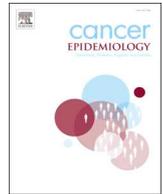




ELSEVIER

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Alcohol consumption and lung cancer risk: A pooled analysis from the International Lung Cancer Consortium and the SYNERGY study

Darren R. Brenner^{a,b,1}, Gord Fehring^{a,1}, Zuo-Feng Zhang^c, Yuan-Chin Amy Lee^d, Travis Meyers^d, Keitaro Matsuo^e, Hidemi Ito^f, Paolo Vineis^g, Isabelle Stucker^h, Paolo Boffettaⁱ, Paul Brennan^j, David C. Christiani^k, Nancy Diao^k, Yun-Chul Hong^l, Maria T. Landi^m, Hal Morgensternⁿ, Ann G. Schwartz^o, Gad Rennert^p, Walid Saliba^p, John R. McLaughlin^q, Curtis C. Harris^r, Irene Orlow^s, Juan M. Barros Dios^t, Alberto Ruano Raviña^{t,F}, Jack Siemiatycki^u, Anita Koushik^u, Michele Cote^u, Philip Lazarus^v, Guillermo Fernandez-Tardon^w, Adonina Tardon^w, Loïc Le Marchand^x, Hermann Brenner^{y,G,H}, Kai-Uwe Saum^y, Eric J. Duell^z, Angeline S. Andrew^A, Dario Consonni^B, Ann Olsson^{C,D}, Rayjean J. Hung^a, Kurt Straif^{E,*}

^a Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

^b Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada

^c Department of Epidemiology, School of Public Health, UCLA, Los Angeles, USA

^d Department of Family and Preventive Medicine, School of Medicine, University of Utah, and Huntsman Cancer Institute, Salt Lake City, USA

^e Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Japan

^f Division of Cancer Information and Control, Aichi Cancer Centre Research Institute, Japan

^g Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK

^h Department of Environmental Epidemiology, INSERM U170, Villejuif, France

ⁱ The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, USA

^j Genetic Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France

^k Harvard School of Public Health, Massachusetts General Hospital/Harvard Medical School, Boston, USA

^l Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, South Korea

^m Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH after National Cancer Institute, Bethesda, USA

ⁿ Departments of Epidemiology and Environmental Health Sciences, School of Public Health and Comprehensive Cancer Center, University of Michigan, Ann Arbor, USA

^o Karmanos Cancer Institute, Wayne State University, Detroit, USA

^p 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

^q Public Health Ontario, Toronto, Canada

^r Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, USA

^s Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, USA

^t Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain

^u CRCHUM (Centre de recherche du CHUM) and Department of Social and Preventive Medicine, Université de Montréal, Montreal, Quebec, Canada

^v Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, USA

^w University Institute of Oncology (IUOPA), University of Oviedo, and CIBERESP, Spain

^x Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii, USA

^y Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

^z Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain

^A Norris Cotton Cancer Center, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United Kingdom

^B Epidemiology Unit, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

^C Environment and Radiation Section, International Agency for Research on Cancer, Lyon, France

^D Institute of Environmental Medicine, Stockholm, Sweden

^E IARC Monographs Section, International Agency for Research on Cancer, Lyon, France

^F CIBER de Epidemiología y Salud Pública, Madrid, Spain

^G Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

^H German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

* Corresponding author.

E-mail address: StraiK@iarc.fr (K. Straif).

¹ Authors contributed equally.

ARTICLE INFO

Keywords:

Alcohol
Lung cancer
Pooled analysis

ABSTRACT

Background: There is inadequate evidence to determine whether there is an effect of alcohol consumption on lung cancer risk. We conducted a pooled analysis of data from the International Lung Cancer Consortium and the SYNERGY study to investigate this possible association by type of beverage with adjustment for other potential confounders.

Methods: Twenty one case-control studies and one cohort study with alcohol-intake data obtained from questionnaires were included in this pooled analysis (19,149 cases and 362,340 controls). Adjusted odds ratios (OR) or hazard ratios (HR) with corresponding 95% confidence intervals (CI) were estimated for each measure of alcohol consumption. Effect estimates were combined using random or fixed-effects models where appropriate. Associations were examined for overall lung cancer and by histological type.

Results: We observed an inverse association between overall risk of lung cancer and consumption of alcoholic beverages compared to non-drinkers, but the association was not monotonic. The lowest risk was observed for persons who consumed 10–19.9 g/day ethanol (OR vs. non-drinkers = 0.78; 95% CI: 0.67, 0.91), where 1 drink is approximately 12–15 g. This J-shaped association was most prominent for squamous cell carcinoma (SCC). The association with all lung cancer varied little by type of alcoholic beverage, but there were notable differences for SCC. We observed an association with beer intake (OR for ≥ 20 g/day vs nondrinker = 1.42; 95% CI: 1.06, 1.90).

Conclusions: Whether the non-monotonic associations we observed or the positive association between beer drinking and squamous cell carcinoma reflect real effects await future analyses and insights about possible biological mechanisms.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality globally [1]. Tobacco consumption is unquestionably the predominant risk factor for the disease with 80–90% of cases occurring among former or current smokers [2,3]. As larger cohorts and consortia efforts mature, the ability to estimate less prominent risk factors in large datasets emerge. A multitude of risk additional factors for lung cancer have been identified [4–7]. One additional risk factor of potential interest is the intake of alcohol and the interaction between alcohol and tobacco consumption [8]. Alcohol has shown to be inconsistently associated with lung cancer risk in previous meta-analyses of case-control and cohort studies, with several previous studies reporting an increased risk for high doses [9,10] in a non-linear fashion [11], while others reporting that the associations are dependent upon beverage type with increased risks for liquor and beer and an inverse relationship with consumption of red wine [12]. While meaningful associations have been observed across different studies designs, many of these studies have been unable to reach conclusive associations due to the potential for residual confounding or inadequate statistical power. Systematic reviews by the International Agency for Research on Cancer and the World Cancer Research Fund/American Institute for Cancer Research stated that there is inadequate evidence to support an association between alcohol consumption and lung cancer risk [13]. An examination of the associations between alcohol and lung cancer by beverage type, histology groups as well as the interaction with tobacco consumption within a standard analytical framework confounders is warranted.

To address these questions we pooled data from twenty one studies participating in the International Lung Cancer Consortium (ILCCO) and the SYNERGY consortium and standardized exposure and covariate data across studies.

2. Methods

2.1. Data collection

ILCCO and SYNERGY study inclusion and details have been previously published [14] and are available on the web portals (<http://ilcco.iarc.fr>) (<http://synergy.iarc.fr>). Twenty two participating studies contributed data ascertaining alcohol and agreed to participate in this pooled analysis (Table 1 & Supplementary Table 1). Eleven studies were conducted in North America, eight studies in Europe and three in Asia. There were twenty one case-control studies, of which ten were

population-based, eight hospital-based and three studies with mixed (hospital and population) controls (Supplementary Table 2). There was one large population-based cohort study, the European Prospective Investigation into Cancer (EPIC) study [15]. The control groups in all case-control studies were, either individually or, frequency-matched with cases on age and sex. The analyses included in this manuscript examine the associations between alcohol consumption and lung cancer risk across all tobacco consumption groups. Given the importantly different baseline risk profile among never smokers, we have presented detailed analyses of alcohol consumption and lung cancer risk restricted to never smokers in a separate publication [16]. Written informed

Table 1

Population characteristics for combined International Lung Cancer Consortium and Synergy Consortium Study population (N cases=16,808) (N controls=21,258). The European Prospective Investigation into Cancer and Nutrition (EPIC) study characteristics are presented in Supplementary Table 1.

	Controls n	(%)	Cases n	(%)
Sex				
Female	7,243	34.1	5,774	34.4
Male	14,015	65.9	11,034	65.6
Age groups				
< 50	3,384	15.9	1,987	11.8
50 < 55	2,663	12.5	2,056	12.2
55 < 60	3,466	16.3	2,853	17.0
60 < 65	3,427	16.1	2,731	16.2
65 < 70	3,672	17.3	2,961	17.6
70+	4,646	21.9	4,220	25.1
Age years (mean \pm sd)	60.3 (11.1)		61.7 (10.5)	
Education level				
Basic/elementary	4,708	22.1	4,637	27.6
Up to high school graduate	7,286	34.3	6,209	36.9
Some postsecondary and higher	5,299	24.9	2,910	17.3
Missing or unspecified	3965	18.7	3052	18.2
Race/ethnicity				
White	15,636	73.6	13,737	81.7
Black, African-American	1,198	5.6	721	4.3
Asian	3,981	18.7	2,149	12.8
Hispanic	258	1.2	101	0.6
Other unknown	185	0.9	100	0.6
Smoking groups				
Never	7,992	37.6	2,067	12.3
Former	7,694	36.2	5,977	35.6
Current	5,540	26.1	8,748	52.0
Unknown	32	0.2	16	0.1
Pack-years (mean \pm sd)	18.3 (25.1)		41.6 (32.3)	

consents were obtained from all study subjects, and ethics review boards at each study center approved the studies.

The data submitted from all studies were checked for inadmissible values, aberrant distributions, inconsistencies and missing values. Queries were sent to the investigators to resolve all discrepancies and possible errors. A total of 19,149 cases and 362,340 controls were available for the present investigation.

Alcohol intake was collected in each study using questionnaire data. The entry formats and questions varied across studies. A full description of the different types of questions asked is shown in Supplementary Table 3. Wherever possible, we converted the question responses into standardized drink units based on the quantities inquired by the questionnaires. These were converted into grams of alcohol per day based on data from the International Agency for Research on Cancer (<http://cancer-code-europe.iarc.fr/>) for alcoholic beverages. The duration of alcohol consumption was calculated wherever possible through the use of duration questions or questions aimed at drinking during particular periods or decades of the life. From the available measures, drink-years (drinks/day*years of drinking) and average grams of ethanol per day consumed during adulthood for alcohol intake overall and for each beverage type were calculated. Regular drinkers were defined as those consuming at least one alcoholic drink per week. We used non-drinkers as the reference group for our analyses. This choice was made to enable comparison with other large pooled [9] and meta-analyses [12,17] of alcohol intake and, in particular, to estimate the effects of low volumes of habitual consumption. In the beverage type analyses, non-drinkers that did not consume alcohol of any type were used as the reference group.

2.2. Statistical analyses

The frequency distribution of demographic variables and putative risk factors for lung cancer, including age, sex, ethnicity, and smoking, were examined among all cases and controls. The ethnicity of the subjects were categorized according to the National Institutes of Health (NIH) definition as non-Hispanic Whites, Blacks or African Americans, Hispanic or Latinos, Asians, Native Hawaiians or other Pacific islanders, American Indians or others. Former smokers were defined as smokers who quit smoking at least two years before the interview or diagnosis. Cumulative tobacco consumption was calculated as the product of smoking duration and intensity throughout the life-course standardized across studies and expressed as pack-years.

For the case-control studies, unconditional logistic regression was used to estimate odds ratios (OR) and their associated confidence intervals (95% CI), adjusted for age, sex, cumulative tobacco smoking (in pack-years), and country or study center (when the study was conducted in multiple countries or centers) for the effects of each type and measure of alcohol consumption. For the cohort study, we used Cox proportional hazards regression (with time since enrollment as the time scale) to estimate hazard ratios (HR) and their associated 95% CIs adjusted for the same factors as case-control studies. Follow-up time at risk was calculated as the time between study enrollment and lung-cancer diagnosis (for cases) or the last known date of query (for non-cases) from the cancer registry. We estimated pooled effects across studies employing the inverse variance method and using fixed and random-effects models to account for variability between study populations. We conducted sensitivity analyses with and without the cohort study to examine for excess influence on the results to the size of the population.

We conducted a stratified analysis by histological subtypes to examine for potential differential effects with models conducted in each study and then pooled using random effects. Of great interest were potential synergistic interactions between alcohol and tobacco consumption. In order to examine the interaction between alcohol and tobacco consumption, we pooled data into a single population and

employed a fixed-effects analysis adjusted for study. We then examined a departure from an additive scale by comparing observed effect estimates in combined tobacco and alcohol exposure groups. We also conducted a test of a multiplicative interaction between pack-years of smoking and grams of ethanol per day. In order to examine graded risk with the lower risk for both smoking and alcohol consumption categories, we used the 0 < 20 g/day group as the reference group as non-drinkers had an increased risk compared to light drinkers. We also analyzed ethanol consumption as a continuous variable. Non-linear effects were examined through the use of restricted cubic splines in a combined dataset. A 5-knot term was used, as this best fit the data based on the log-likelihood.

As several of the studies included in the pooled analysis contained lifetime occupational data, we evaluated whether the effect estimates we observed were potentially confounded by ever employment in occupations and industries known to present an excess risk of lung cancer (List A) [18] or occupations and industries suspected to present an excess risk of lung cancer (List B) [19]. We also evaluated potential confounding due to the presence of a previous lung disease. Several of the studies collected self-reported previously diagnosed tuberculosis at the time of interview. As the presence of a lung disease may have impacted the amount of regular alcohol consumption, we compared the average lifetime alcohol consumption across those with and without a history of tuberculosis.

Heterogeneity was evaluated for each of the summary estimates based on a test of the Cochrane Q statistic as well as the I² statistic [20]. Where there was evidence of heterogeneity across studies, we evaluated the source of heterogeneity by meta-regression using continent (North America, Europe, Asia, etc.), control type (population, hospital, mixed), prevalence of ever smoking among controls (continuous), % male of the population, % Caucasian and median year of the study period (continuous) as predictors. Statistical analyses were conducted using SAS version 9.3, STATA software version 10 and R version 2.15.

3. Results

3.1. Overall drinking

Among regular drinkers the average number of grams of ethanol per day consumed from all types of alcoholic drinks was 24 g. This corresponds to 2 drinks per days. We observed a slight inverse association for low doses of alcohol in the range of less than 20 g of alcohol per day (Table 2). This effect persisted across all histologic subtypes including adenocarcinoma and squamous cell carcinoma. No inverse associations or increased risks were observed for high levels of overall alcohol consumption on lung cancer risk. The non-linear effects of ethanol per day on lung cancer risk can be seen in Fig. 1. A clear dip in the odds of being a case is seen at low to moderate levels of drinking. As expected we observed heterogeneity in the main effects of alcohol on lung cancer risk ($p < 0.001$) due to differences across populations. Study-specific results are presented across alcohol consumption categories with corresponding I² and p-values for heterogeneity are presented in Supplementary Fig. 1. When we examined the main effects of alcohol consumption in a meta-regression using continent, control type, prevalence of ever smoking among controls (continuous) and median year of the study period (continuous) as predictors, no single study characteristic appeared to drive the heterogeneity.

When comparing the overall effect estimates with the EPIC cohort study included or removed from analyses, the pooled effect estimates did not differ materially. For example, the effects among the > 0-4.9 g/day group compared to non-drinkers including the cohort study OR = 0.79, 95%CI = 0.72–87 and without the cohort study OR = 0.79, 95%CI = 0.70-0.89. For this reason the cohort was retained in the combined results.

Table 2

Associations with categories of grams of alcohol consumption combined from all types of drinks in the combined International Lung Cancer Consortium and Synergy Consortium Study population. Effect estimates from random effects models across studies. (N cases = 19,149) (N controls = 362,340).

Group	Number of studies	n cases	n controls	OR ¹	95% CI
Overall					
Non-drinkers	21	4,204	31,950	1.00	REF
0–4.9 g per day	21	3,439	124,752	0.79	0.72–0.87
5–9.9 g per day	21	2,342	66,107	0.85	0.74–0.96
10–19.9 g per day	21	3,022	68,975	0.78	0.67–0.91
20–29.9 g per day	20	1,796	30,438	0.98	0.85–1.12
30–44.9 g per day	20	1,639	20,334	0.92	0.82–1.04
≥ 45 g per day	19	2,707	19,784	0.94	0.77–1.15
Adenocarcinoma					
Non-drinkers	21	1,776	31,912	1.00	REF
0–4.9 g per day	21	1,384	124,751	0.78	0.71–0.86
5–9.9 g per day	21	870	66,104	0.88	0.76–1.02
10–19.9 g per day	21	1,067	68,984	0.82	0.70–0.97
20–29.9 g per day	19	561	30,422	0.99	0.85–1.15
≥ 30 g per day	18	1,189	40,017	0.88	0.73–1.05
Squamous Cell Carcinoma					
Non-drinkers	20	860	31,846	1.00	REF
0–4.9 g per day	20	639	124,668	0.71	0.59–0.86
5–9.9 g per day	20	531	66,080	0.78	0.64–0.95
10–19.9 g per day	20	782	68,907	0.77	0.62–0.94
20–29.9 g per day	18	510	30,345	0.96	0.79–1.18
≥ 30 g per day	18	1,466	39,870	1.01	0.80–1.28
Small Cell Lung Cancer					
Non-drinkers	14	347	3,883	1.00	REF
0–4.9 g per day	14	273	3,587	0.81	0.66–0.99
5–9.9 g per day	14	199	2,354	0.94	0.67–1.31
10–19.9 g per day	14	285	2,995	0.91	0.66–1.25
20–29.9 g per day	13	177	1,409	1.08	1.80–1.46
≥ 30 g per day	13	448	2,813	0.91	0.66–1.25

Models adjusted for sex, age group, pack-years, education, ethnicity and center/country where appropriate.

3.2. Alcoholic beverage type

When examining the effects of consuming different alcoholic beverage types adjusted for other types of beverages, an inverse association between drinking and lung cancer risk was observed for wine and liquor consumption, but not for beer consumption, where risk estimates were elevated for higher categories of grams of ethanol from beer compared with non-drinkers (OR = 1.09, 95% CI = 0.94–1.27, for ≥ 20 g/day) (Table 3). Increases in risk associated with beer consumption were observed among subgroup analyses of squamous cell carcinoma (OR = 1.42, 95% CI = 1.06–1.90, for ≥ 20 g/day). In accordance with the results in the overall analyses, a decrease in risk was also observed for wine consumption with the strongest effects observed for squamous cell carcinoma (OR = 0.71, 95% CI = 0.53–0.94, for 10–19.9 g/day).

3.3. Interaction with smoking

We divided the population into groups according to alcohol consumption (non-drinkers (0 g/day), 0– < 20 g/day and ≥ 20 g/day) and tobacco consumption (0 pack-years, 0– < 10 pack-years, ≥ 10 pack-years). An interaction analysis between the smoking and drinking categories suggested, as expected that lung cancer risk was associated with higher levels of tobacco consumption. An interaction was observed for those in the highest alcohol and tobacco consumption groups, where the effect estimate deviated from that expected on the additive scale (OR = 11.23, 95% CI = 10.29–12.26, ≥ 20 g/day, ≥ 10 pack-years). The test for multiplicative interaction between alcohol consumption and smoking intensity was also significant (P < .001) (Table 4).

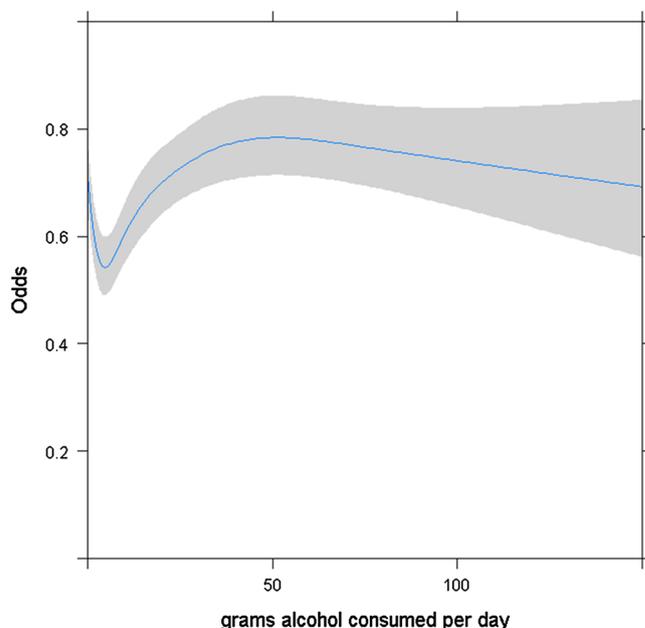


Fig. 1. Odds of lung cancer associated with grams of alcohol consumption in the combined International Lung Cancer Consortium and Synergy Consortium Study population.

*See PNG file attachment

Figure represent the odds of being a case compared to a control across the distribution of grams of ethanol consumed in the study populations estimated from the combined population. The blue line represents the point estimate and the grey shaded area represents a 95% confidence interval. Models were adjusted for age, sex, pack-years, education, ethnicity and center/country where appropriate.

3.4. Investigation of potential confounding

When we evaluated whether the effect estimates we observed were potentially confounded by ever employment in occupations and industries known to present an excess risk of lung cancer, we did not observe any notable differences between ORs with and without adjustment for List A or List B (Supplementary Table 4). When we examined the presence of reporting a history of tuberculosis at diagnosis or interview we saw no appreciable difference in the proportions between never drinkers and drinkers (Supplementary Table 5).

4. Discussion

4.1. Summary of effects

We observed no increased risk of lung cancer associated with high intakes of total alcohol consumption alcoholic beverages. Similar null effects were observed across lung cancer histologic subtypes. However, specifically for higher level of beer consumption, we observed increased risks of lung squamous cell carcinoma. On the other hand, a slight inverse association (i.e. protective effect) was observed for low to moderate alcohol consumption compared to non-drinkers. We also observed evidence of increased risks of adenocarcinoma and overall lung cancer for the highest categories of beer consumption, as well as evidence of increased risk of squamous cell carcinoma for the highest level of liquor consumption. In contrast, we did not observe any evidence of an increased in overall or sub-type specific risk with higher levels of wine consumption. Our study findings are more robust than previous analyses due to the large sample size from 21 pooled studies as well as standardized variable characterization and adjustment across the studies.

Table 3

Associations with categories of grams of alcohol consumption combined by beverage type, adjusted for other types of consumption combined in the International Lung Cancer Consortium and Synergy Consortium Study population. Effect estimates from random effects models across studies.

Group	All lung cancer					Adenocarcinoma					Squamous cell carcinoma				
	n studies	n cases	n controls	OR ¹	95% CI	n studies	n cases	n controls	OR ¹	95% CI	n studies	n cases	n controls	OR ¹	95% CI
Beer															
Non- drinkers	17	7,749	107,023	1.00	REF	15	2,584	106,364	1.00	REF	12	1,624	105,114	1.00	REF
0–4.9 g per day	17	4,525	186,320	0.95	0.86–1.04	15	1,521	186,113	1.00	0.88–1.13	12	1,069	185,635	0.99	0.88–1.12
5–9.9 g per day	17	1,575	30,667	1.06	0.97–1.16	15	463	30,621	1.04	0.88–1.24	12	439	30,486	1.18	1.01–1.38
10–19.9 g per day	17	1,240	20,625	1.06	0.91–1.23	15	376	20,597	1.13	0.93–1.37	12	318	20,463	1.17	0.90–1.51
≥ 20 g per day	17	1,849	13,746	1.09	0.94–1.27	15	527	13,722	1.13	0.92–1.38	12	525	13,566	1.42	1.06–1.90
Liquor															
Non- drinkers	17	7,683	119,126	1.00	REF	15	2,592	118,422	1.00	REF	12	1,528	117,212	1.00	REF
0–4.9 g per day	17	5,444	194,741	0.83	0.76–0.91	15	1,850	194,552	0.81	0.72–0.91	12	1,236	193,885	0.80	0.67–0.95
5–9.9 g per day	17	1,228	23,502	0.81	0.70–0.95	15	356	23,475	0.77	0.62–0.95	12	319	23,368	0.84	0.63–1.10
10–19.9 g per day	17	1,118	13,041	0.93	0.83–1.03	15	332	13,013	1.03	0.86–1.24	12	320	12,925	0.90	0.71–1.15
≥ 20 g per day	17	1,465	7,971	0.96	0.81–1.13	15	341	7,955	0.91	0.74–1.12	12	572	7,874	1.16	0.97–1.40
Wine															
Non-drinkers	17	7,322	53,161	1.00	REF	15	2,268	52,626	1.00	REF	12	1,657	51,606	1.00	REF
0–4.9 g per day	17	3,959	181,822	0.80	0.71–0.89	15	1,320	181,541	0.81	0.72–0.90	12	801	180,960	0.69	0.54–0.88
5–9.9 g per day	17	1,542	56,636	0.87	0.68–1.10	15	535	56,571	0.88	0.68–1.15	12	370	56,459	0.67	0.43–1.03
10–19.9 g per day	17	1,461	38,760	0.88	0.74–1.04	15	527	38,701	0.98	0.84–1.14	12	361	38,582	0.72	0.54–0.97
≥ 20 g per day	17	2,654	28,002	0.95	0.77–1.18	15	821	27,978	0.94	0.78–1.15	12	786	27,657	0.84	0.59–1.19

Non-drinkers that did not consume alcohol of any type were used as the reference group for all beverage types.

Table 4

Joint effects of alcohol and tobacco consumption combined in International Lung Cancer Consortium and Synergy Consortium Study population. Effect estimates from a fixed effects model in a single combined population.

Odds ratios for smoking and alcohol Categories		
Drinking and smoking categories	OR ¹	95% CI
0 < 20 g Alc per day, 0 pack-years	1.00	REF
0 < 20 g Alc per day, 0 < 10 pack-years	1.31	1.16–1.48
0 < 20 g Alc per day, 10+ pack-years	7.74	7.14–8.39
0 g Alc per day, 0 pack-years	1.64	1.48–1.82
0 g Alc per day, 0 < 10 pack-years	1.85	1.54–2.23
0 g Alc per day, 10+ pack-years	9.81	8.92–10.80
20+ g Alc per day, 0 pack-years	0.86	0.72–1.03
20+ g Alc per day, 0 < 10 pack-years	1.57	1.32–1.87
20+ g Alc per day, 10+ pack-years	11.23	10.29–12.26

Controlling for sex, age, pack-years, education, ethnicity and study.

Our results are in line with previous meta-analyses [12,17] and analyses of large datasets [9] that suggested a J-shaped association for overall consumption of grams of alcohol per day. Freudenheim et al. (2005) observed an inverse association (OR = 0.81, 95% CI = 0.68–0.97 (5- < 15 g/day vs 0 g/day) among women, OR = 0.86, 95% CI = 0.76–1.28 (> 0- < 5 g/day vs 0 g/day among men)) when compared to never drinkers in a pooled analyses of multiple prospective cohort studies [9]. This suggests a level of consistency between our study and the other largest studies done to date, which includes a large proportion of the published data available on this association.

4.2. Inverse associations among light/low levels of drinking

Our beverage type-specific results are also consistent with previous analyses of large datasets [9]. Freudenheim et al. also observed an inverse association for 1–2 glasses of wine per day (OR = 0.66, 95% CI = 0.51–0.87 (5- < 15 g/day vs 0 g/day) among men, OR = 0.78, 95% CI = 0.52–1.07 (5- < 15 g/day vs 0 g/day) among women) and increased risk observed with beer drinking (OR = 1.88, 95% CI = 1.45–2.42 (5- < 15 g/day vs 0 g/day) among women) and liquor consumption (OR = 1.34, 95% CI = 1.09–1.66 (5- < 15 g/day) among women). The authors concluded that the associations at higher levels of consumption may be in part explained by residual confounding from tobacco, lung diseases and other confounders. A meta-analysis of case-

control and cohort studies conducted by Chao also suggested an inverse association for wine drinking 0.79 (0.65–0.95) and an increased risk associated with the highest category of beer drinking at 1.23 (1.06–1.41) [12] when comparing highest to lowest intakes in the studies. In consideration of potential residual confounding due to tobacco smoking, it is relevant to examine the effects of alcohol consumption among never smokers. In a companion analyses, we examined the effects of alcohol in the same set of studies included here, focused solely on never smokers [16]. We observed similar small inverse associations with moderate drinkers.

Before considering a possible causal interpretation of the potential inverse association with low alcohol consumption, there are at least two alternative explanations. First, there may be confounding by a correlate of low alcohol consumption, that might be characterized by the phrase “balanced-lifestyle” and that might entail habits such as low smoking percentages, increased cruciferous vegetable intake [21], citrus fruit intake [22], garlic [23], tea consumption [24] and/or elevated levels of recreational physical activity [25,26]. While these may individually have small protective effects, the collective presence of these factors may entail a larger effect which could confound the wine-cancer association. In the University of North Carolina Alumni Heart Study, the lowest prevalence of cigarette smoking was observed among drinkers who preferred wine compared to liquor and beer, respectively [27]. The second possible explanation would be that those who are abstaining from drinking are not doing so by choice, but by necessity. For example, an exposure such as a previous lung disease or family history has altered alcohol and or tobacco consumption. This imbalanced exposure profile would artificially place the reference group at a higher risk than those in the moderate consumption categories. However, further adjusting history of tuberculosis did not affect our results.

A causal interpretation is compatible with the finding that there are anti-carcinogenic properties in alcohol beverages. In particular, poly-phenolic compounds including flavonoids in red wine have well characterized anti-carcinogenic properties [28]. Evidence from other population studies suggests that flavonoids, such as quercetin intake may reduce the risk of lung cancer through anti-oxidative pathways [29–31]. Additional ingredients of alcoholic beverages, such as xanthohumol and resveratrol have also been shown to have cancer chemopreventive properties [32,33].

Further investigation and future analyses are required to support and justify the findings of this study. Additional analytical approaches

such as Mendelian Randomization [34] to reduce differential measurement error and instrumental variable analyses [35] to control for unmeasured confounding where consumption patterns vary widely enough to act as strong instruments may provide additional support to our results through a triangulation [36] of approaches. From a biological pathway perspective additional mouse model studies examining the hypothesized carcinogenic components of alcohol and tobacco exposure may also provide additional triangulation support [36] of the interactive effects we observed.

4.3. Increased risk with high levels of beer consumption among squamous cell carcinoma

We observed a greater relative risk associated with high levels of beer consumption for squamous cell carcinoma than for adenocarcinoma. As squamous cell carcinomas are more frequently observed among heavy smokers, this association might further reflect residual confounding from tobacco in the use, particularly when assessing alcohol consumption. This follows the previously suggested contention that residual confounding from smoking is likely to be stronger in the highest consumption categories, due to an excess of extremely heavy smokers among these cases [10].

4.4. Interaction with smoking

We observed a positive interaction between high pack-years of smoking and elevated levels of drinking. This may reflect some type of biological interaction of the combination of the two exposures or it may also reflect a different exposure profile across drinking categories where those at higher levels of both alcohol and tobacco consumption may be exposed to other factors, such as second-hand smoke from time spent in bars.

From a biological perspective, alcohol may interact with and enhance the carcinogenicity of tobacco smoke by inducing the activity of cytochrome P-450 enzymes, which could activate the harmful substances, such as ethanol, present in alcoholic beverages [8,37]. Our study is in agreement with the vast majority of the literature where synergistic effects among categories of high levels of both alcohol and tobacco consumption have been observed [38]. Both alcohol and nicotine are known to impact the same mesolimbic dopamine system [39]. This mediates the rewarding and reinforcing properties of both substances and may lead heavy drinkers to smoke more and vice versa.

4.5. Limitations

As 21 of 22 studies included in this analyses were case-control studies, the limitations of assessing association within the case-control design are a limitation of this larger pooled analysis. We were able to compare the associations observed within the single cohort study included in this analyses and we observed relatively similar findings, however, the impact of recall bias and differential misclassification on these associations cannot be ruled out. Alcohol intake was determined by questionnaires inquiring about lifetime intake. As with other food frequency questionnaires, the measurements are influenced by notable misclassification due to various factors influencing responses. The level of detail from questionnaires used to estimate the average intake of ethanol weighted over adulthood varied across studies. This variation may have contributed to the heterogeneity observed across study-specific estimates. Some questionnaires asked a simple question about average number of alcoholic drinks per day over adulthood, while others asked specific questions about the type of drink and consumption over small windows of time over the life-course. This may have introduced varying degrees of misclassification into our measures, therefore complicating an estimation of the potential effect on the relationship between our estimates and the true risk estimates associated with exposure. However, we did attempt to minimize any effect on the

result from such misclassification through standardizing measurements across studies, removing aberrant measurements, and controlling for common confounders between the studies.

In order to determine the causality of this association, controlling confounding due to tobacco is paramount. Although we have used pack-years of smoking for adjustment, which is a relatively detailed combined construct of cumulative duration and intensity, it is possible that some degree of residual confounding remains. Furthermore, despite a large number of studies we were unable to investigate the differential effects of the alcohol tobacco interaction across histology groups due to a lack of statistical power.

4.6. Strengths

This is one the largest datasets queried to date to assess the question of whether alcohol consumption and the varying types of alcohol drinks that are consumed is associated with lung cancer risk. A previous meta-analysis of alcohol consumption and lung cancer cited an inability to examine effect across histology groups¹². This analysis was able to examine these associations by drink across histologic sub-types with adequate precision. The generalizability of this investigation is strengthened of this particular investigation is the existence of data from multiple studies from three continents. This analysis is also strengthened by the ability to examine the potential for confounding due to the history of tuberculosis and occupational exposures in a subgroup of the included studies. Furthermore, detailed data on smoking also allowed for a more standardized adjustment than in previous analyses.

4.7. Conclusions

Although we cannot advocate for alcohol consumption to reduce the risk of lung cancer as alcohol has multiple known adverse effects, our results replicate a slight inverse association with wine consumption at low to moderate levels warrant further research into the mechanisms involved. This result is also compatible with the explanation based on balanced lifestyle typically seen among low to moderate drinker.

Conflict of interest statement

None declared.

Author contributions

Study concepts DB, GF, RH, KS, AO, AC, ZZ
 Study design DB, RH, KS, AO, AC, ZZ, GF
 Data acquisition TM, KM, HI, PV, IS, PB, PB, DC, ND, YH, MT, HM, AS, MBD, AR, JS, AK, MC, PZ, GT, AT, LL, HB, KS, ED, AS, DC, AO
 Quality control of data and algorithms DB, GF, RH, KS, AO, AC, ZZ
 Data analysis and interpretation DF, GF
 Statistical analysis DB, RH, KS, AO, AC, ZZ
 Manuscript preparation DB, GF, RH, KS, AO, AC, ZZ
 Manuscript editing All
 Manuscript review DB, RH, KS, AO, AC, ZZ

Acknowledgements

The ILCCO Data management is supported by Cancer Care Ontario Research Chair of Population Studies to R. J. H. The SYNERGY project was funded by the German Social Accident Insurance (DGUV), grant FP 271. Grant Number P20RR018787 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). The Aichi Study was supported by MEXT Kakenhi (Nos. 17015018 and 26253041) from the Japanese Ministry of Education, Culture, Sports, Science and Technology by a Grant-in-Aid for the Third Term Comprehensive 10-year Strategy for Cancer Control from the

Ministry of Health, Labour and Welfare of Japan and the Health. The CAPUA Study, was financed by FIS-FEDER/Spain grant numbers FIS-01/310, FIS-PI03-0365, FIS-PI 06-0604; FICYT/Asturias grant numbers FICYT PB02-67 and FICYT IB09-133, the IUOPA, University of Oviedo and the CIBERESP, Spain. The ESTHER study was supported by a grant from the Baden-Württemberg Ministry of Science, Research and Education. We gratefully acknowledge most valuable contributions of Hartwig Ziegler, Christa Stegmaier, Sonja Wolf and Volker Herrmann in the conduct of the ESTHER study. The Hawaii Case-control study was partially funded by NCI grant R01-CA55874. Darren Brenner is supported by a Capacity Development Award in Prevention from the Canadian Cancer Society Research Institute (703917). The Detroit studies were partially funded by NIH R01CA060691, R01CA8795, HHSN261201300011I and P30CA22453. The Montreal study was supported by the Canadian Institutes of Health Research and by the Guzzo-CRS Research Chair.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2018.10.006>.

References

- [1] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, *CA. Cancer J. Clin.* 61 (2) (2011) 69–90.
- [2] R. Doll, R. Peto, K. Wheatley, R. Gray, I. Sutherland, Mortality in relation to smoking: 40 years' observations on male British doctors, *BMJ* 309 (6959) (1994) 901–911.
- [3] R. Peto, S. Darby, H. Deo, P. Silcocks, E. Whitley, R. Doll, Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies, *BMJ* 321 (7257) (2000) 323–329.
- [4] A.J. Alberg, M.V. Brock, J.G. Ford, J.M. Samet, S.D. Spivack, *Epidemiology of lung cancer: diagnosis and management of lung cancer*, 3rd ed: American College of chest physicians evidence-based clinical practice guidelines, *Chest* 143 (5 Suppl) (2013) e1S–29S.
- [5] J.M. Samet, E. Avila-Tang, P. Boffetta, L.M. Hannan, S. Olivo-Marston, M.J. Thun, C.M. Rudin, Lung cancer in never smokers: clinical epidemiology and environmental risk factors, *Clin. Cancer Res.* 15 (18) (2009) 5626–5645.
- [6] M. Johansson, C. Relton, P.M. Ueland, S.E. Vollset, O. Midttun, O. Nygard, N. Slimani, P. Boffetta, M. Jenab, F. Clavel-Chapelon, M.C. Boutron-Ruault, G. Fagherazzi, R. Kaaks, S. Rohrmann, H. Boeing, C. Weikert, H.B. Bueno-de-Mesquita, M.M. Ros, C.H. van Gils, P.H. Peeters, A. Agudo, A. Barricarte, C. Navarro, L. Rodriguez, M.J. Sanchez, N. Larranaga, K.T. Khaw, N. Wareham, N.E. Allen, F. Crowe, V. Gallo, T. Norat, V. Krogh, G. Masala, S. Panico, C. Sacerdote, R. Tumino, A. Trichopoulos, P. Lagiou, D. Trichopoulos, T. Rasmussen, G. Hallmans, E. Riboli, P. Vineis, P. Brennan, Serum B vitamin levels and risk of lung cancer, *JAMA : J. Am. Med. Assoc.* 303 (23) (2010) 2377–2385.
- [7] D.R. Brenner, P. Boffetta, E.J. Duell, H. Bickeböller, A. Rosenberger, V. McCormack, J.E. Muscat, P. Yang, H.-E. Wichmann, I. Brueske-Hohlfeld, Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium, *Am. J. Epidemiol.* 176 (7) (2012) 573–585.
- [8] G. Poschl, H.K. Seitz, Alcohol and cancer, *Alcohol Alcohol.* 39 (3) (2004) 155–165.
- [9] J.L. Freudenheim, J. Ritz, S.A. Smith-Warner, D. Albanes, E.V. Bandera, P.A. van den Brandt, G. Colditz, D. Feskanich, R.A. Goldbohm, L. Harnack, A.B. Miller, E. Rimm, T.E. Rohan, T.A. Sellers, J. Virtamo, W.C. Willett, D.J. Hunter, Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies, *Am. J. Clin. Nutr.* 82 (3) (2005) 657–667.
- [10] J.E. Korte, P. Brennan, S.J. Henley, P. Boffetta, Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk, *Am. J. Epidemiol.* 155 (6) (2002) 496–506.
- [11] V. Bagnardi, G. Randi, J. Lubin, D. Consonni, T.K. Lam, A.F. Subar, A.M. Goldstein, S. Wacholder, A.W. Bergen, M.A. Tucker, A. Decarli, N.E. Caporaso, P.A. Bertazzi, M.T. Landi, Alcohol consumption and lung cancer risk in the environment and genetics in lung cancer etiology (EAGLE) study, *Am. J. Epidemiol.* 171 (1) (2010) 36–44.
- [12] C. Chao, Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis, *Cancer Epidemiol. Biomarkers Prev.* 16 (11) (2007) 2436–2447.
- [13] R. Baan, K. Straif, Y. Grosse, B. Secretan, F. El Ghissassi, V. Bouvard, A. Altieri, V. Coglianò, W.H.O.I.A.f.R.o.C.M.W. Group, Carcinogenicity of alcoholic beverages, *Lancet Oncol.* 8 (4) (2007) 292–293.
- [14] R.J. Hung, D.C. Christiani, A. Risch, O. Popanda, A. Haugen, S. Zienoldiny, S. Benhamou, C. Bouchardy, Q. Lan, M.R. Spitz, H.E. Wichmann, L. LeMarchand, P. Vineis, G. Matullo, C. Kiyohara, Z.F. Zhang, B. Pezeshki, C. Harris, L. Mechanic, A. Seow, D.P. Ng, N. Szeszenia-Dabrowska, D. Zaridze, J. Lissowska, P. Rudnai, E. Fabianova, D. Mates, L. Foretova, V. Janout, V. Bencko, N. Caporaso, C. Chen, E.J. Duell, G. Goodman, J.K. Field, R.S. Houlston, Y.C. Hong, M.T. Landi, P. Lazarus, J. Muscat, J. McLaughlin, A.G. Schwartz, H. Shen, I. Stucker, K. Tajima, K. Matsuo, M. Thun, P. Yang, J. Wiencke, A.S. Andrew, S. Monnier, P. Boffetta, P. Brennan, International Lung Cancer Consortium: pooled analysis of sequence variants in DNA repair and cell cycle pathways, *Cancer Epidemiol. Biomarkers Prev.* 17 (11) (2008) 3081–3089.
- [15] E. Riboli, R. Kaaks, The EPIC project: rationale and study design. European prospective investigation into cancer and nutrition, *Int. J. Epidemiol.* 26 (Suppl. 1) (1997) S6–14.
- [16] G. Fehrer, D.R. Brenner, Z.F. Zhang, Y.A. Lee, K. Matsuo, H. Ito, Q. Lan, P. Vineis, M. Johansson, K. Overvad, E. Riboli, A. Trichopoulos, C. Sacerdote, I. Stucker, P. Boffetta, P. Brennan, D.C. Christiani, Y.C. Hong, M.T. Landi, H. Morgenstern, A.G. Schwartz, A.S. Wenzlaff, G. Rennert, J.R. McLaughlin, C.C. Harris, S. Olivo-Marston, I. Orlov, B.J. Park, M. Zauderer, J.M. Barros Dios, A. Ruano Ravina, J. Siemiatycki, A. Koushik, P. Lazarus, A. Fernandez-Somoano, A. Tardon, L. Le Marchand, H. Brenner, K.U. Saum, E.J. Duell, A.S. Andrew, N. Szeszenia-Dabrowska, J. Lissowska, D. Zaridze, P. Rudnai, E. Fabianova, D. Mates, L. Foretova, V. Janout, V. Bencko, I. Holcatova, A.C. Pesatori, D. Consonni, A. Olsson, K. Straif, R.J. Hung, Alcohol and lung cancer risk among never smokers: a pooled analysis from the international lung cancer consortium and the SYNERGY study, *Int. J. Cancer* 140 (9) (2017) 1976–1984.
- [17] V. Bagnardi, M. Rota, E. Botteri, I. Tramacere, F. Islami, V. Fedirko, L. Scotti, M. Jenab, F. Turati, E. Pasquali, C. Pelucchi, C. Galeone, R. Bellocchio, E. Negri, G. Corrao, P. Boffetta, C. La Vecchia, Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis, *Br. J. Cancer* 112 (3) (2015) 580–593.
- [18] W. Ahrens, F. Merletti, A standard tool for the analysis of occupational lung cancer in epidemiologic studies, *Int. J. Occup. Environ. Health* 4 (4) (1998) 236–240.
- [19] D. Mirabelli, M. Chiusolo, R. Calisti, S. Massacesi, L. Richiardi, M. Nesti, F. Merletti, [Database of occupations and industrial activities that involve the risk of pulmonary tumors], *Epidemiol. Prev.* 25 (4-5) (2001) 215–221.
- [20] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, *BMJ* 327 (7414) (2003) 557–560.
- [21] T.K. Lam, L. Gallicchio, K. Lindsley, M. Shiels, E. Hammond, X.G. Tao, L. Chen, K.A. Robinson, L.E. Caulfield, J.G. Herman, E. Guallar, A.J. Alberg, Cruciferous vegetable consumption and lung cancer risk: a systematic review, *Cancer Epidemiol. Biomarkers Prev.* 18 (1) (2009) 184–195.
- [22] F.L. Buchner, H.B. Bueno-de-Mesquita, J. Linseisen, H.C. Boshuizen, L.A. Kiemeneij, M.M. Ros, K. Overvad, L. Hansen, A. Tjønneland, O. Raaschou-Nielsen, F. Clavel-Chapelon, M.C. Boutron-Ruault, M. Touillaud, R. Kaaks, S. Rohrmann, H. Boeing, U. Nöthlings, A. Trichopoulos, D. Zyllis, V. Dilis, D. Palli, S. Sieri, P. Vineis, R. Tumino, S. Panico, P.H. Peeters, C.H. van Gils, E. Lund, I.T. Gram, T. Braaten, C. Martinez, A. Agudo, L. Arriola, E. Ardanaz, C. Navarro, L. Rodriguez, J. Manjer, E. Wirfalt, G. Hallmans, T. Rasmussen, T.J. Key, A.W. Roddam, S. Bingham, K.T. Khaw, N. Slimani, P. Boffetta, G. Byrnes, T. Norat, D. Michaud, E. Riboli, Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European prospective investigation into cancer and nutrition (EPIC), *Cancer Causes Control* 21 (3) (2010) 357–371.
- [23] Z.Y. Jin, M. Wu, R.Q. Han, X.F. Zhang, X.S. Wang, A.M. Liu, J.Y. Zhou, Q.Y. Lu, Z.F. Zhang, J.K. Zhao, Raw garlic consumption as a protective factor for lung cancer, a population-based case-control study in a Chinese population, *Cancer Prev. Res. (Phila)* 6 (7) (2013) 711–718.
- [24] H.X. Zhang, W.B. Yin, L.J. Zhang, Z.Y. Yang, Z.X. Zhang, M. Wang, D.F. Chen, X.Z. Gu, Curative radiotherapy of early operable non-small cell lung cancer, *Radiother. Oncol.* 14 (2) (1989) 89–94.
- [25] J.Y. Sun, L. Shi, X.D. Gao, S.F. Xu, Physical activity and risk of lung cancer: a meta-analysis of prospective cohort studies, *Asian Pac. J. Cancer Prev.* 13 (7) (2012) 3143–3147.
- [26] A. Tardon, W.J. Lee, M. Delgado-Rodriguez, M. Dosemeci, D. Albanes, R. Hoover, A. Blair, Leisure-time physical activity and lung cancer: a meta-analysis, *Cancer Causes Control* 16 (4) (2005) 389–397.
- [27] J.C. Barefoot, M. Gronbaek, J.R. Feaganes, R.S. McPherson, R.B. Williams, I.C. Siegler, Alcoholic beverage preference, diet, and health habits in the UNC alumni heart study, *Am. J. Clin. Nutr.* 76 (2) (2002) 466–472.
- [28] M.K. Chahar, N. Sharma, M.P. Dobhal, Y.C. Joshi, Flavonoids: a versatile source of anticancer drugs, *Pharmacogn. Rev.* 5 (9) (2011) 1–12.
- [29] Y. Cui, H. Morgenstern, S. Greenland, D.P. Tashkin, J.T. Mao, L. Cai, W. Cozen, T.M. Mack, Q.Y. Lu, Z.F. Zhang, Dietary flavonoid intake and lung cancer—a population-based case-control study, *Cancer* 112 (10) (2008) 2241–2248.
- [30] T.K. Lam, M. Rotunno, J.H. Lubin, S. Wacholder, D. Consonni, A.C. Pesatori, P.A. Bertazzi, S.J. Chanock, L. Burdette, A.M. Goldstein, M.A. Tucker, N.E. Caporaso, A.F. Subar, M.T. Landi, Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk, *Carcinogenesis* 31 (4) (2010) 634–642.
- [31] L. Le Marchand, S.P. Murphy, J.H. Hankin, L.R. Wilkens, L.N. Kolonel, Intake of flavonoids and lung cancer, *J. Natl. Cancer Inst.* 92 (2) (2000) 154–160.
- [32] C. Gerhauser, Beer constituents as potential cancer chemopreventive agents, *Eur. J. Cancer* 41 (13) (2005) 1941–1954.
- [33] S.K. Goswami, D.K. Das, Resveratrol and chemoprevention, *Cancer Lett.* 284 (1) (2009) 1–6.
- [34] J. Yarmolinsky, K.H. Wade, R.C. Richmond, R.J. Langdon, C.J. Bull, K.M. Tilling, C.L. Relton, S.J. Lewis, G. Davey Smith, R.M. Martin, Causal inference in cancer

- epidemiology: what is the role of mendelian randomization? *Cancer Epidemiol. Biomarkers Prev.* 27 (9) (2018) 995–1010.
- [35] C. Canan, C. Lesko, B. Lau, Instrumental variable analyses and selection bias, *Epidemiology* 28 (3) (2017) 396–398.
- [36] D.A. Lawlor, K. Tilling, G. Davey Smith, Triangulation in aetiological epidemiology, *Int. J. Epidemiol.* 45 (6) (2016) 1866–1886.
- [37] G. Poschl, F. Stickel, X.D. Wang, H.K. Seitz, Alcohol and cancer: genetic and nutritional aspects, *Proc. Nutr. Soc.* 63 (1) (2004) 65–71.
- [38] International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 83 Tobacco Smoke and Involuntary Smoking, IARC, Press, Lyon, France, 2004.
- [39] A. Larsson, J.A. Engel, Neurochemical and behavioral studies on ethanol and nicotine interactions, *Neurosci. Biobehav. Rev.* 27 (8) (2004) 713–720.