Original Article

Serum iron status and the risk of lung cancer: a two-sample Mendelian-randomization study

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Background: Previous epidemiological studies have reported controversial findings about the potential causal association between iron status and lung cancer. This study sought to assess the potential causality of serum iron status and lung cancer using the Mendelian-randomization (MR) method.

Methods: We selected the genetic variables for iron status from the Genetics of Iron Status (GIS) consortium comprising 48,972 samples from European populations. The following two analysis strategies for instrumental variables (IVs) were applied: a conservative approach (instruments related to four iron status markers), and a liberal approach (instruments related to each iron status marker). The summary-level data for lung cancer were obtained from the International Lung Cancer Consortium comprising 27,209 individuals from European populations. The causality between serum iron status and lung cancer was examined.

Results: Using the conservative approach, a higher serum iron status was found to be causally correlated with lower risks of lung squamous cell carcinoma. The odds ratios of lung squamous cell carcinoma per standard deviation (SD) unit increment in the four iron status markers were 0.73 [95% confidence interval (CI): 0.60–0.89; P=0.002] in serum iron, 0.50 (95% CI: 0.33–0.77; P=0.002) in ferritin, 1.35 (95% CI: 1.09–1.67; P=0.006) in transferrin, and 0.80 (95% CI: 0.69–0.92; P=0.001) in transferrin saturation based on the inverse variance–weighted method. Similar results were found using the liberal approach.

Conclusions: Genetically, a high serum iron status was inversely associated with the risk of lung squamous cell carcinoma. More research needs to be conducted to explore the underlying mechanisms and to determine the potential application value about preventing the occurrence of cancer.

Keywords: Serum iron status; lung cancer; single nucleotide; Mendelian randomization; causality

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Introduction

Accounting for more than 130,000 cancer deaths and 235,760 new cases in 2021, lung cancer is one of the most frequently diagnosed malignancies and the major cause of cancer mortality in the United States of America (1). At 21%, the 5-year survival rate for lung cancer patients is low (1). To date, smoking behavior is still the primary cause of death in lung cancer patients and resulted in 107,870 deaths; thus, approximately 20,000 lung cancer patients died from causes other than smoking in USA, 2021 (1,2). Smoking behavior is the principal causative factor of lung cancer; however, the underlying causality of other risk factors, such as iron status, is still unclear.

Epidemiological evidence that iron status is a causative factor of lung cancer remains inconclusive. A retrospective

study of 440 lung cancer cases and 1,320 healthy controls indicated that the population with high serum iron tended to have a lower risk for lung cancer [relative risk (RR): 0.86, 95% confidence interval (CI): 0.68–1.08] (3). Similarly, numerous epidemiological studies have shown that a high-iron diet elevated the risk of lung cancer (4-8). The inconsistent results could be attributed to potential confounding variables, such as the small sample sizes, the iron status and dietary iron intake assessments, and the clinical stages of lung cancer (8-10). Thus, high-powered causal inference methods need to be used to reassess the causal link between iron status and lung cancer.

A Mendelian-randomization (MR) approach was applied to estimate the potential causal relationship between the risk factors and disease using single nucleotide polymorphisms (SNPs) as the instrumental variables (IVs) (11,12). As genetic variants are allocated randomly during conception, the causal inference related to the use of genetic variants could eliminate the interference caused by confounding factors, such as environmental factors (12,13). Moreover, this approach removes the bias of reverse causation because of genetic variants allocated preceding the onset of illness (12,13).

Our study examined whether serum iron status contributes to the occurrence of lung cancer by performing two-sample MR analyses. We present this article in accordance with the STROBE-MR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1645/rc).

Highlight box

Key findings

- Higher serum iron status was inversely related to the risk of lung squamous cell carcinoma by performing two-sample Mendelian-randomization analyses.

What is known and what is new?

- Epidemiological evidence supporting the causality of iron status on lung cancer remains inconclusive.
- Serum iron status had a negative causal effect on the risk of lung squamous cell carcinoma. Conversely, serum iron status was not found to be correlated with the risk of lung cancer overall and lung adenocarcinoma in general.

What is the implication, and what should change now?

- These findings have promising underlying clinical and public health implications about preventing the occurrence of lung cancer.

Methods

Genetic associations with serum iron status

We retrieved a large summary data set for serum iron status from the Genetics of Iron Status (GIS) consortium and performed a MR analysis. This data set from 11 discovery and 8 replication cohorts contained 48,972 samples from European populations (14). Iron status indicators for serum iron, ferritin, transferrin, and transferrin saturation were included in our study. Before the genome-wide analyses were performed, adjustments for population characteristics were made to ensure the consistency of the analysis (14). The diagnostic criteria for diseases was showed in Table S1.

Genetic associations with lung cancer

The summary-level genome-wide association studies (GWAS) data for lung cancer were obtained from the International Lung Cancer Consortium (ILCCO, https://ilcco.iarc.fr/). The lung cancer database comprised 11,348 individuals from European populations with lung cancer and 15,861 healthy individuals. In the patient cohort, 3,442 individuals had adenocarcinoma and 3,275 individuals had squamous cell carcinoma (15,16). The diagnostic criteria for diseases was showed in Table S1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Selection of IVs

The SNPs for the IV analysis, which were robustly correlated with iron status, were obtained from the GIS consortium ($P<5\times10^{-8}$). The linkage disequilibrium of all the SNPs was performed with an R^2 threshold of 0.01 to ensure that the selected SNPs were independent. None of the SNPs was related to lung cancer ($P>0.05$). The critical assessment indicators were acquired from the GIS consortium and ILCCO, and the selected SNPs corresponded to the European population.

The following two analysis strategies were used to select the SNPs: a conservative approach, and a liberal approach (17,18). Under the conservative approach, three SNPs (*rs855791*, *rs1800562*, *rs1799945*) were selected that were robustly related to elevated levels of serum iron and ferritin, elevated transferrin saturation, and a reduced level of transferrin ($P<5\times10^{-8}$). Improved serum iron status was consistent with the elevated levels of serum iron and

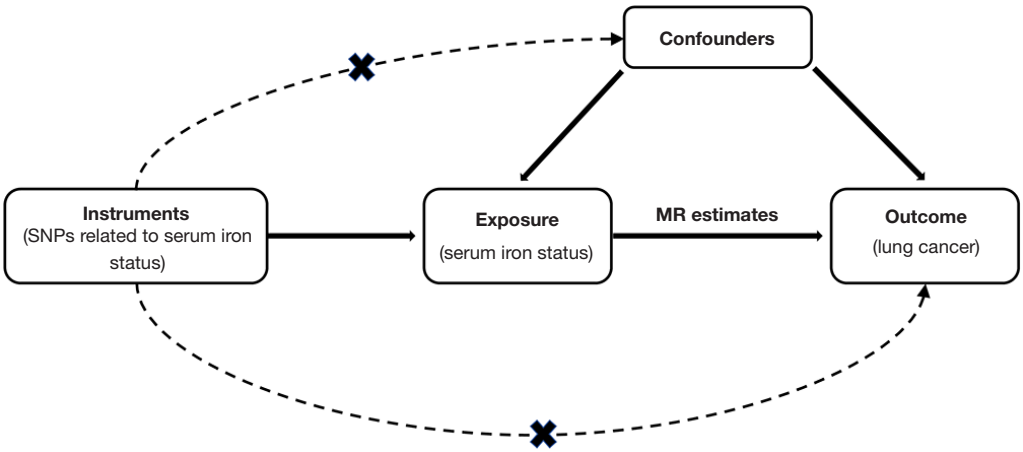

Figure 1 Diagram view of the two-sample MR study design. MR, Mendelian-randomization; SNP, single nucleotide polymorphism.

ferritin, elevated transferrin saturation, and a reduced level of transferrin (19). As a result, the correlation between the IVs and serum iron status would be correlated with these four markers.

Under the liberal approach, we selected the SNPs robustly related to each iron status marker in the GWAS ($P<5\times10^{-8}$): five SNPs for serum iron (*rs8177240*, *rs1800562*, *rs7385804*, *rs855791*, *rs1799945*), five SNPs for ferritin (*rs744653*, *rs1800562*, *rs1799945*, *rs411988*, *rs855791*), nine SNPs for transferrin (*rs744653*, *rs8177240*, *rs9990333*, *rs1800562*, *rs1799945*, *rs4921915*, *rs174577*, *rs6486121*, *rs855791*), and five SNPs for transferrin saturation (*rs8177240*, *rs1800562*, *rs1799945*, *rs7385804*, *rs855791*). The descriptive statistics for the specific SNPs are shown in the published research(17,18). Notably, all of the IVs were not related to the risk of lung cancer (all P>0.05).

Statistical analysis

To ensure the effectiveness of the MR estimates, three key assumptions for the MR analysis were crucial (20). First, the selected SNPs were strongly related to the exposure (iron status). In this analysis, the F statistic was used to evaluate the effect of weak instrument bias, and the F statistic for all the IVs was set to above 10 to avoid this bias (21). Second, the IVs only influenced the outcome (lung cancer) by the risk factor and not by any other causal pathway. Finally, The IVs were independent of confounders of the exposure-outcome relationship (*Figure 1*).

To test the causality between serum iron status and lung cancer, we used two-sample MR approaches. Moreover, adenocarcinoma and squamous cell carcinoma were included in the analysis according to the pathological diagnosis. In the conservative and liberal approaches, the primary MR analysis for the effect of serum iron status on lung cancer was inverse variance-weighted (IVW). In the liberal approach, the causal association was also evaluated using other approaches, such as MR-Egger regression and the weighted median.

To explore the influence of serum iron status on lung cancer risk factors, the IVW method was used to assess whether genetic variants of serum iron status were related to the risk factors of lung cancer, including body mass index (BMI), smoking, triglycerides, and total cholesterol, based on the liberal approach. Genetic instruments for smoking status (cigarettes smoked per day; ever *vs.* never smoked; former *vs.* current smoker) were acquired from the Tobacco and Genetics Consortium (TAG) (22). The correlation between triglycerides and total cholesterol for lung cancer was assessed according to the summary-level GWAS data from the Global Lipids Genetics Consortium (GLGC) (23). The genetic correlation for BMI was acquired from the Genetic Investigation of Anthropometric Traits consortium (GIANT) (24).

In the sensitivity analysis, the MR-Egger regression method was used to examine horizontal pleiotropy and heterogeneity (25). The MR-Egger regression examines horizontal pleiotropy by determining whether the intercept associated with the causal inference differs from zero. The conservative sets were not included in the sensitivity analysis, as it was difficult to ensure the inferences were credible according to a line formed by only three points.

Table 1 Causal effects between the four iron status biomarkers and potential confounding factors

Outcomes	Iron		Ferritin		Transferrin		Transferrin saturation	
	Causal effect (95% CI)	P value	Causal effect (95% CI)	P value	Causal effect (95% CI)	P value	Causal effect (95% CI)	P value
Cigarettes smoked per day	0.99 (0.55–1.78)	0.968	0.59 (0.19–1.88)	0.372	0.99 (0.69–1.41)	0.944	0.96 (0.62–1.48)	0.852
Ever *vs.* never smoked	1.05 (0.93–1.18)	0.416	1.10 (0.81–1.49)	0.553	0.98 (0.92–1.05)	0.569	0.96 (0.97–1.14)	0.255
Former *vs.* current smoker	0.93 (0.83–1.05)	0.230	1.02 (0.72–1.45)	0.922	1.00 (0.92–1.08)	0.997	0.96 (0.88–1.05)	0.365
Body mass index	0.99 (0.96–1.01)	0.316	0.97 (0.94–1.01)	0.148	1.00 (0.98–1.02)	0.778	0.99 (0.97–1.01)	0.300
Triglycerides	1.03 (1.00–1.06)	0.046*	1.07 (1.02–1.13)	0.006*	0.98 (0.88–1.08)	0.638	1.03 (1.01–1.04)	0.005*
Total cholesterol	0.92 (0.87–0.98)	0.006*	0.83 (0.74–0.94)	0.003*	1.01 (0.90–1.13)	0.926	0.94 (0.90–0.98)	0.002*

*, P<0.05. CI, confidence interval.

Heterogeneity for each SNP was estimated through Cochran's Q statistic based on the MR-Egger regression test (26,27). Tests of influence were complemented by a leave-one-out sensitivity analysis to estimate the influence of each SNP and to confirm which SNPs affected the causal correlation abnormally.

All the analyses were conducted using the TwoSampleMR package (version 0.5.5) in R (version 3.6.1) (16). The study protocol and details were not pre-registered anywhere.

Results

The genetic instruments for serum iron status

Under the conservative approach, three SNPs were used that were associated with all four biomarkers of serum iron status. Under the liberal approach, five SNPs were definitely related to serum iron, ferritin, and transferrin saturation, and nine SNPs were definitely related to transferrin. The F statistic values for all the SNPs were more than 10 (minimum =40, maximum =2,947) to effectively avoid weak instrument bias (28).

The genetic instruments and lung cancer risk factors

To explore the underlying risk factors affecting the interaction effects between serum iron status and lung cancer, we examined whether a high serum iron status was related to any underlying confounding factors. As *Table 1* shows, a high serum iron status (iron, ferritin, and transferrin saturation) was positively related to triglycerides and was inversely related to total cholesterol (all P<0.05). No significant correlations were found between the serum iron status and other factor risks, including smoking status (cigarettes smoked per day; ever *vs.* never smoked; former *vs.* current smoker) and BMI (all P>0.05).

MR estimates

In general, a genetically predicted higher serum iron status was negatively correlated with lung squamous cell carcinoma but was not correlated with lung cancer overall and lung adenocarcinoma (*Figures 2*,*3*). Under the conservative approach, all of the serum iron status biomarkers were correlated with lung squamous cell carcinoma, but only serum iron was correlated with lung cancer overall [odds ratio (OR): 0.86; 95% CI: 0.76–0.98; P=0.025]. Based on the IVW method, the ORs of lung squamous cell carcinoma per standard deviation (SD) unit increment in the four iron status markers were as flow: iron, 0.73 (95% CI: 0.60–0.89; P=0.002); ferritin, 0.50 (95% CI: 0.33–0.77; P=0.002); and transferrin saturation, 0.80 (95% CI: 0.69–0.92; P=0.001). In addition, a higher transferrin level was correlated with a lower serum iron status, indicating a increased lung squamous cell carcinoma risk (OR: 1.35; 95% CI: 1.09–1.67; P=0.006). Similar results were found using the weighted median method (all P<0.05) (*Figure 2*). A similar trend was observed between iron status and lung cancer under the liberal approach.

Conversely, under the liberal approach, the only different result was that the little correlation was found

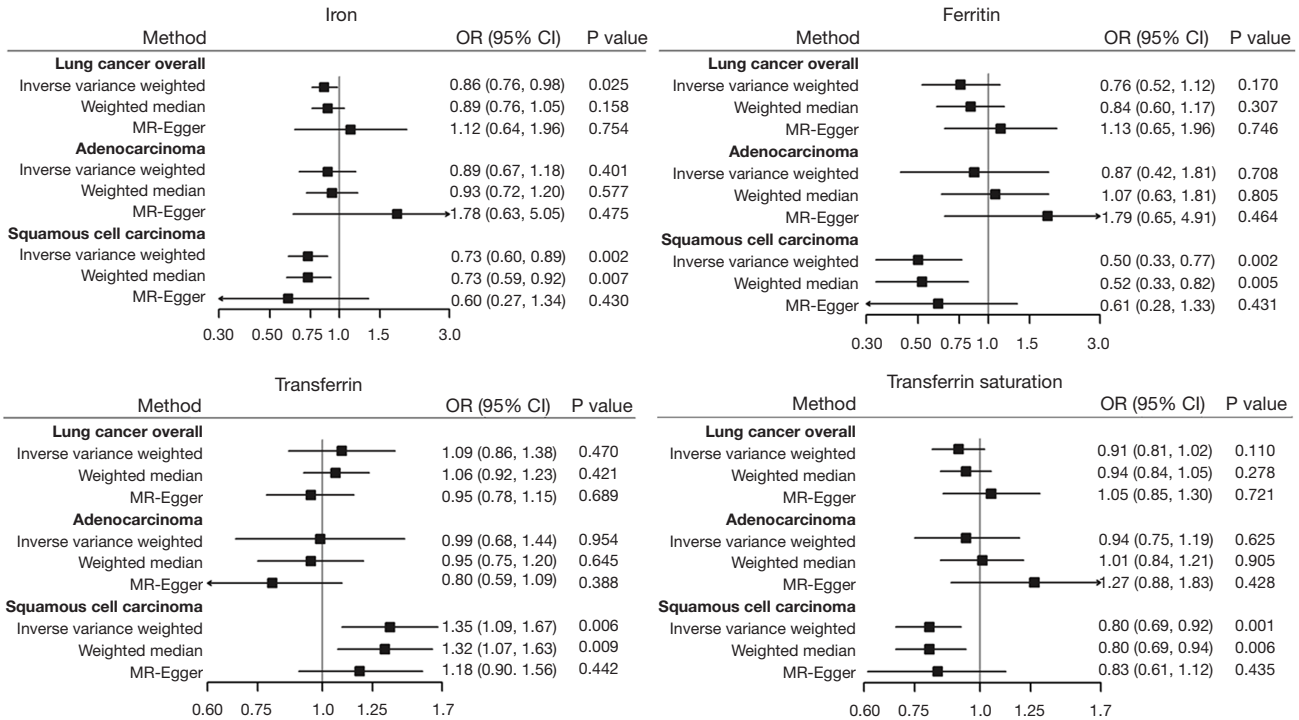

Figure 2 The association between genetically predicted iron status and the risk of lung cancer under the conservative approach. The ORs for lung cancer and their histological subtypes per SD increase in each iron status biomarker. Three SNPs (*rs1800562*, *rs1799945*, and *rs855791*) associated with all four iron status biomarkers ($P<5\times10^{-8}$) were used as the instrumental variables in the conservative approach. The IVW method was the primary method used to calculate the MR estimates. OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian-randomization; MR-Egger, Mendelian-randomization-Egger regression method; SD, standard deviation; SNP, single nucleotide polymorphism; IVW, inverse variance-weighted.

between the transferrin level and the risk of lung squamous cell carcinoma (OR: 1.05; 95% CI: 0.88–1.26; P=0.572) compared to the conservative approach. However, no evidence was found of any casual link between all the markers of serum iron status and lung cancer overall and lung adenocarcinoma (P>0.05) (*Figure 3*).

Sensitivity analyses

The liberal instruments for the MR estimates with the MR-Egger method was used to examine the heterogeneity of lung cancer overall, lung adenocarcinoma, and lung squamous cell carcinoma, but no statistically significant results were found (for lung cancer overall: intercept 0.019(Iron), –0.01(Ferrtin), –0.011(Transferrin), and –0.012(Transferrin saturation); for lung adenocarcinoma: intercept 0.013(Iron), –0.03(Ferrtin), –0.012(Transferrin) and –0.031(Transferrin saturation); for lung squamous cell carcinoma: intercept 0.027(Iron), 0.002(Ferrtin), –0.02(Transferrin) and 0.014(Transferrin saturation); all P>0.05) (*Table 2*).

The Cochran's Q test results showed that there was no heterogeneity in the liberal instrument for all the analyses, except for the transferrin-related estimates (for lung cancer overall: Q=18.694; for lung adenocarcinoma: Q=16.055; for lung squamous cell carcinoma: Q=17.530; all P<0.05) (Table S2). In the leave-one-out analysis, the MR analysis was not materially changed by any single SNP, and the directions of causal estimates had not changed (Figures S1-S4).

Discussion

In this two-sample MR analysis of serum iron status and lung cancer risk using large-scale GWAS data sets, we found that genetically predicted higher serum iron status was inversely related to the risk of lung squamous cell

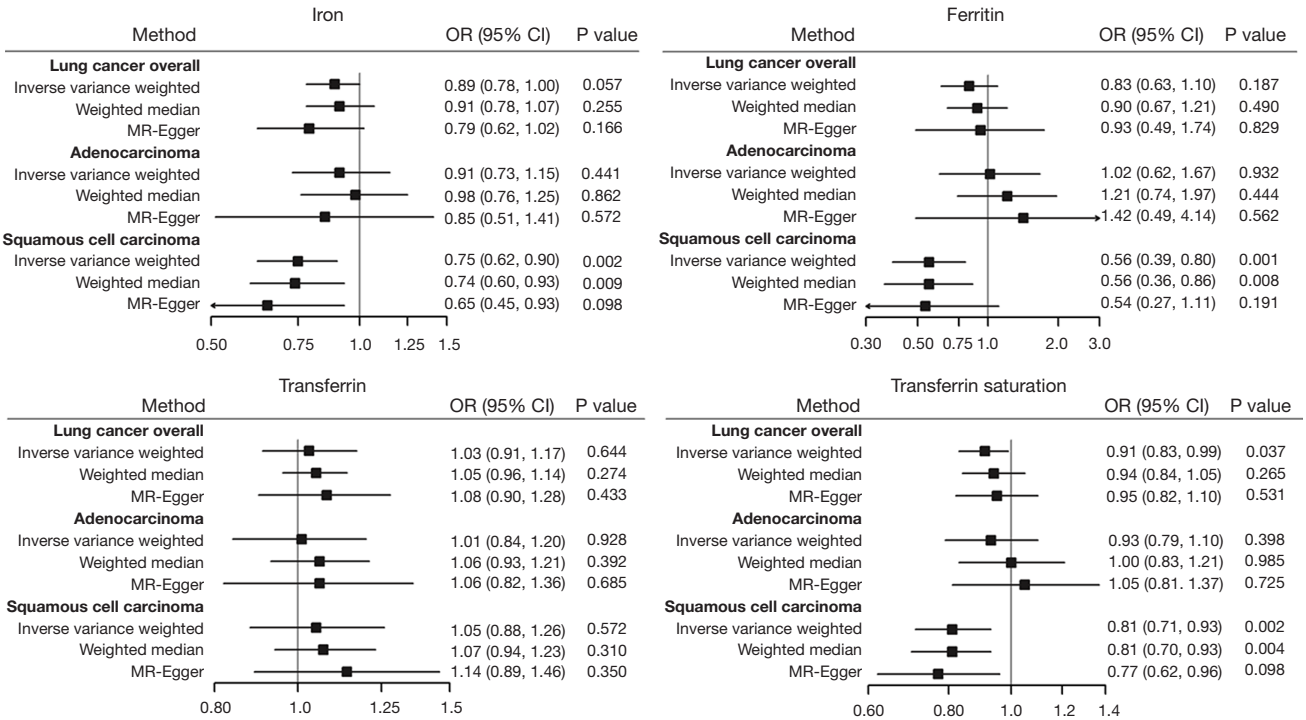

Figure 3 The association between genetically predicted iron status and the risk of lung cancer under the liberal approach. The ORs for lung cancer and their histological subtypes per SD increase in each iron status biomarker. The SNPs associated with serum iron, ferritin, transferrin, and transferrin saturation ($P<5\times10^{-8}$) were used as the instrumental variables in the liberal approach. OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian-randomization; MR-Egger, Mendelian-randomization-Egger regression method; SD, standard deviation; SNP, single nucleotide polymorphism.

Table 2 MR-Egger pleiotropy test for the instrumental variables associated with the four iron status biomarkers and the risk of lung cancer overall and the histological subtypes

Outcome	Iron		Ferritin		Transferrin		Transferrin saturation	
	Intercept	P value	Intercept	P value	Intercept	P value	Intercept	P value
Lung cancer over all	0.019	0.391	–0.010	0.716	–0.011	0.483	–0.012	0.514
Adenocarcinoma	0.013	0.760	–0.030	0.533	–0.012	0.612	–0.031	0.325
Squamous cell carcinoma	0.027	0.417	0.002	0.948	–0.020	0.411	0.014	0.587

MR-Egger, Mendelian-randomization-Egger regression method

carcinoma. Conversely, serum iron status was not found to be correlated with the risk of lung cancer overall and lung adenocarcinoma in general. We also found that serum iron status was genetically correlated with underlying risk factors for lung cancer, such as triglycerides and total cholesterol, which might be the mediating mechanisms between serum iron status and lung cancer. These results provide a novel theoretical basis that suggests that serum iron status could serve as a prospective target for the prevention of lung cancer.

Studies on the association between diet or circulating iron and the risk of lung cancer are controversial and the results are inconclusive (4,7,29-31). In a prospective population-based cohort study of 5,435 participants aged 55 years or older at the baseline, of whom 211 suffered from lung cancer during the 22-year follow-up period, a

high intake of iron was reported to be related to reductions in the risk of lung cancer [hazard ratio (HR): 0.58, 95% CI: 0.37–0.92; P=0.021] (29). Conversely, multiple observational studies have suggested that a high-iron diet increases the risk of lung cancer significantly (4,7,30,31). In two cross-sectional studies with small sample sizes, circulating ferritin and transferrin receptor 1 were elevated in lung cancer patients (30,31). A multi-center prospective cohort of 416,746 participants recruited from ten European countries found a positive correlation between haem iron intake and the risk of lung cancer (HR: 1.03, 95% CI: 1.00–1.07) after adjusting for smoking history (7). Similarly, a large meta-analysis of 11 cohort studies and 23 case-control studies found a positive correlation between red meat and the RR of lung cancer (RR: 1.34, 95% CI: 1.18–1.52) after adjusting for smoking (4). The inconsistent results may be partly attributed to the inherent restrictions of these studies, such as the diverse assessment criteria for dietary iron intake, single time-point evaluations, different pathological types of lung cancer, and sample sizes (9,29-31). Moreover, serum iron status may not be influenced by a slightly higher dietary iron intake. Recently, the MR approach was used in some studies and the results showed that the IVs for iron status were not related to other disease outcomes, such as pan-cancer and breast cancer (18,32). To date, this is the first MR study to investigate the causal association between serum iron status and lung cancer and its histological types.

Lung cancer is a complicated disease, and its occurrence and development are affected by multiple gene mutations and risk factors (33). Given that tobacco smoking is the main environmental exposure of lung cancer, we investigated whether the causal relationship between serum iron status and lung squamous cell carcinoma was mediated by smoking status (33,34). However, smoking status was not associated with serum iron status; thus, smoking status cannot fully explain the causal association. Further, BMI is correlated with iron status and the risk of lung cancer (35,36). There is no correlation between genetic serum iron status and BMI by MR estimates. In addition, our MR analysis indicated that a higher serum iron status was related to higher triglycerides and lower total cholesterol, which are both underlying risk factors for lung cancer (37-41). However, the accuracy and the potential mechanism of their mediation require further investigation. Interestingly, other iron status indicators, such as ferroptosis and intracellular iron accumulates, play an important role in the occurrence, development, and apoptosis of lung cancer (10,42). Further, iron accumulation in the tumor microenvironment does not indicate a change in systemic iron homeostasis at advanced stages of lung cancer (10). In our MR analyses, we only assessed the causality between serum iron status and lung cancer; thus, further investigations are required to evaluate the causality between other iron status indicators and lung cancer.

The present study had several strengths. It was the first to systematically assess the causality between serum iron status and lung cancer using a MR analysis. All the statistical data sets were derived from the large meta-GWASs database for iron status and lung cancer. Randomization was carried out based on genetic variants to ensure the random assignment of participants, similar to a randomized controlled trial. The MR approach eliminiates potential confounding factors and the bias of reverse causation that are commonly found in observational studies. Moreover, two analysis approaches (a conservative and liberal approach) were used to select the IVs to stabilize the causal inferences.

However, this study also had several limitations. First, all of the study individuals were white with a European ancestry. Thus, it is doubtful whether our findings would apply to other populations. Second, as with almost MR studies, it was difficult to perform stratified analyses of other potential factors in the MR analysis using summary association data, such as age and body mass index. Further, we used the liberal approach to include more SNPs as IVs, but this approach is inevitably susceptible to the effects of pleiotropy, even though the MR-Egger test did not reveal any detectable directional pleiotropy. Moreover, larger sample sizes should be used to obtain more reliable results in MR analyses; however, the sample size may have been large enough in our study. Iron status could be affected by a variety of innate or environmental factors, such as coffee consumption, alcohol intake, and inflammatory diseases (43-45). Whether these confounding factors interact with iron status was difficult to assess in our study using data from the large meta-GWASs database, but the confounding effects of the above factors might be slight. In addition, dietary iron intake may not reflect the real serum iron status. The results of this study should not be used to make direct inferences about the influence of higher dietary iron intake or iron deficiency anemia.

Conclusions

In general, our present MR study showed that serum iron status had a negative causal effect on the risk of lung squamous cell carcinoma. These findings have promising

underlying clinical and public health implications. Future studies need to be conducted to replicate this finding and to investigate the underlying mechanisms that mediate the causality between serum iron status and lung cancer.

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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-23-1645/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1645/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1645/coif). 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).

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Supplementary

Table S1 Diagnostic criteria used by databases about iron status and lung cancer

Phenotype	Consortium	Diagnostic criteria/Method
Iron status	GIS	Serum iron: colorimetric assay, ferrozine measurement. Ferritin: latex particle immunoturbidimetry. Transferrin: immunoturbidimetric, Electro-chemiluminescence immunoassay. Transferrin saturation: Serum iron/ Transferrin×100%
Lung cancer	ILCCO	Histology, immunohistochemistry

GIS, Genetics of Iron Status; ILCCO, International Lung Cancer Consortium.

Table S2 Heterogeneity test for the instrumental variables associated with the four iron status biomarkers and the risk of lung cancer overall and the histological subtypes

Outcome	Iron		Ferritin		Transferrin		Transferrin saturation	
	Q	P value	Q	P value	Q	P value	Q	P value
Lung cancer overall	3.013	0.390	4.814	0.186	18.694	0.009*	2.750	0.432
Adenocarcinoma	5.207	0.157	5.453	0.141	16.055	0.025*	3.605	0.307
Squamous cell carcinoma	0.095	0.992	1.209	0.751	17.530	0.014*	0.768	0.857

*, P<0.05.

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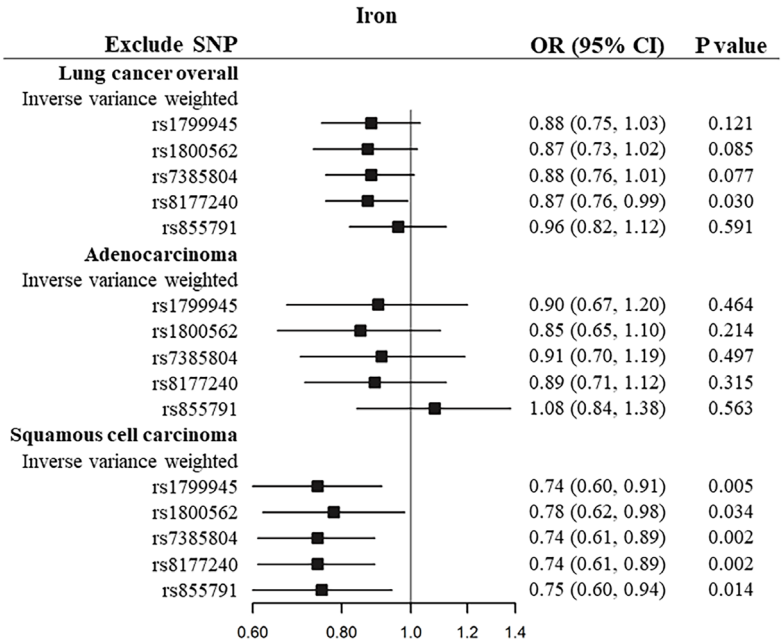

Figure S1 Leave-one-out analysis for the MR estimates for serum iron and the risk of lung cancer. The ORs of lung cancer and their histological subtypes risk per standard deviation increment in the level of serum iron excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

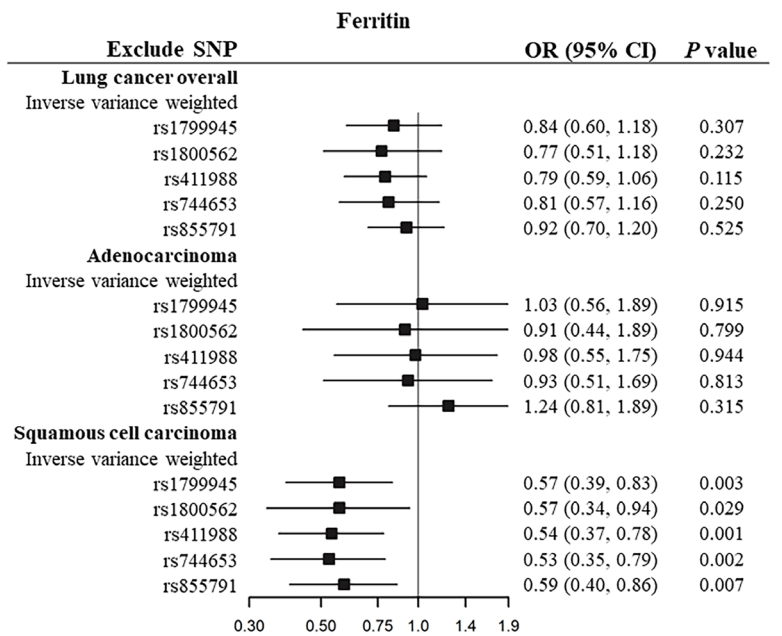

Figure S2 Leave-one-out analysis for the MR for between ferritin and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of ferritin excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

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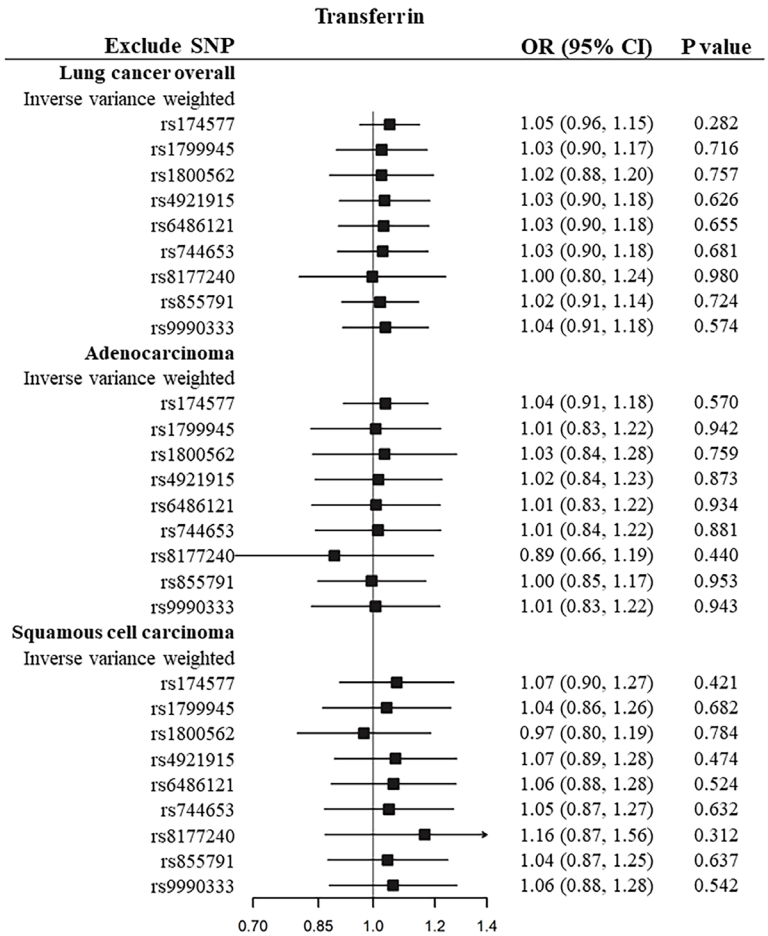

Figure S3 Leave-one-out analysis for the MR estimates for transferrin and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of transferrin excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

https://dx.doi.org/10.21037/jtd-23-1645

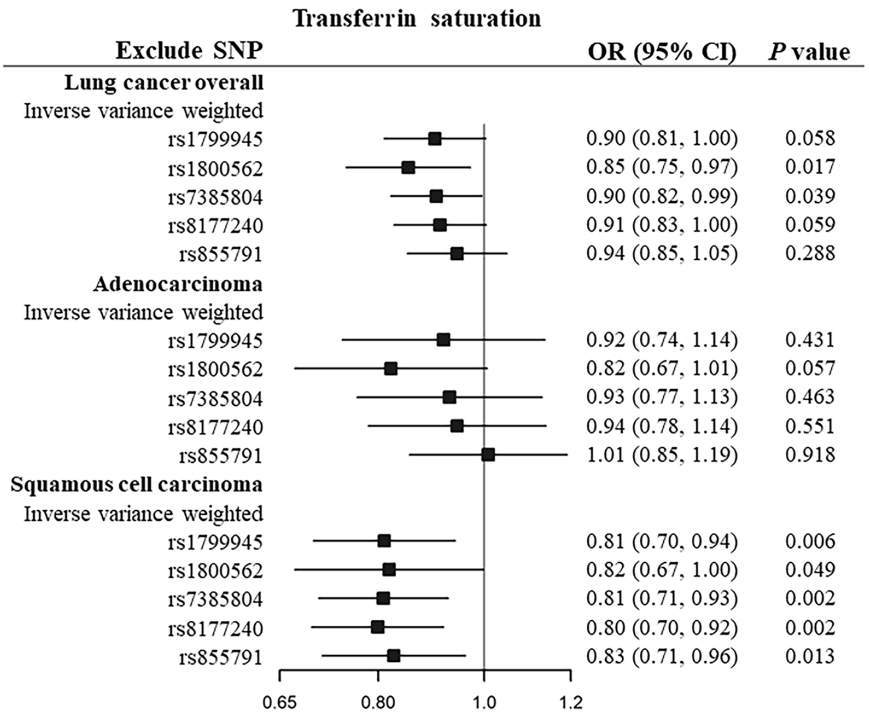

Figure S4 Leave-one-out analysis for the MR estimates for transferrin saturation and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of transferrin saturation excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

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