IJC
International Journal of Cancer

Cancer Epidemiology

Alcohol and lung cancer risk among never smokers: A pooled analysis from the international lung cancer consortium and the SYNERGY study

Gordon Fehringer[1], Darren R. Brenner[1,2,3], Zuo-Feng Zhang[4], Yuan-Chin Amy Lee[5], Keitaro Matsuo[6], Hidemi Ito[7], Qing Lan[8], Paolo Vineis[9], Mattias Johansson[2], Kim Overvad[10], Elio Riboli[11], Antonia Trichopoulou[12,13], Carlotta Sacerdote[14], Isabelle Stucker[15], Paolo Boffetta[16], Paul Brennan[2], David. C. Christiani[17], Yun-Chul Hong[18], Maria Teresa Landi[8], Hal Morgenstern[19], Ann G. Schwartz[20], Angela S. Wenzlaff[20], Gad Rennert[21], John R. McLaughlin[22], Curtis C. Harris[23], Susan Olivo-Marston[24], Irene Orlow[25], Bernard J. Park[26], Marjorie Zauderer[27,28], Juan M. Barros Dios[29,30], Alberto Ruano Raviña[29,30], Jack Siemiatycki[31], Anita Koushik[31], Philip Lazarus[32], Ana Fernández-Somoano[33], Adonina Tardon[33], Loic Le Marchand[34], Hermann Brenner[35,36,37], Kai-Uwe Saum[35], Eric J. Duell[38], Angeline S. Andrew[39], Neonila Szeszenia-Dabrowska[40], Jolanta Lissowska[41], David Zaridze[42], Peter Rudnai[43], Eleonora Fabianova[44], Dana Mates[45], Lenka Foretova[46], Vladimir Janout[47], Vladimir Bencko[48], Ivana Holcatova[48], Angela Cecilia Pesatori[49,50], Dario Consonni[49], Ann Olsson[2,51], Kurt Straif[2] and Rayjean J. Hung[1]

[1] Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Canada
[2] International Agency for Research on Cancer, Lyon, France
[3] Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada
[4] Department of Epidemiology, School of Public Health, UCLA, Los Angeles, CA
[5] Department of Family and Preventive Medicine, School of Medicine, University of Utah, Salt Lake City, UT
[6] Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
[7] Division Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
[8] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD
[9] Division of Epidemiology, Public Health and Primary Care, Faculty of Medicine, Imperial College London, London, United Kingdom
[10] Department of Public Health, Section for Epidemiology, Aarhus University, Denmark
[11] Department of Epidemiology and Biostatistics, Imperial College, London, United Kingdom
[12] Hellenic Health Foundation, Athens, Greece
[13] World Health Organization Collaborating Center for Food and Nutrition Policies, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece
[14] Unit of Cancer Epidemiology, Piedmont Children Cancer Registry, Città della Salute e della Scienza di Torino Hospital and CPO Piemonte, Turin, Italy
[15] Department of Environmental Epidemiology, INSERM, Villejuif, U170, France
[16] Mount Sinai School of Medicine, The Tisch Cancer Institute, New York, NY
[17] Harvard School of Public Health, Massachusetts General Hospital/Harvard Medical School, Boston, MA
[18] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

Key words: alcohol, lung cancer, wine, beer, liquor
Additional Supporting Information may be found in the online version of this article.
This article was published online on 27 February 2017. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 14 March 2017.
Grant sponsor: Canadian Cancer Society; **Grant number:** CCSRI no. 020214; **Grant sponsor:** Ministry of Education, Science, Sports, Culture and Technology of Japan (AICHI: MEXT Kakenhi); **Grant numbers:** 170150181 and 26253041; **Grant sponsor:** European Commission's INCO-COPERNICUS Program; **Grant number:** IC15-CT96-0313; **Grant sponsor:** National Institutes of Health; **Grant numbers:** NIH R01CA060691, NIH R01CA87895, NIH P30CA022453, NIH P30 CA008748, HHSN261201200011; **Grant sponsor:** National Cancer Institute; **Grant numbers:** CA092824, CA074386, CA090578; **Grant sponsor:** FIS-FEDER/Spain; **Grant numbers:** FIS-01/310, FIS-PI03-0365, and FIS-07-BI060604; **Grant sponsor:** FICYT/Asturias; **Grant numbers:** FICYT PB02-67, FICYT IB09-133; **Grant sponsor:** National Center for Research Resources; **Grant number:** P20RR018787; **Grant sponsor:** Research Intention PRVOUK; **Grant number:** PRVOUK P28/1LF/6; **Grant sponsors:** Intramural Research Program of the National Institutes of Health; Third Term Comprehensive 10-Year Strategy for Cancer Control from Ministry Health, Labour and Welfare of Japan; Steps for Breath, the Labrecque Foundation and the Society of Memorial Sloan-Kettering Cancer Center; The University of Oviedo, Asturias, Spain; The Fundacion Caja de Ahorros de Asturias and the Ciber de Epidemiologia y Salud Publica, CIBERESP, Spain; Baden-Württemberg State Ministry of Research, Science and Arts; Danish Cancer Society
DOI: 10.1002/ijc.30618
History: Received 29 Aug 2016; Accepted 19 Dec 2016; Online 24 Jan 2017
Correspondence to: Rayjean J. Hung, Ph.D., M.S. Lunenfeld-Tanenbaum Research Institute, Sinai Health System, University of Toronto, 60 Murray St. Toronto ON M5T 3L9. Canada, E-mail: rayjean.hung@lunenfeld.ca

[19] Departments of Epidemiology and Environmental Health Sciences, School of Public Health and Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI
[20] Karmanos Cancer Institute, Wayne State University, Detroit, MI
[21] Department of Community Medicine and Epidemiology, Carmel Medical Center and Bruce Rappaport Faculty of Medicine, Israel Institute of Technology and Clalit Health Services National Cancer Control Center, Haifa, Israel
[22] Public Health Ontario, Toronto, Canada
[23] Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD
[24] College of Public Health, The Ohio State University, Columbus, OH
[25] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY
[26] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[27] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[28] Weill Cornell Medical College, Cornell University, New York, NY
[29] Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain
[30] CIBER de Epidemiología y Salud Pública, Madrid, Spain
[31] University of Montreal Hospital Research Center (CRCHUM) and School of Public Health, Montreal, Canada
[32] Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, Spokane, Washington
[33] IUOPA, University Institute of Oncology, University of Oviedo, and CIBERESP, Spain
[34] University of Hawaii Cancer Center, Honolulu, Hawaii
[35] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
[36] Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany
[37] German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
[38] Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain
[39] Norris Cotton Cancer Center, Geisel School of Medicine, Dartmouth College, Lebanon, USA
[40] The Nofer Institute of Occupational Medicine (NIOM), Lodz, Poland
[41] Department of Cancer Epidemiology and Prevention, Cancer Center Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland
[42] Institute of Carcinogenesis, Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia
[43] National Institute of Environmental Health, Budapest, Hungary
[44] Specialized Institute of Hygiene and Epidemiology, Banská Bystrica, Slovakia
[45] National Institute of Public Health, Bucharest, Romania
[46] Masaryk Memorial Cancer Institute, Brno, Czech Republic
[47] Palacky University, Olomouc, Czech Republic
[48] Institute of Hygiene and Epidemiology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
[49] Epidemiology Unit, Department of Preventive Medicine, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy
[50] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[51] The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

It is not clear whether alcohol consumption is associated with lung cancer risk. The relationship is likely confounded by smoking, complicating the interpretation of previous studies. We examined the association of alcohol consumption and lung cancer risk in a large pooled international sample, minimizing potential confounding of tobacco consumption by restricting analyses to never smokers. Our study included 22 case-control and cohort studies with a total of 2548 never-smoking lung cancer patients and 9362 never-smoking controls from North America, Europe and Asia within the International Lung Cancer Consortium (ILCCO) and SYNERGY Consortium. Alcohol consumption was categorized into amounts consumed (grams per day) and also modelled as a continuous variable using restricted cubic splines for potential non-linearity. Analyses by histologic sub-type were included. Associations by type of alcohol consumed (wine, beer and liquor) were also investigated. Alcohol consumption was inversely associated with lung cancer risk with evidence most strongly supporting lower risk for light and moderate drinkers relative to non-drinkers (>0–4.9 g per day: OR = 0.80, 95% CI = 0.70–0.90; 5–9.9 g per day: OR = 0.82, 95% CI = 0.69–0.99; 10–19.9 g per day: OR = 0.79, 95% CI = 0.65–0.96). Inverse associations were found for consumption of wine and liquor, but not beer. The results indicate that alcohol consumption is inversely associated with lung cancer risk, particularly among subjects with low to moderate consumption levels, and among wine and liquor drinkers, but not beer drinkers. Although our results should have no relevant bias from the confounding effect of smoking we cannot preclude that confounding by other factors contributed to the observed associations. Confounding in relation to the non-drinker reference category may be of particular importance.

Lung cancer continues to be the most common cancer and the leading cause of cancer death worldwide, with 1.8 million new cases and 1.6 million deaths reported annually.[1] Tobacco smoking is the primary cause of lung cancer accounting for >80% of all lung cancer diagnoses.[2] Other known risk factors include exposure to occupational and environmental

What's new?

When considering how alcohol affects lung cancer risk, it's been challenging to tease out the impact of alcohol from that of smoking. Now, these authors have pooled data from 22 international studies involving only people who have never smoked. They've conducted the largest case-control analysis to date looking at alcohol and lung cancer risk in the absence of tobacco. People who drank low to moderate amounts of wine and liquor particularly – not beer – did have a lower risk of lung cancer, although confounding by factors other than smoking, particularly in relation to the non-drinkers reference group, cannot be ruled out.

carcinogens such as asbestos and radon.[3,4] Although less common than lung cancer in smokers, lung cancer among never smokers still impacts a significant portion of the population, and is recognized as the seventh most common cause of cancer mortality worldwide.[5]

Alcohol is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, and it has been hypothesized that alcohol consumption may modulate lung cancer risk. However, definite conclusions could not be drawn from previous epidemiologic investigations because of inconsistent results across studies.[6–9] Since alcohol intake is strongly correlated with tobacco smoking,[9] the confounding effect poses the main methodological challenge when investigating alcohol consumption and lung cancer risk. Although few previous studies have investigated the association between alcohol consumption and lung cancer risk in never smokers, they were limited in precision. Furthermore, associations by histologic subtype and beverage type (e.g., wine, beer and liquor) have not been thoroughly investigated among never smokers.[8,10,11]

In this study, we investigated the association of alcohol consumption and lung cancer risk in never smokers in a large pooled dataset of 22 studies from the International Lung Cancer Consortium (ILCCO)[12] and the SYNERGY project,[13] in order to obtain sufficient sample size to thoroughly examine this association stratified by histologic subtype and beverage type while minimizing the effect of residual confounding by smoking.

Material and Methods

Study populations

Details regarding ILCCO and SYNERGY have been reported previously[12,13] and are available on web portals http://ilcco.iarc.fr and http://synergy.iarc.fr. Twenty-two studies from these consortia provided data for this analysis, including 10 studies in North America, seven studies in Europe and five studies in Asia or other areas. All studies were either case-control or analyzed as nested case-control data sets, with 11 population-based, seven hospital-based, three with mixed control groups and one cohort (Supporting Information Table 1 for further details). Control groups were at minimum matched on age and sex. Each study received approval from local ethics review boards.

Assessments of alcohol consumption

Consumption of alcohol and tobacco smoking was collected in each study by questionnaire. Never-smokers were defined as those who smoked <100 cigarettes in their lifetime whenever this information is available, or based on study questionnaire. Non-drinkers were defined as those who did not consume alcohol, or at least occasionally, in their lifetime (Supporting Information Table 2). Most studies ($n = 18$) included details regarding quantity and type of alcohol consumed (*e.g.*, beer, wine and liquor) and duration of drinking. Some questionnaires included additional types of alcohol (*e.g.*, Aperatif, Soku, Sachi), which were included in the estimation of average lifetime alcohol consumption (Supporting Information Table 2). Duration of drinking data were generally available for multiple time periods (Supporting Information Table 2).

Amount of alcohol consumption was converted to standardized drink units. These were then converted to grams per day using 12 g of alcohol per drink unit based on on-line data from the International Agency for Research on Cancer (http://cancer-code-europe.iarc.fr/) and the Canadian Nutrient File by Health Canada. Lifetime average grams of alcohol consumed per day (overall and separately by beverage types) were estimated based on consumption frequency, changes in consumption patterns over the lifetime and beverage-specific alcohol content. For four studies where duration data were not available, we used current drinking as a proxy for average lifetime alcohol consumption. Non-drinkers were chosen as the reference category (instead of combining non-drinkers with low-level drinkers) to ensure that lung cancer risk related to low amounts of alcohol consumption could be assessed and that our results were comparable to previous large studies which also chose non-drinkers as the reference group. We also created detailed categories to capture the dose-response relationship for moderate and heavy alcohol consumption.

Statistical analysis

We applied unconditional logistic regression to estimate odds ratios and confidence limits for the association of average lifetime alcohol consumption with lung cancer risk based on the pooled dataset. To understand the association for different lung cancer histological subtypes we examined associations separately by histology. We also modelled average lifetime grams per day of wine consumption, beer consumption and liquor consumption separately for lung cancer risk, mutually adjusted by beverage type. The potential non-linear dose-response relationship was assessed using restricted cubic splines. All models were adjusted for sex, age, ethnicity, education and study centre/sub-centre. Race/ethnicity was

Table 1. Demographic characteristics of study subjects

Characteristics	Case no. (%)	Control no. (%)
Overall	2548	9362
Sex		
Female	1978 (77.6)	5351 (57.2)
Male	570 (22.4)	4011 (42.8)
Age (years)		
Mean	60.8	60.5
Standard deviation	11.8	11.6
Age groups		
<50	453 (17.8)	1710 (18.3)
50 < 60	657 (25.8)	2274 (24.3)
60 < 70	810 (31.8)	3155 (33.7)
70+	628 (24.6)	2223 (23.7)
Race/ethnicity		
White, European	1511 (59.3)	6600 (70.5)
Black, African-American	67 (2.6)	463 (4.9)
Asian	906 (35.6)	2077 (22.2)
Latino	41 (1.6)	124 (1.3)
Other unknown	23 (0.9)	98 (1.0)
Education		
Basic/elementary	567 (22.3)	2152 (23.0)
Up to high school graduate	572 (22.4)	2791 (29.8)
Some postsecondary and higher	903 (35.4)	2011 (21.5)
Missing or unspecified	506 (19.9)	2408 (25.7)

collected according to investigator chosen categories (Table 1). We chose to adjust for race/ethnicity because alcohol consumption and lung cancer risk in non-smokers has been found to vary across race/ethnicity groups[14,15] indicating that race/ethnicity could confound the association between alcohol intake and lung cancer risk.

Because metabolism of alcohol varies between sexes, we conducted sex-specific analyses for overall alcohol consumption. To evaluate potential biases created by study design, stratified analysis (hospital- verses population-based/cohort) was conducted. For studies where data were available, we examined whether potential confounders might at least in part influence the observed associations between overall alcohol intake and lung cancer risk. We examined confounding by occupational exposure (data available for 5 studies) by adjusting for study subjects' job history (whether they held jobs known or suspected to be associated with excess risk of lung cancer such as mining, chemical industry, metal refining, and others).[16,17] We also adjusted for previous medical history of tuberculosis, chronic pulmonary disorder, emphysema or pneumonia (five studies) and exposure to environmental tobacco smoke (10 studies) in regression models. Statistical analyses were performed with SAS (SAS Institute, Inc., Cary, NC) and R (Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2548 never-smoking lung cancer patients and 9362 never-smoking controls from the 22 studies were included in this investigation (Table 1). Mean age of cases and controls were similar (60.8 for cases, 60.5 for controls). There were more females among cases (78%) than controls (57%), resulting from the original frequency matching by sex being performed in both ever and never smokers combined, with the tendency for females to be over-represented among cases in never smoking samples. Cases were slightly more educated than controls. The majority of the subjects were of European descent. Cases were less likely to be of European descent than controls due to the large number of controls from the European-based EPIC study where frequency matching included five controls per case.

Overall alcohol consumption

The associations between average lifetime alcohol consumption and lung cancer risk by consumption categories are presented in Table 2. Low to moderate alcohol consumption was shown to be inversely associated with lung cancer risk when compared to non-drinkers with ORs of 0.80 (95%CI = 0.70–0.90), 0.82 (95%CI = 0.69–0.99) and 0.79 (95%CI = 0.65–0.96) for the consumption of >0–4.9 g per day, 5–9.9 g per day, and 10–19.9 g per day, respectively. Results from analyses stratified by histologic subtype showed inverse associations of low, moderate and heavier drinking with lung adenocarcinoma and squamous cell carcinoma. The inverse association with squamous cell carcinoma appeared to be more prominent. However, sample size for squamous cell carcinoma was limited, given the particularly strong association of this sub-type with tobacco. In contrast to these histologic sub-types, risk for small cell carcinoma of the lung was elevated ranging from 1.2 to 1.7 for all categories of alcohol consumption above 0–4.9 g per day, although the confidence limits were wide given the small sample size (Table 2).

Figure 1 shows the dose-response relationship of average lifetime alcohol consumption in grams per day against the odds of being a case for all lung cancer, adenocarcinoma, squamous cell carcinoma and small cell lung cancer. A notable drop in the odds of being a case was seen for drinkers with low to moderate consumptions compared to non-drinkers for lung cancer overall, adenocarcinoma and squamous cell carcinoma. With increasing alcohol consumption, the confidence limits widened considerably which did not permit firm conclusions of the precise dose-response relationship for higher levels of alcohol intake.

Type of alcohol consumed

The associations between lung cancer risk and lifetime average consumption by different alcoholic beverage types (wine,

Table 2. Risk estimates and 95% CI by histological type and average amount of alcohol consumed per day.

Histological type	Average alcohol consumption (g/day)	Case no. (%)	Control no. (%)	OR	95% CI
All lung cancer[1]					
	Non-drinker	1338 (52.5)	3488 (37.3)	1.00	Reference
	>0-4.9	632 (24.8)	2607 (27.8)	0.80	0.70, 0.90
	5-9.9	217 (8.5)	1111 (11.9)	0.82	0.69, 0.99
	10-19.9	189 (7.4)	1100 (11.7)	0.79	0.65, 0.96
	20-29.9	78 (3.1)	445 (4.8)	0.82	0.62, 1.09
	30-44.9	36 (1.4)	306 (3.3)	0.68	0.47, 0.99
	45+	58 (2.3)	305 (3.3)	0.91	0.65, 1.29
Adenocarcinoma[1]					
	Non-drinker	702 (50.9)	3488 (37.3)	1.00	Reference
	>0-4.9	376 (27.3)	2607 (27.8)	0.82	0.70, 0.96
	5-9.9	132 (9.6)	1111 (11.9)	0.91	0.72, 1.14
	10-19.9	98 (7.1)	1100 (11.7)	0.74	0.58, 0.96
	20-29.9	34 (2.5)	445 (4.8)	0.67	0.45, 0.99
	30-44.9	13 (0.9)	306 (3.3)	0.46	0.26, 0.83
	45+	24 (1.7)	305 (3.3)	0.72	0.44, 1.18
Squamous cell carcinoma[2]					
	Non-drinker	91 (52.9)	3271 (37.7)	1.00	Reference
	>0-4.9	36 (20.9)	2407 (27.7)	0.51	0.33, 0.78
	5-9.9	15 (8.7)	1066 (12.3)	0.49	0.28, 0.89
	10-19.9	15 (8.7)	1040 (12.0)	0.51	0.28, 0.92
	20+	15 (8.7)	903 (10.4)	0.51	0.27, 0.95
Small cell lung cancer[3]					
	Non-drinker	27 (43.5)	2266 (32.6)	1.00	Reference
	>0-4.9	8 (12.9)	2033 (29.3)	0.47	0.21, 1.10
	5-9.9	9 (14.5)	849 (12.2)	1.45	0.64, 3.29
	10-19.9	7 (11.3)	862 (12.4)	1.23	0.49, 3.07
	20+	11 (17.7)	933 (13.4)	1.68	0.70, 4.06

[1]Adjusted for age group, sex, ethnicity, education and center/sub-centre. Includes all studies.
[2]Adjusted for age group, sex, ethnicity, education, and centre (included: Aichi, CAPUA, CE, China, EAGLE, EPIC, ESTHER, FHS, HSPH, Hawaii, ICARE, Israel, Montreal, NCI-Maryland, Moffitt, Seoul, Toronto, UCLA).
[3]Adjusted for age group, sex, ethnicity, education, and centre (included: Aichi, CAPUA, CE, China, EAGLE, EPIC, ESTHER, FHS, ICARE, Spain, Toronto, UCLA).

beer and liquor) are reported in Table 3. Risk estimates for wine and liquor consumption were similar to those for overall consumption, whereas beer drinking showed statistically non-significant elevations in risk for alcohol consumption of 10 g a day and higher. Low and moderate amounts of wine drinking were associated with reduced lung cancer risk (>0–4.9 g per day: OR = 0.80, 95% CI = 0.69–0.94; 20–29 g per day: OR = 0.62, 95% CI = 0.43–0.89), while low amount of liquor drinking was associated with reduced lung cancer risk (0–4.9 g per day: OR = 0.77, 95% CI = 0.66–0.91). Trends for beer consumption differed from those for wine and liquor with point estimates being above 1 for moderate to high drinking categories (>10 g per day) suggesting positive associations (Table 3).

Evaluation of effect modifiers and potential confounders

Associations between alcohol consumption and lung cancer risk were similar when stratified by gender. A significant inverse association with lower amounts of drinking was observed in females with OR of 0.80 (95% CI = 0.69–0.93), while the estimate in males was comparable with OR of 0.89 (0.68–1.17) (Supporting Information Table 3). The lack of significance in males may simply be due to the smaller sample size.

When we analyzed population-based and cohort studies separately from hospital-based studies, we found that significantly reduced odds ratios were restricted to the population-based/cohort studies. Risk estimates for the hospital-based study group did not provide strong evidence for an association with lung cancer risk (Supporting Information Table 4).

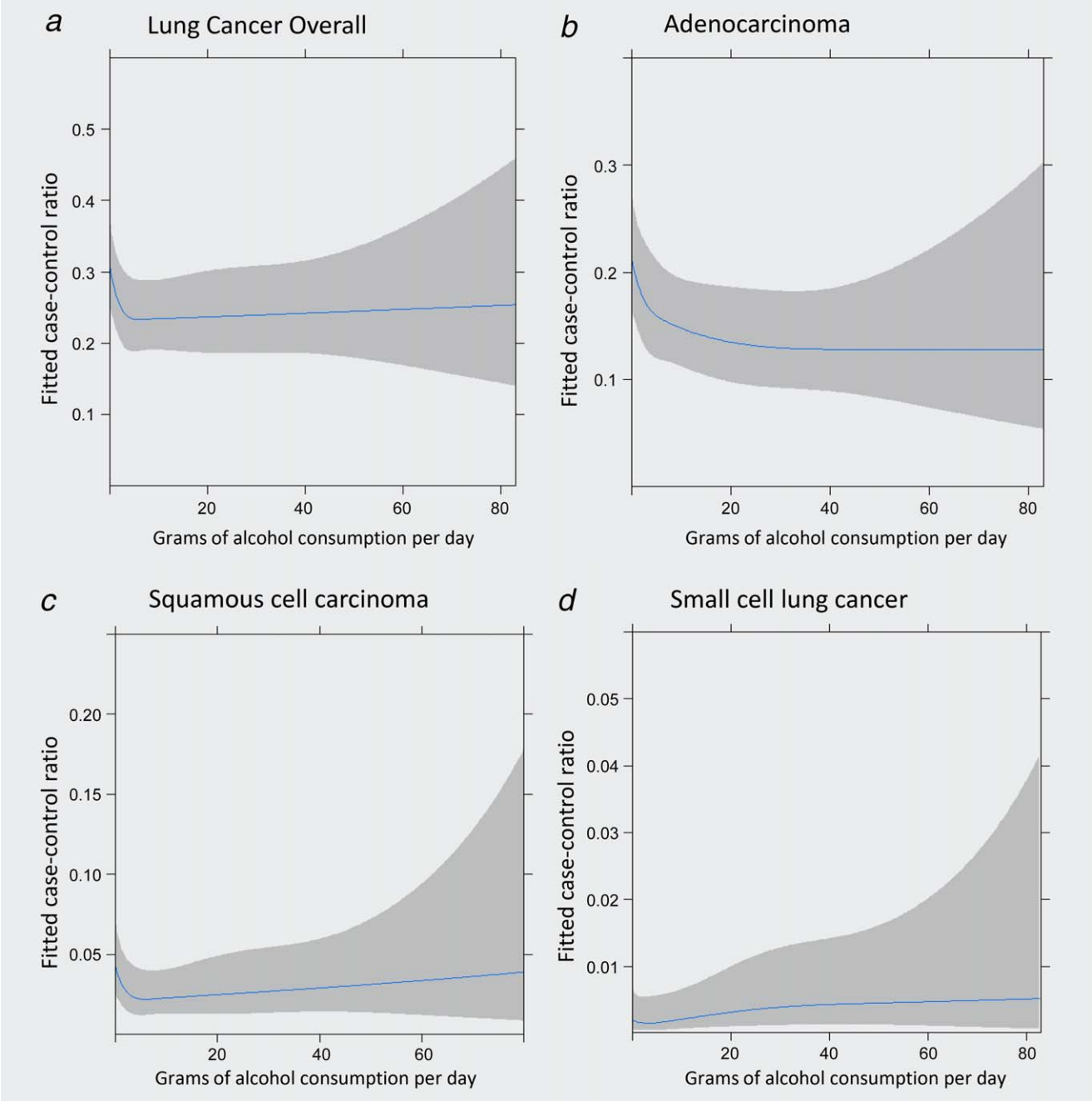

Figure 1. Non-linear dose response relationship between alcohol consumption and lung cancer risk among never smokers based on restricted cubic splines. *X*-axis is grams of alcohol consumed per day and *Y*-axis is the fitted odds of being a case versus being a control, adjusted for sex, age, ethnicity, education and center. [Color figure can be viewed at wileyonlinelibrary.com]

Data for occupational exposure were available for 5 studies (CE, CAPUA, EAGLE, Montreal, Toronto: 494 cases, 2496 controls). No appreciable changes in odds ratios were found when variables representing lung cancer related occupational exposures were added to logistic regression models. Adjustment for medical history of tuberculosis, chronic pulmonary disorder, emphysema or pneumonia for 5 studies for which data were available (CE, FHS, NELCS, Toronto, UCLA, WELD: 516 cases, 2439 controls) also had negligible effects on odds ratios. We found no appreciable differences in odds ratios when controlling for exposure to environmental tobacco smoke (10 studies CE, EPIC, UCLA, FHS, Harvard, Hawaii, Moffitt, NELCS, Toronto, WELD: 851 cases, 3261 controls) (data not shown).

Discussion

In this study, the largest conducted on the association of alcohol consumption with lung cancer risk among never

Table 3. Risk estimates and 95% CI by beverage type and average amount of alcohol consumed per day.

Beverage type	Average alcohol consumption (g/day)	Case no. (%)	Control no. (%)	OR	95% CI
Wine					
	Non-drinker	1138 (58.6)	3377 (43.7)	1.00	Reference
	>0–4.9	480 (24.7)	2387 (30.9)	0.80	(0.69,0.94)
	5–9.9	133 (6.9)	767 (9.9)	0.87	(0.69,1.10)
	10–19.9	102 (5.3)	552 (7.2)	0.84	(0.65,1.09)
	20–29.9	41 (2.1)	372 (4.8)	0.62	(0.43,0.89)
	30+	47 (2.4)	266 (3.5)	0.94	(0.64,1.38)
Beer					
	Non-drinker	1427 (73.5)	4647 (60.2)	1.00	Reference
	>0–4.9	378 (19.5)	2221 (28.8)	0.95	0.81, 1.11
	5–9.9	55 (2.8)	453 (5.9)	0.91	0.66, 1.26
	10–19.9	41 (2.1)	229 (3.0)	1.20	0.82, 1.75
	20–29.9	19 (1.0)	79 (1.0)	1.54	0.90, 2.65
	30+	21 (1.1)	92 (1.2)	1.35	0.78, 2.33
Liquor					
	Non-drinker	1459 (75.2)	4806 (62.3)	1.00	Reference
	>0–4.9	383 (19.7)	2382 (30.9)	0.77	(0.66, 0.91)
	5–9.9	42 (2.2)	233 (3.0)	0.82	(0.56, 1.19)
	10–19.9	30 (1.6)	137 (1.8)	0.87	(0.56, 1.36)
	20–29.9	18 (0.9)	73 (1.0)	1.03	(0.59, 1.81)
	30+	9 (0.5)	90 (1.2)	0.41	(0.19, 0.86)

Adjusted for alcohol type (i.e. mutual adjustment for wine, beer, and liquor) age group, sex, ethnicity, education, and centre/sub-center. Includes: CAPUA, CE, China, EAGLE, EPIC, ESTHER, FHS, HSPH, HAWAII, ICARE, Israel, Montreal, NCI-Maryland, NELC, Moffitt, Spain, Toronto, UCLA, WELD.

smokers, we found an inverse association between overall alcohol consumption and lung cancer risk with reduced risk estimates most consistently observed for low and moderate drinking. We also found alcohol consumption was associated with lower risk of both adenocarcinoma and squamous cell carcinoma. Analysis by alcoholic beverage type revealed that wine drinkers and liquor drinkers were at lower risk for lung cancer, with beer drinkers having modest non-significant increases in risk relative to non-drinkers for most drinking categories.

Consistent with our results, other large studies (including both ever and never smokers) found reduced lung cancer risk for lower levels of alcohol consumption. The NIH-AARP Diet and Health Study, a prospective cohort study, reported lower risk among drinkers who consumed <12 g (1 drink) of alcohol per day[18] while Freudenheim *et al.* using a pooled analysis of cohort studies, found lower risk for women who drank <15 g of alcohol per day.[8] A comprehensive meta-analysis by Bagnardi *et al.* (26,509 cases), also reported reduced risk for low levels of drinking (<12.5 g per day).[19] Specifically for never smokers, previous studies have not provided consistent evidence regarding alcohol consumption to lung cancer risk. A meta-analysis by Bagnardi *et al.* found no differences in risk between ever and never drinkers[10]. Among larger prospective cohort studies, one study found lung cancer risk increased with increased drinking in never smoking males but not females,[8] while two other studies reported null results.[15,18]

We found differential associations by beverage type with inverse associations found for both wine and liquor consumption, but not beer consumption. Among larger studies that investigated association by beverage type (including both ever and never smokers), inverse associations for low levels of wine drinking (<12 g or 1 drink per day), but positive associations with liquor drinking.[7] However, similar to our results, the NIH-AARP Diet and Health Study (the largest cohort study investigating this association with 10,227 lung cancer cases) also found low to moderate consumption of wine or liquor was associated with reduced lung cancer risk.[18] Consistent with our data, larger studies have reported positive associations between beer consumption and lung cancer risk.[7,18]

Our results are compatible with the hypothesis that flavonoids found in wine may reduce the risk of some cancers. Support for a beneficial role of flavonoids is provided by several studies where higher dietary intake of flavonoids (including flavonols, flavanones and quercetin) was inversely associated with lung cancer risk.[20–22] The inverse association

between liquor consumption and lung cancer risk is more difficult to explain. It is possible that constituents of different beverage types have no direct effect on risk, but instead beverage type is correlated with lifestyle factors that are associated with lung cancer risk. For example, wine drinkers have been reported to have healthier diets than beer drinkers in several studies.[23–26] A healthier diet for both wine and liquor drinkers relative to beer drinkers has also been reported, but not consistently.[23,24,26]

We observed differential association of lung cancer risk across different histologic sub-types, with inverse associations found between alcohol consumption and adenocarcinoma and squamous cell carcinoma but not for small cell lung carcinoma. Our finding of reduced risk for squamous cell carcinoma among alcohol consumers is in part supported by the NIH-AARP Diet and Health Study where reduced risk of squamous cell carcinoma was found among low and moderate drinkers (<3 drinks per day) of alcohol.[18] However, in general, results pertaining to the association of alcohol consumption with histologic sub-type of lung cancer in combined samples of ever and never smokers have been mixed.[8,18,27] In addition to random variation it is possible that heterogeneity in results could be at least partially attributed to confounding by smoking, which can vary across populations and is differentially associated with different histologic subtypes. Even though our study is restricted to never smokers, we cannot preclude the possibility of residual confounding by tobacco smoking. However validation studies have shown that misclassification of never smokers with ever smokers is unlikely to have an important effect on results[28]; therefore the potential residual confounding by tobacco smoking is not expected to be a driving factor of associations observed in our study.

In general, neither our categorical data analysis nor our analysis of non-linearity using restricted cubic splines indicated that heavy consumers of alcohol have higher lung cancer risk when comparing to non-drinkers, although we did observe a suggestive positive association with increased beer consumption. In most analyses, we found risk estimates were generally below the null for subjects who were categorized as heavier drinkers (30 or more grams per day) of total alcohol, wine or liquor. In contrast, results from several large cohort studies and a recent comprehensive meta-analysis indicated increased risk for heavier drinkers.[8,11,18,19] As these studies included smokers, residual confounding by smoking in heavier drinkers may explain the observed increased risk of lung cancer. Two recent cohort studies and a meta-analysis did not find heavier drinkers to be at higher risk for lung cancer among never smokers.[10,11,18]

The observed inverse associations we found between alcohol consumption and lung cancer risk may be explained by confounding related to differences between non-drinkers and drinkers. It has been postulated that non-drinkers may represent a unique subgroup of the population with either lower socio-economic status or medical conditions that could confound associations with lung cancer. Although we have controlled for confounding by socio-economic status by adjusting for education in logistic regression models, it is possible that this measure did not fully capture socio-economic status. To account for potential comorbidity, we also adjusted for medical history of tuberculosis, chronic pulmonary disorder, emphysema or pneumonia in a subset of our study where these data were available. We found no appreciable effects on odds ratios. Even though we did not observe any evidence of confounding based on socio-economic status or medical conditions, our results are compatible with the hypothesis that non-drinkers are a unique group of individuals which can drive the dose response relationship to show inverse associations with point estimates below the null throughout different categories of drinking.

To investigate whether study design could have introduced bias into our results, we compared results by study design (cohort, population-based and hospital-based case-control studies). Interestingly, inverse associations between alcohol consumption and lung cancer risk were found only for the population-based studies. The most noticeable difference between the three sub-groups was that controls in hospital based studies were more likely to identify themselves as never drinkers than those in the population-based or cohort studies (Supporting Information Table 4). A possible explanation for this is that controls recruited in the hospital-based studies may be more likely to abstain from alcohol due to other health conditions, and this resulted in associations remaining near the null in this sub-group. Given that most of the studies are based on case-control design, we cannot preclude the possibility of recall bias, which could further explain the lack of dose response, although it would not explain how recall bias would result in the observed association particularly in population-based case-control studies. Ideally, one would hope to address the recall issue in the prospective study; however we had limited number of non-smoking lung cancer cases from cohort study to be informative (Supporting Information Table 4). We also stratified our subjects by sex since men and women metabolize alcohol differently. However, we did not find important differences in risk estimates between the sexes.

Although our results are consistent with wine and liquor consumption associated with a reduced risk of lung cancer, we cannot rule out residual confounding from known or unknown factors influencing observed associations with lung cancer risk. Recent results from Mendelian randomization studies conflict with the commonly cited view that light to moderate alcohol consumption is causally linked to lower risk for ischaemic heart disease, with results from genetic analyses clearly indicating that genetic variation that predisposes to less drinking is associated with lower risk in both light/moderate and heavier drinkers.[29] This emphasizes the potential importance of confounding in studies that investigate associations between alcohol consumption and chronic diseases.

In summary, based on the largest study of alcohol consumption and lung cancer for never smokers to date, we investigated detailed dose-response relationships and potential effect modifiers by beverage type and histological subtype. We found an inverse association between wine and liquor consumption and lung cancer risk in never smokers. We cannot, however, rule out residual confounding from known or unknown risk factors influencing the observed associations with lung cancer risk, particularly those related to non-drinkers. Further research is needed to clarify associations between alcohol consumption and lung cancer risk with a focus on reducing or elucidating the role of confounding a priority for future studies.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr.
2. Dela Cruz CS, Tanoue LT, Matthay RA, Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med* 2011;32:605–44.
3. Field RW, Withers BL, Occupational and environmental causes of lung cancer. *Clin Chest Med* 2012;33:681–703.
4. Vineis P, Hoek G, Krzyzanowski M, et al. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 2007;6:7.
5. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
6. Bagnardi V, Randi G, Lubin J, et al. Alcohol consumption and lung cancer risk in the Environment and Genetics in Lung Cancer Etiology (EAGLE) study. *Am J Epidemiol* 2010;171:36–44.
7. Chao C. Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2007; 16:2436–47.
8. Freudenheim JL, Ritz J, Smith-Warner SA, et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr* 2005;82:657–67.
9. Korte JE, Brennan P, Henley SJ, et al. Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am J Epidemiol* 2002;155:496–506.
10. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. *Ann Oncol* 2011;22:2631–9.
11. Klatsky AL, Li Y, Nicole Tran H, et al. Alcohol intake, beverage choice, and cancer: a cohort study in a large kaiser permanente population. *Perm J* 2015;19:28–34.
12. Hung RJ, Christiani DC, et al. International Lung Cancer Consortium: pooled analysis of sequence variants in DNA repair and cell cycle pathways. Cancer. *Epidemiol Biomarkers Prev* 2008;17:3081–9.
13. Olsson AC, Gustavsson P, Kromhout H, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. *Am J Respir Crit Care Med* 2011;183:941–8.
14. Esser MB, Hedden SL, Kanny D, et al. Prevalence of alcohol dependence among US adult drinkers, 2009-2011. *Prev Chronic Dis* 2014;11:E206.
15. Thun MJ, Hannan LM, Adams-Campbell LL, et al. Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. *PLoS Med* 2008;5:e185.
16. Ahrens W, Merletti F, A standard tool for the analysis of occupational lung cancer in epidemiologic studies. *Int J Occup Environ Health* 1998;4: 236–40.
17. Mirabelli D, Chiusolo M, Calisti R, et al. [Database of occupations and industrial activities that involve the risk of pulmonary tumors]. *Epidemiol Prev* 2001;25:215–21.
18. Troche JR, Mayne ST, Freedman ND, Shebl FM, Abnet CC, The association between alcohol consumption and lung carcinoma by histological subtype. *Am J Epidemiol* 2016; 183110–21.
19. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015;112:580–93.
20. Lam TK, Rotunno M, Lubin JH, et al. Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk. *Carcinogenesis* 2010;31:634–42.
21. Le Marchand L, Murphy SP, Hankin JH, et al. Intake of flavonoids and lung cancer. *J Natl Cancer Inst* 2000;92:154–60.
22. Woo HD, Kim J. Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis. *PloS One* 2013;8:e75604.
23. Adjemian MK, Volpe RJ, Adjemian J. Relationships between diet, alcohol preference, and heart disease and type 2 diabetes among Americans. *PloS One* 2015;10:e0124351.
24. Barefoot JC, Gronbaek M, Feaganes JR, et al. Alcoholic beverage preference, diet, and health habits in the UNC Alumni Heart Study. *Am J Clin Nutr* 2002;76:466–72.
25. Ruidavets JB, Bataille V, Dallongeville J, et al. Alcohol intake and diet in France, the prominent role of lifestyle. *Eur Heart J* 2004;25:1153–62.
26. Sluik D, van Lee L, Geelen A, et al. Alcoholic beverage preference and diet in a representative Dutch population: the Dutch national food consumption survey 2007-2010. *Eur J Clin Nutr* 2014;68:287–94.
27. Chao C, Li Q, Zhang F, et al. Alcohol consumption and risk of lung cancer in the VITamins and lifestyle study. *Nutr Cancer* 2011;63:880–8.
28. Nyberg F, Agudo A, Boffetta P, et al. A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. *Cancer Causes Control* 1998;9:173–82.
29. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* 2014;349:g4164.