Original Article

Causal effect of beta-blockers on the risk of lung cancer: a Mendelian randomization study

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Background: It remains uncertain whether there is a causal association of the use of beta-blockers (BBs) on lung cancer risk. We used a two-sample Mendelian randomization (MR) approach to identify the causal association of BBs and lung cancer risk.

Methods: Twenty-two BB-related single-nucleotide polymorphisms (SNPs) were obtained from the UK Biobank as the instrumental variables (IVs). Genetic summary data information of lung cancer was extracted from the International Lung Cancer Consortium, with a total of 11,348 cases and 15,861 controls. We adopted the inverse-variance weighted (IVW) approach to conduct the MR analyses. Egger-intercept analysis was further performed as sensitivity analysis for pleiotropy evaluation. Additionally, we investigated whether BBs could causally affect the risk of lung cancer through their pharmacological effects.

Results: The current IVW analysis suggested a decreased lung cancer risk in BB users [odds ratio (OR) =0.83; 95% confidence interval (CI): 0.73–0.95; P<0.01]. Results of Egger-intercept analysis demonstrated that no pleiotropy was found (P=0.94), which suggested the robustness of the causality. However, there was little evidence that pharmacological effects mediate the association between BBs and lung cancer.

Conclusions: The current analysis suggested that BBs could decrease the risk of lung cancer but may be not via its pharmacological effects. Further research is in need for elucidating the underlying mechanisms.

Keywords: Mendelian randomization (MR); beta-blockers (BBs); lung cancer; risk factors

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Introduction

Lung cancer, with an 11.4% of diagnosed incidence and 18.0% of mortality among the total of cancer deaths, was supposed to be the second most commonly diagnosed cancer (1). Although the treatment of lung cancer has been changing with each passing day and emergence of immunotherapy has offered the hope to cure lung cancer permanently, the 5-year survival rate of lung cancer remains low. Hence, the prevention of lung cancer is exceedingly significant, especially to know about the risks and precautions from the aspects of epidemiology and bioinformatics, including cigarette smoking, environmental pollution and pressure (2,3).

Beta-blockers (BBs) are commonly used in the treatment of many cardiovascular diseases (4). It is implicated in recent studies that beta-adrenergic receptor (β-AR) acts as a significant mediator in the growth and/or invasiveness of many malignancies, that is, it could promote tumorigenesis and cancer metastasis (5,6), and enhance suppressive immunity (7); these exciting discoveries of BBs have inspired a new round of research boom. A nested case-control study provided by Saad *et al.* (8) suggested that long-standing use of BBs seems to relate to reduce the risk of pancreatic cancer. Thiele *et al.* (9) proved that non-selective BBs may play a preventive role on cirrhosis patients who would probably suffer from hepatocellular carcinoma in a meta-analysis. However, whether BBs-taken can decrease the risk of lung cancer remains controversial and inconsistent in epidemiological studies.

Mendelian randomization (MR) analysis is not only an epidemiological method to assess the latent pathogenic factors of diseases, but also a novel approach for predicting possibilities of drug repurposing (10,11). MR uses public genetic variants as instrumental variables (IVs) to infer causal effects, with the purpose of eliminating all confounding factors between genetic polymorphism and disease theoretically (12). Moreover, using two-sample MR analysis which is based on the published summary data from large-scale genome-wide association studies (GWASs) can greatly enhance cost efficiency of MR analysis and alleviate the bias of MR caused by overestimation of genetic effect sizes which are induced by GWASs (13,14). This approach has not been used to evaluate the association of BBs and lung cancer, and to verify whether it is caused by the pharmacological effects of BBs including lowering blood pressure, decreasing heart rate, and increasing the level of triglycerides (15-18). In this study, we implemented a two-sample MR analysis to explore the potential causal association between BBs and the risk of lung cancer by using single-nucleotide polymorphisms (SNPs) from large-scale GWAS. We present this article in accordance with the STROBE-MR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1098/rc).

Highlight box

Key findings

- This study suggested a decreased lung cancer risk in beta-blocker users (odds ratio =0.83; 95% confidence interval: 0.73–0.95; P<0.01) using Mendelian randomization study. No pleiotropy was found (P=0.94) according to Egger-intercept analysis.

What is known and what is new?

- Observational studies have found that the use of beta-blockers (BBs) affects the risk of developing multiple types of cancer. Many previous studies have suggested that β-adrenergic signaling is associated with lung cancer.
- The causal relationship between the use of BBs and the risk of developing lung cancer is not clear.

What is the implication, and what should change now?

- The intake of BBs may potentially serve as a preventive medication to assist clinical professionals in treating patients with lung cancer.

Methods

Genetic variant selection

We used summary statistics from a GWAS of the UK Biobank on the basis of self-reported medication-use data of 23 medication categories among approximately 320,000 European individuals (19). Threshold of $P<5\times10^{-8}$ was set to be genome-wide significant for SNPs selection. To control

Table 1 Details of studies included in MR study

Trait	First author	Consortium	Study participants	Year	PubMed ID	Website
A unit increase dose of BB	Wu Y	UK Biobank	224,024	2019	31015401	https://www.ukbiobank.ac.uk/
Lung cancer	Wang Y	ILCCO	27,209	2014	24880342	ilcco.iarc.fr
SBP	Warren HR	ICBP-1000G	152,249	2017	28135244	http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020
DBP	Warren HR	ICBP-1000G	152,249	2017	28135244	http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=157020
Heart rate	den Hoed M	Global BPgen	174,610	2013	23583979	NA
Triglycerides	Kathiresan S	DGI-GWAS	18,554	2008	18193044	http://www.broad.mit.edu/diabetes
Cigarettes smoked per day	Liu M	GSCAN	341,427	2019	30643251	https://genome.psych.umn.edu/index.php/GSCAN
Alcoholic drinks per week	Liu M	GSCAN	341,427	2019	30643251	https://genome.psych.umn.edu/index.php/GSCAN
BMI	Yengo L	GIANT	681,275	2018	30124842	https://cnsgenomics.com/data.html
Hypertension	Ehret GB	ICBP-GWAS	203,056	2011	21909115	NA
Coronary heart disease*	Schunkert H	UKBCM	86,995	2011	21378990	https://www.ebi.ac.uk/gwas/

*, including myocardial infarction, angina and chromic ischemic heart disease. MR, Mendelian randomization; BB, beta-blocker; ILCCO, International Lung Cancer Consortium; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not available; DGI-GWAS, diabetes genetics initiative genome-wide association study; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; BMI, body mass index; GIANT, Genetic Investigation of ANthropometric Traits; ICBP-GWAS, International Consortium for Blood Pressure Genome-Wide Association Studies; UKBCM, UK Biobank Cardio Metabolic.

the family-wise error rate (FWER), we further performed an exclusion while mutual linkage disequilibrium (LD) shared larger P value ($P>5\times10^{-8}$) and exceeding limits ($R^2<0.001$) through Bonferroni correction. Besides, we measured F-statistics to evaluate instrument strength. We had 80% power at a 0.05 significance level to detect an odds ratio (OR) of 1.04 according to Brion *et al.* (20), β was detected as 0.09 at a 0.05 significance level with 224,024 samples involved when statistical power reached 80%. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

GWAS summary data on lung cancer

Genetic association estimation from GWAS summary data on lung cancer in our study was collected from the International Lung Cancer Consortium (ILCCO) (European population, 11,348 cases and 15,861 controls) including the histological subtypes of lung adenocarcinomas (LUADs) and lung squamous carcinomas (LUSCs) (*Table 1*) (21). Each of the 22 SNPs associated with BBs was used for assessing the effects on those data of lung cancer for determination of the effect sizes and standard errors.

Statistical analysis

Several MR methods were used to confirm MR estimation of BBs intake for the risk of lung cancer. We combined the Wald ratio for individual SNPs by using inverse-variance weighted (IVW) meta-analysis. The methods of MR-Egger regression and weighted median were used to indirectly test whether the IVs associated with BBs intake would influence lung cancer only by the effect on BBs. Directional pleiotropy was evaluated by the intercept obtained from the Egger regression analysis. We performed Cochran's Q test of the IVW and the MR-Egger estimation to identify if there is heterogeneity among the SNPs. Furthermore, two different histological subtypes including LUAD and LUSC were also conducted for the same analysis. The estimations were presented in the form of OR and 95% confidence

Table 2 MR estimates of the associations between beta-blockers and risk of lung cancer

Outcome	IVW method		MR-Egger		Weighted median method	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Lung cancer	0.8342 (0.7294, 0.9540)	0.0081	0.8210 (0.5206, 1.2947)	0.4062	0.8496 (0.7077, 1.0199)	0.0805
Squamous cell lung cancer	0.7123 (0.5515, 0.9201)	0.0094	0.5334 (0.2299, 1.2378)	0.1590	0.7980 (0.5957, 1.0691)	0.1305
Lung adenocarcinoma	0.8370 (0.6863, 1.0209)	0.0790	1.0872 (0.5596, 2.1125)	0.8076	0.8233 (0.6280, 1.0795)	0.1594

MR, Mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval.

intervals (CIs). P values <0.05 represented statistically significance (22).

The MR methods were following by the three assumptions: (I) the IVs are strongly associated with the use of BBs; (II) the IVs affect lung cancer only through their effects on the use of BBs instead of any causal pathway; (III) the IVs are independent and not affected by any confounding factors (23). A leave-one-out analysis was performed in our study to assess whether a single SNP could determine or bias the MR estimation.

It is noteworthy that no matter how prefect an epidemiological research design is or how exact the measuring instruments are, there will always be the underlying, immeasurable, and overlooked confounders. Smoking (24), alcohol (25), and high body mass index (BMI) (26) are considered as the major causes of lung cancer. Individuals with above features are prone to cardiovascular diseases which require treatment with BBs; the clinical applications of BBs are probably related to lung cancer. Therefore, we considered those mentioned factors as confounding factors between BBs and lung cancer. It allowed us to test the (III) assumption more fully. We conducted MR analysis between BBs and each confounding factors, which allowed us to test the (III) assumption more fully. MR analysis can only provide the effect of lifelong exposure on the outcome (27), and IVs required in our study was chosen from a GWAS study where patients taking lifelong BBs medication based on the literature of Oliver *et al.* (28). Then we evaluated them with similar MR methods. *Table 1* shows the source and details of respective GWAS summary data of those confounding factors.

To explore the potential mechanisms, we used the MR methods defined in the preceding section and identified the type of BBs and their pharmacology action in the DrugBank database (29) and selected the major pharmacological functions: lowering blood pressure; systolic blood pressure (SBP) and diastolic blood pressure (DBP); slowing heart rate; increasing the concentration of triglycerides. Genetic effects on SBP and DBP were obtained from the UK Biobank (30) (equal to the drop of SBP or DBP in every 10 mmHg), while the association with heart rate based on the GWAS data from a meta-analysis of GWASs (31). Genetic instruments for triglycerides (equal to the standard deviation increase of triglycerides) were collected from the diabetes genetics initiative (DGI) study, FUSION study and the SardiNIA study (32). All MR analyses were conducted in R (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria) (33). All the P values were 2-tailed.

Results

Genetic instruments

As genetic instruments for BBs, we selected 59 loci that related to BBs at the genome-wide significance threshold of $P<5\times10^{-8}$ (detailed information is shown in Table S1). After selection and exclusion, 22 SNPs in total closely associated with BBs were identified as the final IVs, which explained 3.38% of the variation of using BBs across individuals (table available at https://cdn.amegroups.cn/static/public/jtd-23-1098-1.xlsx). The result of F-statistics was 132.79 which meant that the instruments used in our study would powerfully predict (F >100) the IVs used in our analysis (34).

Causal effect on BBs and lung cancer

The process of conducting two-sample MR analysis is indicated in Figure S1. Firstly, the result based on MR analyses (*Table 2*) showed that genetically predicted BBs were statistically associated with a lower risk of lung cancer and had a protective effect on lung cancer. Each additional unit of BBs reduced the risk of suffering lung cancer by

Table 3 Results of sensitivity analyses between beta-blocking agents and lung cancer

Outcome	MR method	Heterogeneity statistics		MR-Egger regression method	
		Cochran Q [Q_df]	P value	Intercept [SE]	P value
Lung cancer	MR-Egger	23.65 [20]	0.2579	0.0011 [0.015]	0.944
	IVW	23.66 [21]	0.3099		
Squamous cell lung cancer	MR-Egger	36.9 [20]	0.0120	0.02 [0.029]	0.487
	IVW	37.82 [21]	0.0135		
Lung adenocarcinoma	MR-Egger	21.19 [20]	0.3859	−0.018 [0.022]	0.428
	IVW	21.89 [21]	0.4061		

MR, Mendelian randomization; df, degrees of freedom; SE, standard error; IVW, inverse-variance weighted.

Table 4 Causal effects between genetically predicted confounders and beta-blockers and lung cancer

Outcomes	Causal effect (95% CI)	P value
Cigarettes smoked per day	1.0006 (0.9969, 1.0043)	0.7496
Alcoholic drinks per week	0.9987 (0.9934, 1.0039)	0.6156
BMI	0.9996 (0.9984, 1.0007)	0.4741
Hypertension	1.0025 (0.9929, 1.0056)	0.1087
Coronary heart disease*	1.0001 (0.9992, 1.0011)	0.7909

*, including myocardial infarction, angina and chromic ischemic heart disease. CI, confidence interval; BMI, body mass index.

17% (OR =0.83; 95% CI: 0.73–0.95; P<0.01). We obtained the similar causal effect from LUSC subgroup (OR =0.71; 95% CI: 0.55–0.92; P<0.01), while in LUAD subgroup we received the contrary result (OR =0.84; 95% CI: 0.69–1.02; P=0.08) (*Table 2*; Table S2).

Verification of three MR-assumptions

Firstly, we selected SNPs at the genome-wide significance threshold of $P<5\times10^{-8}$ which reached the first MR assumption. Secondly, the Egger intercept was close to zero and P value of it was large (β =0.001, P=0.94) (*Table 3*). It meant that if the effect of horizontal pleiotropy seems to be negligible, it will not contradict the second MR assumption. The MR regression slopes are shown in Figure S2A-S2C. There was no evidence found in the existing GWASs that the included BBs-associated SNPs were dramatically associated with any other phenotypes, which met the requirements of the third assumption. Furthermore, the MR analyses suggested that no confounders interfered with the causality on BBs and lung cancer (*Table 4*).

Heterogeneity, asymmetry, and sensitivity analyses

Table 3 suggested that no directional pleiotropy was found in the MR-Egger regression analysis. Besides, based on Cochran's Q-test and funnel plot, no evidence showed the presence of heterogeneity and asymmetry among these SNPs in the causal effect on BBs and lung cancer or LUAD subgroup. However, heterogeneity was found in subgroup analysis of LUSC (*Table 3*). This may be because the meta-analysis on lung cancer was based on data from four different existing lung cancer GWAS of European populations, meaning that the complexity of case-control studies, identification criteria for primary lung cancer and its classification, composition of series samples, and the traits of the participants themselves were most probably connected with heterogeneity. Individual causal effects of the 22 SNPs on lung cancer are illustrated respectively in Table S2; the results of leave-one-out sensitivity analysis were showed in Table S3 and Figure S3A-S3C.

Causal effect of mediators from BBs on lung cancer

To identify whether the pharmacology effects of BBs could mediate the BBs-lung cancer association, we used the similar MR analysis to investigate it. The results were insufficient to show that IVs of 22 BBs-associated SNPs were genome wide significantly associated with any other phenotypes (*Table 5*), which suggested that the pharmacology effects of BBs may not be the mediator for BBs on lung cancer.

Discussion

In this two-sample MR analysis which involved 31,700 cases and 192,324 controls, it was genetically predicted that the use of BBs was found associated with lung cancer overall

Table 5 Causal effects from the pharmacology effects on lung cancer and its subgroups in using the IVW method

Exposures/ outcomes	Lung cancer		Squamous cell lung cancer		Lung adenocarcinoma	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
SBP	0.9892 (0.9427, 1.0380)	0.6597	0.9522 (0.8992, 1.0084)	0.0941	0.9927 (0.9132, 1.0790)	0.8626
DBP	1.0225 (0.9778, 1.0692)	0.3297	1.0235 (0.9646, 1.0860)	0.4419	1.0167 (0.9588, 1.0782)	0.5793
Heart rate	1.0044 (0.9688, 1.0413)	0.8124	1.0174 (0.9667, 1.0708)	0.5079	1.0208 (0.9712, 1.0728)	0.4185
Triglycerides	1.0200 (0.7543, 1.3794)	0.8975	1.0662 (0.6966, 1.6321)	0.7678	1.0210 (0.6833, 1.5257)	0.9190

IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

and LUSCs, but not with LUAD. Given the additional analysis of mediator exploration, the results suggested that BBs may reduce the risk of lung cancer through another alternative mechanisms, rather than they were being used in the treatment of common diseases.

A growing number of studies have explored the β-AR expression patterns and supported that activation of β-adrenergic signaling is associated with lung cancer progression, which can be reversed by BBs. Several studies have revealed β-AR expression in lung cancer by using bioinformatics analysis (35) or experimental techniques (36,37). According to Nilsson *et al.* (38), β-AR related gene expression was positive in 159 non-small cell lung cancer (NSCLC) clinical samples and 116 lung cancer cell lines tested by quantitative real time polymerase chain reaction (qRT-PCR). Activated β-AR was correlated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance via mitogen-activated protein kinases (MAPKs) pathway in EGFR-mutant NSCLC cells. In a study investigating β-AR expression and its prognostic value on 328 primary NSCLC tumors samples, β2-AR expression was significantly associated with tumor vascularization and cell proliferation and was an independent biomarker of worse progression free survival (PFS) in stage I LUAD patients (39). Besides, some clinical studies like the one conducted by Jafri *et al.* (40) showed that the use of BBs may protect against lung cancer, as the use of BBs was observed significantly higher in patients without lung cancers. Moreover, a cohort study raised by Lin *et al.* (41) demonstrated that long-term use of carvedilol, a nonselective β-blocker, was associated with lower risk of lung cancer and it could be a potential agent in lung cancer prevention. Therefore, the use of BBs may be a potential alternative to control the incidence of lung cancer, which is consistent with our findings.

In this study, the effect of BBs in prevention of lung cancer was not found in all histological subtypes, possibly driven by different mechanisms of anticancer effects. Current studies have found that abnormally activated β-AR signaling pathways which were induced by chronic stress or the nicotine-derived carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) contribute to lung epithelial cell transformation, lung tumourigenesis, and angiogenesis, while BBs can reduce this process (42-44). Data from Min *et al.* found that NNK stimulated malignant transformation of normal human lung epithelial and tumor formation via β-AR-mediated insulin-like growth factor 1 receptor (IGF-1R) phosphorylation. After treated with β-AR antagonists, normal human lung epithelial cell lines showed a significantly suppression in NNK-mediated phenotypic transformation (45). Because duration-related cigarette exposure was more strongly related with LUSC (46,47), our findings in this histological subtype might be supported. As for LUAD, Schuller *et al.* (48) demonstrated that only in LUAD of Clara cell phenotype, a group with non-ciliated small airway epithelial cells features, can BBs block the malignant transformation progression stimulated by β-AR signaling. Smoking or psychological stress leads to the release of catecholamines which bind to β-AR and activate protein kinase A by cyclic adenosine monophosphate (cAMP) accumulation, with vascular endothelial-derived growth factor (VEGF) and arachidonic acid (AA) release downstream, resulting in cancer growth stimulation (49-51). Considering the converse effect of BBs in different histological subtypes, researchers should interpret our findings with caution.

Strengths and limitations

Using two-sample MR analysis to investigate the causal effect is the main strength of our study. It helps in mitigating and addressing certain forms of confounding and reversing

causation in conventional observational studies including environment and lifestyle factors of participants (10). For example, cohort studies face the problems of follow-up loss and the status of participants changed over time, while case-control studies fail to confirm specific susceptibility loci of BBs, determine causality, and eliminate various bias like selection bias. Participants were grouped in our study according to randomly allocated genotype, which mimics the procedure of randomized controlled trial (RCT) and prevents the disadvantages such as complicated research design, long duration, and high cost. Considering our large sample sizes with 224,024 samples, and the close association of IVs (F >100), the causal effect can be estimated with high accuracy under a sufficient power value (100%).

However, like other MR analyses, there are some shortcomings in this study. First, the ethnic consistency is required in MR analysis, so our study only applies to European origin, and other populations remain to be explored. Therefore, our results are regionally limited. Second, given that it is impossible to deal with all the existing confounding factors completely and the pleiotropic nature of genetic variants affecting medication-use, we cannot easily exclude the potential and immeasurable confounding factors and residual pleiotropy. In order to minimize errors as much as possible, several sensitivity analyses were used and potential interference factors were taken into account. Though no evidence of horizontal pleiotropic effects was found, we cannot directly conclude that there were no latent confounding factors. Third, we also faced the fact that MR analysis might generate false-negative findings when testing the effect of drugs. MR analysis estimates the effect of lifelong exposure in most cases while medications generally cannot be as an lifelong exposure in strict terms (52). That means that the null finding in our result may be caused by this default rather than the ineffectiveness of the drug.

Further limitations in our study were caused by the lack of detailed data. Firstly, the summary data of BBs from the UK Biobank lacked reasons, duration, dosage, and the subtypes of BBs-taken, thus we could not identify the associations of SNPs with dosage level by pharmacogenomics analyses. Secondly, it is controversial whether the efficacy of BBs in lung cancer prevention is receptor-dependent. Due to data limitations, we could not have a further discussion on the type, selective or non-selective, of BBs. Thirdly, without detailed data of the instruments, we did not get SNPs of the protein targets of BB drug classes. Though independent SNPs associated with BBs pharmacologic action were used in mechanism investigation, how BBs play a role in lung cancer prevention remains unclear.

Conclusions

Our present MR study provided abundant and preliminary evidence that the use of BBs can decrease the risk of lung cancer. This helps researchers understand an alternative way for lung cancer prevention. However, we found little supportive evidence that the decrease of lung cancer risk was caused by the major pharmacologic effects of BBs with the help of combining SNPs and summary data from different GWAS as IVs. Furthermore, some hypotheses raised in some literature may not be directly verified by MR analysis. Further research is required to obtain a definitive answer to the underlying mechanism.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1098/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1098/coif). J.H. serves as the Executive Editor-in-Chief of *Journal of Thoracic Disease*

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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).

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