Prospective Study of Alcohol Consumption and the Risk of Age-Related Macular Degeneration

Eunyoung Cho, ScD; Susan E. Hankinson, ScD; Walter C. Willett, MD; Meir J. Stampfer, MD; Donna Spiegelman, ScD; Frank E. Speizer, MD; Eric B. Rimm, ScD; Johanna M. Seddon, MD

Objective: To describe the relationship between alcohol consumption and the incidence of age-related macular degeneration (AMD).

Methods: We conducted a prospective study among female nurses between 1980 and 1994 and among male health professionals between 1986 and 1994. We included 32 764 women and 29 488 men who were 50 years or older, without a diagnosis of AMD or cancer at baseline, and added additional subjects to the analysis as they reached 50 years of age. Their alcohol intake was assessed at baseline and updated during follow-up evaluations using a validated semiquantitative food-frequency questionnaire. After separate analyses for women and men, pooled estimates of the relationship of alcohol to the risk of AMD were calculated.

Results: Age-related macular degeneration associated with a visual acuity loss of 20/30 or worse, including the early and dry and wet types, was diagnosed in 298 women (from 697 498 person-years of follow-up) and 153 men (229 180 person-years) by 1994, the end of follow-up. After controlling for age, smoking, and other risk factors, the pooled relative risks (RRs) and 95% confidence intervals (CIs) for AMD compared with nondrinkers were 1.0 (0.7-1.2) for drinkers who consumed 0.1 to 4.9 g/d of alcohol; 0.9 (0.6-1.4) for 5 to 14.9 g/d; 1.1 (0.7-1.7) for 15 to 29.9 g/d; and 1.3 (0.9-1.8) for 30 g/d or more. Among women, there was a suggestion of a modest increased risk of the disease in drinkers who consumed 30 g/d or more (RR, 1.5; 95% CI, 1.0-2.4); this was limited to an increased risk of the early and dry form (RR, 2.0; 95% CI, 1.2-3.4). No specific type of alcohol provided protection against AMD.

Conclusion: This prospective study does not support an inverse relationship between moderate alcohol consumption and risk of AMD.

Arch Ophthalmol. 2000;118:681-688

From the Departments of Nutrition (Drs Cho, Willett, Stampfer, and Rimm), Epidemiology (Drs Hankinson, Willett, Stampfer, Spiegelman, Rimm, and Seddon), and Biostatistics (Dr Spiegelman), Harvard School of Public Health, and the Channing Laboratory, Department of Medicine (Dr Cho), Brigham and Women's Hospital (Drs Hankinson, Willett, Stampfer, Speizer, and Rimm), and the Epidemiology Unit, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary (Dr Seddon), Harvard Medical School, Boston, Mass.

AGE-RELATED macular degeneration (AMD) is the leading cause of blindness among elderly individuals in Western countries.[1,2] Preventing development of the disease is vital, since, in most cases, no effective treatment is available.[3] Although several risk factors or protective factors for AMD have been suggested, few data, with the exception of the link between smoking and AMD, have been accumulated to confirm these possible associations.[4-6] Vascular disease may affect the circulation to the retina and may thus be related to the development of AMD.[7,8] The narrowing of the choriocapillaris caused by atherosclerosis may result in a decreased supply of nutrients and oxygen to the retina and may contribute to the development of ischemia in that region.[9]

Mild to moderate alcohol consumption is a modifiable lifestyle factor known to decrease the risk of coronary heart disease.[10] Therefore, moderate alcohol consumption may protect against AMD through its beneficial effect on cardiovascular disease. This hypothesis was supported by a recent cross-sectional study in which an inverse association was observed between alcohol consumption (particularly wine) and AMD,[11] but, until now, no prospective data have been available. We therefore examined total and specific types of alcohol consumption in relation to the risk of AMD in 2 large prospective follow-up studies of women and men.

RESULTS

During 697 498 person-years of follow-up in women and 229 180 person-years of follow-up in men, we ascertained 451 cases of AMD (298 in women and 153 in men; 271 early and dry AMD and 180 wet AMD).

Among the 32 764 women and 29 488 men eligible for analysis at baseline, 33% of

SUBJECTS AND METHODS

STUDY POPULATION

The Nurses' Health Study (NHS) started in 1976 among 121 701 female registered nurses aged 30 to 55 years who completed a mailed questionnaire regarding medical history and health-related information. The Health Professionals Follow-up Study (HPFS) enrolled 51 529 male health professionals 40 to 75 years of age residing in the United States in 1986. The cohort consisted of dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%). For both cohorts, follow-up questionnaires have been sent biennially to update exposure information and to ascertain new disease diagnoses, including AMD.

ASCERTAINMENT OF DIET AND ALCOHOL INTAKE

In 1980, we sent a semiquantitative food frequency questionnaire (FFQ) with 61 food items, including alcohol, to measure dietary intake in the past year in women. Dietary and alcohol intakes were measured with a similar FFQ with approximately 120 food items in 1984, 1986, and 1990. Intake information was provided on a similar questionnaire by men in 1986 and 1990. Participants were asked how often, on average, they had consumed each type of food or beverage (beer, wine, and liquor) during the past year. Separate questions for red and white wine were asked of men and, from 1984 on, of women. There were 9 possible responses, ranging from never or less than once per month to 6 or more times per day. At baseline in both cohorts, we also asked whether their alcohol use had changed during the past 10 years. The alcohol content was estimated to be 12.8 g per 12-oz (355-mL) can or bottle of beer, 11.0 g per 4-oz (120-mL) glass of wine, and 14.0 g per shot of liquor. Total alcohol intake per individual was calculated as the sum of the contribution from each of these beverages.

The reproducibility and validity of food and alcohol intake as assessed by the FFQs have been documented.[12-14] The Spearman correlation coefficients between total alcohol consumption as assessed by the FFQ and by the diet records were 0.90 for women and 0.86 for men. The correlations for specific beverage types varied from 0.80 to 0.83 in women and from 0.70 to 0.86 in men. In addition, the correlations with serum high-density lipoprotein cholesterol levels, which are sensitive to alcohol intake, were 0.40 for women and 0.35 for men ($P<.001$).

POPULATION FOR ANALYSIS

The baseline population for this study included women who were 50 years or older in 1980 and men who were in the same age range in 1986 (47 806 women and 33 357 men). Participants were included in our analyses only if they had plausible energy intakes (2510-14 640 kJ/d in women and 3350-17 570 kJ/d in men), left fewer than 10 of 61 food items blank on the FFQ (women) or fewer than 70 of 131 items blank (men), and provided information on alcohol intake (36 117 women and 31 978 men). We excluded subjects who reported a diagnosis of AMD or cancer (except nonmelanoma skin cancer) at baseline (2136 women and 1744 men); these exclusions were updated every 2 years. Finally, subjects who did not answer any of the follow-up questionnaires regarding a diagnosis of AMD (1986-1994 in the NHS and 1988-1994 in the HPFS) were also excluded (1217 women and 746 men). A total of 32 764 women and 29 488 men were included at baseline, and others were added as they reached 50 years of age at every 2-year follow-up evaluation. By 1992, 73 849 women and 37 389 men contributed to the analyses. As of 1994, follow-up rates, calculated as total person-years of follow-up divided by potential person-years of follow-up, were 99% in the NHS and 97% in the HPFS.

IDENTIFICATION OF CASES

Questions regarding the diagnosis of AMD were first asked of women in 1986 and of men in 1988. When the cohort member reported a diagnosis of AMD, we requested permission to review medical records. We then asked his or her ophthalmologist to complete a standardized questionnaire regarding best-corrected visual acuity, signs of AMD (including drusen, retinal pigment epithelial hypopigmentation/hyperpigmentation, geographic atrophy, retinal pigment epithelial detachment, subretinal neovascular membrane, or disciform scar), and date of initial diagnosis, or to send us copies of ocular records to confirm the diagnosis. Cases were defined as participants with AMD that was associated with a visual acuity loss of 20/30 or worse in at least one eye and who were first diagnosed after completing baseline FFQs and before June 1, 1994, in the NHS and January 1, 1994, in the HPFS. In addition, the AMD had to be judged by the ophthalmologist to be sufficient alone to cause visual acuity loss of 20/30 or worse. We used the subject as the unit of analysis, with disease status defined by the more severely affected eye.

In addition to the analyses that included all cases, separate analyses were based on subgroups of AMD. Cases were divided into 2 main types: early and dry and wet (exudative)

women and 23% of men reported consuming alcohol never or less than once per month (**Table 1**). The majority in both cohorts reported consuming a low to moderate amount of alcohol (0.1-14.9 g/d). Few reported drinking 50 g or more per day: 1.0% of women and 3.4% of men. Alcohol drinking, especially consumption of 30 g/d or more, was associated with smoking. Heavy drinkers also tended to have more hypertension than any other group. The other characteristics were distributed similarly according to alcohol intake in both women and men.

Compared with nondrinkers, women who drank 30 g/d or more of alcohol had an increased risk of the disease in age-adjusted analyses (**Table 2**) (RR, 1.90; 95% CI, 1.24-2.92; test for trend, $P<.001$). However, after controlling for smoking, the RR was reduced to 1.54 (95% CI, 0.99-2.39) (test for trend, $P = .03$). Additional adjustment for other factors did not affect the RR. The same comparison among men showed a positive but weaker association in age-adjusted analyses. This association also was attenuated substantially by control for smoking. None of the pooled multivariate RRs for alcohol drinkers compared with nondrinkers was significant. Additional analyses using either the average alcohol intake during follow-up evaluation or the most recent alcohol intake as

AMD. The early and dry form of AMD was defined as the presence of drusen, retinal pigment epithelial changes, or geographic atrophy. The wet form of AMD, usually associated with greater visual impairment, included the presence of retinal pigment epithelial detachment, choroidal neovascular membrane, or disciform scar. If the case had different types of AMD in each eye, we chose the more severe type. Our case definition of AMD has been validated by 2 retinal specialists who conducted a standardized review of fundus slides in a subset of cases (those ascertained from the 1990 follow-up in the NHS).[5] Among 42 cases with photographs of sufficient quality to grade, 39 (93%) were judged to have AMD by both reviewers.

Two thousand eighty-seven women and 929 men reported a diagnosis of AMD during follow-up evaluations; 761 women (36%) and 359 men (39%) were confirmed to have AMD by their ophthalmologist. For 199 women (10%) and 79 men (9%), we were not able to contact either the subjects or their ophthalmologists. The remainder of subjects reporting AMD did not grant permission to contact their ophthalmologist (8%, NHS; 12%, HPFS), indicated that the initial report was in error (21%, NHS; 18%, HPFS), or did not have the diagnosis confirmed by their ophthalmologist (25%, NHS; 23%, HPFS). In the last case, the ophthalmologist frequently implicated other maculopathies (eg, macular hole) or other eye diseases (eg, diabetic retinopathy). After excluding women and men who did not have visual acuity loss of 20/30 or worse (358 subjects in NHS and 125 in the HPFS) or whose visual acuity loss was not attributable to AMD (90 subjects in the NHS and 32 in the HPFS), 313 women and 202 men met our case definition. Among them, after excluding subjects without dietary information, with a previous diagnosis of cancer, or a diagnosis of AMD either before completing the baseline FFQ or after the end of follow-up, 298 women and 153 men were eligible for the analysis.

DATA ANALYSIS

We grouped total alcohol intake into 5 categories (nondrinking, 0.1-4.9 g/d, 5.0-14.9 g/d, 15.0-29.9 g/d, and ≥30.0 g/d). Intake of each alcoholic beverage was categorized by frequency (never or <1 drink per month, 1-3 per month, 1-4 per week, 5 per week to 1 per day, and ≥2 per day).

Study participants contributed person-time (months) in each 2-year interval from the time the baseline FFQ was returned or from 50 years of age until a diagnosis of AMD or cancer, death, the time of last questionnaire return, or the end of the follow-up period (June 1, 1994, for women and January 1, 1994, for men), whichever came first.

Age-adjusted rates were calculated with age as a 5-year categorical variable. Analyses to control for other potential confounders employed pooled multivariate logistic regression.[15] The models included potential risk factors for AMD, such as age, smoking, body mass index (calculated as weight in kilograms divided by the square of height in meters), history of hypertension, energy and lutein/zeaxanthin intake, physical activity (metabolic equivalents per week by quintile in men and vigorous activity once or more per week in women), postmenopausal hormone use (women), and occupation (men). To control for smoking, pack-years of smoking (number of years smoked×average number of packs of cigarettes per day) were used, since this measure best reflects the cumulative impact of smoking and is more strongly related to AMD than current smoking status.[5] Among these covariates, nondietary factors, including age, pack-years of smoking, body mass index, history of hypertension, and postmenopausal hormone use, were updated every 2 years, as recent exposure status may be more relevant to the disease. For dietary covariates, we used baseline values for baseline analyses and updated or averaged values in further analyses. For all relative risks (RRs), 95% confidence intervals (CIs) were calculated. Tests for trend across categories of alcohol intake were conducted by using the medians within each category as a continuous variable. Log-likelihood ratio tests were used to compare models with or without interaction terms between alcohol intake and smoking. All *P* values are 2-sided.

We conducted separate analyses for each cohort and then pooled analyses of the 2 study groups. Tests for heterogeneity between the 2 cohorts were performed.[16] Meta-analytic methods using a random-effects model were employed to pool the RRs from the 2 cohorts.[16]

The primary analyses used alcohol intake as reported on the baseline FFQs, but in alternative analyses, we updated alcohol intake with each new assessment to examine the effect of the most recent intake on risk of AMD. In addition, an updated average intake over the follow-up period was examined (eg, in women, 1980 intake for the 1980-1984 follow-up and an average of the 1980 and 1984 intake for the 1984-1986 follow-up).

To confirm the results from the primary analyses, we also performed several restricted analyses in the following groups: (1) never-smokers, (2) subjects who reported unchanged drinking habits in the previous 10 years, (3) subjects without cardiovascular disease (angina, myocardial infarction, stroke, and coronary bypass or angioplasty in men and angina and myocardial infarction in women), and (4) subjects who had eye examinations, either for screening or for symptoms, during follow-up.

the exposure provided qualitatively similar results. Among never-smokers, the RRs for alcohol intake were similar to the overall multivariate estimates. Relative risks were also similar in analyses conducted among subjects who reported unchanged alcohol intake in the 10 years prior to baseline, who reported having 1 or more eye examinations during follow-up, or who did not have cardiovascular disease.

We explored the association of total alcohol intake with early and dry and wet AMD separately, because these types may have different etiologic mechanisms (**Table 3**). In each cohort, approximately 60% of the cases had the early and dry form. After controlling for age, smoking, and other risk factors, alcohol intake of 30 g/d or more was associated with an increased risk of early and dry AMD in women (RR, 2.04; 95% CI, 1.22-3.42; test for trend, $P = .003$). However, among men, the relationship was much weaker (RR, 1.18; 95% CI, 0.62-2.23). The pooled multivariate RR for this category was 1.60 (95% CI, 0.94-2.73; test for trend, $P = .02$; for heterogeneity, $P = .19$). There was no clear association between alcohol intake and wet AMD in either women or men.

We also examined the effect of specific alcoholic beverages in relation to total AMD (**Table 4**). Beer

Table 1. Age-Standardized Baseline Characteristics of Cohorts According to Alcohol Intake Among Participants Who Reported Alcohol Values and Were 50 Years or Older at Baseline (1980 for Women and 1986 for Men)*

Characteristic	Alcohol Intake, g/d				
	0	0.1-4.9	5-14.9	15-29.9	≥30
Women					
No. of subjects	10 822	10 141	7465	2361	1975
Mean age, y	54	54	54	54	54
Currently smoking, %	22	25	32	34	54
Mean body mass index, kg/m^2	26	25	24	24	24
Vigorous activity once or more per week, %	39	43	47	48	40
Postmenopausal hormone use, %	11	12	13	14	14
High blood pressure, %	27	23	22	22	30
High blood cholesterol level, %	10	9	8	9	8
Eye examination in 1988-1994, %	95	96	96	96	94
Energy-adjusted daily mean lutein/zeaxanthin intake, µg	4870	5409	5630	6129	5224
Men					
No. of subjects	6849	6796	8117	3829	3897
Mean age, y	61	60	60	60	61
Currently smoking, %	7	8	9	9	20
Mean body mass index, kg/m^2	26	26	26	25	26
Physical activity, METs/wk	24	22	24	24	23
High blood pressure, %	27	25	26	28	33
High blood cholesterol level, %	14	15	15	15	15
Eye examination in 1990-1994, %	88	90	91	91	88
Energy-adjusted daily mean lutein/zeaxanthin intake, µg	3849	4009	4018	4077	3613

Except for the mean age data, all data shown are standardized to the age distributions of the cohorts at baseline. METs indicates metabolic equivalents.

Table 2. Relative Risk (RR) of Total Age-Related Macular Degeneration by Alcohol Intake*

	Alcohol Intake, g/d					*P*	
	0	0.1-4.9	5-14.9	15-29.9	30+	For Trend†	For Heterogeneity‡
Women							
Median intake, g/d	0	1.8	10.8	19.5	36.5		
No. of cases	85	85	72	28	28		
Person-years	224 360	223 080	159 691	51 446	38 921		
Age-adjusted RR (95% CI)	1.00	1.05 (0.78-1.42)	1.22 (0.89-1.67)	1.48 (0.97-2.27)	1.90 (1.24-2.92)	<.001	
Age- and smoking-adjusted RR (95% CI)	1.00	1.04 (0.77-1.40)	1.14 (0.83-1.57)	1.35 (0.88-2.08)	1.54 (0.99-2.39)	.03	
Multivariate RR (95% CI)§	1.00	1.03 (0.76-1.39)	1.12 (0.81-1.55)	1.31 (0.85-2.04)	1.51 (0.97-2.37)	.04	
Men							
Median intake, g/d	0	1.9	9.6	18.9	40.5		
No. of cases	39	31	35	19	29		
Person-years	52 275	53 816	63 279	30 426	29 384		
Age-adjusted RR (95% CI)	1.00	0.81 (0.51-1.30)	0.80 (0.51-1.27)	0.96 (0.55-1.66)	1.33 (0.82-2.16)	.08	
Age- and smoking-adjusted RR (95% CI)	1.00	0.80 (0.50-1.28)	0.75 (0.47-1.19)	0.85 (0.49-1.49)	1.10 (0.67-1.80)	.38	
Multivariate RR (95% CI)‖	1.00	0.80 (0.50-1.28)	0.74 (0.46-1.17)	0.81 (0.46-1.41)	1.04 (0.63-1.72)	.54	
Pooled Multivariate RR (95% CI)							
Baseline intake (n = 451)	1.00	0.96 (0.74-1.23)	0.94 (0.63-1.41)	1.06 (0.66-1.71)	1.28 (0.89-1.84)	.05	.33
Most recent intake (n = 451)	1.00	0.98 (0.75-1.28)	1.01 (0.74-1.37)	1.03 (0.58-1.85)	1.41 (1.01-1.98)	.02	.73
Average intake during follow-up (n = 451)	1.00	1.04 (0.80-1.35)	0.89 (0.66-1.19)	1.06 (0.75-1.49)	1.48 (0.96-2.30)	.03	.40
In never-smokers (n = 146)	1.00	0.86 (0.58-1.28)	0.73 (0.45-1.19)	1.07 (0.54-2.10)	1.42 (0.68-2.95)	.48	.82
Without change in alcohol intake (n = 322)	1.00	0.99 (0.58-1.71)	1.11 (0.80-1.53)	1.20 (0.80-1.91)	1.32 (0.84-2.08)	.07	.63
With eye examination (n = 437)	1.00	0.95 (0.71-1.26)	0.92 (0.57-1.49)	0.99 (0.62-1.59)	1.26 (0.87-1.85)	.08	.41
Without cardiovascular disease (n = 388)	1.00	0.92 (0.63-1.35)	0.94 (0.61-1.45)	1.10 (0.75-1.59)	1.32 (0.85-2.02)	.05	.44

*A 2-year period is adjusted in every analysis. CI indicates confidence interval.

†The test for trend was calculated using median intake of alcohol in each category as a continuous variable.

‡The test for between-study heterogeneity was calculated using the test for trend.

§The multivariate model controlled for age (50-54, 55-59, 60-64, 65-69, and 70-74 years), smoking (never, 1-9, 10-24, 25-44, 45-64, and 65+ pack-years), high blood pressure (yes or no), total energy intake (quintiles), lutein/zeaxanthin intake (quintiles), body mass index (<21, 21.0-22.9, 23.0-24,9, 25.0-28.9, and 29.0+ kg/m^2), postmenopausal hormone use (premenopausal and never, current, and past users), and vigorous exercise (yes or no).

‖The multivariate model controlled for age (50-59, 60-64, 65-69, 70-74, and 75+ years), smoking (never, 1-9, 10-24, 25-44, 45-64, and 65+ pack-years), high blood pressure (yes or no), total energy intake (quintiles), lutein/zeaxanthin intake (quintiles), body mass index (<21, 21.0-22.9, 23.0-24.9, 25.0-28.9, and 29.0+ kg/m^2), profession (dentist, pharmacist, optometrist, podiatrist, or veterinarian), and physical activity (metabolic equivalent quintiles).

Table 3. Relative Risk (RR) of Early and Dry and Wet Age-Related Macular Degeneration (AMD) by Alcohol Intake*

	Alcohol Intake, g/d					*P*	
	0	0.1-4.9	5-14.9	15-29.9	30+	For Trend†	For Heterogeneity‡
Early and Dry AMD							
Women							
No. of cases	54	49	38	18	23		
Multivariate RR (95% CI)	1.00	0.94 (0.64-1.39)	0.95 (0.62-1.45)	1.36 (0.79-2.36)	2.04 (1.22-3.42)	.003	
Men							
No. of cases	23	17	19	11	19		
Multivariate RR (95% CI)	1.00	0.75 (0.40-1.42)	0.70 (0.38-1.30)	0.80 (0.38-1.66)	1.18 (0.62-2.23)	.31	
Pooled multivariate RR (95% CI)	1.00	0.88 (0.63-1.23)	0.86 (0.61-1.22)	1.10 (0.66-1.84)	1.60 (0.94-2.73)	.02	.23
Wet AMD							
Women							
No. of cases	31	36	34	10	5		
Multivariate RR (95% CI)	1.00	1.19 (0.73-1.93)	1.41 (0.85-2.32)	1.25 (0.60-2.58)	0.69 (0.26-1.83)	.73	
Men							
No. of cases	16	14	16	8	10		
Multivariate RR (95% CI)	1.00	0.86 (0.42-1.78)	0.79 (0.39-1.61)	0.83 (0.35-1.98)	0.86 (0.38-1.95)	.82	
Pooled multivariate RR (95% CI)	1.00	1.07 (0.72-1.61)	1.12 (0.65-1.94)	1.05 (0.60-1.84)	0.78 (0.42-1.47)	.69	.92

*The multivariate models use the same covariates for women and men as in Table 2. CI indicates confidence interval.
†The test for trend was calculated using median intake of alcohol in each category as a continuous variable.
‡The test for between-study heterogeneity was calculated using the test for trend.

consumption was not appreciably related to AMD in either women or men. However, a high intake of wine was positively related to AMD in each cohort. Compared with nondrinkers, women in the highest category of wine intake (≥2 drinks per day) had an age-adjusted RR of 2.20 (95% CI, 1.29-3.76), which was only modestly attenuated after adjustment for smoking and other risk factors (RR, 2.07; 95% CI, 1.20-3.58; test for trend, $P = .02$). Men had a 40% increased risk in the same category of wine intake (RR, 1.40; 95% CI, 0.55-3.53). The pooled multivariate RR for this comparison was 1.87 (95% CI, 1.17-3.00). In an analysis among never-smokers only, the pooled RR was attenuated to 1.37 (95% CI, 0.42-4.46), suggesting possible residual confounding in the overall association.

At baseline, the results for red and white wine separately were only available for men and suggested that the positive association was stronger (although not significant) for white wine. The multivariate RR for men who had 2 or more drinks of white wine per day was 2.16 (95% CI, 0.77-6.11; test for trend, $P = .09$). The limited number of cases precluded a separate analysis of high red wine intake. To further explore this issue in women, we used data on alcohol intake collected in 1984, the first year we collected information on red and white wine separately. As in men, women who consumed 2 or more drinks per day of white wine had a 2-fold increased risk (RR, 1.98; 95% CI, 0.99-3.98).

The relationship of wine drinking with AMD risk seemed limited to the early and dry form of the disease, although the number of cases in these analyses was small. For early and dry AMD, the pooled multivariate RR for 2 or more drinks of wine per day was 2.36 (95% CI, 1.31-4.27); the multivariate RRs for that category were 2.79 (95% CI, 1.50-5.21) in women and 1.37 (95% CI, 0.41-4.53) in men (data not shown).

A high liquor intake (≥2 drinks per day) was associated with a significantly increased risk in age-adjusted analyses in both women and men (RR, 2.03; 95% CI, 1.24-3.30, and RR, 1.76; 95% CI, 1.09-2.83, respectively). However, the association was attenuated in multivariate analyses, primarily because of controlling for smoking (RR, 1.51; 95% CI, 1.05-2.17; test for trend, $P = .009$). Further analyses restricted to never-smokers provided a pooled RR of 1.43 for the same comparison (data not shown). No clear association was observed at lower levels of alcohol intake.

Since smoking is an important risk factor for AMD and usually related to alcohol consumption, we examined the interaction between alcohol and smoking. We found no significant interactions between smoking and either overall alcohol intake or wine consumption specifically.

COMMENT

These prospective data from 111 238 women and men do not support a protective effect of moderate alcohol consumption on the risk of AMD. In our primary analyses, we found no substantial association between total alcohol intake and incidence of AMD. Among women, we observed a moderate adverse effect of alcohol consumption of 30 g/d or more that seemed to be limited to early and dry AMD, the early stage of the disease. The apparent increased risk associated with alcohol was principally caused by wine, particularly white wine. Most of the observed results across the 2 large cohorts of men and women were consistent; we conducted tests for between-study heterogeneity for all effect estimates, and none was significant.

Several studies have provided support for the hypothesis that relates AMD to a predisposition for cardiovascular disease.[7] History of cardiovascular disease has been associated with AMD in some reports,[17,18] but not in others.[19,20] In one cross-sectional study, subjects with

Table 4. Relative Risk (RR) of Total Age-Related Macular Degeneration (AMD) by Intake of Each Alcoholic Beverage*

	Alcohol Intake, No. of Drinks					*P*	
	Never or <1/mo	1-3/mo	1-4/wk	5/wk to 1/d	≥2/d	For Trend†	For Heterogeneity‡
Beer							
Women							
No. of cases	243	19	18	15			
Multivariate RR (95% CI)	1.00	0.68 (0.42-1.09)	0.74 (0.45-1.21)	1.09 (0.64-1.85)		.85	
Men							
No. of cases	80	26	30	13			
Multivariate RR (95% CI)	1.00	0.83 (0.52-1.34)	0.84 (0.53-1.33)	0.80 (0.44-1.48)		.49	
Pooled multivariate RR (95% CI)	1.00	0.75 (0.53-1.05)	0.79 (0.56-1.11)	0.95 (0.64-1.43)		.73	.52
Wine							
Women							
No. of cases	132	68	51	30	15		
Multivariate RR (95% CI)	1.00	1.16 (0.85-1.57)	0.95 (0.67-1.34)	1.23 (0.81-1.87)	2.07 (1.20-3.58)	.02	
Men							
No. of cases	72	16	41	18	5		
Multivariate RR (95% CI)	1.00	0.78 (0.45-1.37)	0.93 (0.61-1.41)	0.86 (0.49-1.49)	1.40 (0.55-3.53)	.65	
Red wine§							
No. of cases	98	34	14	4			
Multivariate RR (95% CI)	1.00	1.26 (0.78-2.03)	0.78 (0.41-1.51)	0.79 (0.28-2.24)		.59	
White wine§							
No. of cases	78	36	21	8	4		
Multivariate RR (95% CI)	1.00	0.83 (0.51-1.35)	0.68 (0.38-1.21)	1.16 (0.54-2.51)	2.16 (0.77-6.11)	.09	
Pooled multivariate RR (95% CI)	1.00	1.02 (0.71-1.46)	0.94 (0.72-1.23)	1.07 (0.76-1.52)	1.87 (1.17-3.00)	.02	.43
Liquor							
Women							
No. of cases	157	44	45	30	18		
Multivariate RR (95% CI)	1.00	0.90 (0.63-1.27)	0.96 (0.68-1.37)	1.10 (0.73-1.65)	1.49 (0.89-2.49)	.10	
Men							
No. of cases	61	17	22	27	24		
Multivariate RR (95% CI)	1.00	0.99 (0.56-1.74)	0.82 (0.48-1.38)	1.43 (0.87-2.33)	1.53 (0.92-2.56)	.04	
Pooled multivariate RR (95% CI)	1.00	0.92 (0.68-1.24)	0.92 (0.68-1.23)	1.22 (0.89-1.67)	1.51 (1.05-2.17)	.009	.78

**The multivariate models use the same covariates for women and men as in Table 2, as well as the other alcoholic beverages in this table, simultaneously. CI indicates confidence interval.*

†The test for trend was calculated using median intake of alcohol in each category as a continuous variable.

‡The test for between-study heterogeneity was calculated using the test for trend.

§The effects of red and white wine were examined only for men.

plaques in carotid arteries had a 4.5-fold (95% CI, 1.9-10.7) increased risk of AMD.[21] Several cardiovascular risk factors, such as smoking, hypertension, and elevated blood cholesterol levels, were directly related to AMD in some studies,[5,18,19,22-24] but not in others.[20,25] Antioxidant nutrients and postmenopausal hormone use, protective factors for cardiovascular disease, may also provide some protection against AMD.[19,26] However, these studies do not distinguish whether the predisposition to cardiovascular disease directly affects the development of AMD (eg, caused by atherosclerosis of retinal vessels) or whether these 2 diseases just share some common risk factors or protective factors that work through different mechanisms. Our results do not support the former idea, since moderate alcohol consumption is an important protective factor in cardiovascular disease,[10] and, if cardiovascular disease promoted AMD, we would expect a protective effect of alcohol on AMD.

There have been few previous studies of alcohol intake and risk of AMD. The Beaver Dam Eye Study reported that beer consumption was positively related to increased retinal pigment and wet AMD.[27] The Blue Mountain Eye Study observed an adverse effect of liquor intake.[28] On the other hand, the study based on the first National Health and Nutrition Examination Survey reported a protective effect of wine.[11] However, these studies were limited by their cross-sectional design and had limited control of possible confounders.

Alcohol consumption may have different associations with early and dry AMD and wet AMD; it may be more strongly related to the wet type. We had limited power to detect such an association. Most studies that have found associations with cardiovascular risk factors and AMD were based on wet AMD cases.[19,21,24,26] In the preliminary report from the Eye Disease Case-Control Study, higher alcohol intake was related to a reduced risk of wet AMD.[29] Alternatively, the proposed protective effect of alcohol may be canceled out by other adverse effects of alcohol on AMD. In one recent study, ethanol exposure caused a decrease in docosahexaenoic acid levels (the most abundant fatty acids in the human retina) in feline retinas.[30] Alcohol also may influence antioxidant vitamin levels, which in turn may increase the risk of AMD. Several studies have shown that alcohol consumption is inversely associated with serum or tissue antioxidant nutrients, such as β-carotene and lutein/

zeaxanthin, even after control for dietary antioxidant intake.[31,32]

We have no good explanation for why the highest consumption of wine was associated with increased risk. Although the association may well have been caused by chance, the finding was consistent in both cohorts. The apparent adverse effect of wine seemed to be limited to the early and dry form of AMD and was pronounced only at high intake. However, since we had only a limited number of wet AMD cases in both cohorts, the results for wet AMD are inconclusive and should be examined further in other studies and in our own study after additional follow-up evaluation.

The positive association of wine with AMD seemed to be limited to white wine drinkers who consumed 2 drinks or more per day. In our study, it was not possible to determine whether only white wine had this adverse effect, since there were few red wine drinkers and a limited number of cases in the high red wine intake group. Some component in wine other than alcohol may have an adverse effect on AMD. Alternatively, wine consumption may serve as a surrogate for other lifestyle risk factors. Contrary to our results, previous studies that examined the effect of different types of alcohol did not find any adverse effect of wine on early and dry AMD.[7,28] However, in the Beaver Dam Eye Study, the results were inconclusive because of the limited number of wine drinkers.[27] The Blue Mountain Eye Study also had inconclusive findings, as other potential risk factors were not accounted for in the analysis.[28] In addition, none of these studies examined red and white wine separately.

Since we took advantage of 2 prospective cohorts in which alcohol intake was measured before the diagnosis of disease, the possibility of recall bias was eliminated. Additionally, loss to follow-up, a potential source of bias in cohort studies, has been low. To minimize the possibility that people who drank alcohol may have had a different pattern of routine eye examinations, and thus of being diagnosed with AMD, we included only cases with visual acuity loss of 20/30 or worse. We also conducted secondary analyses limited to participants who had an eye examination during follow-up and observed essentially the same results. Although we had a strict case definition of visual acuity loss of 20/30 or worse, some cases may still be included among our noncases. However, as long as the threshold for diagnosis is unrelated to alcohol intake and specificity is close to 100%, our RRs will have minimal bias.[33,34] Based on our case validation study, the positive predictive value was 93% (39/42).[5] This high predictive value ensures a high specificity (≥99%).[35] In subgroup analyses employing a stricter case definition of visual acuity loss of 20/50 or worse, the overall RR was 0.81 for subjects who consumed 30 g/d or more of alcohol (data not shown). However, this RR may be lower because cases with visual acuity loss of 20/50 include primarily wet AMD cases. Further analyses of early and dry AMD cases with visual acuity loss of 20/50 (74 cases) provided a pooled RR of 1.24 (0.52-2.96) for the highest category of alcohol intake.

Some degree of random misclassification in alcohol consumption is unavoidable and may bias the results toward the null. However, alcohol consumption has been strongly protective for coronary heart disease in these cohorts.[36,37] We conducted a restricted analysis excluding people who had cardiovascular disease, since they may change their dietary habits because of the disease and their dietary information may not reflect long-term intake; we also evaluated these associations among participants reporting no substantial increase or decrease in alcohol intake in the 10 years prior to baseline. These analyses also did not materially change the overall results.

We had good information for most potentially important known confounders, including smoking, dietary intake (eg, zinc, vitamin E, carotenoids), and other lifestyle factors. Except for age and smoking, none of the other potential risk factors had a substantial influence on the associations. Of course, we cannot rule out with certainty a bias caused by other, unmeasured risk factors (eg, sun exposure). Since smoking is an important risk factor for AMD and highly correlated with drinking (especially heavy drinking), some degree of the positive association we observed in women might have been attributable to residual confounding caused by smoking (although wine drinking specifically is not strongly associated with smoking). To address this possibility, we conducted an analysis in never-smokers only (146 cases): the RR essentially did not change for total alcohol and decreased somewhat for wine. However, because of the small number of cases remaining in this analysis, the effect estimates were unstable, with wide CIs. With additional follow-up, we will be able to address this issue more thoroughly.

These prospective results suggest that moderate alcohol intake has no beneficial effect on the risk of AMD overall. Further studies are needed to address these possible relationships with specific types of AMD.

Accepted for publication November 4, 1999.

This study was supported by research grants CA 40356, CA 55075, EY 09611, and HL 35464 from the National Institutes of Health, Bethesda, Md, and by a research grant from the Alcohol Beverage Medical Research Foundation, Baltimore, Md.

We thank Maureen Ireland, Paula Masto, Kerry Demers, Kaumudi Joshipura, Marcia Goetsch, Jaylyn Olivo, and Karen Corsano for their unfailing help. We also thank the Nurses' Health Study and the Health Professionals Follow-up Study participants.

Reprints: Eunyoung Cho, ScD, Nurses' Health Study, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115 (e-mail: hpeyc@capecod.bwh.harvard.edu).

REFERENCES

1. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:933-943.
2. Evans J, Wormald R. Is the incidence of registrable age-related macular degeneration increasing? *Br J Ophthalmol*. 1996;80:9-14.
3. Bressler NM, Bressler SB. Age-related macular degeneration. *Ophthalmology*. 1995;102:1206-1211.
4. Cho E, Hung S, Seddon JM. Nutrition and age-related macular degeneration: a review. In: Berger JW, Fine SL, Maguire MG, eds. *Age-Related Macular Degeneration*. St Louis, Mo: Mosby–Year Book Inc; 1998:57-67.
5. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA*. 1996; 276:1141-1146.

6. Seddon JM. Epidemiology of age-related macular degeneration. In: Albert DM, Jakobiec FA, eds. *Principles and Practice of Ophthalmology*. Philadelphia, Pa: WB Saunders Inc; 1999:521-531.
7. Verhoeff FH, Grossman HP. Pathogenesis of disciform degeneration of the macula. *Arch Ophthalmol*. 1937;18:561-585.
8. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share commom antecedents? *Ophthalmol Epidemiol*. 1999;6:125-143.
9. Sarks SH, Sarks JP. Age-related macular degeneration: atrophic form. In: Ryan SJ, Schachat AP, Murphy RM, eds. *Retina*. St Louis, Mo: Mosby–Year Book Inc; 1994:149-173.
10. Manson JE, Tosteson HT, Ridker PM, et al. The primary prevention of myocardial infarction. *N Engl J Med*. 1992;326:1406-1416.
11. Obisesan TO, Hirsch R, Kosoko O, Carlson L, Parrott M. Moderate wine consumption is associated with decreased odds of developing age-related macular degeneration in NHANES-1. *J Am Geriatr Soc*. 1998;46:1-7.
12. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51-65.
13. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992; 135:1114-1126.
14. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol*. 1991; 133:810-817.
15. Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med*. 1988;7:205-218.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177-188.
17. Goldberg J, Flowerdew G, Smith E, Brody JA, Tso MO. Factors associated with age-related macular degeneration: an analysis of data from the first National Health and Nutrition Examination Survey. *Am J Epidemiol*. 1988;128:700-710.
18. Hyman LG, Lilienfeld AM, Ferris FL, Fine SL. Senile macular degeneration: a case-control study. *Am J Epidemiol*. 1983;118:213-227.
19. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol*. 1992;110:1701-1708.
20. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1993;100:406-414.
21. Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration is associated with atherosclerosis: the Rotterdam Study. *Am J Epidemiol*. 1995;142:404-409.
22. 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;137:190-200.
23. 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;276:1147-1151.
24. Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Arch Ophthalmol*. 1997;115:741-747.
25. Sanders TA, Haines AP, Wormald R, Wright LA, Obeid O. Essential fatty acids, plasma cholesterol, and fat-soluble vitamins in subjects with age-related maculopathy and matched control subjects. *Am J Clin Nutr*. 1993;57:428-433.
26. Seddon JM, Ajani UA, Sperduto RD, et al, for the Eye Disease Case-Control Study Group. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA*. 1994;272:1413-1420.
27. Ritter LL, Klein R, Klein BE, Mares-Perlman JA, Jensen SC. Alcohol use and age-related maculopathy in the Beaver Dam Eye Study. *Am J Ophthalmol*. 1995;120: 190-196.
28. Smith W, Mitchell P. Alcohol intake and age-related maculopathy. *Am J Ophthalmol*. 1996;122:743-745.
29. Ajani U, Willett W, Miller D, et al. Alcohol consumption and neovascular age-related macular degeneration [abstract]. *Am J Epidemiol*. 1993;138:646.
30. Pawlosky RJ, Salem N Jr. Ethanol exposure causes a decrease in docosahexaenoic acid and an increase in docosapentaenoic acid in feline brains and retinas. *Am J Clin Nutr*. 1995;61:1284-1289.
31. 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;127:283-296.
32. Forman MR, Beecher GR, Lanza E, et al. Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women: a controlled dietary study. *Am J Clin Nutr*. 1995;62:131-135.
33. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little Brown & Co; 1986:87.
34. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105:488-495.
35. Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston, Mass: Little Brown & Co; 1987.
36. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med*. 1988;319:267-273.
37. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*. 1991;338:464-468.