Further Observations on the Association Between Smoking and the Long-term Incidence and Progression of Age-related Macular Degeneration

The Beaver Dam Eye Study

Ronald Klein, MD, MPH; Michael D. Knudtson, MS; Karen J. Cruickshanks, PhD; Barbara E. K. Klein, MD, MPH

Objective: To examine the association between smoking and the 15-year cumulative incidence of age-related macular degeneration (AMD).

Methods: Population-based longitudinal cohort study of people in Beaver Dam, Wisconsin, who were aged 43 to 84 years (N=4926) in 1987-1988. Participants were examined in 1988-1990 and were reexamined at 5-year intervals during a 15-year period. Age-related macular degeneration status was determined by grading stereoscopic color fundus photographs.

Results: Controlling for age, sex, and baseline AMD severity, people who were current smokers at baseline, compared with those who never smoked, were at increased risk of incident early AMD (odds ratio, 1.47; 95% confidence interval, 1.08-1.99; *P*=.01) and for progression of AMD (odds ratio, 1.43; 95% confidence interval, 1.05-1.94; *P*=.02) during a 15-year follow-up. There were few associations of specific characteristics of smoking (eg, intensity, pack-years smoked, duration, and age at initiation and quitting) with AMD outcomes.

Conclusions: Smoking appears to be related to the long-term incidence and progression of AMD. This has important health care implications because early AMD increases the risk of developing late AMD and smoking behavior is modifiable.

Arch Ophthalmol. 2008;126(1):115-121

Author Affiliations:
Departments of Ophthalmology and Visual Sciences (Drs R. Klein, Cruickshanks, and B. E. K. Klein, and Mr Knudtson) and Population Health Sciences (Dr Cruickshanks), University of Wisconsin School of Medicine and Public Health, Madison.

SMOKING IS ONE OF THE FEW modifiable risk factors associated with age-related macular degeneration (AMD).[1-16] Smoking affects risk factors hypothesized to be involved in the pathogenesis of AMD, eg, immune activation, depression of antioxidant levels, reduction of choroidal blood flow, decrease in luteal pigments in retina, reduction of drug detoxification by the retinal pigment epithelium (RPE), and nicotine potentiation of angiogenic activities.[17-23] The purpose of this article is to describe the association between baseline smoking status, age at initiation, duration, intensity, pack-years, age at quitting, and time from the baseline examination since quitting and the 15-year cumulative incidence and progression of AMD in the population-based Beaver Dam Eye Study. Our study builds on earlier observations on smoking and AMD from a shorter follow-up of the same cohort.[14,15] In addition, we describe the association between exposure to environmental tobacco smoke (ETS), first measured during the 10-year follow-up of the Beaver Dam Eye Study, and the 5-year incidence and progression of AMD.

METHODS

POPULATION

Methods used to identify and describe the population have appeared in previous reports.[24-28] In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were aged 43 to 84 years. Of the 5924 eligible individuals, 4926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Ninety-nine percent of the population was white. Of the 4542 surviving subjects, 3684 (81.1%) participated in the 5-year follow-up examination between March 1, 1993, and June 14, 1995. Then, 2764 of the 3334 (82.9%) surviving subjects in the baseline and second examination participated in the second follow-up examination between March 1, 1998, and June 9, 2000. Of the 2480 surviving subjects in the baseline and 5- and 10-year follow-ups, 2119 (85.4%) participated in the third follow-up examination between March 31, 2003, and April 30, 2005. Comparisons between participants and nonparticipants at the time of the baseline and the 5-, 10-, and 15-year follow-up examinations have appeared elsewhere.[24-28] Three thousand five hundred eight people who partici-

pated in at least 1 follow-up examination provided data for the current analysis.

While adjusting for age and sex, people who smoked were more likely to die and, if alive, were less likely to participate in a follow-up examination than former smokers or those who have never smoked (data not shown). However, AMD severity status at baseline did not affect the association between smoking status or pack-years smoked and participation or death.

DESIGN

Similar procedures, used at both baseline and follow-up examinations, have been described in detail elsewhere.[24-35] Informed consent was obtained from each participant at the beginning of the examination. Pertinent parts of the examinations included taking stereoscopic 30° color fundus photographs centered on the macula (Diabetic Retinopathy Study standard field 2). The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions associated with AMD. Grading procedures, lesion descriptions, and detailed definitions for the presence and severity of specific lesions have appeared elsewhere.[32-35]

The incidence of early AMD was defined by the presence of soft, indistinct drusen or any type of drusen associated with RPE depigmentation or increased retinal pigment at follow-up when none of these lesions were seen at baseline. The incidence of exudative macular degeneration and pure geographic atrophy was defined by their presence at follow-up when neither was present at baseline.

For each eye, a 6-level severity scale for AMD was defined as follows:

Level 10. No drusen or hard drusen; or small soft drusen (<125 μm in diameter) only, regardless of area of involvement, and no pigmentary abnormalities (increased retinal pigment or RPE depigmentation).

Level 20. Hard drusen; or small soft drusen (<125 μm in diameter), regardless of area of involvement, with increased retinal pigment but no RPE depigmentation; or soft drusen (≥ 125 μm in diameter) with a drusen area smaller than 196 350 μm^2 (equivalent to a circle with a diameter of 500 μm) and no pigmentary abnormalities.

Level 30. Soft drusen (≥ 125 μm in diameter) with a drusen area smaller than 196 350 μm^2 and RPE depigmentation; or soft drusen (≥ 125 μm in diameter) with an area 196 350 μm^2 or larger with or without increased retinal pigment but no RPE depigmentation.

Level 40. Soft drusen (≥ 125 μm in diameter) with a drusen area involvement 196 350 μm^2 or larger and RPE depigmentation with or without increased retinal pigment.

Level 50. Geographic atrophy in absence of exudative macular degeneration.

Level 60. Exudative macular degeneration with or without geographic atrophy.

Level 10 is equivalent to not having AMD; levels 20, 30, and 40 involve lesions that define early AMD of increasing severity (by type, size, area of drusen, and pigmentary abnormalities); while levels 50 and 60 involve lesions that define late AMD. Progression of AMD was defined as an increase in the AMD severity scale in either eye by 2 or more steps higher from levels 10, 20, or 30 and 1 or more steps higher from levels 40 or 50 at the 5-, 10-, or 15-year follow-up examination.

Age was defined as the age at baseline examination. At baseline examination, subjects were classified as nonsmokers if they had smoked fewer than 100 cigarettes in their lifetime; as past smokers if they had smoked more than 100 cigarettes in their lifetime but had stopped smoking before the examination; and as current smokers if they had not stopped smoking. Smoking duration at baseline was defined by total years smoked. Smoking intensity was defined by the mean number of cigarettes smoked per day; pack-years smoked was calculated as the number of years smoked × (the mean number of cigarettes smoked per day/20). Smoking initiation was defined as the age participants reported when first began. Time since quitting smoking was defined as years elapsed since last smoked to baseline examination.

As part of the study of hearing loss conducted in the same cohort, a scale for exposure to ETS at the 10-year follow-up was developed to allow a single, convenient categorization that used information from reported home, social, and workplace ETS exposure.[36] Nonsmoking participants (past smokers and those who never smoked) were categorized as having high ETS exposure if they (1) had more than 4 hours/d of workplace exposure, (2) were living with a smoker, or (3) were exposed to ETS socially on a daily basis. Participants who did not have high ETS exposure were categorized as having moderate exposure if they reported 1 to 4 hours/d of workplace exposure or exposure to social ETS several times a week. Participants who did not qualify for having high or moderate exposure were categorized as having little or no exposure. This scale has been validated against serum cotinine levels.[36]

The medical history questionnaire contained questions regarding alcohol consumption. A current heavy drinker was defined as a person who consumed 4 or more servings of alcoholic beverages daily; a former heavy drinker had consumed 4 or more servings of alcoholic beverages daily in the past but not in the previous year; and a nonheavy drinker had never consumed 4 or more servings of alcoholic beverages on a regular, daily basis. Vitamin use was defined in 3 levels of current use at baseline: no use, use of multivitamins, or use of a single vitamin or other combination of vitamins (eg, B complex).

STATISTICAL ANALYSIS

For these analyses, we examined the relationships between smoking status, smoking intensity, smoking duration, age at initiation, time since quitting, age at quitting, and ETS exposure and the cumulative incidence of early AMD, exudative AMD, and pure geographic atrophy and the cumulative progression of AMD. SAS, version 9 (SAS Institute Inc, Cary, North Carolina), was used for analyzing the data.[37] Multivariate odds ratios and 95% confidence intervals were calculated from discrete logistic hazard models.[38] These analytical approaches allowed those who were right-censored (not seen after the 5- or 10-year examination owing to death or nonparticipation) to contribute information to the estimates.

Smoking status was considered using indicator variables for smoking in the past vs never smoked and currently smoking vs never smoked. Models were run separately within the category of those who have ever smoked and current smokers for intensity, duration, pack-years, and age at initiation. As described by Leffondré et al,[39] excluding nonsmokers from these analyses eliminates the assumption that the difference between those who have ever smoked and those who have never smoked is quantitative rather than qualitative. Time since quitting and age when a participant quit were only analyzed among past smokers. All variables except for smoking status were analyzed continuously and linearly. No variables had nonlinear effects with any of the AMD outcomes (data not shown). Analyses were stratified by sex and controlled for baseline age in 4 categories (43-54, 55-64, 65-74, and 75-86 years) and baseline severity of AMD. In the models combining men and women, we controlled additionally for sex. We also investigated models stratified by age (<65 and ≥ 65 years) and further controlled for systolic blood pressure, vitamin use, and heavy drinking status. In analyses restricted to cases of incident AMD (eg,

Table 1. Baseline Smoking Characteristics in the Beaver Dam Eye Study

Characteristic	Men		Women			All	
	No. of Subjects at Risk for AMD Outcomes[a]	Value[b]	No. of Subjects at Risk for AMD Outcomes[a]	Value[b]	*P* Value	No. of Subjects at Risk for AMD Outcomes[a]	Value[b]
Smoking status, %							
Never	448	29.2	1129	57.3	<.001	1577	45.0
Past	763	49.6	492	25.0	<.001	1255	35.8
Current	326	21.2	350	17.8	<.001	676	19.3
Intensity, cigarettes/d							
Ever smoked	1087	25.4 (15.8)	838	17.4 (11.5)	<.001	1925	21.9 (14.7)
Current smoker	326	23.8 (11.7)	350	18.2 (9.8)	<.001	676	20.9 (11.1)
Duration, y							
Ever smoked	1086	26.5 (14.4)	839	25.7 (13.5)	.18	1925	26.1 (14.0)
Current smoker	325	35.5 (10.8)	349	33.2 (10.1)	.004	674	34.3 (10.5)
Pack-years[c]							
Ever smoked	1084	35.4 (30.4)	836	24.4 (22.3)	<.001	1920	30.6 (27.7)
Current smoker	325	42.6 (24.4)	349	31.2 (22.1)	<.001	674	36.7 (23.9)
Age at initiation, y							
Ever smoked	1086	20.8 (7.7)	837	24.8 (10.4)	<.001	1923	22.6 (9.2)
Current smoker	325	20.6 (7.2)	349	23.5 (9.8)	<.001	674	22.1 (8.8)
Time since past smokers quit, y	763	17.4 (11.9)	490	13.9 (11.1)	<.001	1253	16.0 (11.7)
Age when past smokers quit, y	763	43.5 (13.5)	490	46.2 (13.8)	<.001	1253	44.6 (13.6)

Abbreviation: AMD, age-related macular degeneration.
[a] Number at risk for incident early AMD, exudative AMD, or geographic atrophy or progression of AMD.
[b] Values are mean (SD) unless otherwise indicated.
[c] Number of years smoked × (mean number of cigarettes smoked per day/20).

incident cases of early AMD), we compared the mean age of onset (ie, age at the examination where the end point was first seen) among never, past, and current smokers.

RESULTS

SMOKING CHARACTERISTICS AT BASELINE AND CUMULATIVE INCIDENCE OF AMD END POINTS

At baseline, 21% of men and 18% of women were current smokers (**Table 1**). The frequencies of current smoking decreased with increasing age and at each subsequent 5-year follow-up examination (data not shown). Men were more likely than women to have greater mean intensity and pack-years of smoking and to have begun smoking and have quit earlier than women (Table 1). Exposure to ETS at the 10-year follow-up in nonsmokers was greater in men than women (58% vs 42%, $P<.001$). Exposure to ETS also decreased with age (test of trend, $P<.001$; data not shown).

The number of participants at risk for a specific AMD outcome and the numbers of incident early and late AMD and progressed AMD events are presented in **Table 2**. There were 391 people who developed early AMD, 63 who developed exudative AMD, 39 who developed pure geographic atrophy, and 400 whose AMD progressed during the 15-year period of the study.

SMOKING AND 15-YEAR CUMULATIVE INCIDENCE OF EARLY AMD

While controlling for age, sex, and baseline AMD severity, current smoking at baseline was associated with a 47% increased odds of developing early AMD during the 15-year period (**Table 3**). This association was statistically significant in men but not women. There was no age interaction of current smoking and incident early AMD (data not shown). There was no relationship between smoking intensity, duration, pack-years smoked, or time since quitting and the cumulative incidence of early AMD (Table 3). Older age at smoking initiation among currently smoking women was marginally related to the cumulative incidence of early AMD. This relationship was independent of the number of pack-years smoked (odds ratio, 1.62; 95% confidence interval, 1.05-2.51; $P=.03$). Individuals who were currently smoking were estimated to have a younger mean age at onset of early AMD (69.2 years; 95% confidence interval, 66.9-71.4) than former smokers (72.3 years; 95% confidence interval, 70.8-73.9) and those who have never smoked (74.4 years; 95% confidence interval, 73.0-75.8).

SMOKING AND THE 15-YEAR CUMULATIVE INCIDENCE OF EXUDATIVE AMD AND GEOGRAPHIC ATROPHY

While controlling for age, sex, and AMD severity level, smoking status at baseline was not associated with the 15-year cumulative incidence of exudative AMD (**Table 4**). Older age at time of quitting among past smokers or longer duration of smoking in men who had ever smoked was related to the cumulative incidence of exudative AMD. Smoking characteristics were not related to the 15-year cumulative incidence of geographic atrophy (**Table 5**).

Table 2. Number of Individuals at Risk and Number of Events[a] for Each Outcome by Sex and History of Smoking Status Among Persons in the Beaver Dam Eye Study

Outcome	Men		Women		All	
	No. of Subjects at Risk	No. of Events	No. of Subjects at Risk	No. of Events	No. of Subjects at Risk	No. Events
Incidence of early AMD						
Never smoked	368	41	896	139	1264	180
Past smoker	598	73	403	70	1001	143
Current smoker	260	32	301	36	561	68
Incidence of exudative AMD						
Never smoked	448	3	1128	31	1576	34
Past smoker	762	11	492	12	1254	23
Current smoker	326	3	350	3	676	6
Incidence of pure GA						
Never smoked	446	8	1123	15	1569	23
Past smoker	761	7	485	8	1246	15
Current smoker	327	1	350	0	677	1
Progression of AMD						
Never smoked	451	35	1132	162	1583	197
Past smoker	760	74	490	64	1250	138
Current smoker	326	32	349	33	675	65

Abbreviations: AMD, age-related macular degeneration; GA, geographic atrophy.
[a]Can occur at 5-, 10-, or 15-year follow-up.

Table 3. Relationship Between Smoking Characteristics at Baseline and the 15-Year Cumulative Incidence of Early AMD[a]

Smoking History Variable	Subset	Men		Women		Both	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Past vs never smokers	Not applicable	1.14 (0.76-1.71)	.54	1.28 (0.93-1.74)	.13	1.16 (0.91-1.48)	.23
Current vs never smokers	Not applicable	1.74 (1.06-2.88)	.03	1.27 (0.85-1.89)	.24	1.47 (1.08-1.99)	.01
Intensity, packs/d	Ever smoked	0.93 (0.72-1.21)	.60	0.97 (0.65-1.44)	.87	0.93 (0.75-1.15)	.50
	Current smokers	1.07 (0.56-2.05)	.83	1.13 (0.55-2.32)	.73	1.06 (0.65-1.73)	.80
Duration, per 10 y	Ever smoked	1.14 (0.98-1.32)	.08	0.91 (0.78-1.06)	.22	1.02 (0.92-1.13)	.71
	Current smokers	1.16 (0.68-1.97)	.59	0.83 (0.56-1.21)	.33	0.98 (0.74-1.30)	.88
Pack-years, per 20 y	Ever smoked	1.04 (0.92-1.19)	.52	0.96 (0.78-1.19)	.72	1.02 (0.91-1.14)	.76
	Current smokers	1.10 (0.81-1.49)	.54	1.09 (0.79-1.49)	.61	1.08 (0.87-1.34)	.50
Age at initiation, per 10 y	Ever smoked	1.06 (0.83-1.36)	.64	1.13 (0.93-1.37)	.22	1.13 (0.97-1.31)	.11
	Current smokers	0.93 (0.54-1.60)	.79	1.43 (0.99-2.06)	.05	1.16 (0.88-1.52)	.30
Time since quitting, per 10 y	Past smokers	0.90 (0.73-1.10)	.30	1.03 (0.82-1.31)	.78	0.97 (0.83-1.13)	.67
Age at quitting, per 10 y	Past smokers	1.17 (0.95-1.44)	.15	0.97 (0.77-1.22)	.77	1.06 (0.91-1.23)	.45

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
[a]Controlling for age (categorically), sex (when appropriate), and baseline AMD severity level.

SMOKING AND THE 15-YEAR PROGRESSION OF AMD

While controlling for age, sex, and AMD severity level, current smoking at baseline was associated with the cumulative 15-year progression of AMD (**Table 6**). The relationship was statistically significant in men but not women. Older age at initiation and older age at quitting was associated with progression of AMD in the whole cohort, the former being statistically significant in women but not in men and the latter being statistically significant in men but not women. There was no relationship between pack-years smoked or smoking intensity and progression of AMD. The association between smoking and incidence or progression of AMD remained largely unchanged in multivariate analyses that further controlled for history of vitamin use, systolic blood pressure, and history of heavy drinking (data not shown).

EXPOSURE TO ETS AND INCIDENCE OR PROGRESSION OF AMD

Exposure to ETS was not associated with the prevalence, 5-year incidence, or progression of AMD in men or women (data not shown). The 5-year incidence of exudative AMD or pure geographic atrophy between the 10- and 15-year follow-up examinations was too low to examine the association between exposure to ETS and these end points.

Table 4. Relationship Between Smoking Characteristics at Baseline and the 15-Year Cumulative Incidence of Exudative AMD[a]

Smoking History Variable	Subset	Men		Women		Both	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Past vs never smokers	Not applicable	2.90 (0.73-11.43)	.13	0.88 (0.43-1.81)	.72	1.12 (0.62-2.01)	.70
Current vs never smokers	Not applicable	3.46 (0.61-19.53)	.16	0.36 (0.10-1.31)	.12	0.69 (0.27-1.76)	.44
Intensity, packs/d	Ever smoked	0.82 (0.43-1.57)	.56	1.27 (0.54-3.01)	.58	0.94 (0.58-1.54)	.81
	Current smokers	0.45 (0.02-12.31)	.64	3.36 (0.42-26.67)	.25	1.12 (0.16-7.84)	.91
Duration, per 10 y	Ever smoked	1.55 (1.01-2.36)	.04	0.90 (0.63-1.28)	.55	1.16 (0.90-1.50)	.26
	Current smokers	0.23 (0.05-1.03)	.05	2.58 (0.21-32.22)	.46	0.76 (0.34-1.70)	.51
Pack-years, per 20 y	Ever smoked	1.10 (0.82-1.47)	.54	0.96 (0.65-1.42)	.85	1.04 (0.83-1.31)	.73
	Current smokers	0.28 (0.04-2.05)	.21	1.72 (0.77-3.85)	.19	0.89 (0.37-2.14)	.79
Age at initiation, per 10 y	Ever smoked	0.82 (0.42-1.60)	.56	1.18 (0.75-1.87)	.48	1.03 (0.72-1.48)	.86
	Current smokers	3.84 (0.97-15.09)	.05	0.58 (0.08-4.51)	.61	1.42 (0.66-3.07)	.37
Time since quitting, per 10 y	Past smokers	0.60 (0.33-1.08)	.09	0.97 (0.61-1.54)	.91	0.78 (0.55-1.11)	.17
Age at quitting, per 10 y	Past smokers	1.87 (1.03-3.40)	.04	1.08 (0.68-1.73)	.74	1.38 (0.96-1.99)	.08

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
[a]Controlling for age (categorically), sex (when appropriate), and baseline AMD severity level.

Table 5. Relationship Between Smoking Characteristics at Baseline and the 15-Year Cumulative Incidence of Geographic Atrophy[a,b]

Smoking History Variable	Subset	Men		Women		Both	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Past vs never smokers	Not applicable	0.38 (0.12-1.24)	.11	1.71 (0.69-4.24)	.25	0.88 (0.41-1.88)	.75
Current vs never smokers	Not applicable	0.16 (0.02-1.62)	.12	No events		0.18 (0.02-1.40)	.10
Intensity, packs/d	Ever smoked	0.99 (0.36-2.71)	.99	3.59 (0.92-14.00)	.07	1.19 (0.58-2.44)	.64
Duration, per 10 y	Ever smoked	1.32 (0.74-2.33)	.34	1.05 (0.62-1.78)	.87	1.13 (0.78-1.64)	.51
Pack-years, per 20 y	Ever smoked	1.06 (0.66-1.70)	.82	1.25 (0.67-2.32)	.48	1.03 (0.73-1.46)	.86
Age at initiation, per 10 y	Ever smoked	0.44 (0.12-1.66)	.23	0.88 (0.46-1.68)	.69	0.73 (0.40-1.33)	.30
Time since quitting, per 10 y	Past smokers	0.76 (0.37-1.60)	.48	0.82 (0.40-1.69)	.59	0.84 (0.51-1.39)	.50
Age at quitting, per 10 y	Past smokers	1.37 (0.66-2.88)	.40	1.29 (0.62-2.67)	.49	1.23 (0.74-2.03)	.42

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]There was only 1 case of incident geographic atrophy among current smokers, prohibiting analysis of this outcome among current smokers.
[b]Controlling for age (categorically), sex (when appropriate), and baseline age-related macular degeneration severity level.

Table 6. Relationship Between Smoking Characteristics at Baseline and the 15-Year Cumulative Progression of AMD Along the 6-Level Beaver Dam Scale[a]

Smoking History Variable	Subset	Men		Women		Both	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Past vs never smokers	Not applicable	1.29 (0.84-1.97)	.24	0.97 (0.71-1.33)	.86	1.03 (0.81-1.32)	.81
Current vs never smokers	Not applicable	2.19 (1.30-3.69)	.003	1.13 (0.75-1.69)	.57	1.43 (1.05-1.94)	.02
Intensity, packs/d	Ever smoked	0.91 (0.70-1.18)	.47	1.15 (0.78-1.69)	.48	0.96 (0.78-1.18)	.68
	Current smokers	0.85 (0.43-1.68)	.64	1.22 (0.59-2.55)	.59	1.07 (0.65-1.75)	.79
Duration, per 10 y	Ever smoked	1.25 (1.08-1.45)	.002	0.96 (0.82-1.12)	.61	1.10 (0.99-1.22)	.08
	Current smokers	0.88 (0.54-1.41)	.59	0.71 (0.49-1.02)	.06	0.82 (0.63-1.07)	.14
Pack-years, per 20 y	Ever smoked	1.06 (0.94-1.20)	.36	1.05 (0.87-1.27)	.59	1.05 (0.95-1.16)	.37
	Current smokers	0.93 (0.68-1.28)	.66	1.05 (0.75-1.46)	.78	1.02 (0.81-1.28)	.85
Age at initiation, per 10 y	Ever smoked	0.94 (0.74-1.20)	.63	1.20 (0.99-1.46)	.06	1.10 (0.95-1.28)	.19
	Current smokers	1.22 (0.76-1.94)	.41	1.57 (1.09-2.25)	.01	1.30 (1.00-1.69)	.05
Time since quitting, per 10 y	Past smokers	0.83 (0.68-1.02)	.08	0.98 (0.77-1.25)	.88	0.90 (0.77-1.05)	.19
Age at quitting, per 10 y	Past smokers	1.28 (1.04-1.58)	.02	1.08 (0.85-1.37)	.51	1.17 (1.00-1.37)	.05

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
[a]Controlling for age (categorically), sex (when appropriate), and baseline AMD severity level.

CONCLUSIONS

Compared with never having smoked, current but not past smoking at the baseline examination was associated with an approximately 45% higher odds of developing early AMD or AMD progression during 15 years of follow-up. There was no relationship between smoking status and the 15-year cumulative incidence of either exudative AMD or geographic atrophy, but because of small numbers, we cannot rule out the possibility of an association. Exposure to ETS in nonsmoking individuals was not associated with the 5-year incidence of early AMD or progression of AMD.

The finding that smoking status is related to the incidence of early AMD or AMD progression is consistent with our earlier reported findings from the 10-year follow-up and with data from other studies.[14-16] It is consistent with hypothesized biological mechanisms linking smoking to the pathogenesis of AMD.[17-23] As in our previous report, we could not find an association between smoking status and incident signs of late AMD. The lack of a strong relationship between smoking status and incident signs of late AMD in our study is in contrast to data from some but not all epidemiological studies that have examined this association.[5,6,15,16]

There may be a number of reasons for not finding a strong association between smoking and the cumulative incidence of late AMD in the Beaver Dam cohort. First, the lack of a relationship between smoking status and incident signs of late AMD may be because of selective survival. While people with early AMD who smoked were more likely to die or not participate at follow-up than nonsmokers with early AMD, AMD severity status at baseline did not affect the relationship between smoking status or pack-years smoked and participation or death, making selective survival less likely of a reason for not finding an association between smoking and AMD incidence. Second, and more likely, is the limited power to observe a relationship between smoking and incidence of late AMD in people aged 65 years or older, as most smokers begin to quit smoking at this age.[4] It is possible that most of those at risk for developing signs of late AMD may have developed them at the time of the baseline examination, which is consistent with our finding of a cross-sectional association.[4] At baseline, there were only 44 current smokers who returned for follow-up who were aged 65 years or older and had signs of early AMD in our study, a group with the highest risk to progress to late AMD. This number declined at each subsequent examination. To overcome this limitation, in the past we have pooled our data with those from other large populations and have shown a statistically significant relationship between current smoking and the 5-year incidence of pure geographic atrophy but not exudative AMD.[15] Third, it is possible that other unmeasured factors—eg, inhalation, filtration, nicotine levels, additives to cigarettes, and other tobacco-related differences in cigarettes smoked, which were not measured in our study—might, in part, explain differences in these associations found among other smoking and AMD studies. Fourth, it is possible that smoking may not increase the risk of progression of early to late AMD in our population.

Few of the specific smoking characteristics studied provided further insights into the relationship between smoking and the incidence or progression of AMD. Using the traditional measures of pack-years smoked, no association with progression of AMD in either current or former smokers in the whole cohort was found. However, the associations of older age at initiation in current female smokers with incident early AMD and older age of quitting in former male smokers with incident exudative AMD suggest that age at smoking exposure may also be important in determining risk of AMD. However, use of such historical information may be limited by lack of precision. In addition, these findings may be a result of chance owing to multiple comparisons.

We found no relationship between exposure to ETS and incidence or progression of AMD. This may be because of the relatively short interval of 5-year follow-up with limited incidence and progression of AMD or the imprecision of this past exposure. Decrease in ETS in the population may also, in part, explain not finding an association. There are no other population-based data, to our knowledge, regarding the relationship between passive smoking and the incidence of AMD.

In summary, while controlling for other factors, smoking appears to be related to the incidence and progression of AMD in our population. This has important health care implications, because early AMD is associated with an increase in the risk of developing late AMD and smoking behavior is modifiable.

Submitted for Publication: November 22, 2006; final revision received January 23, 2007; accepted February 10, 2007.
Correspondence: Ronald Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin, 610 N Walnut St, 417 WARF, Madison, WI 53726-2336 (kleinr@epi.ophth.wisc.edu).
Financial Disclosure: None reported.
Funding/Support: This study was funded by grant EY06594 from the National Eye Institute (Drs R. Klein and B. E. K. Klein) and by grant AG11900 from the National Institute of Aging (Dr Cruickshanks) and was also supported in part by Research to Prevent Blindness (Drs R. Klein and B. E. K. Klein, Senior Scientific Award), New York, NY.
Additional Information: Reprints not available from the author.

REFERENCES

1. Paetkau ME, Boyd TA, Grace M, Bach-Mills J, Winship B. Senile disciform macular degeneration and smoking. *Can J Ophthalmol.* 1978;13(2):67-71.
2. Hyman LG, Lilienfeld AM, Ferris FL III, Fine SL. Senile macular degeneration: a case-control study. *Am J Epidemiol.* 1983;118(2):213-227.
3. Risk factors for neovascular age-related macular degeneration: The Eye Disease Case-Control Study Group. *Arch Ophthalmol.* 1992;110(12):1701-1708.
4. Klein R, Klein BE, Linton KL, DeMets DL. The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *Am J Epidemiol.* 1993;137(2):190-200.
5. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA.* 1996; 276(14):1141-1146.
6. Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA.* 1996;276(14):1147-1151.

7. Vingerling JR, Klaver CC, Hofman A, de Jong PT. Epidemiology of age-related maculopathy. *Epidemiol Rev*. 1995;17(2):347-360.
8. Smith W, Mitchell P, Leeder SR. Smoking and age-related maculopathy: The Blue Mountains Eye Study. *Arch Ophthalmol*. 1996;114(12):1518-1523.
9. Delcourt C, Diaz JL, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration: The POLA Study, Pathologies Oculaires Liees a l'Age. *Arch Ophthalmol*. 1998;116(8):1031-1035.
10. Risk factors associated with age-related macular degeneration: a case-control study in the age-related eye disease study, Age-Related Eye Disease Study report No. 3. *Ophthalmology*. 2000;107(12):2224-2232.
11. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration: pooled findings from three continents. *Ophthalmology*. 2001;108(4): 697-704.
12. West SK, Rosenthal FS, Bressler NM, et al. Exposure to sunlight and other risk factors for age-related macular degeneration. *Arch Ophthalmol*. 1989;107(6): 875-879.
13. Klein R, Klein BE, Moss SE. Relation of smoking to the incidence of age-related maculopathy: The Beaver Dam Eye Study. *Am J Epidemiol*. 1998;147(2):103-110.
14. Klein R, Klein BE, Tomany SC, Moss SE. Ten-year incidence of age-related maculopathy and smoking and drinking: the Beaver Dam Eye Study. *Am J Epidemiol*. 2002;156(7):589-598.
15. Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology*. 2004;111(7):1280-1287.
16. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. *Eye*. 2005;19 (9):935-944.
17. Pryor WA, Hales BJ, Premovic PI, Church DF. The radicals in cigarette tar: their nature and suggested physiological implications. *Science*. 1983;220(4595): 425-427.
18. Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *Am J Epidemiol*. 1988;127(2):283-296.
19. Bettman JW, Fellows V, Chao P. The effect of cigarette smoking on the intraocular circulation. *AMA Arch Ophthalmol*. 1958;59(4):481-488.
20. Friedman E. Choroidal blood flow: pressure-flow relationships. *Arch Ophthalmol*. 1970;83(1):95-99.
21. Hammond BR Jr, Wooten BR, Snodderly DM. Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration. *Vision Res*. 1996; 36(18):3003-3009.
22. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol*. 2000; 45(2):115-134.
23. Suñer IJ, Espinosa-Heidmann DG, Marin-Castano ME, Hernandez EP, Pereira-Simon S, Cousins SW. Nicotine increases size and severity of experimental choroidal neovascularization. *Invest Ophthalmol Vis Sci*. 2004;45(1):311-317.
24. Linton KL, Klein BE, Klein R. The validity of self-reported and surrogate-reported cataract and age-related macular degeneration in the Beaver Dam Eye Study. *Am J Epidemiol*. 1991;134(12):1438-1446.
25. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98(8):1310-1315.
26. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population: The Beaver Dam Eye Study. *Ophthalmology*. 1996;103(8):1169-1178.
27. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: The Beaver Dam Eye Study. *Ophthalmology*. 2001;108(10):1757-1766.
28. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;142(4):539-549.
29. Klein R, Klein BE. *The Beaver Dam Eye Study: Manual of Operations*. Springfield, VA: US Dept of Commerce; 1991:B91-B149823. NTIS accession No. P.
30. Klein R, Klein BE. *The Beaver Dam Eye Study, II: Manual of Operations*. Springfield, VA: US Dept of Commerce; 1995:B95-B273827. NTIS accession No. P.
31. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98(7):1128-1134.
32. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. *The Wisconsin Age-Related Maculopathy Grading System*. Springfield, VA: US Dept of Commerce; 1991:B91-B184267. NTIS accession No. P.
33. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: The Beaver Dam Eye Study. *Ophthalmology*. 1992;99(6):933-943.
34. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7-21.
35. Klein R, Klein BE, Knudtson M, Meuer SM, Swift M, Gangnon RE. The fifteen-year cumulative incidence of age-related macular degeneration: The Beaver Dam Eye Study. *Ophthalmology*. 2007;114(2):253-262.
36. Nondahl DM, Cruickshanks KJ, Schubert CR. A questionnaire for assessing environmental tobacco smoke exposure. *Environ Res*. 2005;97(1):76-82.
37. SAS Institute Inc. *SAS/STAT User's Guide, Version 9*. Cary, NC: SAS Institute Inc; 2004.
38. Hosmer DW Jr, Lemeshow S. *Applied Logistic Regression*. In: Hosmer DW Jr, Lemeshow S, eds. New York, NY: John Wiley & Sons; 1989.
39. Leffondré K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: a comparison of different approaches. *Am J Epidemiol*. 2002;156(9): 813-823.

From the Archives of the Archives

My colleagues and I use 000000 mild chromic surgical gut in all cases of cataract surgery, both for the corneoscleral wound and the conjunctival flap. With loss of vitreous, it is necessary when using absorbable surgical sutures to make a surgeon's knot, since the suture becomes so slippery when covered with vitreous that the ordinary square knot will not hold.

Reference: Fralick FB. 000000 Chromic absorbable surgical suture U. S. P. (surgical gut) in wound closure after cataract extraction. *Arch Ophthalmol*. 1952;47:113