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Research Article

A Pooled Analysis of Alcohol Consumption and Risk of Multiple Myeloma in the International Multiple Myeloma Consortium

Gabriella Andreotti[1], Brenda Birmann[3], Anneclaire J. De Roos[4], John Spinelli[5], Wendy Cozen[6], Nicola J. Camp[7], Kirsten Moysich[8], Brian Chiu[10], Emily Steplowski[2], Joseph Krzystan[2], Paolo Boffetta[9,14], Véronique Benhaim-Luzon[15], Paul Brennan[15], Silvia de Sanjosé[17], Laura Costas[17,18], Adele Seniori Costantini[19], Lucia Miligi[19], Pierluigi Cocco[20], Nikolaus Becker[21], Lenka Foretová[23], Marc Maynadié[16], Alexandra Nieters[22], Anthony Staines[24], Guido Tricot[11], Kevin Milliken[4], Dennis Weisenburger[12], Tongzhang Zheng[13], Dalsu Baris[1], and Mark P. Purdue[1]

Abstract

Background: Recent findings suggest that alcohol consumption may reduce risk of multiple myeloma.

Methods: To better understand this relationship, we conducted an analysis of six case–control studies participating in the International Multiple Myeloma Consortium (1,567 cases, 7,296 controls). Summary ORs and 95% confidence intervals (CI) relating different measures of alcohol consumption and multiple myeloma risk were computed by unconditional logistic regression with adjustment for age, race, and study center.

Results: Cases were significantly less likely than controls to report ever drinking alcohol (men: OR = 0.72; 95% CI, 0.59–0.89; women: OR = 0.81; 95% CI, 0.68–0.95). The inverse association with multiple myeloma was stronger when comparing current to never drinkers (men: OR = 0.57; 95% CI, 0.45–0.72; women: OR = 0.55; 95% CI, 0.45–0.68), but null among former drinkers. We did not observe an exposure–response relationship with increasing alcohol frequency, duration, or cumulative lifetime consumption. Additional adjustment for body mass index, education, or smoking did not affect our results; and the patterns of association were similar for each type of alcohol beverage examined.

Conclusions: Our study is, to our knowledge, the largest of its kind to date, and our findings suggest that alcohol consumption may be associated with reduced risk of multiple myeloma.

Impact: Prospective studies, especially those conducted as pooled analyses with large sample sizes, are needed to confirm our findings and further explore whether alcohol consumption provides true biologic protection against this rare, highly fatal malignancy. *Cancer Epidemiol Biomarkers Prev; 22(9); 1620–7. ©2013 AACR.*

Authors' Affiliations: [1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Rockville; [2]Information Management Services, Inc., Silver Spring, Maryland; [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [4]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [5]Cancer Control Research, BC Cancer Agency and School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada; [6]Department of Preventive Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California; [7]Division of Genetic Epidemiology, University of Utah School of Medicine, Salt Lake City, Utah; [8]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo; [9]Mount Sinai School of Medicine, New York, New York; [10]Department of Health Studies, University of Chicago, Chicago, Illinois; [11]Department of Internal Medicine, University of Iowa, Iowa City, Iowa; [12]Pathology and Microbiology Department, University of Nebraska Medical Center, Lincoln, Nebraska; [13]Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut; [14]International Prevention Research Institute; [15]International Agency for Research on Cancer, Lyon; [16]Registry of Hematological Malignancies of Côte d'Or, EA4184, University of Burgundy, Dijon, France; [17]Unit of Infections and Cancer, Catalan Institute of Oncology, IDIBELL, University of Barcelona, Barcelona, Spain; [18]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada; [19]Center for Study and Prevention of Cancer, Unit of Occupational and Environmental Epidemiology, Florence; [20]Department of Public Health, Occupational Health Section, University of Cagliari, Cagliari, Italy; [21]German Cancer Center, Division of Cancer Epidemiology; [22]Division of Clinical Epidemiology, German Cancer Research Centre, Heidelberg, Germany; [23]Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic; and [24]Department of Public Health, Public Health University College, Dublin, Ireland

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Novelty and Impact: To our knowledge, this is the largest analysis of alcohol consumption and multiple myeloma risk in men and women; therefore, we had excellent power to detect modest associations. Also, we were able to evaluate confounding and effect modification by putative risk factors. Our findings suggest that alcohol consumption may be associated with reduced risk of multiple myeloma, and point to the need for pooled analyses of cohort studies to better understand this relationship.

Corresponding Author: Gabriella Andreotti, National Cancer Institute, 6909 Medical Center Dr., Rm 6E622, MSC 9704, Bethesda, MD 20892-9704. Phone: 240-276-7284; Fax: 240-276-7835; E-mail: andreotg@mail.nih.gov

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Introduction

Multiple myeloma is a rare B-cell malignancy characterized by abnormal monoclonal plasma cells in the bone marrow, monoclonal immunoglobulin in serum and/or urine, lytic bone lesions, and in some patients, end-organ damage. Multiple myeloma is highly fatal, with a 5-year survival rate of less than 30% (1). In the United States, multiple myeloma is responsible for one third of all lymphoma-related deaths, despite accounting for only one fifth of diagnosed lymphoid malignancies (1).

The etiology of multiple myeloma is poorly understood. Established risk factors include older age, male sex, African ancestry, and obesity (2). Findings suggestive of a protective effect of alcohol consumption on multiple myeloma risk are less consistent, as shown in some case–control studies (3–6) and cohort investigations (7–10), but not others (11–14). Given the rarity of multiple myeloma many of these past investigations had limited statistical power to detect an alcohol effect of moderate size. To better understand the relationship between alcohol consumption and multiple myeloma, we conducted a pooled analysis of data from 6 case–control studies participating in the International Multiple Myeloma Consortium (IMMC).

Materials and Methods

Population

For this analysis, we pooled individual-level questionnaire data from the 6 case–control studies in the IMMC that had collected information on alcohol consumption (1,567 cases, 7,296 controls). Methods of previously published studies have been described (1, 4, 5, 15, 16). Enrollment period, age eligibility, study design (source of controls: hospital, population), number of cases and controls, and the centers within each study are summarized in Table 1. The European EpiLymph collaboration included studies that used both population and hospital-based controls, and Utah included spouse and population controls, which we considered as population controls for our analysis. Four of the studies were conducted in North America and the remaining in Europe. Participants with histologically confirmed incident primary diagnoses of multiple myeloma (ICD-O-3 diagnostic codes of 9731.3, 9732.3, 9734.3, ICD-9 of 203, and the equivalent) that occurred during the respective enrollment periods were eligible for inclusion in this analysis. However, one study, Utah, enrolled both prevalent and incident cases of multiple myeloma identified at a major regional myeloma clinic. In our sensitivity analysis, we examined associations for incident and prevalent cases separately, and found that the associations were not measurably different, therefore we included both types of cases in this analysis. The original data for each study were collected in-person by trained interviewers or by self-administered questionnaire. Protocols for the participating case–control studies were approved by the respective local institutional review boards, and study participants provided written informed consent.

Alcohol data

For this pooled analysis we requested data from each participating study, including variables on alcohol consumption, case–control status, and various demographic and lifestyle factors. We examined several measures of alcohol consumption, including usual alcohol drinking status (never, ever), former or current drinker, frequency (drinks per week), duration (years), and cumulative intake (drinks in lifetime). Alcohol drinking status was based on question(s) about their usual drinking behaviors prior to any current illness. Among ever drinkers, former/current status was calculated from questions about duration of drinking, therefore, we were unable to determine

Table 1. IMMC Lifestyle Factors Pooling Project (LFPP): studies with alcohol data

Case–control studies	Enrollment period	Age eligibility (years)	Study design[a]	Cases	Controls	% Caucasian
Italy[b]	1991–1993	20–74	Population	270	1,161	100
NCI-Connecticut	1996–2000	21–84	Population	183	716	91
NCI Population Health Study[c]	1986–1989	30–79	Population	573	2,131	57
Salt Lake City, Utah	2008–present	≥18	Population	119	247	98
EpiLymph[d]	1998–2004	≥17	Population	92	1,046	97
EpiLymph[e]	1998–2004	≥17	Hospital	186	1,419	96
Roswell Park Cancer Institute (RPCI), Buffalo, NY	1982–1998	≥20	Hospital	144	576	100

[a]Based on source of controls. Utah also included spouse controls.
[b]Italy: Firenze, Forli, Imperia, Latina, Ragusa, Siena, Torino.
[c]NCI Population Health Study: Atlanta, GA; Detroit, MI; NJ.
[d]EpiLymph: Italy, Germany (Ludwigshafen/Upper Palatinate, Heidelberg/Rhine-Neckar County, Wurzburg/Lower Frankonia, Hamburg, Bielefeld, and Munich).
[e]EpiLymph: Czech Republic, Ireland, France (Amiens, Fijon, Monepellier), Spain (Barcelona, Tortosa, Reus, Madrid).

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former/current status for subjects who did not provide drinking duration (229 cases, 1,140 controls). In our sensitivity analysis we examined the associations between ever drinking and multiple myeloma for subjects with and without current/former drinking status, and found that the associations were not measurably different. We also examined associations for former drinkers excluding participants who recently quit (i.e., ceased drinking within 2 years prior to completion of the questionnaire), as well as current drinkers including the participants who recently quit.

We defined alcohol drinking duration as the total number of years beverage-specific (beer, wine, liquor) or total alcohol was consumed. When not directly provided we calculated beverage-specific consumption frequencies (the average number of standard drinks per week) within each study by multiplying the reported number of beverage-specific drinks per week by the estimated volume per serving in North America (350 mL beer, 120 mL wine, 45 mL liquor) or Europe (250 mL beer, 100 mL wine, 35 mL liquor; ref. 17). This product was multiplied by the estimated ethanol content of each beverage (beer 5%, wine 12%, liquor 40%), and then divided by the reported average volume of ethanol per serving across the 3 beverage types, 15.6 mL (17). The consumption frequency for total alcohol was calculated by dividing cumulative intake by duration for total alcohol. Beverage-specific estimates of cumulative intake were calculated by multiplying the duration and consumption frequencies for each beverage type. The cumulative intake of total alcohol was calculated as the sum of beverage-specific cumulative intake. Alcohol sources beyond beer, wine, and liquor, if provided, were minimal and not included in any harmonized alcohol variables.

Statistical analysis

Data were checked for internal consistency, outliers, and missing values before pooling across studies. In a sensitivity analysis, we assessed the impact of excluding subjects with values above the 95th percentile for alcohol frequency, duration, and cumulative intake, and found that it did not measurably impact risk estimates. Therefore, we decided not to drop outliers. We found no outliers for the nondrinking covariates. Missing data for both the alcohol drinking variables and other covariates were retained in the models, because we found that dropping missing data did not impact our results.

Because of differences in alcohol drinking by sex, we categorized the quantitative alcohol variables using sex-specific cut points based on the tertiles among the pooled controls: frequency (men: <8.7, ≤21.4, >21.4, women: <1.6, ≤7.1, >7.1 drinks per week); duration (men: <30, ≤43, >43, women: <23, ≤40, >40 years); cumulative intake (men: 16.882, ≤48,400, >48,400, women: <2,743, ≤12,600, >12,600 drinks). These cut points were also used to categorize beverage-specific consumption measures.

All analyses were conducted using SAS unless otherwise specified. Within each study, we computed sex-specific ORs with 95% confidence intervals (95% CI) relating the aforementioned alcohol variable categories to multiple myeloma risk through unconditional logistic regression, with adjustment for age group (<50, 50–59, 60–69, 70+ years), race (White, Black, other), and study center. Tests of trend for alcohol frequency, duration, and cumulative intake were conducted by linear regression analysis. We used the R package MiMa (18) to conduct a meta-analysis of study-specific findings using both random and fixed effects models. Heterogeneity between studies in the meta-analysis was assessed using the Q statistic.

We also conducted a pooled analysis in a single harmonized data set, with ORs and 95% CIs for alcohol measures computed using unconditional logistic regression with adjustment for age, race, and study center. We evaluated potential confounding in analyses additionally adjusted for education level (<12 years of study; 12+ years or high school graduate; some attendance at college, technical, or vocational school after high school; graduation from college without further studies; or, other), body mass index (BMI: <18.5, <25, <30, <35, 35+ kg/m^2), and smoking status (ever, never). To assess effect modification of alcohol–multiple myeloma associations, we investigated associations of alcohol consumption across strata of study design, smoking status, and BMI using the likelihood ratio test.

Results

In the pooled study population, approximately 45% of cases and 50% of controls were male; close to 85% of cases and controls were white (Supplementary Table S1). Distributions of other covariables differed slightly but not dramatically between pooled cases and controls.

Age-adjusted study-specific associations for ever versus never drinking alcohol were fairly homogeneous in both random and fixed effects models. In the random effects models, tests of heterogeneity between studies did not achieve statistical significance among men ($P = 0.61$) or women ($P = 0.40$; Fig. 1). Because the results from the meta-analysis and pooled analysis were virtually identical, we present results from the pooled analysis, unless otherwise specified.

In the pooled analysis of ever versus never consumption of alcohol, ever consumption was associated with a decreased risk of multiple myeloma for men (OR = 0.72; 95% CI, 0.59–0.89) and women (OR = 0.81; 95% CI, 0.68–0.95; Table 2). The inverse association was stronger for current drinkers (men: OR = 0.57; 95% CI, 0.44–0.72; women: OR = 0.55; 95% CI, 0.45–0.68), as well as for current drinkers combined with participants who recently quit (i.e., ceased drinking within 2 years prior to questionnaire). The risks for former drinkers compared to never drinkers were elevated, however, after excluding those who recently quit, the associations were null. Among current drinkers, including those who recently quit, there was no evidence of a monotonic trend of multiple myeloma risk with increasing alcohol drinking frequency, duration, or cumulative intake for either men

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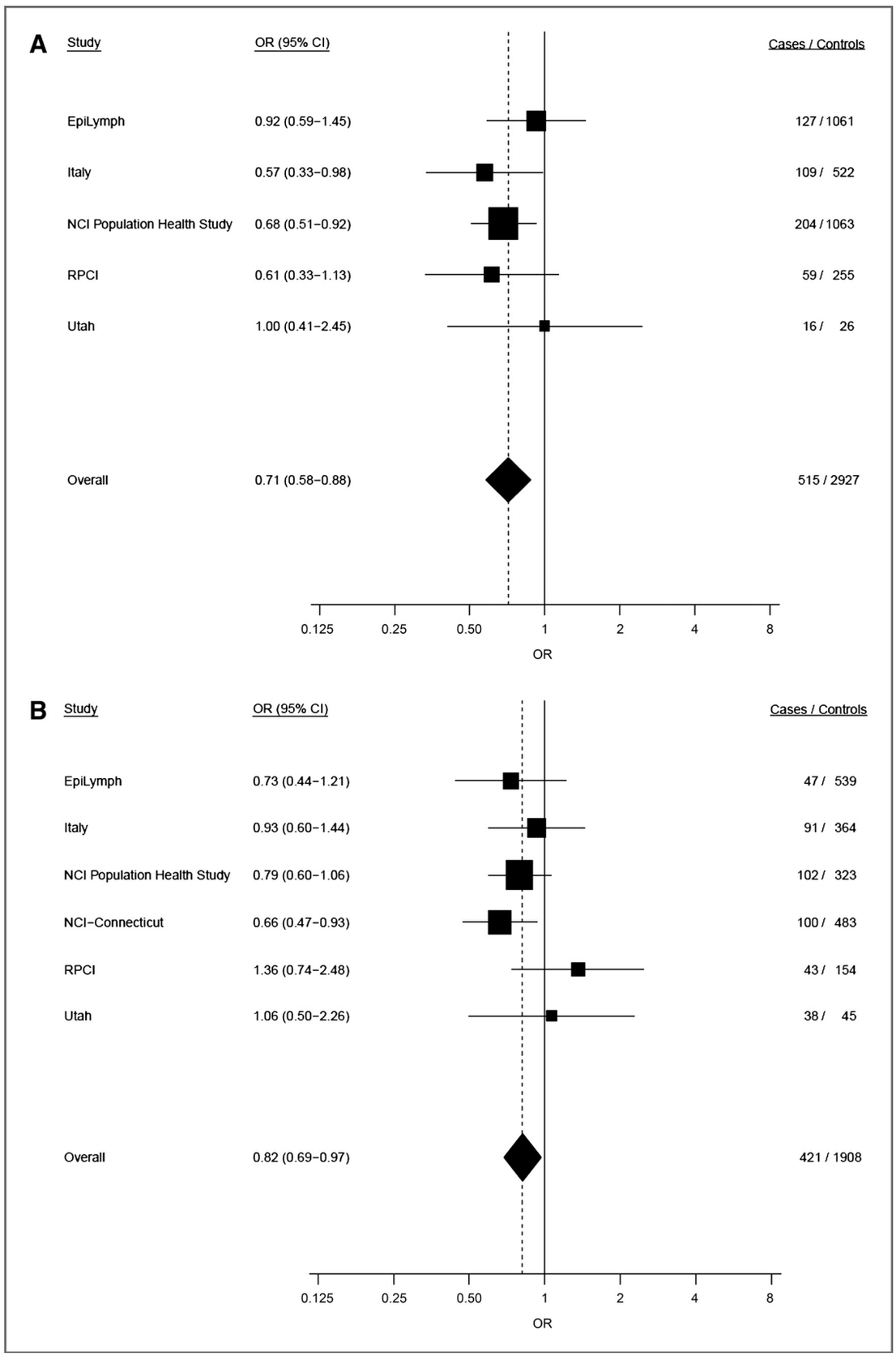

Figure 1. A, study-specific risks of multiple myeloma for ever versus never drinking alcohol among males. P-heterogeneity = 0.61. B, study-specific risks of multiple myeloma for ever versus never drinking alcohol among females. P-heterogeneity = 0.40.

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Table 2. Risk of multiple myeloma associated with alcohol consumption in pooled study population by gender

Alcohol consumption	Male				Female				$P_{interaction}$
	Case	Control	OR (95% CI)[a,b]	OR (95% CI)[a,c]	Case	Control	OR (95% CI)[a,b]	OR (95% CI)[a,c]	
Total	699	3674	–	–	856	3541	–	–	
Never drinker	184	747	**1.00** (–)	–	435	1633	**1.00** (–)	–	
Ever drinker	515	2927	0.72 (0.59–0.89)	–	421	1908	0.81 (0.68–0.95)	–	0.59
Current	257	1803	0.57 (0.45–0.72)	–	202	1179	0.55 (0.45–0.68)	–	
Current[d]	289	1851	0.65 (0.52–0.82)	–	226	1199	0.62 (0.51–0.77)	–	
Former	126	449	1.11 (0.84–1.47)	–	122	264	1.32 (1.02–1.70)	–	
Former[e]	94	401	0.90 (0.66–1.24)	–	98	244	1.11 (0.85–1.47)	–	
Current[d] drinker frequency[f]									
T1	61	317	0.70 (0.50–0.98)	**1.00** (–)	43	279	0.55 (0.38–0.79)	**1.00** (–)	
T2	54	412	0.49 (0.34–0.70)	0.74 (0.48–1.12)	67	296	0.62 (0.45–0.85)	1.01 (0.64–1.59)	
T3	74	461	0.62 (0.45–0.87)	0.95 (0.63–1.41)	86	348	0.77 (0.57–1.04)	1.22 (0.79–1.91)	0.21
P_{trend}			(0.01)	(0.90)			(0.23)	(0.36)	
Current[d] drinker duration[g]									
T1	63	571	0.64 (0.45–0.92)	**1.00** (–)	37	359	0.51 (0.34–0.75)	**1.00** (–)	
T2	95	578	0.71 (0.52–0.96)	1.12 (0.73–1.73)	93	404	0.76 (0.58–1.01)	1.45 (0.91–2.31)	
T3	122	645	0.61 (0.46–0.81)	0.98 (0.61–1.58)	95	426	0.57 (0.43–0.75)	0.99 (0.59–1.65)	0.27
P_{trend}			(0.001)	(0.84)			(0.001)	(0.86)	
Current[d] drinker cumulative[h]									
T1	61	370	0.65 (0.46–0.91)	**1.00** (–)	49	288	0.63 (0.44–0.91)	**1.00** (–)	
T2	59	403	0.56 (0.40–0.80)	0.90 (0.60–1.36)	59	317	0.56 (0.41–0.78)	0.79 (0.51–1.23)	
T3	71	419	0.61 (0.44–0.86)	1.02 (0.67–1.54)	88	318	0.76 (0.57–1.02)	0.99 (0.64–1.53)	0.53
P_{trend}			(0.01)	(0.87)			(0.16)	(0.79)	

[a]Adjusted for age, race, and center.
[b]Reference group is never drinkers.
[c]Reference group is among drinkers.
[d]Includes participants who ceased drinking within 2 years prior to completion of questionnaire.
[e]Excludes participants who ceased drinking within 2 years prior to completion of questionnaire.
[f]Average number of standard drinks per week.
Male tertiles: <8.7, ≤21.4, >21.4.
Female tertiles: <1.6, ≤7.1, >7.1.
[g]Number of years consumed.
Male tertiles: <30, ≤43, >43
Female tertiles: <23, ≤40, >40
[h]Lifetime number of standard drinks (frequency × duration).
Male tertiles: <16,882, ≤48,400, >48,400
Female tertiles: <2,743, ≤12,600, >12,600

or women, even though some P_{trend} values were statistically significant when compared to never drinkers (Table 2). Similar patterns of association were seen among ever and former drinkers (excluding those who recently quit; Supplementary Table S2). These associations did not change with additional adjustment for education, smoking status, or BMI (data not shown).

In the analysis stratified by study design, the inverse association of ever alcohol drinking with multiple myeloma was significant among population-based studies (OR = 0.73; 95% CI, 0.63–0.84), but not among hospital-based studies (OR = 0.90; 95% CI, 0.68–1.18; Table 3). The interaction of ever versus never alcohol drinking with study design was statistically significant ($P = 0.01$). In contrast, the associations were not significantly different by smoking status or BMI. We also found consistent results among black participants (cases = 231, controls = 992).

Similar patterns of association were seen for each type of alcohol beverage (beer, wine, liquor; Supplementary Table S3). We found reduced risks of multiple myeloma among ever drinkers of beer, wine, and liquor, but no meaningful dose–response associations.

Discussion

In this pooled analysis of 1,567 cases and 7,296 controls, participants who ever drank alcohol had a lower risk of multiple myeloma compared to those who never drank.

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Table 3. Risk of multiple myeloma associated with alcohol consumption in pooled study population by various factors

	Case	Control	OR (95% CI)[a,b]	Case	Control	OR (95% CI)[a,b]	$P_{interaction}$
	Study design						
Alcohol status	**Hospital**			**Population**			
Never drinker	128	810	**1.00** (–)	491	1570	**1.00** (–)	
Ever drinker	197	1,148	0.90 (0.68–1.18)	739	3687	0.73 (0.63–0.84)	0.01
Current	79	637	0.76 (0.54–1.07)	380	2345	0.53 (0.45–0.63)	
Current[c]	91	666	0.81 (0.58–1.14)	424	2384	0.60 (0.51–0.71)	
Former	31	166	1.04 (0.66–1.64)	217	547	1.21 (0.99–1.48)	
Former[d]	19	156	0.79 (0.45–1.37)	173	508	1.02 (0.82–1.27)	
	Smoking status						
	Ever smoker			**Never smoker**			
Never drinker	207	849	**1.00** (–)	412	1528	**1.00** (–)	
Ever drinker	576	3,223	0.74 (0.61–0.89)	356	1611	0.84 (0.70–1.01)	0.50
Current	278	2,017	0.53 (0.43–0.66)	179	965	0.65 (0.52–0.81)	
Current[c]	315	2,070	0.61 (0.49–0.76)	197	980	0.71 (0.57–0.88)	
Former	161	512	1.16 (0.90–1.50)	86	201	1.34 (1.00–1.80)	
Former[d]	124	459	0.95 (0.72–1.26)	68	186	1.10 (0.80–1.51)	
	BMI						
	BMI <25 kg/m^2			**BMI ≥ 25 kg/m^2**			
Never drinker	217	881	**1.00** (–)	318	1149	**1.00** (–)	
Ever drinker	320	1,382	0.79 (0.64–0.98)	392	2023	0.73 (0.60–0.88)	0.77
Current	143	1,106	0.54 (0.41–0.69)	164	1014	0.57 (0.45–0.72)	
Current[c]	169	1,136	0.62 (0.48–0.79)	193	1051	0.66 (0.52–0.83)	
Former	109	309	1.38 (1.03–1.84)	134	380	1.10 (0.86–1.42)	
Former[d]	83	279	1.11 (0.80–1.52)	105	343	0.94 (0.71–1.24)	

[a]Adjusted for sex, age, race, and center.
[b]Reference group is never drinkers.
[c]Includes participants who ceased drinking within 2 years before completion of questionnaire.
[d]Excludes participants who ceased drinking within 2 years before completion of questionnaire.

This significant inverse association persisted for current drinkers, but not for former drinkers. We found no dose–response relationships with frequency, duration, or cumulative intake of alcohol. The alcohol–multiple myeloma associations were similar by different types of alcoholic beverage.

An association between alcohol drinking and decreased risk of multiple myeloma has also been observed in some cohort studies (7, 10, 19, 20). The largest of these studies, an analysis within the Million Women cohort that included 1,584 cases followed for a mean of 10 years, reported a relative risk of 0.88 (95% CI, 0.80–0.98) per 10 g of alcohol consumed per day (10). A cohort study in Japan with 89 multiple myeloma cases followed for an average of 13 years found a nonsignificant 53% decreased relative risk for high versus occasional alcohol intake among current drinkers (7), and a cohort study of female teachers in California with 101 multiple myeloma cases followed for more than 10 years found a nonsignificant decreased risk for current drinkers, particularly for lighter drinkers (RR = 0.65; 95% CI, 0.39–1.09), compared to nondrinkers (8). No clear evidence of an association was seen in the CPSII cohort (9), the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (20), or in the San Francisco Health Care program (14). A large pooled case–control analysis of alcohol intake and non-Hodgkin lymphoma (NHL), a collection of lymphoid malignancies that are predominantly B-cell in origin, like multiple myeloma, had findings very similar to our own, with alcohol consumption associated with reduced risk, particularly for current drinkers, but no dose–response relationship with consumption frequency or duration (21).

The lack of dose–response associations in this study limits our interpretation for a true protective effect.

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Furthermore, the biological effects of alcohol and relationship to cancer are not clear. It has been suggested that light to moderate alcohol intake can attenuate proinflammatory cytokines and chemokines that may promote lymmphomagenesis (22–24), improve cellular and humoral immune responses, and improve DNA repair capacity (25). Also, antioxidants such as resveratrol in wine and flavonoids in beer may have anticarcinogenic effects (26, 27). In contrast, heavy alcohol consumption has been shown to impair immune function and increase susceptibility to infection (28).

Our study is, to our knowledge, the largest investigation of alcohol consumption and multiple myeloma risk in men and women. As a consequence, we had excellent power to detect associations of weak magnitude, whereas the majority of previous investigations had low power to detect a statistically significant association of the magnitude (OR = 0.73) that we observed in this study. Another strength of our analysis was the availability of extensive data on other putative demographic and lifestyle risk factors for multiple myeloma with which we were able to evaluate confounding and effect modification.

An inherent limitation of this study is the retrospective case–control design of the participating studies, in which information on alcohol consumption was collected after disease diagnosis. Although alcohol drinking status was based on participants' usual drinking behavior prior to illness, the critical window of exposure may not be captured in retrospective case–control studies because the effects of alcohol are based on consumption close to time of diagnosis. Not having a clearly defined reference period, such as 1 to 3 years before diagnosis, across all studies limited our ability to rule out potential disease effects before diagnosis. We were able to exclude former drinkers who had ceased drinking within the 2 years before the completion of the questionnaire because these participants would be most subject to some influence of preclinical disease on alcohol use. Nevertheless, we cannot rule out the possibility that our findings could be due to confounding of unascertained or unknown risk factors, or a reflection of selection bias due to differential participation or exposure misclassification between cases and controls. We did not have data on the presence of other medical conditions, such as autoimmune disorders, that may have led to participants avoiding alcohol. However, we note that the results from several prospective cohorts, including the largest cohort analysis of alcohol and multiple myeloma conducted to date, support our findings.

In conclusion, our pooled analysis suggests that people who drink alcoholic beverages have a lower risk of multiple myeloma. A pooled analysis among prospective cohorts with sufficiently detailed alcohol consumption data would be a valuable source of further confirmation of the present findings. If confirmed, the data collectively suggest that alcohol consumption may protect against this rare, highly fatal malignancy. Nevertheless, the biologic mechanisms underlying this association need to be elucidated further before we can state that alcohol consumption may confer true biologic protection, particularly because alcohol is linked to an increased risk of some adverse health outcomes and so may have limited value in prevention of multiple myeloma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G. Andreotti, B.M. Birmann, A.J. De Roos, N.J. Camp, K.B. Moysich, P. Boffetta, S. De Sanjose, A. Staines, K. Milliken, T. Zheng, D. Baris, M.P. Purdue

Development of methodology: G. Andreotti, A.J. De Roos, K.B. Moysich, A. Staines, G. Tricot, T. Zheng, M.P. Purdue

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Andreotti, W. Cozen, N.J. Camp, K.B. Moysich, P. Boffetta, P. Joseph Brennan, S. De Sanjose, L. Costas, A.S. Costantini, L. Miligi, P. Cocco, N. Becker, L. Foretova, M. Maynadié, A. Nieters, A. Staines, G. Tricot, K. Milliken, T. Zheng, D. Baris, M.P. Purdue

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Andreotti, B.M. Birmann, A.J. De Roos, N.J. Camp, K.B. Moysich, E. Steplowski, J. Krzystan, S. De Sanjose, T. Zheng, D. Baris, M.P. Purdue

Writing, review, and/or revision of the manuscript: G. Andreotti, B.M. Birmann, A.J. De Roos, J.J. Spinelli, W. Cozen, N.J. Camp, B.C. Chiu, E. Steplowski, P. Boffetta, P. Joseph Brennan, S. De Sanjose, L. Costas, L. Miligi, P. Cocco, N. Becker, L. Foretova, A. Staines, D.D. Weisenburger, T. Zheng, D. Baris, M.P. Purdue

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Andreotti, E. Steplowski, J. Krzystan, V. Benhaim-Luzon, L. Foretova

Study supervision: G. Andreotti, N.J. Camp, K. Milliken, T. Zheng, D. Baris, M.P. Purdue

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