Habitual consumption of alcohol with meals and lung cancer: a Mendelian randomization study

Chongxiang Chen[1,2#], Qiaozhen Hu[1#], Jiaojiao Wang[3#], Tianmeng Wen[4], Chaoyang Zhu[5], Weiyan Tan[5], Xuelin Chen[5], Qingyu Zhao[1], Wei Wang[6], Huijiao Cao[1], Huan Li[1]

[1]Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; [2]Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, Guangzhou, China; [3]Fuzhou Pulmonary Hospital of Fujian, Fuzhou, China; [4]School of Public Health, Sun Yat-sen University, Guangzhou, China; [5]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China; [6]Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-sen University, Guangzhou, China

Contributions: (I) Conception and design: H Li, H Cao, C Chen, Q Zhao; (II) Administrative support: H Li, H Cao; (III) Provision of study materials or patients: C Chen, Q Hu, J Wang; (IV) Collection and assembly of data: J Wang, T Wen, C Zhu, W Tan, X Chen; (V) Data analysis and interpretation: H Li, H Cao, C Chen, Q Hu, J Wang, W Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
[#]These authors contributed equally to this work.

Correspondence to: Huan Li; Huijiao Cao. Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China. Email: lihuan@sysucc.org.cn; caohj@sysucc.org.cn.

Background: The objective of this study was to determine the causal relationship between habitual alcohol consumption with meals and lung cancer.

Methods: Public genetic summary data from two large consortia [the Neale Lab and the International Lung Cancer Consortium (ILCCO)] were used for analysis. As the instrumental variables of habitual alcohol consumption with meals, data on genetic variants were retrieved from Neale Lab. Additionally, genetic data from other consortia [Global Lipid Genetics Consortium (GLGC), Tobacco, Alcohol and Genetics (TAG), Genetic Investigation of Anthropocentric Traits (GIANT)] were utilized to determine whether alcohol could causally alter some general risk factors for lung cancer. The primary outcome was the risk of lung cancer (11,348 cases and 15,861 controls in the ILCCO). The R package TwoSampleMR was used for analysis.

Results: Based on the inverse variance weighted method, the results of the two-sample Mendelian randomization (MR) analyses indicated that commonly consuming alcohol with meals was a protective factor, reducing lung cancer risk [odds ratio (OR) 0.175, 95% confidence interval (CI): 0.045–0.682, P=0.012]. The heterogeneity analysis revealed that the causal relationship analyses of different types of lung cancer all had low heterogeneity (P>0.05). The horizontal pleiotropic study showed that major bias was unlikely. The MR assumptions did not seem to be violated. The causal relationship analyses between habitual alcohol consumption with meals and some risk factors for cancers showed that this alcohol consumption habit was a beneficial factor for reducing body mass index (BMI) and the number of cigarettes smoked per day.

Conclusions: Habitual appropriate alcohol consumption with meals is a protective factor for the development of lung cancer.

Keywords: Mendelian randomization; alcohol; lung cancer

Submitted Apr 01, 2020. Accepted for publication Nov 02, 2020.
doi: 10.21037/atm-20-3063
View this article at: http://dx.doi.org/10.21037/atm-20-3063

Introduction

Conventionally, alcohol consumption has been thought to cause many risk factors towards various diseases, such as obesity; however, a study conducted by Arif *et al.* (1) indicated that an appropriate alcohol consumption habit (fewer than 5 drinks per week) could decrease the incidence of obesity. Furthermore, for various diseases, several studies have shown that appropriate alcohol consumption (light-to-moderate, less than 30 g/d) is beneficial for patients' health and can not only reduce the risk of type 2 diabetes (2), arterial hypertension (3), and cardiovascular diseases (4) but can also decrease patient mortality (5).

It is estimated that lung cancer, as the first leading cause of cancer death in the USA, will result in more than 130 thousand patient deaths in 2020 (6), with a total 5-year survival rate of 19% (6). It is crucial to clarify modifiable risk factors and beneficial factors to improve the prevention of lung cancer because of the increasing burden (7). Regarding risk factors, smoking has been identified as the most frequent cause of lung cancer (8), and because of tobacco control policies, lung cancer mortality has significantly decreased (6,9,10). In addition, regarding beneficial factors, the study by Zhou *et al.* (11) showed that education was one of the protective factors for lung cancer, which was proposed by Mendelian randomization (MR).

Worldwide interest in MR has greatly increased over the last 10 years; this method uses genome-wide association study (GWAS) data to demonstrate the exact causal relationship between A and B (using instrumental variable analysis with genetic instruments), which can avoid the influences of other exposure factors on the outcomes (12). Previously, several observational studies have shown that appropriate alcohol consumption (amount per day and frequency per week) could prevent lung cancer (13,14). Among these studies, the study by Brenner *et al.* (13) demonstrated that alcohol intake of less than 20 g/d was a beneficial factor for the prevention of lung cancer. Moreover, Li *et al.* (14) indicated that occasionally consuming alcohol throughout the week was a favorable factor for the survival of Chinese men with lung cancer. Therefore, we conducted an MR study to confirm the causal relationship between the habitual consumption of alcohol with meals and lung cancer. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3063).

Methods

Genetic variants associated with lung cancer

The exposure factor data (habitual alcohol consumption with meals) in this study were based on the Neale Lab. The outcome data (incidence of lung cancer, lung adenocarcinoma, and lung squamous cell cancer) were retrieved from the International Lung Cancer Consortium (ILCCO) (15), and the data for small cell lung cancer were obtained from the UK BioBank. In terms of other risk factors, the data of triglycerides and total cholesterol were obtained from the Global Lipid Genetics Consortium (GLGC) (16); the data of smoking habits (including cigarettes smoked per day, former *vs.* current smoker, age of smoking initiation, and ever *vs.* never smoker) were obtained from the Tobacco, Alcohol and Genetics (TAG) consortium (17); and the data of obesity class 1–3, waist circumference (adjusted by body mass index, BMI), hip circumference (adjusted by BMI), and waist-to-hip ratio (adjusted by BMI) were retrieved from the Genetic Investigation of Anthropocentric Traits (GIANT) (18,19). (*Table 1*).

Statistical analyses

To determine MR estimates of habitual alcohol consumption with meals for lung cancer, we used several MR approaches. In our study, habitual consumption of alcohol meant appropriate alcohol consumption habit (light-to-moderate, less than 30 g/d). We conducted a random effect inverse variance weighted (IVW) meta-analysis of the Wald ratio for individual single nucleotide polymorphisms (SNPs). Other statistical tests (the weighted median and MR-Egger regression methods) were used to estimate the effects. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Three assumptions were the basis of the MR method: (I) the instrumental variables are strongly associated with the habitual consumption of alcohol with meals; (II) the instrumental variables influence lung cancer only through their effect on habitual alcohol consumption with meals; and (III) the instrumental variables are independent of any confounder (20). We assessed the directional pleiotropy based on the intercept obtained from the MR-Egger analysis (21).

The common risk factors for lung cancer were identified in previous studies (22,23). Analyses were performed by

Table 1 Details of studies included in Mendelian randomization analyses

Variable	Consortium	PMID	Population	Gender
Lung cancer	ILCCO	24880342	11,348	European
Habitual consumption of alcohol with meals	Neale Lab	UK BioBank	–	–
Obesity 1–3 (waist circumference, hip circumference, waist-to-hip ratio)	GIANT	23563607, 25673412;	European (for obesity 1–3); mixed (waist circumference, hip circumference, waist-to-hip ratio)	Mixed
Triglycerides, total cholesterol	GLGC	24097068	Mixed	Mixed
Cigarettes smoking	TAG	20418890	European	Mixed

ILCCO, International Lung Cancer Consortium; TAG, Tobacco, Alcohol and Genetics; GLGC, Global Lipids Genetics Consortium; GIANT, Genetic Investigation of Anthropocentric Traits.

Table 2 Results from two sample MR

Cancer	Method	Numbers of SNPs	P value	OR	95% CI
Lung cancer	MR-Egger	14	0.375	0.002	2.01E–09 to 1,355.308
	Weighted median	14	0.034*	0.201	0.046–0.885
	Inverse variance weighted	14	0.012*	0.175	0.045–0.682
Small cell lung cancer	MR-Egger	14	0.777	0.998	0.985–1.012
	Weighted median	14	0.796	1.000	0.998–1.002
	Inverse variance weighted	14	0.900	1.000	0.999–1.001
Lung adenocarcinoma	MR-Egger	14	0.887	3.108	7.18E–07 to 13,449,061.81
	Weighted median	14	0.059	0.139	0.018–1.079
	Inverse variance weighted	14	0.078	0.247	0.052–1.169
Squamous cell lung cancer	MR-Egger	14	0.149	2.36E–06	1.64E–13 to 33.966
	Weighted median	14	0.016*	0.065	0.007–0.605
	Inverse variance weighted	14	0.004*	0.075	0.013–0.429

*, P value <0.05. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidential index.

using the package TwoSampleMR (version 0.3.4) in R (version 3.4.2).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Causal relationships between appropriate alcohol consumption and lung cancer

The IVW analysis results indicated that habitual appropriate alcohol consumption with meals was a protective factor for lung cancer (OR 0.175, 95% CI: 0.045–0.682, P=0.012) and lung squamous cell cancer (OR 0.075, 95% CI: 0.013–0.429, P=0.004). However, the two-sample MR results of habitual appropriate alcohol consumption with meals and lung adenocarcinoma (OR 1.000, 95% CI: 0.999–1.001, P=0.900), as well as small cell lung cancer (OR 0.247, 95% CI: 0.052–1.169, P=0.078), did not show causal relationships (*Table 2*, *Figures 1-5*).

The heterogeneity study showed that the heterogeneity in the causal relationship analysis between habitual appropriate alcohol consumption with meals and the incidence of lung cancer was high (P=0.033 for Egger, P=0.039 for IVW); however, the heterogeneities in different types of lung cancer were low (P>0.05 for MR-Egger, and

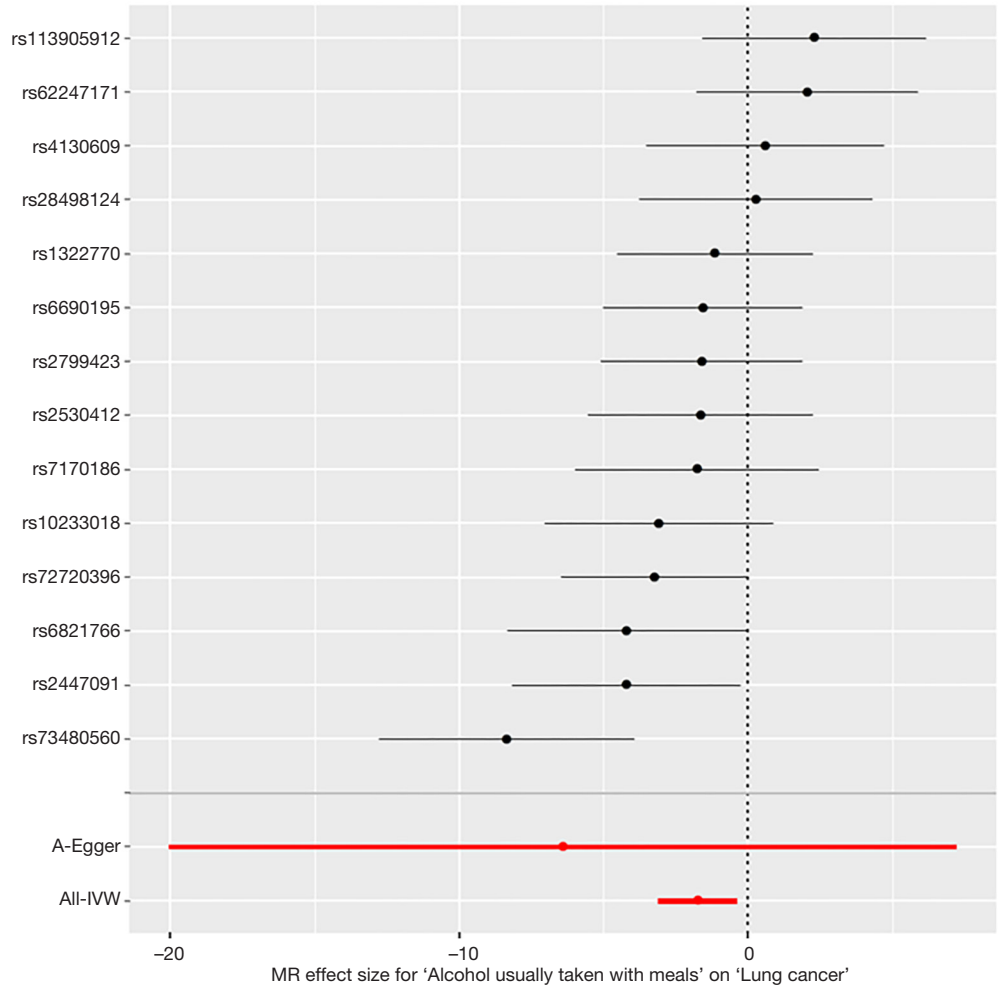

Figure 1 Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung cancer. MR, Mendelian randomization.

IVW) (*Table 3*). The horizontal pleiotropy study showed that habitual appropriate alcohol consumption with meals did not have multiple effects on other factors of lung cancer (P>0.05) (*Table 4*). The direction of the causal relationship of all MR analyses showed forward causal relationships (P<0.05) (*Table 5*).

Causal relationship between appropriate alcohol consumption and risk factors

The MR analyses between habitual appropriate alcohol consumption with meals and other risk factors for lung cancers showed that the former was a protective factor associated with reduce BMI (OR 0.701, 95% CI: 0.577–0.852, P<0.001) and fewer cigarettes smoked per day (OR 0.002, 95% CI: 3.500E−06 to 0.901, P=0.046). However, other risk factors, including age of smoking initiation (OR 1.140, 95% CI: 0.961–1.354, P=0.133), former *vs.* current smoker (OR 1.778, 95% CI: 0.532–5.949, P=0.350), total cholesterol (OR 0.707, 95% CI: 0.420–1.189, P=0.192), and triglycerides (OR 0.762, 95% CI: 0.542–1.072, P=0.119), did not show significant causal relationships with habitual appropriate alcohol consumption with meals (*Table 6*).

Discussion

The results of our MR study verified the causal relationship between habitual appropriate alcohol consumption with

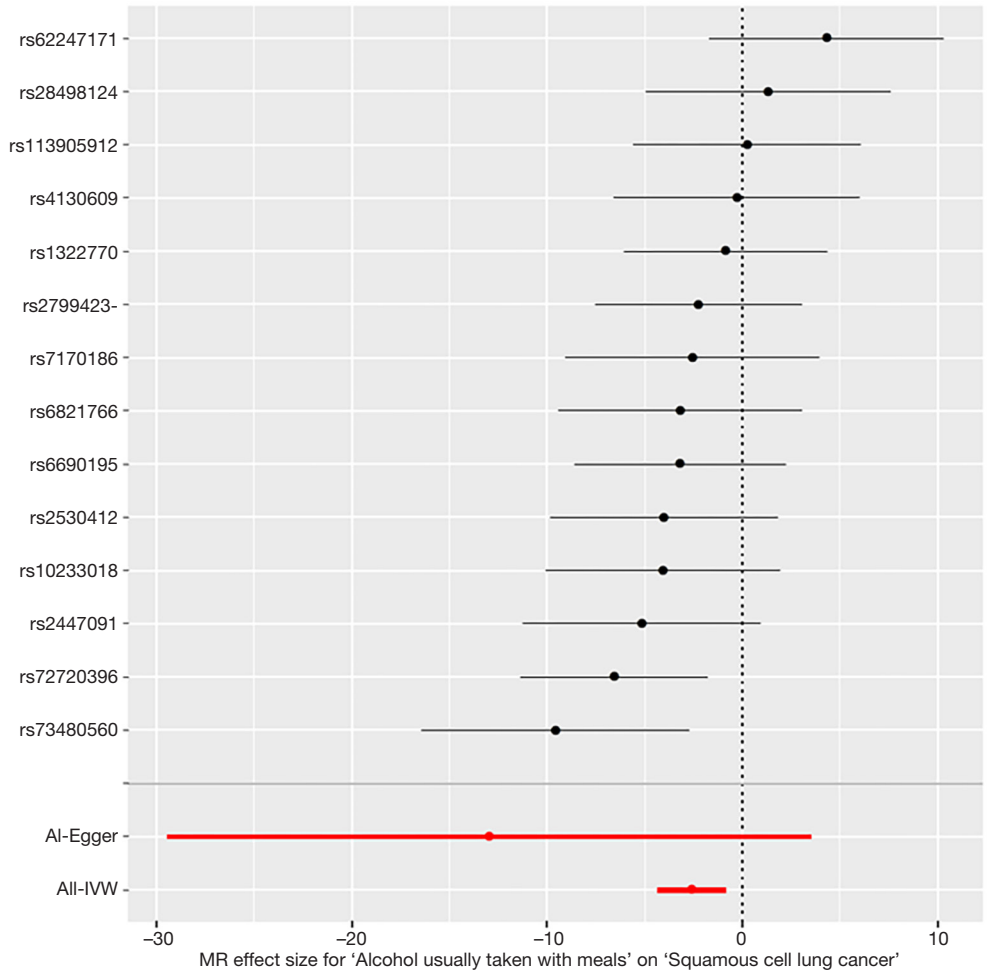

Figure 2 Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung squamous cell cancer. MR, Mendelian randomization.

meals and lung cancer. Several studies have supported the idea that light-to-moderate alcohol consumption could not only decrease the incidence of lung cancer (13,24), but could also benefit lung cancer patients' prognosis. Additionally, light-to-moderate alcohol consumption showed benefits in the studies of many different diseases, including type 2 diabetes (2), arterial hypertension (3), and cardiovascular diseases (4). In this case, we are inclined to conclude that appropriate alcohol consumption is important for health (13,25).

The MR analyses between habitual alcohol consumption with meals and some risk factors for lung cancer demonstrated that this causal relationship probably resulted from the phenomenon that people with this habit care more about their health by avoiding some risk factors, such as smoking (fewer cigarettes smoked per day) and so on. On the one hand, the deduced effect above seems reasonable when patients are smokers. On the other hand, for non-smoking lung cancer patients, the study conducted by Fehringer *et al.* (26) indicated that light-to-moderate alcohol consumers (less than 20 g per day) had lower lung cancer risk than non-drinkers. Furthermore, Garcia Lavandeira *et al.* (27) suggested that the consumption of almost all kinds of alcohol, except spirits, posed no risk to lung cancer patient survival.

To explore the mechanism, we hypothesized that flavonoids found in wine may reduce the risk of some cancers. Support for a beneficial role of flavonoids is

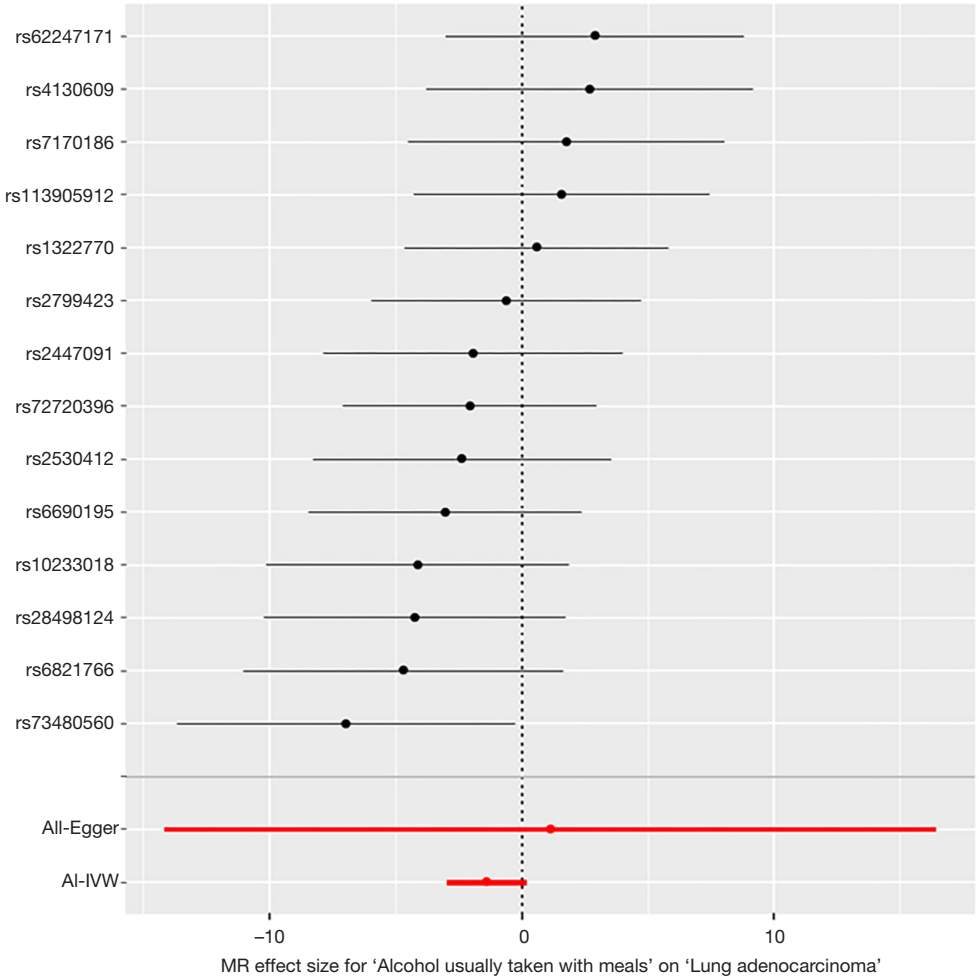

Figure 3 Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on lung adenocarcinoma. MR, Mendelian randomization.

provided by several studies where higher dietary intake of flavonoids (including flavonols, flavanones and quercetin) was inversely associated with lung cancer risk (28).

For these SNPs included in our MR study, rs4130609 reflected single nucleotide variation in *SOX5* gene, which reduced expression by alcohol exposure (29). Moreover, rs113905912 represented single nucleotide variation in *KMT2E* gene, and the mutation of this gene was associated with various diseases, such as some intellectual disability disorders (30), leukemia (31), and vasculopathy (32). Besides, rs62247171 meant Single nucleotide variation in *FOXP1* gene, which could be also related to multiple sclerosis (33), and ischemic stroke (33).

The MR results showed that habitual alcohol consumption with meals had an inverse effect on BMI. The study conducted by Arif *et al.* (1) also demonstrated that compared with nondrinkers, subjects with moderate alcohol consumption (fewer than 5 drinks per week) had a lower BMI. One interesting MR study (34) indicated that regular light-to-moderate alcohol consumption could increase high-density lipoprotein and reduce total glycerides, total cholesterol, and low-density lipoprotein, and according to previous studies, these lipid indicators were associated with lung cancer (35,36).

Randomized controlled trials (RCTs) are widely accepted to verify causality, but they are associated with a high cost. Because of the consistently long latency between the exposures and the occurrence of diseases, it is impractical

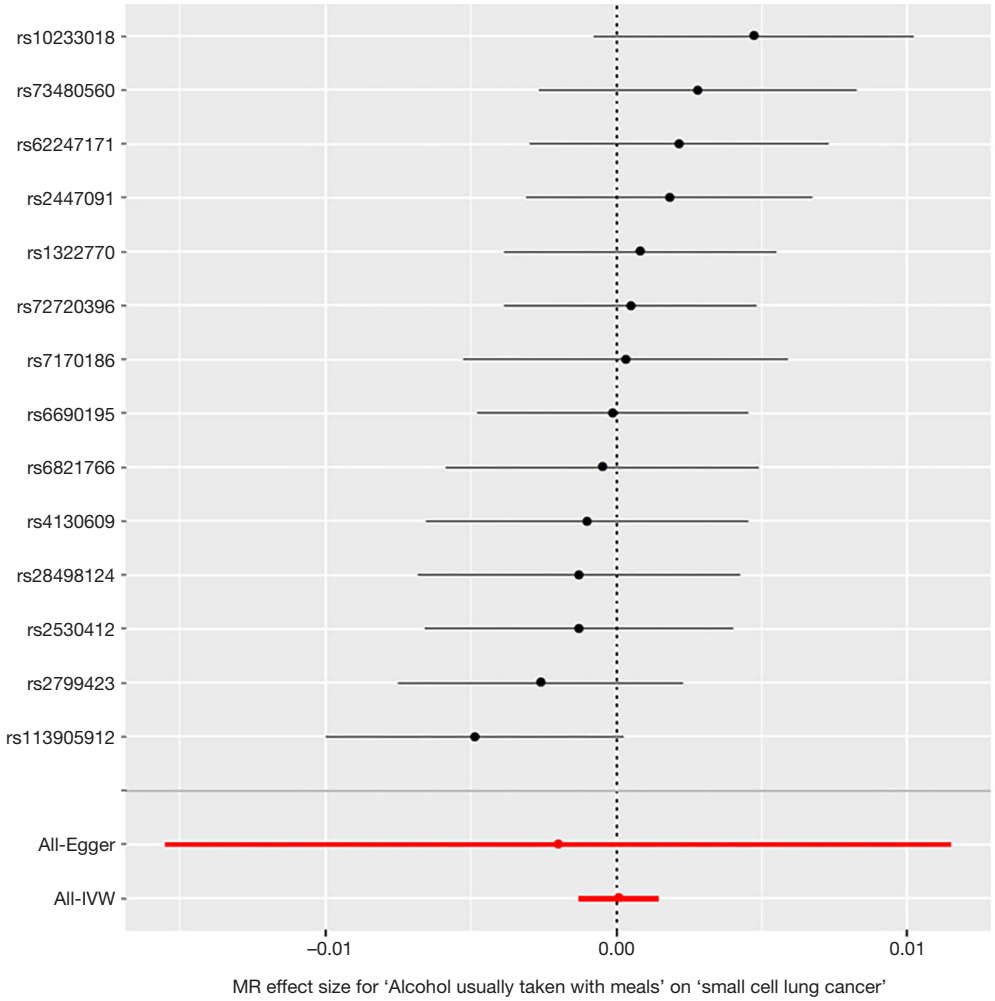

Figure 4 Forest plot of the causal effects of alcohol usually taken with meals-associated single nucleotide polymorphisms on small cell lung cancer. MR, Mendelian randomization.

and impossible to investigate all these causal associations through RCTs. However, in MR, genetic markers are used as variables of exposure instead of the exposure itself to facilitate causal inference (37). This method is rarely affected by confounding, reverse causality, and measurement error (38). Additionally, we can implement MR design by using two-sample MR analysis based on published summary data from large-scale GWASs, which greatly increases the scope and statistical power of MR studies (39,40).

Our study is the first MR study about alcohol consumption habits (alcohol habitually consumed with meals) and lung cancer. Participants were grouped based on their randomly allocated genotype, mimicking an RCT. However, limitations still exist in our study. First, all the participants included in our study were of European origin. Thus, whether the results can be generalized to other populations still needs to be studied and verified. Moreover, the summary data we used for two-sample MR did not allow for stratified analyses by covariates of interests, such as age and smoking status.

Conclusions

Habitual alcohol consumption with meals has a causal relationship with lung cancer. Furthermore, more work is needed to elucidate the potential mechanisms that mediate the associations between habitual alcohol consumption with meals and lung cancer.

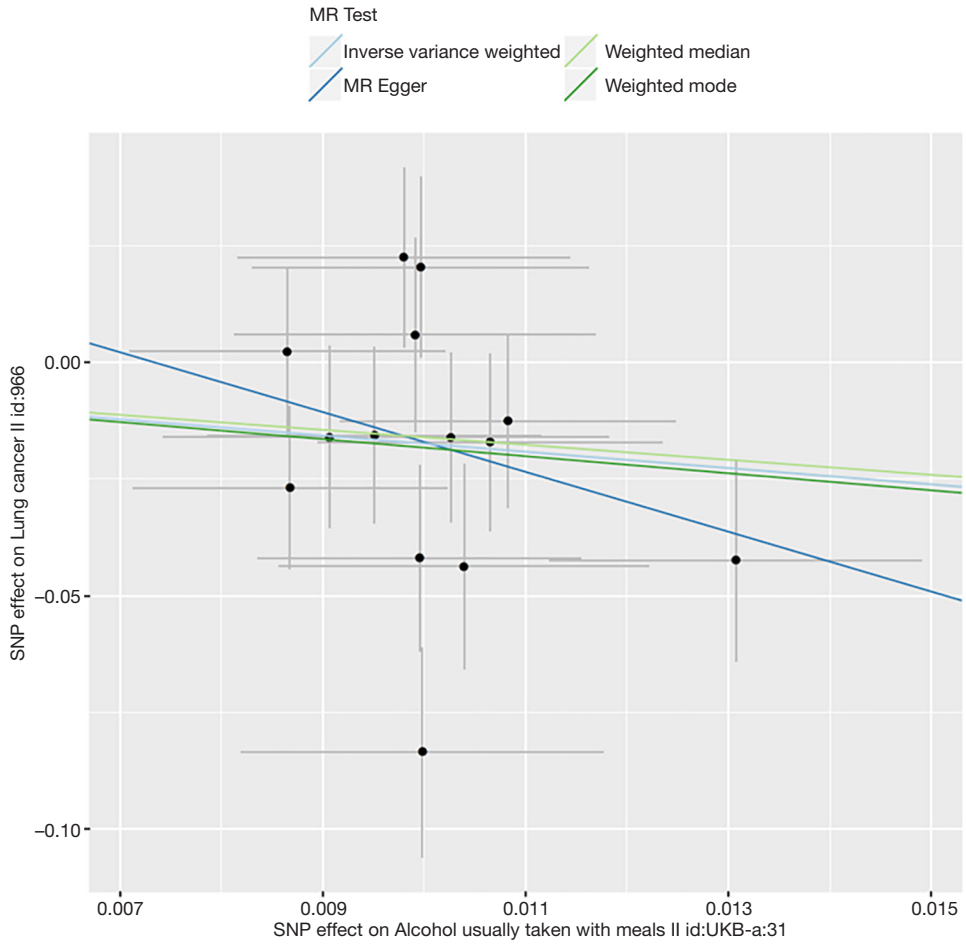

Figure 5 Scatter plots of genetic associations with alcohol usually taken with meals against the genetic associations with lung cancer. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Table 3 Heterogeneity tests

Cancer	Method	Q	Q_df	P value
Lung cancer	MR-Egger	22.379	12	0.033*
	Inverse variance weighted	23.229	13	0.039*
Small cell lung cancer	MR-Egger	10.322	12	0.588
	Inverse variance weighted	10.414	13	0.660
Lung adenocarcinoma	MR-Egger	12.042	12	0.442
	Inverse variance weighted	12.148	13	0.516
Squamous cell lung cancer	MR-Egger	14.548	12	0.267
	Inverse variance weighted	16.411	13	0.228

*, P value <0.05. MR, Mendelian randomization.

Table 4 Test for directional horizontal pleiotropy

Cancer	Egger_intercept	SE	P value
Lung cancer	0.047	0.070	0.512
Small cell lung cancer	2.10E−05	6.91E−05	0.766
Lung adenocarcinoma	−0.025	0.078	0.750
Squamous cell lung cancer	0.105	0.084	0.239

*, P value <0.05. SE, standard error.

Table 5 Test that the exposure is upstream of the outcome

Cancer	Snp_r2. exposure	Snp_r2. outcome	Correct_causal_direction	Steiger_P value
Lung cancer	0.003	0.001	True	0.007*
Small cell lung cancer	0.003	2.31E−05	True	<0.001*
Lung adenocarcinoma	0.003	0.001	True	0.001*
Squamous cell lung cancer	0.003	0.001	True	0.026*

*, P value <0.05. SNPs, single nucleotide polymorphisms.

Table 6 Two sample MR of alcohol consumption and risk factors

Risk factors	Numbers of SNPs	P value	OR	95% CI
Age of smoking initiation	8	0.133	1.140	0.961–1.354
BMI	14	<0.001*	0.701	0.577–0.852
Total cholesterol	8	0.192	0.707	0.420–1.189
Triglycerides	8	0.119	0.762	0.542–1.072
Cigarettes smoked per day	8	0.046*	0.002	3.50E−06 to 0.901
Former *vs.* current smoker	8	0.350	1.778	0.532–5.949

*, P value <0.05. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidential index; BMI, body mass index.

Acknowledgments

Funding: This work was supported by the funds from the Medical Research Fund of Guangdong Province (No. A2018237). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-3063

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/atm-20-3063). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Arif AA, Rohrer JE. Patterns of alcohol drinking and its association with obesity: data from the Third National Health and Nutrition Examination Survey, 1988-1994. BMC Public Health 2005;5:126.
2. Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes Care 2015;38:1804-12.
3. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2012;14:792-8.
4. Di Castelnuovo A, Rotondo S, Iacoviello L, et al. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002;105:2836-44.
5. Gronbaek M, Johansen D, Becker U, et al. Changes in alcohol intake and mortality: a longitudinal population-based study. Epidemiology 2004;15:222-8.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
7. Chen C. Analysis of Cell Division Cycle Associated genes expression and its prognostic significance in human lung carcinoma: a review of literature databases. Biomed Research International 2020. doi: 10.1155/2020/6412593.
8. Volk RJ, Mendoza TR, Hoover DS, et al. Reliability of self-reported smoking history and its implications for lung cancer screening. Prev Med Rep 2020;17:101037.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
11. Zhou H, Zhang Y, Liu J, et al. Education and lung cancer: a Mendelian randomization study. Int J Epidemiol 2019;48:743-50.
12. Zeng P, Zhou X. Causal Association Between Birth Weight and Adult Diseases: Evidence From a Mendelian Randomization Analysis. Front Genet 2019;10:618.
13. Brenner DR, Fehringer G, Zhang ZF, et al. Alcohol consumption and lung cancer risk: A pooled analysis from the International Lung Cancer Consortium and the SYNERGY study. Cancer Epidemiol 2019;58:25-32.
14. Li W, Tse LA, Au JS, et al. Prognostic value of alcohol consumption and some other dietary habits for survival in a cohort of Chinese men with lung cancer. Chin J Cancer 2017;36:21.
15. Wang Y, McKay JD, Rafnar T, et al. Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. Nat Genet 2014;46:736-41.
16. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet 2013;45:1274-83.
17. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet 2010;42:441-7.
18. Berndt SI, Gustafsson S, Magi R, et al. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. Nat Genet 2013;45:501-12.
19. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-96.
20. Boef AG, Dekkers OM, le Cessie S. Mendelian randomization studies: a review of the approaches used and the quality of reporting. Int J Epidemiol 2015;44:496-511.
21. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017;32:377-89.
22. Brennan P, McKay J, Moore L, et al. Obesity and cancer: Mendelian randomization approach utilizing the FTO genotype. Int J Epidemiol 2009;38:971-5.
23. Gao C, Patel CJ, Michailidou K, et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. Int J Epidemiol 2016;45:896-908.
24. Alvarez-Avellon SM, Fernandez-Somoano A, Navarrete-Munoz EM, et al. Effect of alcohol and its metabolites in lung cancer: CAPUA study. Med Clin (Barc) 2017;148:531-8.
25. Kakino K, Kiyohara C, Horiuchi T, et al. CYP2E1 rs2031920, COMT rs4680 Polymorphisms, Cigarette Smoking, Alcohol Use and Lung Cancer Risk in a Japanese Population. Asian Pac J Cancer Prev 2016;17:4063-70.
26. Fehringer G, Brenner DR, Zhang ZF, et al. Alcohol and lung cancer risk among never smokers: A pooled analysis from the international lung cancer consortium and the SYNERGY study. Int J Cancer 2017;140:1976-84.
27. Garcia Lavandeira JA, Ruano-Ravina A, Kelsey KT, et

al. Alcohol consumption and lung cancer risk in never smokers: a pooled analysis of case-control studies. Eur J Public Health 2018;28:521-7.
28. 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.
29. Zhou FC, Zhao Q, Liu Y, et al. Alteration of gene expression by alcohol exposure at early neurulation. BMC Genomics 2011;12:124.
30. Conforti R, Iovine S, Santangelo G, et al. ODLURO syndrome: personal experience and review of the literature. Radiol Med 2020. [Epub ahead of print]. doi: 10.1007/s11547-020-01255-2.
31. Liquori A, Ibañez M, Sargas C, et al. Acute Promyelocytic Leukemia: A Constellation of Molecular Events around a Single PML-RARA Fusion Gene. Cancers (Basel) 2020;12:624.
32. Fan Q, Cheung CMG, Chen LJ, et al. Shared genetic variants for polypoidal choroidal vasculopathy and typical neovascular age-related macular degeneration in East Asians. J Hum Genet 2017;62:1049-55.
33. Tian Z, Song Y, Yao Y, et al. Genetic Etiology Shared by Multiple Sclerosis and Ischemic Stroke. Front Genet 2020;11:646.
34. Vu KN, Ballantyne CM, Hoogeveen RC, et al. Causal Role of Alcohol Consumption in an Improved Lipid Profile: The Atherosclerosis Risk in Communities (ARIC) Study. PLoS One 2016;11:e0148765.
35. Şahin F, Aslan AF. Relationship between Inflammatory and Biological Markers and Lung Cancer. J Clin Med 2018;7:160.
36. Lyu Z, Li N, Wang G, et al. Independent and joint associations of blood lipids and lipoproteins with lung cancer risk in Chinese males: A prospective cohort study. Int J Cancer 2019;144:2972-84.
37. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1-22.
38. Scosyrev E. Identification of causal effects using instrumental variables in randomized trials with stochastic compliance. Biom J 2013;55:97-113.
39. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol 2013;178:1177-84.
40. Burgess S, Scott RA, Timpson NJ, et al. Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol 2015;30:543-52.

Cite this article as: Chen C, Hu Q, Wang J, Wen T, Zhu C, Tan W, Chen X, Zhao Q, Wang W, Cao H, Li H. Habitual consumption of alcohol with meals and lung cancer: a Mendelian randomization study. Ann Transl Med 2021;9(3):263. doi: 10.21037/atm-20-3063

