies Oculaires Liées à l’Age (POLA) study is an epidemiological study that took place in Sète, France, and was designed to identify risk factors for cataract and ARMD. Sète is a harbor town of 40,000 inhabitants located on the French Mediterranean Sea. Its principal economic activities are fishing, oyster farming, tourism, and industry. This town is located near our research center and was chosen because of the various types and amounts of sunlight exposure in its population (eg, fishers and oyster farmers with high lifetime-exposure to sunlight, people from other countries in southern Eu-
PARTICIPANTS, MATERIALS, AND METHODS

STUDY POPULATION

The objective of the POLA study was to examine age-related eye diseases (cataract and ARMD) and their risk factors. The methods of this study have already been published elsewhere. The following criteria were necessary for inclusion: (1) being a resident of the town of Sète; and (2) being 60 years or older on the day of the baseline examination. According to the 1990 population census, almost 12000 residents were eligible. Our objective was to recruit 3000 participants so that we would have sufficient statistical power to detect associations between the studied risk factors and age-related eye diseases. Between June 1995 and July 1997, we recruited 2584 participants, including 1133 men and 1451 women with an average age of 70.9 years. Participants gave written consent for their inclusion. The design of this study was approved by the ethical committee of the University Hospital of Montpellier, Montpellier, France.

OPHTHALMOLOGIC EXAMINATION

This examination included a record of ophthalmologic history and iris color (blue or gray, green or light brown, or dark brown) and a measure of best-corrected far visual acuity in the right and left eyes. After pupil dilation, a standardized assessment of lens opacities using a slitlamp and one 50° color photograph (Kodak Gold 100 ASA; Eastman Kodak Co, Rochester, NY) centered on the macular area was obtained for each eye.

CLASSIFICATION OF ARMD

Late ARMD and early signs of ARMD were defined according to an international classification system on the basis of 50° color photographs centered on the macular area in each eye. Late ARMD was defined by the presence of neovascular ARMD or geographic atrophy within the grid (3000 µm from the foveola). 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 drusen included soft intermediate drusen (>63 µm but ≤125 µm) and soft distinct and indistinct drusen (>125 µm with uniform density and sharp edges or with decreasing density from the center outward and fuzzy edges, respectively). Pigmentary abnormalities were defined as areas of hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels). Early signs of ARMD included the presence of soft drusen and/or pigmentary abnormalities.

The participants were classified according to their worse eye. 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 subjects, 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 for 2196 subjects (85%). Among those, 1992 participants (90.7%) hadgradable photographs in both eyes.

INTERVIEW DATA

Data were collected by trained study personnel who were unaware of ARMD status. A standardized interview was performed to assess sociodemographic variables (eg, marital status, educational level, and major lifetime occupation), medical history (eg, hypertension, cardiovascular disease, diabetes, or osteoarthritis), use of medications, and smoking history.

The subject was then asked about residential history, professional exposure to sunlight (work on the sea [eg, fishing or oyster farming], driving, agriculture, the construction industry, and others) or to artificial light (arc welding, photography, the entertainment industry, and others), duration of this professional exposure (years), leisure exposure to sunlight (beachgoing, sailing, fishing, skiing, and others), use of sunglasses, and sunbathing habits. Locations in France were divided into 101 geographical areas, corresponding to the 101 administrative departments. The

**RESULTS**

**Table 1** presents the prevalence of ARMD according to age and sex. The prevalence of late ARMD increased sharply with age, from 0.3% for subjects younger than 70 years to 10.1% for those 80 years and older. There were no differences between men and women. In men, the prevalence of soft drusen increased from 19.4% for participants younger than 70 years to 27.5% for those 80 years and older. The prevalence was slightly higher in women, varying from 20.5% for those younger than 70 years to 33.1% for subjects 80 years and older. The prevalence of pigmentary abnormalities was higher in men than in women: in men, it varied from 11.8% for subjects younger than 70 years to 17.6% for those 80 years and older, and in women, from 7.5% for participants younger than 70 years to 14.2% for those 80 years and older.

**Table 2** presents the distribution of the light exposure variables in the POLA study. The median of the annual ambient solar radiation was 562 kJ/cm² with a range of about 300 kJ/cm², showing an important interindividual variability. This variability was due to differences in geographic origin: almost 60% of the participants were born in the South of France, about 20% were born in other parts of France, more than 15% were born in northern Africa (the latter remained there for a median

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of 33 years, which corresponds to these countries gaining independence in the 1960s), and about 5% were born in southern Europe. Professional exposure to sunlight was frequent in men (32.5%) and rare in women (2.7%). Professional exposure to artificial light was rare in both sexes (4.5% in men and 0.4% in women). Leisure exposure to sunlight was extremely common: three fourths of the participants lived in Sete after age 60 years.

In France, statistics regarding hours of sunshine for the past 30 years are available in 72 departments. Depart-ments without this information were given the value of data from the nearest available location. For foreign countries, annual solar radiation was generally estimated for the capital; when the capital was situated far from the middle of the country, a more centralized location was chosen. Very large countries (for example, the United States or China) were excluded from this analysis because an estimation of solar radiation in a single geographic location is meaningless for these areas.

For several countries, statistics on hours of sunshine were unavailable, impeding the estimation of solar radiation. When the amount of time spent in such areas was 3 years or less for a particular subject, these countries were eliminated from the calculations. Thus, for 56 subjects the average ambient solar radiation was based on 57, 58, or 59 years instead of 60.

Of the 2196 subjects with available ARMD status, 79 subjects were excluded from the analysis because they had spent more than 3 years in countries where solar radiation could not be estimated, and 28 subjects were excluded because they had missing data for other variables related to sunlight exposure (leisure and/or professional exposure, use of sunglasses, etc). Therefore, data on sunlight exposure were available for 2089 (95.1%) of 2196 subjects.

### BIOLIGIC MEASUREMENTS

Biologic measurements were made from fasting blood samples obtained at subjects’ homes on the morning of the examination. They included measurements on plasma (cholesterol, triglycerides, and vitamins A, E, and C) and on red blood cells (reduced glutathione). In particular, retinol and α-tocopherol were measured by high-performance liquid chromatography according to the method previously described by Catignani and Bieri. One sample of the liotrol mixture was measured in each series as an internal standard to prevent any shift during the study.

### STATISTICAL ANALYSIS

For each light exposure variable, age- and sex-adjusted odds ratios (ORs) were obtained using logistic regression with either late ARMD, soft drusen, or pigmentary abnormalities as the dependent variable and age, sex, and light exposure as the independent variables. Annual ambient solar radiation was divided into 3 groups (lower quartile, intermediate quartiles, upper quartile).

For each retinal variable (late ARMD, soft drusen, and pigmentary abnormalities), a multivariate logistic model was performed using age, sex, all light exposure variables that were close to significance in the first model (P < .10), and potential confounding factors (smoking [current, former], history of cardiovascular disease [coronary heart disease and/or stroke and/or angioplasty], obesity [body mass index ≥ 30 kg/m²], lipid-standardized α-tocopherol [lower quartile, intermediate quartiles, upper quartile], and educational level [grade school, middle school, completion of high school or university]). Subjects with missing data for the confounding factors were excluded from multivariate analyses. Of the 2089 subjects with available ARMD status and sunlight exposure data, we excluded 53 subjects. Therefore, the multivariate analyses were performed on 2036 subjects. All statistical analyses were done using SAS statistical software (SAS Institute Inc, Cary, NC).

| Table 3 presents the association between light exposure variables and characteristics of ARMD. Late ARMD was not significantly associated with any of the light exposure variables. Pigmentary abnormalities were less frequent in participants exposed to higher ambient solar radiation (P = .02) and in those who spent regular leisure time by the sea (P = .02). This was also true globally for early signs of ARMD (P = .04 and P = .05, respectively); the same tendency was observed for soft drusen, although this association did not reach statistical significance (P = .07 for annual ambient solar radiation; P = .11 for leisure time by the sea). Participants who claimed to have used sunglasses regularly had a reduced risk of soft drusen (P = .05). The same tendency was observed for late ARMD, but it did not reach statistical significance (P = .13). No association was observed for pigmentary abnormalities or early signs of ARMD. Finally, we observed no strong |
The association between eye color and any characteristics of ARMD was not significantly associated with an increased risk of ARMD. The risk of early signs of ARMD even decreased in subjects exposed to high ambient solar radiation (OR=0.73; \( P = .04 \)). The associations were similar but did not reach statistical significance for late ARMD (OR=0.44; \( P = .14 \)). Previous studies generally found no association between ARMD and UV-B exposure\(^*\); some even found a significant negative association.\(^{12} \)

Using identical methods, the same studies consistently found a positive association between UV-B exposure and cortical cataract.\(^{15,18,19,21} \) Therefore, it is unlikely that the lack of association between UV-B exposure and ARMD is due to inappropriate estimation of exposure. Moreover, nearly all UV light is absorbed by the cornea and lens.\(^{22} \) Phakic subjects are naturally protected against the potentially harmful effect of UV light on the retina. On the basis of epidemiologic data and biologic plausibility, it seems unlikely that UV light increases the risk of ARMD in phakic subjects.

Blue light in the visible spectrum may be harmful to the retina: in the Watermen Study,\(^{10} \) although UV light was not related to ARMD, there was a significant association with blue light. In our study, we could only estimate ambient solar radiation, including all wavelengths (infrared, visible, and UV). It is difficult to analyze the effects of the different wavelengths because they are naturally highly correlated. The use of eyeglasses, which attenuate UV light but not visible light, may make a difference. In the Watermen Study, the association between ARMD and blue light was mainly due to a more frequent use of eyeglasses in subjects with ARMD. The association between ARMD and blue light needs to be examined further.

In addition to ambient solar radiation, we studied the association between professional and leisure exposure to light and the different characteristics of ARMD. Consistent with the findings for ambient solar radia-
tion, leisure exposure by the sea was negatively associated with pigmentary abnormalities (OR = 0.70; \( P = 0.02 \)).

A negative association between ARMD and ocular light exposure was also found in an Australian study.\(^{12} \) It has been suggested that the relationship between ARMD and sunlight exposure may be confounded by sun sensitivity. In 2 studies, ARMD patients showed higher sun sensitiv-

ity than controls.\(^{12,23} \) Sun sensitivity was related to lower sunlight exposure. Unfortunately, we have no esti-
mation of sun sensitivity in our study and could not take into account its potential confounding effect.

By contrast, frequent use of sunglasses was associated with a reduction in the soft drusen (OR = 0.81; \( P = 0.05 \)) but not of late ARMD or pigmentary abnormalities. Other light-related variables were not significantly associated with early or late ARMD. We found no signif-
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Our study has several limitations. First, our sample underrepresents the older population and overrepresents the middle and upper social classes in comparison with the total eligible population.\(^{13} \) Thus, the subjects in this study may be healthier and may have different lifestyle habits (in particular, concerning light exposure) than the general population. This is likely to have affected the prevalence of ARMD or the distribution of sunlight exposure variables. However, it is unlikely to have affected the association between ARMD and light exposure. Moreover, our sample is probably not highly biased because the prevalence rates of late ARMD and early signs of ARMD are similar to those of previous studies using the same grading protocol.\(^{24,26} \)

Another limitation is the small number of cases of late ARMD, leading to low statistical power to detect any association between light exposure variables and late ARMD. This was also the case in most of the previous studies.\(^{8,10,11} \) In the 2 studies with sufficient statistical power, either no association\(^{9} \) or a negative association was found.\(^{12} \) In our study, the association between late ARMD and ambient solar radiation is also in the negative direction. Although statistical power is limited, it is unlikely that the true association is positive.

Our finding of a protective, biologically implausible association between light exposure and ARMD lesions raises concerns about possible spurious associations due to uncontrolled confounding. These associations remained signif-
nicant after adjustment for the previously identified risk factors (smoking, cardiovascular disease, body mass index, plasma \( \alpha \)-tocopherol level) for ARMD and for socioeconomic status. Other potential confounders include differences in dietary habits; diets in the South of France are known to be different from those in the northern part of the country. There may also be genetic differences, particularly in the genotype of apolipoprotein E, which has recently been shown to be related to ARMD.\(^{27,28} \) Unfortunately, we have no data for these potential confounders.

Misclassification is also a concern in epidemiologi-

cal studies because we usually have limited information on the pathologic characteristics of the disease. Validation studies using the same international classification have demonstrated good reproducibility for the classification of early and late ARMD lesions.\(^{26,20,30} \) However, with only a single photograph of variable quality per eye, misclassification may occur and may bias the estimations toward the null hypothesis. Therefore, we may have underestimated the associations between light exposure and ARMD.

Because this study is cross-sectional, recall bias may have affected the results, particularly concerning professional and leisure exposure to sunlight. All previous studies were either cross-sectional or case-control and may have been equally subject to recall bias. However, because soft drusen and pigmentary abnormalities are asymptomatic, recall bias is unlikely to have affected the associations between light exposure variables and early signs of ARMD.

In conclusion, this study gives no support to a del-
eterious effect of sunlight exposure in ARMD. The nega-

Table 3. Sex- and Age-Adjusted Odds Ratios and 95% Confidence Intervals Between Light Exposure Variables and Age-Related Macular Degeneration in the POLA Study*
ative association between ambient solar radiation and early signs of ARMD needs to be examined further.

Accepted for publication March 30, 2001.

This study is supported by the Institut National de la Santé et de la Recherche Médicale, Paris, France; by grants from the Fondation de France, Department of Epidemiology of Ageing, Paris; the Région Languedoc-Roussillon, Montpellier, France; the Fondation pour la Recherche Médicale, Paris; and the Association Retina-France, Toulouse; and by Rhône Poulenc, Essilor, and the Centre de Recherche et d’Information Nutritionnelles, Paris.

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