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ORIGINAL CONTRIBUTIONS

Ten-Year Incidence of Age-related Maculopathy and Smoking and Drinking

The Beaver Dam Eye Study

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The authors examined associations between smoking and alcohol consumption and the long-term incidence of age-related maculopathy (ARM) in people in the Beaver Dam Eye Study who were aged 43–86 years (n = 3,684) in 1988–1990 and examined over a 10-year period. ARM status was determined by grading stereoscopic color fundus photographs. After controlling for age, sex, and other factors, the authors found that people who had smoked more were more likely to develop large (≥250 μm in diameter) soft drusen (risk ratio (RR) per 10 pack-years smoked = 1.08, 95% confidence interval (CI): 1.02, 1.14) and pigmentary abnormalities (RR = 1.09, 95% CI: 1.04, 1.14) and to have progression of early ARM (RR = 1.05, 95% CI: 1.00, 1.10) than people who had smoked less. Smoking was not associated with the incidence of late ARM. People who reported being heavy drinkers at baseline were more likely to develop late ARM (RR = 6.94, 95% CI: 1.85, 26.1) than people who reported never having been heavy drinkers. Smoking appears to have a modest, positive association with early but not late signs of ARM, and heavy drinking appears to be related to an increased risk of late ARM, although the exposure and outcome were infrequent, and the effect is based on few exposed cases.

alcohol drinking; incidence; macular degeneration; population; risk factors; smoking

Abbreviations: ARM, age-related maculopathy; CI, confidence interval; RR, risk ratio.

Age-related maculopathy (ARM), a common cause of severe visual loss in Americans aged 65 years or more, is estimated to affect 16–26 percent of people in this age group (1–5). At present, there are few medical interventions that have been shown to prevent the incidence or progression of this disease (6). Although surgical interventions in some cases prevent further loss of vision, they usually do not restore vision in patients with neovascular macular degeneration (7, 8). In addition, there are no surgical interventions for those who develop geographic atrophy, an advanced stage of ARM that causes loss of central vision. For these reasons, identification of modifiable factors related to this disease has great public health importance. One such factor, cigarette smoking, has been found to be related to late ARM in some (9–19), but not all (20–23), epidemiologic studies. Most studies have not shown an association of alcohol consumption with ARM (11, 21, 24–30). The purpose of this report is to examine the relation of cigarette smoking and

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alcohol consumption to the 10-year cumulative incidence and progression of ARM.

MATERIALS AND METHODS

Population

The methods used to identify and describe the population have appeared in previous reports (31–34). 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 43–84 years of age. Of the 5,924 eligible individuals, 4,926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Ninety-nine percent of the population was White. A total of 3,684 individuals (81.1 percent) participated in the 5-year follow-up examination between March 1, 1993, and June 14, 1995. Comparisons between participants and nonparticipants at the time of the baseline and 5-year follow-up examinations have appeared elsewhere (32, 33).

Prior to the start of the 10-year follow-up examination on March 1, 1998, 350 (9.5 percent) of the participants had died. Of the 3,334 surviving participants in the baseline and second examinations, 2,764 (82.9 percent or 56.1 percent of the original cohort) participated in the second follow-up examination between March 1, 1998, and June 9, 2000. One participant could not be located, 42 (1.3 percent) permitted an interview only, 38 (1.1 percent) moved out of the area and did not participate, 337 (10.1 percent) refused to participate, and 152 (4.6 percent) died after the start of the 10-year follow-up prior to being examined. The mean and median times between the baseline and 10-year follow-up examinations were 10.1 years and 10.0 years, respectively, and the standard deviation was 0.4 years.

Comparisons between participants and nonparticipants at the 10-year follow-up have been presented elsewhere (34). Persons who were deceased before their scheduled examinations for the 10-year follow-up were older at baseline than those who did participate (69.2 years vs. 58.7 years, $p < 0.001$). Persons who were alive but did not participate in the 10-year follow-up ($n = 418$) were older at baseline than those who did (61.1 years vs. 58.7 years, $p < 0.001$). Of those participants alive at the third examination, after adjustment for age and sex, the people who smoked at the baseline were less likely to participate in the 10-year follow-up than those who did not smoke at baseline. There was no association of heavy drinking status at baseline or early ARM status at the 5-year follow-up with participation at the 10-year follow-up.

Procedures

Similar procedures, used at both the baseline and follow-up examinations, have been described in detail elsewhere (31–39). Informed consent was obtained from each participant at the beginning of the examination. Pertinent parts of the examination at both baseline and follow-up consisted of taking stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye. For the purposes of this report, the 2,625 (3,571 at the first two examinations) people with at least one eye free of confounding lesions (e.g., retinal detachment or non-age-related chorioretinal scarring) at all three examinations are included in the analyses (40).

The Wisconsin Age-related Maculopathy Grading System was used to assess the presence and severity of lesions associated with ARM. Grading procedures, lesion descriptions, and detailed definitions for the presence and severity of specific lesions have appeared elsewhere (37–40). Detailed definitions for the incidence of specific lesions have also appeared elsewhere (40). In brief, incidence implies the appearance of a lesion at follow-up when it was absent at baseline. Progression implies the presence of a lesion at baseline with a worsening at follow-up (40).

The incidence of early ARM was defined by the presence of either soft indistinct drusen or the presence of any type of drusen associated with retinal pigment epithelium depigmentation or increased retinal pigment at follow-up when none of these lesions was present at baseline. The incidence of late ARM was defined by the appearance of either exudative macular degeneration or pure geographic atrophy at follow-up when neither was present at baseline.

For each eye, a six-level severity scale for age-related maculopathy was defined as follows:

- Level 10: no drusen or the presence of hard drusen, or small soft drusen (<125 μm in diameter) only, regardless of area of involvement, and no pigmentary abnormality (increased retinal pigment or retinal pigment epithelium depigmentation) present;
- Level 20: hard drusen or small soft drusen (<125 μm in diameter), regardless of area of involvement, with increased retinal pigment present but no retinal pigment epithelium depigmentation present or soft drusen (≥125 μm in diameter) with drusen area of less than 196,350 μm^2 (equivalent to a circle with a diameter of 500 μm) and no pigmentary abnormalities present;
- Level 30: soft drusen (≥125 μm in diameter) with drusen area of less than 196,350 μm^2 and retinal pigment epithelium depigmentation present or soft drusen (≥125 μm in diameter) with drusen area of ≥196,350 μm^2 with or without increased retinal pigment but no retinal pigment epithelium depigmentation present;
- Level 40: soft drusen (≥125 μm in diameter) with drusen area involvement of ≥196,350 μm^2 and retinal pigment epithelium depigmentation present with or without increased retinal pigment;
- Level 50: pure geographic atrophy in the absence of exudative macular degeneration; and
- Level 60: exudative macular degeneration with or without geographic atrophy present.

The first level on the scale is equivalent to having no ARM, the next three levels on the scale involve lesions defining early ARM of increasing severity (by type, size, area of drusen, and presence of pigmentary abnormalities), and the last two levels involve lesions defining late ARM.

Progression for a participant was defined as an increase in the maculopathy severity in either eye by two steps or more

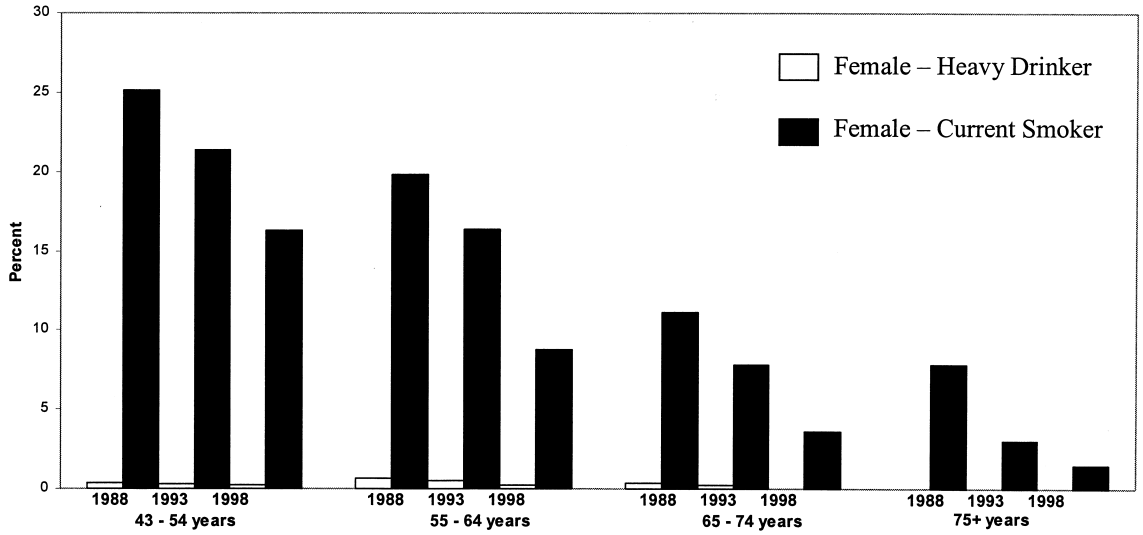

FIGURE 1. Change in current smoking and heavy drinking by age over three examinations (1988–1990, 1993–1995, and 1998–2000) in women in the Beaver Dam Eye Study.

from level 10 through level 30 and one step or more from level 40 or level 50 at the 5-year or 10-year follow-up examination.

Age was defined as the age at the time of the baseline examination. Cigarette smoking status at the time of the baseline examination was determined as follows. A subject was classified as a nonsmoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, as a former smoker if he/she had smoked this number of cigarettes or more in his/her lifetime but had stopped smoking before the examination, and as a current smoker if he/she had not stopped smoking. The total pack-years smoked was defined as the number of cigarettes smoked per day divided by 20, multiplied by the number of years smoked. Of the 3,684 persons who participated in the baseline and follow-up examinations, one was missing information on smoking status and 12 were missing pack-year information.

The medical history questionnaire contained questions regarding alcohol consumption. No people declined to answer any alcohol-related questions. Subjects were asked about their average weekly use of beer, wine, and liquor in the previous year. In addition, they were asked about past periods of drinking including whether or not they ever consumed four or more drinks daily. From these data, a current drinker was defined as a person who had consumed alcoholic beverages within the past year, a former drinker

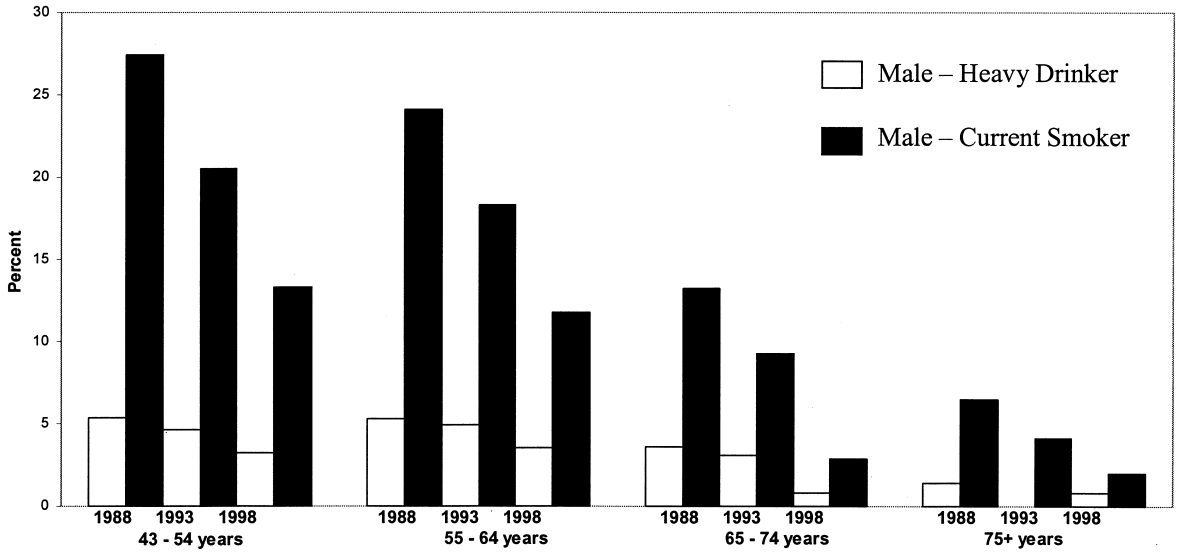

FIGURE 2. Change in current smoking and heavy drinking by age over three examinations (1988–1990, 1993–1995, and 1998–2000) in men in the Beaver Dam Eye Study.

TABLE 1. Cigarette smoking and heavy alcohol consumption at baseline examination (1988–1990) by gender, Beaver Dam Eye Study

Smoking status by gender	Heavy drinking status							
	Never heavy drinker		Former heavy drinker		Current heavy drinker		Total*	
	No.	%†	No.	%†	No.	%†	No.	%†
Males								
Never smoked	381	34.1	73	18.3	5	6.8	459	28.9
% by drinking status		83.0		15.9		1.1		
Former smoker	536	48.0	220	55.3	35	47.9	791	49.8
% by drinking status		67.8		27.8		4.4		
Current smoker	199	17.8	105	26.4	33	45.2	337	21.2
% by drinking status		59.1		31.4		9.8		
Total	1,116		398		73		1,587	
% by drinking status		70.3		25.1		4.6		
Females								
Never smoked	1,187	60.1	26	24.3	1	11.1	1,214	58.1
% by drinking status		97.8		2.1		0.1		
Former smoker	462	23.4	40	37.4	6	66.7	508	24.3
% by drinking status		90.9		7.9		1.2		
Current smoker	326	16.5	41	38.3	2	22.2	369	17.6
% by drinking status		88.3		11.1		0.5		
Total	1,975		107		9		2,091	
% by drinking status		94.5		5.1		0.4		

* Incidence of 3,678 people with complete smoking and drinking history data who participated at the baseline and 5-year follow-up examinations.

† Percent by smoking status.

was a person who had consumed alcoholic beverages in the past but not within the previous year, and a nondrinker had never consumed alcoholic beverages. A current heavy drinker was defined as a person consuming four or more servings of alcoholic beverages daily, a former heavy drinker had consumed four or more servings daily in the past but not in the previous year, and a non-heavy drinker had never consumed four or more servings daily on a regular basis. To investigate whether the amount of alcohol currently consumed was associated with ARM, we computed the amount of alcohol consumed in a usual week. In the questionnaire, one serving of alcoholic beverage was defined as 12 ounces (0.355 liter) of beer, 4 ounces (0.118 liter) of wine, or 1.5 ounces (0.044 liter) of liquor or distilled spirits. Each serving of beer, wine, and liquor was considered to contain 12.96 g, 11.48 g, and 14.00 g of alcohol (ethanol), respectively (41). The amounts of alcohol from beer, wine, and liquor were summed to obtain the average grams of alcohol consumed from any source in a week. The average alcohol consumed in a week from each individual source was also examined. The participants were subdivided into three nonexclusive groups of persons drinking beer, wine, and liquor.

Statistical methods

For these analyses, we examined the relations among smoking status, pack-years smoked, total amount of alcohol (and type) reported to be consumed, and status of heavy drinking at baseline to the incidence or progression of each of the specific maculopathy lesions and to the incidence of two endpoints of disease severity, early and late ARM. SAS software was used for analyzing the data (42). Cumulative events were estimated using the Kaplan-Meier (product limit) survival approach (43). Multivariate risk ratios and 95 percent confidence intervals were calculated from the discrete linear logistic model (44). These analytic approaches allowed those persons who were right censored (not seen after the 5-year examination because of death or nonparticipation) to contribute information to the estimates. Tests of trend were done treating categorical risk factors as continuous variables in the discrete linear logistic model and computing the chi-square statistic for the parameter estimate. In these models, smoking status was considered using two indicator variables (former smoker vs. never smoked and current smoker vs. never smoked), and alcohol status was considered using two indicator variables (former heavy drinkers vs. never heavy drinker and current heavy drinker vs. never heavy drinker).

RESULTS

Cigarette smoking and alcohol consumption status at baseline by age and sex have been reported previously (12, 29). A larger proportion of those reporting a history of current smoking and current or past heavy drinking of alcohol at baseline were in the younger age groups, and the proportions decreased in the older age groups (figures 1 and 2). Men were more likely than women to currently smoke (21.2 percent vs. 17.6 percent), to have smoked in the past (49.8 percent vs. 24.3 percent), to be current heavy drinkers (4.6 percent vs. 0.4 percent), or to have been heavy drinkers (25.1 percent vs. 5.1 percent). Fewer people reported being current smokers (Cochran-Armitage p test of trend < 0.0001 for men and p test of trend < 0.0001 for women) or current heavy drinkers (p test of trend = 0.007 for men and p test of trend = 0.04 for women) at each of the follow-up examinations (figures 1 and 2). Smoking was strongly associated with heavy drinking (table 1).

The age- and sex-adjusted 10-year incidence of early and late ARM and lesions associated with various manifestations of ARM by smoking status and pack-years smoked are shown in table 2. While controlling for age and sex, we found that those who reported they were currently smoking at baseline were more likely to develop large soft drusen and early ARM than those who had never smoked (table 2). Men who were current smokers at baseline had a risk ratio of developing exudative macular degeneration of 4.45 and women, a risk ratio of 0.28; in neither case was the association statistically significant ($p > 0.10$). There was a statistically significant increase in the age- and sex-adjusted incidence of large soft drusen and of pigmentary abnormalities with increasing number of pack-years smoked (table 2).

Total alcohol consumption at baseline was not associated with the incidence of early or late ARM or progression of ARM in the population (data not shown). Few beverage-specific associations were found (table 3). For beer consumption, those who drank 78 or more g of alcohol from beer per week at baseline had an increased risk of developing large soft drusen greater than 250 μm in diameter compared with those who had not consumed any beer. Men who drank 56 or more g of alcohol from liquor per week had an increased risk of developing exudative macular degeneration (risk ratio (RR) = 6.09, 95 percent confidence interval (CI): 1.50, 21.80; $p = 0.01$) compared with men who did not drink liquor. This relation was not found in women (RR = 0.40, 95 percent CI: 0.05, 3.04).

Heavy drinking was associated with the incidence of late ARM (table 4). The risk ratio of developing exudative macular degeneration in former heavy drinkers was 2.55 ($p = 0.04$), and in current heavy drinkers at baseline it was 6.51 ($p = 0.02$). These associations were due mainly to the effect

TABLE 2. Relation of smoking status and pack-years smoked at baseline (1988–1990) to age- and gender-adjusted 10-year incidence of age-related maculopathy, Beaver Dam Eye Study

	Incidence of early ARM*				Incidence of large soft drusen				Incidence of pigmentary abnormalities			
	No.	%	RR*	95% CI*	No.	%	RR	95% CI	No.	%	RR	95% CI
Smoking status												
Never smoked	1,263	12.4	1.00		1,535	6.0	1.00		1,394	8.5	1.00	
Former smoker	1,005	12.4	1.12	0.85, 1.47	1,211	6.6	1.36	0.96, 1.94	1,103	9.3	1.16	0.85, 1.58
Current smoker	563	11.1	1.37	0.98, 1.94	654	6.9	2.19	1.44, 3.32	616	7.1	1.32	0.89, 1.98
Pack-years smoked												
0†	1,273	12.5	1.00		1,546	6.0	1.00		1,404	8.5	1.00	
<15	488	12.9	1.24	0.89, 1.72	579	5.1	1.11	0.70, 1.75	539	7.2	1.00	0.67, 1.50
15–34	540	9.2	1.03	0.72, 1.47	632	6.1	1.67	1.08, 2.58	573	5.3	0.88	0.56, 1.37
≥35	521	13.5	1.24	0.89, 1.74	632	8.7	2.00	1.34, 2.98	588	13.1	1.71	1.20, 2.44
	Incidence of late ARM				Incidence of exudative ARM				Progression of ARM			
	No.	%	RR	95% CI	No.	%	RR	95% CI	No.	%	RR	95% CI
Smoking status												
Never smoked	1,580	2.9	1.00		1,573	1.8	1.00		1,472	12.1	1.00	
Former smoker	1,244	1.6	0.61	0.33, 1.13	1,250	1.1	0.75	0.36, 1.58	1,173	10.9	1.00	0.76, 1.31
Current smoker	671	0.8	0.51	0.18, 1.46	670	0.8	0.85	0.28, 2.51	630	9.2	1.34	0.94, 1.91
Pack-years smoked												
0†	1,591	2.9	1.00		1,584	1.8	1.00		1,483	12.1	1.00	
<15	591	1.0	0.42	0.16, 1.08	591	0.4	0.29	0.07, 1.22	557	8.7	0.85	0.59, 1.23
15–34	645	1.1	0.63	0.26, 1.55	645	0.9	0.95	0.34, 2.59	612	8.9	1.13	0.79, 1.62
≥35	657	1.9	0.76	0.36, 1.62	662	1.7	1.25	0.54, 2.89	612	13.2	1.33	0.96, 1.84

* ARM, age-related maculopathy; RR, risk ratio; CI, confidence interval.

† Number of nonsmokers not equal to number with pack-years = 0 because of rounding (if pack years < 0.05, then pack-years = 0).

TABLE 3. Relation of beverage-specific alcohol consumption at baseline (1988–1990) to age- and gender-adjusted 10-year incidence of age-related maculopathy, Beaver Dam Eye Study

	Incidence of early ARM*				Incidence of large soft drusen				Incidence of pigmentary abnormalities			
	No.	%	RR*	95% CI*	No.	%	RR	95% CI	No.	%	RR	95% CI
Beer consumption (g)												
0	1,925	12.5	1.00		2,295	6.5	1.00		2,113	8.4	1.00	
<26	342	10.9	0.98	0.67, 1.45	420	6.6	1.20	0.76, 1.91	379	8.7	1.15	0.76, 1.76
26–77	281	12.8	1.48	0.98, 2.23	334	5.3	1.38	0.79, 2.42	308	10.7	1.89	1.22, 2.93
≥78	281	9.3	1.14	0.71, 1.83	349	6.1	1.84	1.07, 3.14	311	6.4	1.15	0.67, 1.99
Liquor consumption (g)												
0	1,869	12.8	1.00		2,249	7.1	1.00		2,050	9.1	1.00	
<14	284	12.0	1.02	0.68, 1.52	335	5.1	0.85	0.49, 1.46	311	6.9	0.84	0.51, 1.38
14–55	297	9.3	0.98	0.54, 1.30	359	6.3	1.07	0.66, 1.75	329	7.7	1.01	0.64, 1.60
≥56	378	11.1	0.93	0.64, 1.34	454	4.1	0.62	0.36, 1.06	420	7.6	0.84	0.54, 1.29
Wine consumption (g)												
0	2,470	12.3	1.00		2,975	6.4	1.00		2,724	8.8	1.00	
<23	235	11.7	0.88	0.57, 1.35	276	5.8	0.86	0.49, 1.50	251	6.5	0.73	0.42, 1.25
≥23	124	8.3	0.63	0.32, 1.25	147	6.5	1.21	0.61, 2.42	136	7.2	0.85	0.43, 1.70
	Incidence of late ARM				Incidence of exudative ARM				Progression of ARM			
	No.	%	RR	95% CI	No.	%	RR	95% CI	No.	%	RR	95% CI
Beer consumption (g)												
0	2,359	2.3	1.00		2,361	1.7	1.00		2,200	12.3	1.00	
<26	432	1.9	0.93	0.41, 2.14	432	0.8	0.56	0.17, 1.88	405	9.1	0.78	0.53, 1.16
26–77	346	<0.1	0.24	0.03, 1.78	344	0.4	0.34	0.04, 2.55	327	9.0	1.02	0.65, 1.59
≥78	356	2.2	1.82	0.71, 4.64	354	1.1	1.24	0.35, 4.39	340	8.1	1.11	0.70, 1.76
Liquor consumption (g)												
0	2,312	2.1	1.00		2,306	1.3	1.00		2,153	12.3	1.00	
<14	339	1.9	1.06	0.41, 2.73	339	1.5	1.35	0.46, 3.94	315	8.5	0.80	0.51, 1.26
14–55	371	1.9	1.12	0.46, 2.69	373	1.2	1.23	0.42, 3.61	355	10.0	0.93	0.62, 1.38
≥56	470	1.9	1.17	0.53, 2.56	472	1.8	1.70	0.71, 4.04	448	8.5	0.74	0.50, 1.10
Wine consumption (g)												
0	3,056	2.0	1.00		3,054	1.4	1.00		2,869	11.2	1.00	
<23	286	2.8	1.39	0.62, 3.11	287	1.3	0.82	0.25, 2.69	262	11.9	1.07	0.71, 1.62
≥23	151	1.5	0.88	0.21, 3.70	150	0.9	0.62	0.08, 4.57	142	8.4	0.87	0.46, 1.64

* ARM, age-related maculopathy; RR, risk ratio; CI, confidence interval.

seen in men, as there were only nine women who were current heavy drinkers at baseline.

To determine whether smoking status, pack-years smoked, or a history of heavy drinking made a significant contribution to the incidence and progression of ARM or specific lesions associated with ARM after controlling for other factors, we developed separate discrete linear logistic regression models. The incidences of early ARM, late ARM, and the specific lesions were considered as separate dependent variables. After including age, vitamin supplement use, systolic blood pressure, and heavy drinking status at baseline as independent variables, we included smoking status and pack-years in separate models. For both men and women, a history of current smoking was associated with an increased 10-year incidence of large soft drusen compared with people who had a history of never having smoked (table 5). The amount smoked was associated with the incidence of large soft drusen, pigmentary abnormalities, and the progression of ARM. With the exception of the incidence of large soft drusen, these associations were stronger in men compared with women.

While controlling for smoking status at baseline, age, sex, vitamin use, and systolic blood pressure, we found that people with a history of current or past heavy drinking at baseline were more likely to develop exudative macular degeneration (table 5) than were people who reported never being heavy drinkers. The interaction term for smoking and heavy drinking was not statistically significant.

There were 198 persons who had quit smoking between the baseline and 5-year follow-up. While controlling for age, we found that there were no associations between quitting smoking by the second examination and the subsequent 5-

TABLE 4. Relation of history of heavy drinking status at baseline (1988–1990) to age- and gender-adjusted 10-year incidence of age-related maculopathy by sex, Beaver Dam Eye Study

	Incidence of early ARM*				Incidence of large soft drusen				Incidence of pigmentary abnormalities			
	No.	%	RR*	95% CI*	No.	%	RR	95% CI	No.	%	RR	95% CI
Never heavy drinker	2,396	12.7	1.00		2,846	6.5	1.00		2,627	8.8	1.00	
Former heavy drinker	373	7.8	0.78	0.51, 1.20	475	5.6	1.24	0.77, 2.01	417	6.8	0.99	0.64, 1.55
Current heavy drinker	60	12.6	1.50	0.67, 3.35	76	5.7	1.59	0.56, 4.50	66	7.2	1.14	0.41, 3.20
	Incidence of late ARM				Incidence of exudative ARM				Progression of ARM			
	No.	%	RR	95% CI	No.	%	RR	95% CI	No.	%	RR	95% CI
Never heavy drinker	2,927	1.9	1.00		2,924	1.3	1.00		2,738	11.4	1.00	
Former heavy drinker	486	2.4	1.91	0.88, 4.91	490	1.7	2.55	1.03, 6.34	459	9.4	1.17	0.79, 1.72
Current heavy drinker	79	4.3	5.82	1.65, 20.5	76	3.6	6.51	1.41, 30.2	74	12.2	1.94	0.90, 4.16

* ARM, age-related maculopathy; RR, risk ratio; CI, confidence interval.

year incidence of ARM in men or women (data not shown). There were too few persons (n = 27) who were heavy drinkers at baseline who had quit at the 5-year follow-up to assess the association with incident ARM.

DISCUSSION

Heavy alcohol consumption, defined as four or more drinks per day, was found to be independently associated with an increased risk of developing exudative macular degeneration in Beaver Dam, but the confidence intervals about the risk ratio are large. Although heavy drinking may be related to an increased risk of late ARM, both this exposure and outcome are too infrequent (nine persons with a history of past heavy drinking developed late ARM and three with a history of current heavy drinking developed late ARM). The effect of drinking on late ARM cannot be reliably distinguished from its relation with early disease.

Our hypothesis about an alcohol effect stems from the observation that alcohol intake, by increasing oxidant stress or affecting mechanisms that protect against oxidative damage, has been shown to cause tissue damage in the other organs (45, 46). Data from experimental studies in animals suggest that the retina is susceptible to oxidative damage and that this damage may be minimized by the presence of antioxidant nutrients (47). Heavy drinkers have also been found to have low serum carotene, vitamin E, and zinc, all factors postulated to protect again the development of ARM (48). However, only a few studies have found a relation between alcohol consumption and ARM (11, 21, 24–27, 49, 50). A cross-sectional association of alcohol consumption with early ARM (RR = 1.61, 95 percent CI: 1.07, 2.41) was reported in the Blue Mountains Eye Study (24). In the Nurses' Health Study, an increased risk of self-reported macular degeneration was reported in heavy drinkers; however, the association was not statistically significant (51).

In contrast, there is a suggestion that wine consumption in Beaver Dam was associated with a reduction in the incidence of early ARM; however, the association did not reach statistical significance. In the National Health and Nutrition Examination Survey I, a negative association (RR = 0.66, 95 percent CI: 0.55, 0.79) between ARM and wine consumption was reported (28). The authors speculated that antioxidant phenolic compounds found in high concentration in red wine may explain their finding. The type of wine consumed in Beaver Dam is unknown to us. Neither wine nor beer has been found to be associated with ARM in other studies (24). Contrary to our findings at baseline, consumption of beer in the past year was not associated with the incidence of pigmentary abnormalities and exudative macular degeneration (29).

Smoking in Beaver Dam was associated with the incidence of large soft drusen and pigmentary abnormalities, early signs of ARM that are predictive of development of signs of late ARM (40, 52). These findings are consistent with our 5-year incidence data, which showed that cigarette smoking was related to the development of large soft drusen (20). Smoking, by its depression of serum antioxidant levels (53, 54) and its alterations of choroidal blood flow (55, 56) and the retinal pigment epithelium drug detoxification pathways, has been postulated to cause ARM. In addition, smoking has been shown to decrease luteal pigments in the human retina (57). This has been hypothesized to increase the risk of damage to the macula by light and oxidative damage, leading to an increased risk of developing ARM (58).

There appeared to be no association of the amount smoked with the incidence of late ARM in Beaver Dam, and current smokers at baseline were less likely to develop late ARM than were those who had never smoked. These findings are inconsistent with our earlier findings of a strong cross-sectional association of smoking with the presence of exudative macular degeneration and findings from other cross-

TABLE 5. Logistic regression model of relation of smoking status and drinking status at baseline (1988–1990) to lesions associated with the 10-year incidence of age-related maculopathy, Beaver Dam Eye Study

	Men*		Women*		Men and women†	
	RR‡	95% CI‡	RR	95% CI	RR	95% CI
Incidence of early ARM‡						
Per 10 pack-years§	1.04	0.98, 1.10	1.01	0.92, 1.11	1.03	0.98, 1.08
Former smoker§	1.01	0.65, 1.57	1.30	0.91, 1.85	1.12	0.85, 1.48
Current smoker§	1.57	0.89, 2.75	1.18	0.74, 1.87	1.35	0.95, 1.92
Former heavy drinker	0.66	0.40, 1.09	1.04	0.46, 2.35	0.74	0.48, 1.14
Heavy drinker	1.39	0.59, 3.24	0.00¶		1.33	0.59, 3.02
Incidence of large soft drusen						
Per 10 pack-years§	1.06	0.99, 1.14	1.11	1.02, 1.21	1.08	1.02, 1.14
Former smoker§	1.17	0.64, 2.16	1.52	0.98, 2.37	1.32	0.93, 1.89
Current smoker§	2.40	1.14, 5.04	1.93	1.14, 3.27	2.13	1.40, 3.25
Former heavy drinker	1.10	0.62, 1.97	1.17	0.49, 2.79	1.12	0.70, 1.82
Heavy drinker	1.44	0.47, 4.42	0.00¶		1.28	0.44, 3.69
Incidence of pigmentary abnormalities						
Per 10 pack-years§	1.09	1.03, 1.16	1.08	0.98, 1.81	1.09	1.04, 1.14
Former smoker§	1.05	0.64, 1.72	1.33	0.88, 2.00	1.17	0.86, 1.60
Current smoker§	1.43	0.74, 2.73	1.10	0.63, 1.91	1.27	0.84, 1.92
Former heavy drinker	0.88	0.52, 1.48	1.20	0.50, 2.86	0.96	0.61, 1.50
Heavy drinker	1.04	0.35, 3.05	0.00¶		1.04	0.36, 2.95
Incidence of late ARM						
Per 10 pack-years§	0.99	0.87, 1.13	0.91	0.72, 1.15	0.96	0.86, 1.08
Former smoker§	0.51	0.19, 1.36	0.64	0.27, 1.52	0.53	0.28, 1.01
Current smoker§	0.51	0.11, 2.31	0.20	0.03, 1.52	0.38	0.13, 1.14
Former heavy drinker	2.48	0.91, 6.78	1.87	0.41, 8.53	2.14	0.95, 4.83
Heavy drinker	7.34	1.62, 33.1	0.00¶		6.94	1.85, 26.1
Incidence of exudative ARM abnormalities						
Per 10 pack-years§	1.06	0.92, 1.22	0.87	0.65, 1.16	1.00	0.89, 1.13
Former smoker§	1.61	0.32, 7.99	0.46	0.15, 1.39	0.64	0.29, 1.39
Current smoker§	2.76	0.39, 19.4	0.26	0.03, 1.94	0.66	0.21, 2.04
Former heavy drinker	2.25	0.65, 7.75	3.18	0.68, 14.9	2.62	1.01, 6.79
Heavy drinker	4.63	0.76, 28.1	0.00¶		5.91	1.20, 29.1
Progression of ARM						
Per 10 pack-years§	1.05	1.00, 1.12	1.05	0.97, 1.14	1.05	1.00, 1.10
Former smoker§	1.19	0.75, 1.90	0.95	0.65, 1.38	0.98	0.74, 1.30
Current smoker§	1.61	0.88, 2.97	1.08	0.67, 1.73	1.24	0.86, 1.78
Former heavy drinker	1.14	0.72, 1.80	1.15	0.53, 2.48	1.12	0.75, 1.66
Heavy drinker	2.00	0.88, 4.53	0.00¶		1.75	0.81, 3.80

* Controlled for age, vitamin use, and systolic blood pressure.
† Controlled for age, vitamin use, systolic blood pressure, and gender.
‡ RR, risk ratio; CI, confidence interval; ARM, age-related maculopathy.
§ Model further adjusted for heavy drinking.
¶ Confidence interval not estimable.

sectional and cohort studies (12–16, 18, 19). Data from the Physicians' and Nurses' Health Study showed that male physicians who smoked 20 or more cigarettes per day at baseline were 2.5 times more likely to report developing age-related macular degeneration over 12 years of follow-up compared with those who had never smoked (13, 14). However, the Macular Photocoagulation Study Group (59) reported no relation of cigarette smoking to the risk of devel-

oping choroidal new vessels in unaffected fellow eyes. It is possible that smoking, by itself, does not increase the risk of developing signs of exudative macular degeneration. Further follow-up and study of large population-based cohorts will be necessary to further evaluate this association of smoking and the progression to exudative macular degeneration and geographic atrophy.

Caution should be exercised when interpreting the findings reported herein. First, men and women with early ARM, who were at higher risk for developing late ARM, and those who were smokers at the second examination were less likely to participate in the 10-year follow-up in Beaver Dam. This might have resulted in not observing an association of smoking with ARM. Second, the incidence of the late ARM endpoints was low, reducing the ability to find significant associations. In addition, older persons, who are at greatest risk of developing late age-related macular degeneration, were less likely to be smoking or drinking heavily at the time of the baseline examination and over the course of the study. This reduces the power available for finding associations. Third, underreporting of alcohol consumption or cigarette smoking in people at risk for developing ARM would lead to an underestimate of the association between them. Fourth, the analyses conducted for this report included the examination of many associations. As is the case in all studies, some statistically significant associations may be type I errors (i.e., may be due to chance when in fact no association exists). Thus, it is important to consider the reported results not in isolation but in a context that includes other available evidence and biologic plausibility or mechanisms relating the risk factor to the disease. Finally, because of the small number of observations in some strata of the risk factors examined, sparse-data biases may exist (60).

In summary, in Beaver Dam smoking appears to be related to the incidence of large soft drusen and pigmentary abnormalities, lesions that define early ARM, and heavy drinking with exudative macular degeneration, a lesion that defines late ARM. The associations are for the most part found in men and not women. Further follow-up of this and other large aging cohorts will provide an ability to examine the relation of smoking and alcohol consumption to late ARM. Although these data do not permit us to provide definitive evidence regarding whether stopping smoking and heavy drinking will prevent the development of late age-related macular degeneration, patients should be advised not to smoke or drink heavily because of their significant known adverse affects on health (48, 61, 62).

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