CASE REPORT

# Gut Microbiota and Lung Cancer: A Mendelian Randomization Study

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## Introduction

Gut microbiota deeply influences the host's homeostasis. The imbalance of gut microbiota has been linked to common diseases, including various cancers.[1] Nowadays, the role of gut microbiota in cancer immunotherapies also sparked the interest of researchers.[2] There is a growing attention in targeting these microbiotas for cancer treatment. However, the interactions among drugs, gut microbiota, and cancer are complex and a deeper understanding of microbiome-cancer interactions is critical.[3] Though several studies have mentioned the association between gut microbiota and lung cancer,[2,4] robust epidemiologic evidence was able to discern that this causal relationship does not exist. It is not clear whether certain genera of microbiota is causally associated with lung cancer; and if so, the specific genus is unknown. Mendelian randomization (MR) studies gave us a novel approach, which could clarify the causality on the basis of the principle of independent assortment.[5] It can be regarded as a natural analog of randomized controlled trials without the influence of confounding and reverse causation bias. Therefore, we aimed to investigate whether gut microbiota is causally associated with lung cancer through a two-sample MR approach.

## Methods and Results

Genetic instrumental variables of 23 genera at genome-wide significance ($p < 5 \times 10^{-8}$) were obtained from five available genome-wide association studies (GWAS) of the gut microbiota according to the method of Yang et.al.[6] We obtained the available GWAS summary data of lung cancer from the International Lung Cancer Consortium (11,348 lung cancer cases and 15,861 controls).[7] We conducted a two-sample MR analysis to assess the causality between 23 genera of gut microbiota and lung cancer on the basis of the publicly available GWAS summary data from different consortiums. We applied several different MR methods for deriving causal estimates: Wald ratio, inverse-variance weighted average, weighted median, and MR-Egger. Additional sensitivity analyses were used to detect potential pleiotropy bias. All statistical analyses were conducted using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Among the 23 genera, a one-allele increase in single nucleotide polymorphisms related to increased *Oscillospira* population was associated with a 26.1% lower risk of lung cancer (OR 0.739, 95% confidence interval: 0.570–0.959, $p = 0.023$) (Table 1). We also identified genetic predisposition toward increased *Weissella* population on the basis of one single nucleotide

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Drs. Zhou and Liu contributed equally to this work and are both considered first authors.

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**Table 1.** Mendelian Randomization Estimates of the Associations Between 23 Gut Microbiota and Risk of Lung Cancer

| | | IVW/(Wald Ratio, SNP <3) | | IVW/(Wald Ratio, SNP <3) | | MR-Egger | |
|---|---|---|---|---|---|---|---|
| Microbiota | SNP | OR (95% CI) | *p* value | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| *Acidaminococcus* | 5 | 1.001 (0.999-1.004) | 0.355 | 1.001 (0.998-1.004) | 0.424 | 1.000 (0.996-1.005) | 0.894 |
| *Acinetobacter* | 1 | 1.193 (0.984-1.447) | 0.073 | | | | |
| *Aggregatibacter* | 1 | 0.960 (0.884-1.043) | 0.335 | | | | |
| *Anaerostipes* | 2 | 0.989 (0.933-1.048) | 0.701 | | | | |
| *Atopobium* | 1 | 0.940 (0.876-1.008) | 0.083 | | | | |
| *Bacteroides* | 5 | 0.999 (0.997-1.000) | 0.134 | 0.999 (0.997-1.000) | 0.152 | 0.999 (0.997-1.000) | 0.213 |
| *Bifidobacterium* | 2 | 1.008 (0.934-1.087) | 0.844 | | | | |
| *Coprococcus* | 1 | 1.138 (0.732-1.769) | 0.567 | | | | |
| *Desulfovibrio* | 2 | 0.992 (0.958-1.028) | 0.658 | | | | |
| *Dorea* | 1 | 1.058 (0.984-1.137) | 0.128 | | | | |
| *Eggerthella* | 1 | 1.001 (0.998-1.005) | 0.442 | | | | |
| *Eubacterium* | 1 | 0.999 (0.922-1.083) | 0.987 | | | | |
| *Faecalibacterium* | 3 | 1.004 (0.952-1.058) | 0.889 | 1.002 (0.947-1.060) | 0.949 | 0.990 (0.907-1.080) | 0.852 |
| *Lachnospira* | 1 | 1.028 (0.925-1.141) | 0.609 | | | | |
| *Lactobacillus* | 2 | 0.972 (0.897-1.054) | 0.497 | | | | |
| *Leuconostoc* | 1 | 0.964 (0.860-1.081) | 0.533 | | | | |
| *Megamonas* | 3 | 1.016 (0.990-1.043) | 0.231 | 1.016 (0.985-1.048) | 0.307 | 0.908 (0.725-1.137) | 0.556 |
| *Mogibacterium* | 1 | 0.998 (0.897-1.110) | 0.973 | | | | |
| *Oscillospira* | 1 | 0.739, (0.570-0.959) | 0.023[a] | | | | |
| *Pseudobutyrivibrio* | 1 | 0.961 (0.877-1.053) | 0.397 | | | | |
| *Roseburia* | 1 | 0.980 (0.843-1.140) | 0.796 | | | | |
| *Slackia* | 1 | 0.980 (0.935-1.027) | 0.401 | | | | |
| *Weissella* | 1 | 0.804 (0.693-0.933) | 0.004[a] | | | | |

[a]*p* value less than 0.05.
CI, confidence interval; IVW, inverse-variance weighting; MR-Egger, Mendelian randomization-Egger; OR, odds ratio.

polymorphism, which was associated with a lower risk of lung cancer (OR 0.804, 95% confidence interval: 0.693–0.933, $p = 0.004$). No associations were found for the other 21 genera, namely *Acidaminococcus*, *Acinetobacter*, *Aggregatibacter*, *Anaerostipes*, *Atopobium*, *Bacteroides*, *Bifidobacterium*, *Coprococcus*, *Desulfovibrio*, *Dorea*, *Eggerthella*, *Eubacterium*, *Faecalibacterium*, *Lachnospira*, *Lactobacillus*, *Leuconostoc*, *Megamonas*, *Mogibacterium*, *Pseudobutyrivibrio*, *Roseburia*, and *Slackia*. The above findings have generally robust sensitivity analysis.

## Discussion

To our knowledge, our work is the first MR study focused on the topic of gut microbiota in relation to the risk of lung cancer. We found that not all gut microbiota is associated with lung cancer. This study raises the possibility of a beneficial association between *Oscillospira* and *Weissella* and a lower risk for lung cancer, suggesting that these could be a focus of future research. Identification of these gut microbiota features in relation to lung cancer might contribute to the development of microbiota-targeted therapies. To date, there is no formal report about the potential roles of these two genera in lung cancer. Further studies are needed to confirm this causality and elucidate the potential mechanisms.

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