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RESEARCH

Association between idiopathic pulmonary fibrosis and risk of different pathological types of lung cancer: a Mendelian randomization study

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Abstract

Background Many epidemiological studies have shown that idiopathic pulmonary fibrosis (IPF) is a risk factor for lung cancer (LC), but these studies do not provide direct evidence of a causal association between the two diseases. We investigated the causal association between IPF and different pathological types of LC based on the Mendelian randomization (MR) study.

Methods The genome-wide association study (GWAS) data of IPF and LC were obtained from the latest published articles, and instrumental variables (IVs) for analysis were obtained after screening and eliminating the confounders. MR Analysis was carried out with the help of random effects inverse variance weighting (re-IVW), MR-egger, and weighted median method, and a comprehensive sensitivity test was conducted.

Results The results of re-IVW analysis showed that IPF may increase the risk of lung squamous cell carcinoma (LUSC) (OR = 1.045, 95% CI 1.011 to 1.080, $P = 0.008$). In addition, no causal relationship was found between IPF and overall LC (OR = 0.977, 95% CI 0.933 to 1.023, $P = 0.32$), lung adenocarcinoma (LUAD) (OR = 0.967, 95% CI 0.903 to 1.036, $P = 0.345$) and small cell lung carcinoma (SCLC) (OR = 1.081, 95% CI 0.992 to 1.177, $P = 0.074$). A comprehensive sensitivity analysis ensured the reliability of the study.

Conclusion In conclusion, from the perspective of genetic association, we found that IPF is an independent risk factor for LUSC and may increase the risk of LUSC, but no such causal relationship was found in LUAD and SCLC.

Keywords Cancer · Idiopathic pulmonary fibrosis · Lung cancer · European · Mendelian randomization

Introduction

Lung cancer (LC) is a common malignant tumor that seriously endangers human health. According to statistics, there were about 2.2 million new cases of LC and about 1.8 million deaths worldwide in 2020, making it the second most common cancer and the leading cause of cancer deaths (Sung et al. 2021). The high incidence and mortality rate of LC poses a great threat to human health and also has a serious socio-economic impact. There have been many encouraging breakthroughs in research on LC, such as the use of low-dose spiral CT in screening, which has allowed more patients to be diagnosed at an earlier stage, and the advent of targeted therapy and immunotherapies, which has provided patients with more treatment options (Aberle et al. 2011a, 2011b; Arbour and Riely 2019). All of these methods have improved the prognosis of LC patients to varying degrees. In addition, the exploration of the etiology and risk factors of LC has been ongoing. Although smoking is still considered to be the most important risk factor for LC, other risk factors are gaining attention from researchers as the rate of smoking declines and the rate of LC in nonsmokers increases (Bade and Dela Cruz 2020). For example, marijuana use, biomass burning, air pollution, occupational exposure, and chronic lung disease are all common risk factors for LC.

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More in-depth studies of these risk factors will help reduce the incidence of LC at the root cause.

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia whose etiology has not yet been fully elucidated. A close relationship between IPF and LC was proposed back in 1965 (Meyer and Liebow 1965). As research has progressed, the disease is now considered an important risk factor for LC. It was found that patients with interstitial fibrosis had a significantly increased incidence of LC and that this effect was independent of smoking (Hubbard et al. 2000). In addition, many common pathogenic mechanisms between IPF and LC have been continuously explored and striking advances have been made, and these studies have elucidated the link between the two diseases based on genetic, molecular, and cellular processes and have attempted to explore the causal relationship between them (Ballester et al. 2019; Kinoshita and Goto 2019). Based on these studies, many treatment options have been proposed for patients with IPF combined with LC (Otsubo et al. 2022; Kanayama et al. 2020). However, neither the epidemiologically observed findings nor the currently revealed common pathogenesis has directly demonstrated a clear causal relationship between them. And since many of the risk factors for IPF are also risk factors for LC, such as smoking and occupational exposure, these reasons may interfere with the epidemiological study and affect the accuracy of the results (Meyer 2017).

Mendelian randomization study is a research method to infer the causal relationship between exposure and outcome, which uses single nucleotide polymorphism (SNP) as a genetic instrumental variable (IV) to eliminate various biases caused by known and unknown confounding factors, thus avoiding reverse causality and various errors commonly found in epidemiological studies. In this study, we used an MR study to assess the causal relationship between genetically predicted IPF and LC and its various pathological types.

Materials and methods

Acquisition of IVs representing IPF

The genome-wide association study (GWAS) data for IPF were obtained from a genome-wide association study that included a total sample size of 24,589 cases (4,124 cases, 20,465 controls), all from European ancestry and including both males and females. The study's data consisted of two parts: 2668 cases and 8591 controls from other previous studies after quality control (Noth et al. 2013; Allen et al. 2017; Fingerlin et al. 2013); two independent case–control collections as replication data sets containing 1456 cases and 11874 controls (Allen et al. 2020). We selected IVs based on the three major assumptions of MR, namely, that SNPs are strongly associated with exposure, SNPs are independent of the outcome, and SNPs are independent of confounders. Firstly, we screened SNPs using a genome-wide significance threshold ($P < 5E\text{-}08$) as a threshold and performed structural clustering based on linkage disequilibrium (LD) to retain the index SNPs with the smallest *P* values ($R2 < 0.001$, any other relevant SNPs within 10 Mb). Secondly, we examined the phenotypes associated with IVs by PhenoScanner v2 (http://www.phenoscanner.medschl.cam.ac.uk/, *P*-value = 5E-8, proxy: EUR, $R2 = 0.8$, Build = 37) and removed SNPs associated with LC and confounding factors (Smoking, radon exposure, occupational exposure, history of cancer, history of lung cancer in first-degree relatives, chronic lung disease, lung function, etc.) (Bade and Dela Cruz 2020; Kang et al. 2022) to ensure that the IVS selected could only affect LC by affecting IPF. Thirdly, we harmonized exposure and outcome datasets to ensure allelic consistency. Finally, we calculate the F values of the IVs by the formula F = [R2/(1-R2)] * [(n-k-1)/k], delete the IVs with *F* values less than 10, and keep the IVs that are strongly correlated with exposure (Burgess et al. 2013).

Acquisition of GWAS data for LC and its various pathological types

The GWAS data for LC were derived from a large-scale association analysis of 29,266 cases and 56,450 controls in a pooled genome-wide association study, with all samples from European ancestry and including both males and females (McKay et al. 2017). The study further refined the pathological types of LC, including lung squamous cell carcinoma (LUSC), lung adenocarcinoma (LUAD), and small cell lung carcinoma (SCLC), and the contents of each pathological type of LC are shown in Table S1.

After obtaining data on IPF and LC, we extracted the SNPs associated with IPF that could be used as IVs from each LC dataset in turn for subsequent analysis. Additionally, all the data came from published articles, so there was no need for informed consent or ethical review.

MR analysis

This study was analyzed using random effects inverse variance weighting (re-IVW), MR-Egger, and weighted median methods. Combining the statistical characteristics of each of the three methods and the presence or absence of heterogeneity and multiplicity of IVs, different analytical methods were selected to prioritize the basis for the determination of results.

Sensitivity analysis

The sensitivity analysis included a horizontal multiplicity test and heterogeneity test. In this study, horizontal multiplicity was tested with the help of the MR-Egger regression test, and if there was a statistically significant intercept term in the MR-Egger analysis, it indicated that the study had significant horizontal multiplicity. Heterogeneity was assessed with the help of the IVW method and MR-Egger regression. In this study, outliers were also detected using the MR-PRESSO method, and if outliers were detected, they were removed and re-analyzed using the remaining IVs. Finally, the robustness of the results was assessed by the "leave-one-out" method. All statistical analyses and results visualization in this study was performed with the help of R statistical software (version 4.1.2, https://www.R-project.org), mainly involving the "TwoSampleMR" "MRPRESSO" and "forestplot" packages.

Results

Acquisition of IVs

A total of 24 SNPs significantly associated with IPF were obtained as IVs after screening, and after further screening by the PhenoScanner v2 tool, three SNPs with confounding factors (rs3785884, rs2076295, and rs7100920, which were directly related to lung function and chronic obstructive pulmonary disease) were excluded, resulting in 21 SNPs. The F values of the included SNPs were all greater than 10, indicating that all of these SNPs were strongly associated with IPF, as shown in Table 1. These 21 SNPs were intersected with the data of LC and its various pathological types, and finally, 21 SNPs related to LC, LUSC, and LUAD and 18 for SCLC were obtained for analysis.

Results of MR analysis

re-IVW methods provide reliable causal estimates in the absence of directional pleiotropy. The results of the re-IVW analysis in the current study showed that IPF may increase the risk of LUSC (OR = 1.045, 95% CI 1.011 to 1.080, $p = 0.008$). Although the MR-Egger method and the weighted median method had $P > 0.05$, their β values were all in the same direction as those calculated by the re-IVW method, so it can still be concluded that IPF may increase the risk of LUSC. In addition, no causal relationship was found between IPF and overall LC (OR = 0.977, 95% CI 0.933 ~ 1.023, $P = 0.32$), LUAD(OR = 0.967, 95% CI 0.903 ~ 1.036, $P = 0.345$), and SCLC(OR = 1.081, 95% CI 0.992 ~ 1.177, $P = 0.074$). The detailed analysis results are shown in Table 2 and Fig. 1.

Table 1 Instrumental variables of idiopathic pulmonary fibrosis

SNP	Effect/other	EAF	BETA	SE	*P*-value	*F*
rs4233306	C/T	0.198109392	0.2068	0.034989398	3.41E-09	338.6868944
rs2292181	G/C	0.052345105	− 0.4199	0.057858974	3.95E-13	437.7414064
rs9860874	C/A	0.276486228	− 0.2572	0.0298253	6.49E-18	668.4158726
rs2609259	C/A	0.223972679	− 0.2642	0.031616926	6.47E-17	611.421945
rs7725218	G/A	0.329474643	0.3464	0.029403741	4.90E-32	1376.533422
rs1214759	G/A	0.320606455	0.1652	0.029298351	1.71E-08	295.8309092
rs12537430	G/A	0.374963996	0.2468	0.028455233	4.20E-18	722.6038267
rs2897075	C/T	0.381896285	− 0.2628	0.027612115	1.77E-21	828.6846971
rs10808505	G/T	0.42737335	− 0.1786	0.027295946	6.03E-11	389.9521689
rs11788059	C/T	0.341887354	0.1547	0.028349844	4.85E-08	267.6713698
rs79684490	G/A	0.046295221	− 0.3347	0.060704498	3.52E-08	245.648766
rs1135628	G/C	0.240652692	0.1802	0.032881603	4.25E-08	282.2912936
rs35705950	G/T	0.145216522	− 1.6219	0.039099598	1.00E-20	44241.76504
rs35859077	G/A	0.147777307	− 0.2373	0.037413362	2.26E-10	353.7494837
rs9577395	G/C	0.208160697	− 0.2558	0.0339355	4.78E-14	542.0545735
rs2304645	G/C	0.473865733	− 0.2466	0.027085166	8.66E-20	768.8583763
rs11073517	C/T	0.326986398	− 0.175	0.028876792	1.36E-09	335.9377857
rs74614704	G/A	0.056472577	− 0.4013	0.057332026	2.57E-12	429.3227675
rs12610495	G/A	0.306019	0.2495	0.030457639	2.58E-16	638.3315005
rs75451331	G/T	0.084169828	0.2893	0.050903251	1.32E-08	321.3986571
rs41308092	G/A	0.020636054	− 0.5576	0.094113049	3.13E-09	312.9279711

Results of sensitivity analysis

MR-Egger intercept analysis showed no horizontal pleiotropy in any of the four MR analyses ($P > 0.05$). In terms of heterogeneity, after the SNPs with heterogeneity were removed by MR-Presso, there was still heterogeneity in the MR analysis of overall LC and LUAD ($P < 0.05$), but this study mainly used the re-IVW model for analysis, so this heterogeneity did not affect the results. In addition, the "leave-one-out" test further demonstrates the robustness of the study results. The specific results of the sensitivity test are shown in Table 3 and Figures S1-3.

Discussion

In this large-scale genetic association study, we evaluated the causal relationship between IPF and LC using GWAS data. Our results found that IPF may increase the risk of developing LUSC, but no such causal relationship was found in LUAD and SCLC.

Many studies have shown that IPF is a risk factor for LC and can increase the risk of developing LC. Yuichi Ozaw a et al. observed the follow-up of 103 patients with IPF who did not have LC at initial diagnosis and found that 20.4% developed LC during the follow-up period and that the cumulative incidence of LC increased with increasing follow-up time (Ozawa et al. 2009). A comprehensive study of the literature between 1999 and 2013 showed that the prevalence of LC was much higher in patients with IPF (4.8–48%) than in those without IPF (2.0–6.4%) (Li et al. 2014). Further studies found that, as in the general population, patients with non-small cell lung cancer made up the majority of all patients, but differed in that LUSC was the most common type of pathology in patients with IPF, rather than LUAD (Yoon et al. 2018; Tomassetti et al. 2015; Kato et al. 2018; Guyard et al. 2017; Khan et al. 2015). Although these studies have revealed a relationship between IPF and LC to some extent, epidemiological associations do not prove a causal relationship, there is still a lack of studies supporting a direct association between IPF and LC, and further studies need to take into account possible confounding factors such as age, smoking, and gender (Karampitsakos et al. 2017). Our study provides evidence for the causal study between the two by inferring the causal relationship from the perspective of genetic prediction with the help of MR and avoiding confounding factors to some extent.

Many studies have explored the common pathogenesis of IPF and LC. It is now believed that repeated micro-damage to the alveolar epithelium triggers abnormal repair mechanisms, and with the involvement of multiple growth factors, the balance between pro- and anti-fibrosis is disrupted, leading to a persistent fibrotic process in which epithelial cells are constantly transformed to mesenchymal cells, ultimately leading to the development of pulmonary fibrosis. Growth factors such as TGF-β, PDGF, FGF, and TGF-α play an important role in the pro-fibrotic process, while keratinocyte growth factor and hepatocyte growth factor resist the fibrotic process to some extent (Kinoshita and Goto 2019). The same abnormal fibrotic process is present in the pathology of LC, and lung fibroblasts present around the malignant tumor are thought to be the primary factor in damaging the lung (Kalluri 2016). Meanwhile, related studies suggest that platelet-derived growth factor-BB can induce the differentiation of pericytes in tumor microvasculature into stromal fibroblasts, thus assisting tumor invasion and metastasis (Hosaka et al. 2016). In addition, cellular processes such as apoptosis and autophagy, cell proliferation, intercellular communication, senescence, tissue invasion, and inflammation have been used to elucidate the relationship between IPF and LC (Ballester et al. 2019). However, these co-existing pathogenic mechanisms do not directly explain the causal relationship between the two diseases. Encouragingly, studies at the genetic level found that the majority of somatic mutations detected in LC-IPF patients showed a predominance of C > T somatic transitions, whereas C > A transitions were most common in non-IPF squamous carcinoma subtypes, suggesting a potential association between cytidine deaminase-related mutations and the development of

Table 2 results of MR analysis

Disease	Method	β	SE	OR (95%CI)	P
LC	re-IVW	− 0.023	0.023	0.977 (0.933–1.023)	0.320
	MR-Egger	− 0.076	0.088	0.927 (0.781–1.101)	0.404
	Weighted median	− 0.016	0.026	0.984 (0.934–1.036)	0.538
LUSC	re-IVW	0.044	0.017	1.045 (1.011–1.080)	0.008
	MR-Egger	0.014	0.028	1.014 (0.961–1.071)	0.614
	Weighted median	0.038	0.023	1.039 (0.994–1.086)	0.091
LUAD	re-IVW	− 0.033	0.035	0.967 (0.903–1.036)	0.345
	MR-Egger	− 0.095	0.139	0.909 (0.693–1.193)	0.503
	Weighted median	0.014	0.038	1.014 (0.941–1.092)	0.720
SCLC	re-IVW	0.077	0.043	1.081 (0.992–1.177)	0.074
	MR-Egger	0.258	0.166	1.295 (0.936–1.792)	0.141
	Weighted median	0.081	0.057	1.085 (0.971–1.212)	0.150

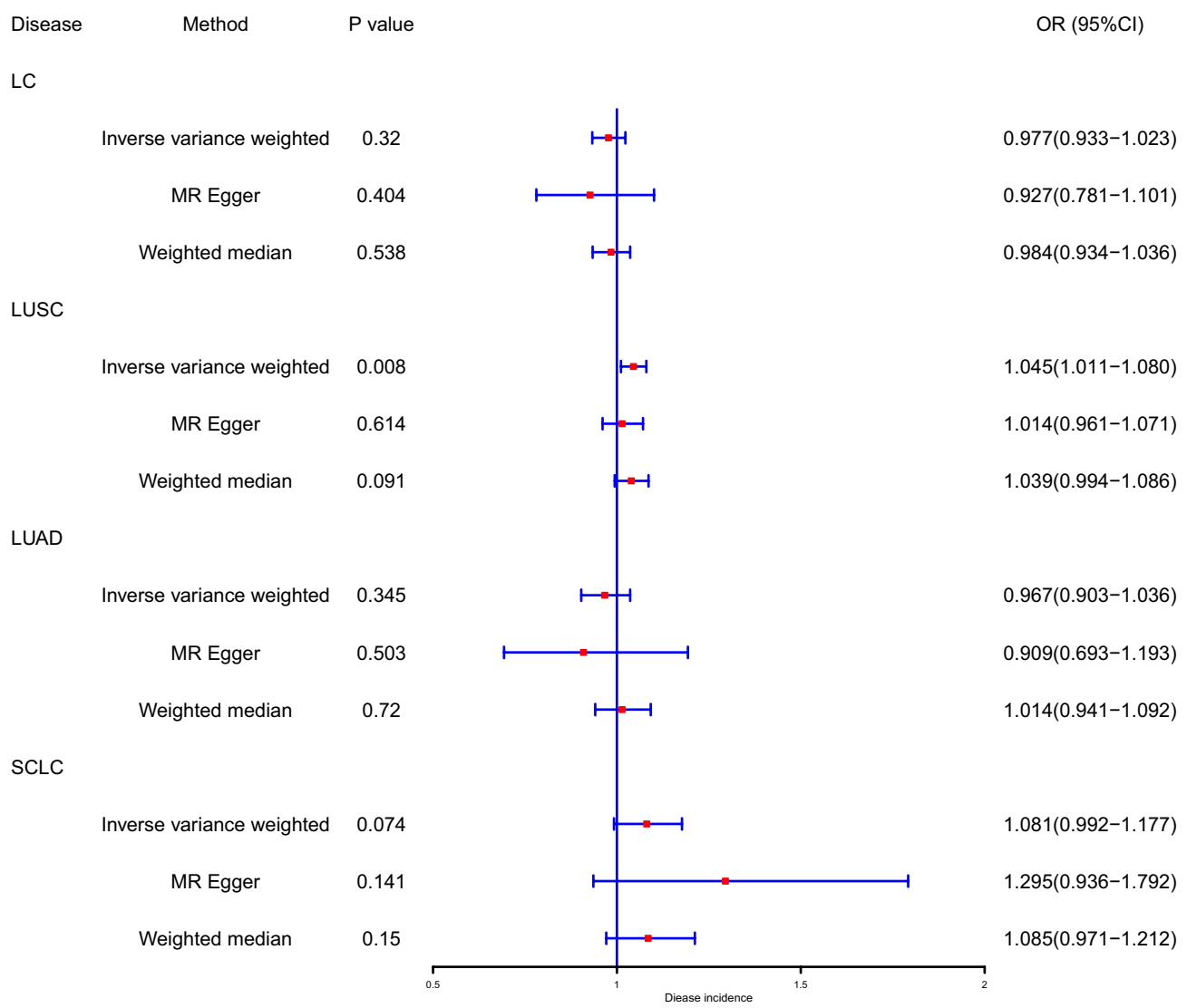

Fig. 1 Forest plot showing OR and 95% confidence interval (CI) to evaluate the causal association between idiopathic pulmonary fibrosis and risk of different pathological types of lung cancer

Table 3 sensitivity analysis of the MR result

Disease	*P*-value		
	Heterogeneity		Pleiotropy
	re-IVW	MR Egger	
LC	0.014	0.012	0.547
LUSC	0.481	0.535	0.196
LUAD	0.003	0.002	0.650
SCLC	0.309	0.331	0.277

lung fibrosis-associated lung cancer, explaining to some extent that IPF is a risk factor for LC and not the other way around (Govindan et al. 2012; Hwang et al. 2018).

Our study explored the causal relationship between IPF and different pathological types of LC with the help of MR. During the study, we used the largest known GWAS data on IPF and LC, and the rich sample size made our findings more reliable. In addition, we removed confounding factors that might have influenced the results during the study, which to some extent compensated for the lack of observational studies.

The present study also has some limitations. Our data are all from European ancestry, which makes our findings somewhat limited, and it is not yet clear that the same causal relationship exists between the two diseases in other races. In addition, we have only reported a causal relationship between the diseases, and further studies are needed to

elaborate on the specific mechanisms by which IPF increases the risk of LUSC.

Conclusions

In conclusion, from the perspective of genetic association, we found that IPF is an independent risk factor for LUSC and may increase the risk of its development, but no such causal relationship was found in either LUAD or SCLC.\

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-023-04727-w.

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Data availability The data used in this study can be obtained from the corresponding literature.

Declarations

Conflict of interest The authors claim that there were no potential conflicts of interest in the study due to business or financial relationships.

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