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Original Article

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Causal Relationships Between Gut Microbiota, Immune Cell and Pancreatic Cancer: A Two-Step, Two-Sample Mendelian Randomization Study

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Abstract

Background: Gut microbiota (GM) is associated with both the occurrence and development of pancreatic cancer (PC), and immune cells potentially play a role in this process. This study sought to evaluate the causative effect of GM on PC and to ascertain possible immune cell mediators.

Methods: The study primarily employed a two-step, two-sample Mendelian randomization (MR) analysis to explore the causal relationship between GM and PC within the European population, placing particular emphasis on the application of the inverse variance weighted (IVW) approach. Additionally, mediation analysis was conducted to explore the potential influence of immune cells as mediators.

Results: The MR analysis revealed a significant association between Geminocystis and the risk of PC. Increased abundance of Geminocystis was positively associated with the risk of PC (odds ratio (OR): 2.580, 95% confidence interval (CI): 1.050 - 6.342). The validity of the outcomes was also verified by the sensitivity analysis. The mediation MR analysis showed that the B-cell absolute count served as a partial intermediary in the causal link between Geminocystis and the risk of PC, contributing to 15.321% of the mediating impact.

Conclusion: This MR study demonstrated that Geminocystis has a causal relationship with PC and potentially mediates B-cell absolute count in the TBNK panel.

Keywords: Gut microbiota; Immune cell; Pancreatic cancer; Mendelian randomization

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Introduction

Pancreatic cancer (PC) is frequently identified as a common malignant neoplasm in the digestive system across numerous countries, and it is characterized as a lethal form of cancer [1]. Data have shown that PC ranks as the third highest cause of cancer deaths in the United States, and its occurrence continues to increase annually. Despite advancements in PC treatment strategies such as targeted therapy and immunotherapy, the overall prognosis of PC remains unfavorable, with a 5-year survival rate of approximately 7.2% [2]. Additionally, the efficacy of various immunotherapies for PC treatment has been less than optimal [3]. Most PC patients do not respond to single immune checkpoint blockade therapy, and the targeted mesothelin-directed chimeric antigen receptor (CAR) T-cell therapy shows limited effectiveness in PC, failing to achieve the expected results [4, 5]. PC has become a major public health issue threatening public health. Accordingly, it is imperative to delve into the processes that drive the onset and escalation of PC and to promote updates in prevention, diagnosis, and treatment methods for this disease.

The gut microbiota (GM) forms a substantial and intricate microbial community that is intimately linked to the well-being of the host. The GM generates metabolites such as short-chain fatty acids (SCFAs), tryptophan, and bile acid derivatives, which influence not just genetic and epigenetic controls but also the metabolic activities of immune cells, including those with immunosuppressive and inflammatory functions [6]. Enhancing evidence suggests that the composition and distribution of GM vary across different cancers, and an altered GM profile can potentially result in the occurrence

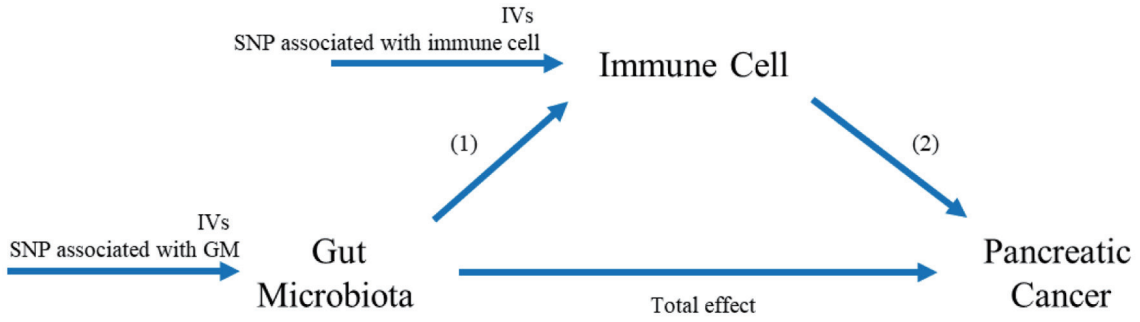

Figure 1. The study design. A two-step Mendelian randomization study of GM on PC mediated by immune cell. IVs: instrumental variables; SNP: single nucleotide polymorphism.

of various diseases, including PC, colorectal tumors, and lung cancer. Research indicates that butyrate, a metabolic product of the GM, can delay the progression of PC by neutralizing the immunosuppressive effects of CD11b cells and enhancing the immunological responses of $CD8^+$ lymphocytes [6, 7]. Thus, the GM not only affects nutritional absorption and metabolism but also co-evolves with the host's immune system to form a complex interplay.

Mendelian randomization (MR) serves as an analytical technique used to explore causal relationships and ascertain the linkage between an exposure and its subsequent outcome [8]. Previous evidence has extensively confirmed the role of GM in PC and its impact on people's immunological system [9]. Yet, whether GM affects the progression of PC through immune cell regulation remains unclear. This research is designed to probe the causal relationships between GM and PC, as well as to determine whether immune cells may mediate this process. The MR method employs genetic variation as an instrumental variable (IV) to infer causal impacts, which, in theory, bypasses the effects of confounding elements or the issue of reverse causality. Two-sample MR analysis is a typical MR method and can be used to access causal connections from two independent samples. In this study, we investigated the influence of GM on immune cell properties and computed the percentage of the impact of GM on PC that is mediated through immune cell features, in order to determine whether GM can affect PC by regulating immunological system.

Materials and Methods

Study design

This study aimed to evaluate the causal relationship from GM to PC through immune cells using genetic instruments. The detailed layout and procedural sequence of this MR study consisted of two principal elements: 1) the examination of the causal impacts of 473 GM on PC, as well as the assessment of the causal influences exerted by 731 immune-related genomic characteristics on PC; 2) and mediation analysis of 731 immune-related whole-genome features in the pathway from GM to PC. The overview of research design is illustrated in Figure 1.

In the MR analysis, three key assumptions must be satisfied to yield valid results: 1) The IVs must exhibit a robust and reliable correlation with the exposure under investigation. 2) The IVs should be unrelated to any confounders that are associated with both genetic variants and the outcome being studied. 3) The IVs must affect the outcome solely via their association with the exposure, excluding any additional intermediary processes [10]. The STROBE-MR checklist of the study is shown in Supplementary Material 1 (www.wjon.org).

Data sources

The datasets utilized in this research were accessible to the general public, and the individuals involved in the database were of European descent. The genetic associations of GM were derived from the NHGRI-EBI GWAS Catalog from accession GCST90032172 to GCST90032644 [11].

Access to the immune cells data is unrestricted through the GWAS Catalog, with a range of accession numbers from GCST0001391 to GCST0002121 [12]. This dataset consists of 731 immunophenotypic measurements including six panels: TBNK (B cells, natural killer (NK) cells, T cells), T regulatory cells, myeloid cells, maturation stages of T cells, B cells and conventional dendritic cells (CDCs).

For the outcome dataset, GWAS summary statistics for PC were sourced from the FinnGen Consortium R10 release. This study used the "adenocarcinoma and ductal carcinoma of pancreas" phenotype and included 314,924 participants (731 PC cases and 314,193 controls).

Statistical analysis

Significant single nucleotide polymorphisms (SNPs) at the threshold $P < 1 \times 10^{-5}$ were recognized as potential IVs [13]. To mitigate bias arising from substantial linkage disequilibrium (LD), we removed SNPs with an $r^2 < 0.001$ from a 10,000 kb window. To avoid the bias of weak IVs, we calculated R^2 and F statistics of the selected SNPs. The methods of calculation for R^2 and F statistics were used as previously reported [14, 15]. The equation for R^2 was: $(2 \times Effect^2 \times eaf \times (1 - eaf))/(2 \times Effect^2 \times eaf \times (1 - eaf) + se^2 \times 2 \times N \times eaf \times (1 - eaf))$. The F statistic was calculated as: $(R^2 \times (N - 2)/(1 - R^2))$. R^2 represented the proportion of GM variance accounted for by genetic

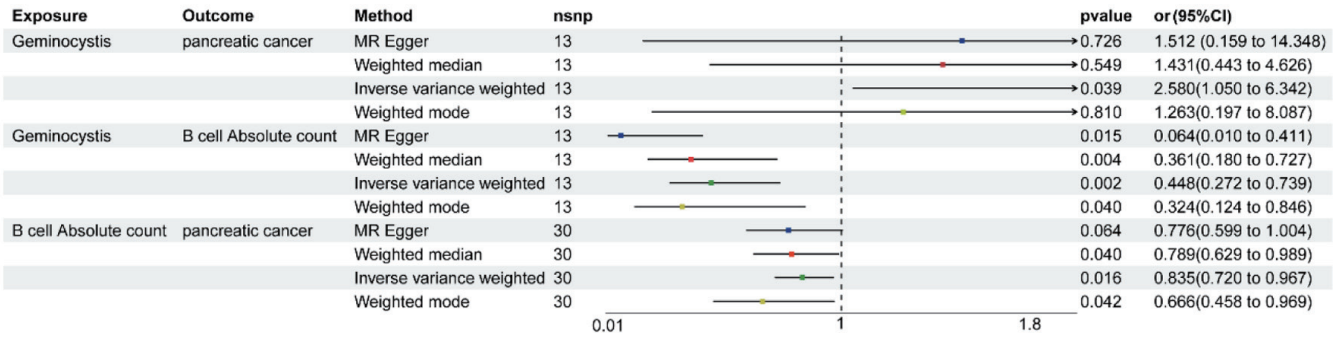

Figure 2. MR analysis showing the causality of Geminocystis on pancreatic cancer is significant. MR: Mendelian randomization; CI: confidence interval; OR: odds ratio; SNP: single nucleotide polymorphism.

instruments, and we excluded SNPs with F statistics below 10. The minimal allele frequency (MAF) was set to 0.01 and we decided not to employ the SNP proxy [16]. After integrating the effect alleles from the GWAS studies of exposure and outcome, the causality between GM and PC was estimated with several MR approaches, including the IVW, weighted median, MR-Egger and weighted mode. Among them, the IVW method was considered the main outcome, which can provide the most accurate assessments [17]. Sensitivity analysis has played a crucial role in MR analysis to evaluate potential pleiotropy, and the heterogeneity for MR estimations can be seriously violated. The heterogeneity of the study was quantified by Cochran's Q test. We applied the MR-Egger intercept and MR-PRESSO to determine whether pleiotropy existed [18]. Leave-one-out analysis was applied to examine whether the MR results were affected by singular SNP. We conducted MR analysis using R software (version 4.4.0) [19] along with the "Two-Sample MR" package (version 0.6.3). $P < 0.05$ was considered to denote statistical significance.

This study is a secondary analysis conducted through existing GWAS data. No ethics approval was needed due to the re-analysis of published data.

Results

Association of GM with PC

The IVW, weighted median, MR-Egger and weighted mode were used to estimate the causal relationship between genetically predicted GM and PC. Detailed information on SNPs included for analyses is presented in Supplementary Material 2 (www.wjon.org). The two-sample MR analysis demonstrated the causality of Geminocystis on PC. While alternative methods did not indicate statistically significant results, the IVW strategy disclosed that elevated levels of Geminocystis corresponded with an escalated probability of developing PC (odds ratio (OR): 2.580, 95% confidence interval (CI): 1.050 - 6.342, P = 0.039) (Fig. 2). The statistical methods of Cochran's Q, the MR-Egger intercept test, and MR-PRESSO indicated no presence of heterogeneity and horizontal pleiotropy within the context of the MR study (Supplementary Material 3, www.wjon.org). Furthermore, during a leave-one-out sensitivity analysis, no SNP significantly altered the consistent relationship between GM and the incidence of PC (Fig. 3a). Similarly, the reverse MR analysis failed to detect any reverse causation (Supplementary Material 4, www.wjon.org).

Association of immune cell with PC

Protective effect of B-cell absolute count (AC) traits on PC was identified with the IVW, weighted median, MR-Egger and weighted mode (Fig. 1, Supplementary Material 5, www.wjon.org). No apparent heterogeneity and horizontal pleiotropy were found in the current study (Supplementary Material 3, www.wjon.org). The leave-one-out sensitivity analysis substantiated the stability of the findings, demonstrating that the exclusion of any individual SNP did not alter the inferred causal relationships (Fig. 3b).

Association of GM with immune cell

Previously, we identified Geminocystis and B-cell AC traits vital to PC. Then, we verified the causal role of Geminocystis on B-cell AC traits. The MR study revealed a correlation between Geminocystis and B-cell AC (OR: 0.448, 95% CI: 0.272 - 0.739, P = 0.002, Fig. 1 and Supplementary Material 6, www.wjon.org). Neither heterogeneity nor horizontal pleiotropy was observed, and the leave-one-out sensitivity analysis showed that no SNP notably modified the stable association (Supplementary Material 3, www.wjon.org and Fig. 3c).

Mediation analysis

We conducted an analysis to determine if B-cell AC acts as an intermediary in the pathway linking Geminocystis to PC. We found that higher levels of Geminocystis were associated with descending levels of B-cell AC, and this reduction was subsequently linked to a higher probability of developing PC. As shown in Table 1, our study showed that B-cell AC accounted for 15.32% of the increased risk of PC associated with Geminocystis.

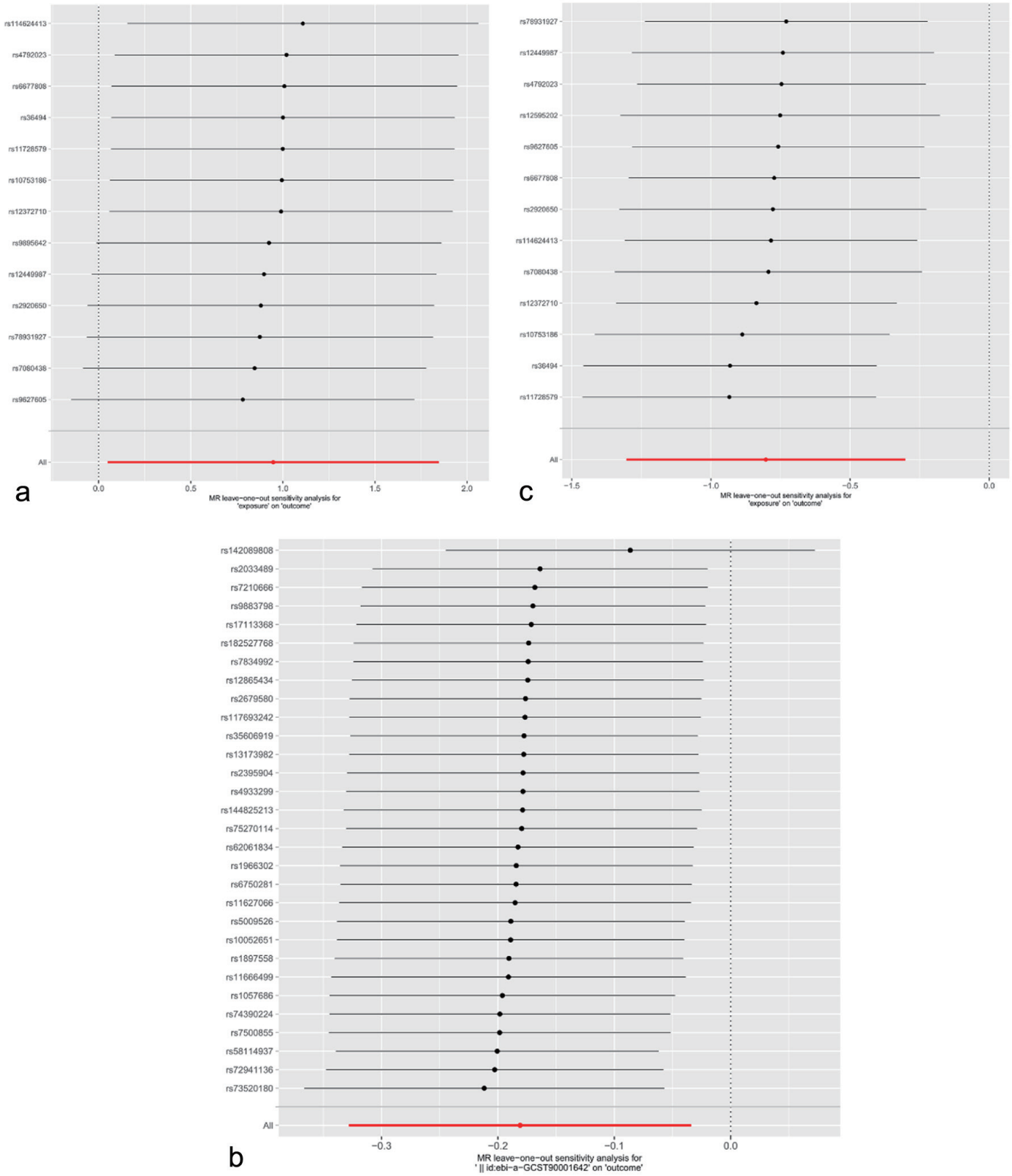

Figure 3. Leave-one-out plots for MR analyses. (a) The causal effect of GM on PC. (b) The causal effect of immune cell on PC. (c) The causal effect of GM on immune cell. SNPs: single nucleotide polymorphisms; MR: Mendelian randomization; GM: gut microbiota; PC: pancreatic cancer.

Table 1. Mediation Effect of Geminocystis on PC via B-Cell Absolute Count in TBNK Panel

Total effect β	Direct effect A β	Direct effect B β	Mediation effect β	Mediated proportion (%)
0.948	-0.803	-0.181	0.145	15.321

Total effect: The causal role of GM on PC. Direct effect A: The causal role of GM on immune cell traits. Direct effect B: The causal role of immune cell traits on PC. β(Indirect effect) = β(Direct effect A) × β(Direct effect B). The mediated proportion = β(indirect effect)/β(total effect). GM: gut microbiota; PC: pancreatic cancer.

Discussion

This research sought to demonstrate the potential causal relationship between GM and PC. We deployed MR analysis to evaluate the correlation between GM and PC, as evidenced by existing GWAS data, and to determine whether immune cells mediate the causal relationship between these factors. Our results indicated that Geminocystis elevated the risk of PC by suppressing the functionality of immune cells, and 15.321% of this effect was mediated through B-cell AC trait of TBNK panel.

The GM, a diverse assembly of archaea, fungi, bacteria, viruses and phages, resides within the digestive tract. This intricate community is fundamental to the proper functioning of the digestive system and the overall health of the individual. Previous studies have emphasized the importance of GM in the pathophysiological processes of various gastrointestinal tumors, including PC. An MR study indicated that the phylum Verrucomicrobia was associated with a reduced risk of intrahepatic cholangiocarcinoma, whereas the Bacillales is associated with an increased risk of PC [20]. Another research showed that Senegalimassilia acts as a safeguard against PC, while Odoribacter, Ruminiclostridium 9, Ruminococcaceae (UCG011), and Streptococcus are linked to an increased likelihood of the disease's onset [21].

The GM may have an effect on regulating the host's immune system and maintaining a stable internal environment [22]. The GM can promote the development of the gut-associated lymphoid tissue (GALT), and regulate the function of the mucosal barrier and the secretion of cytokines. Furthermore, the GM metabolites have the ability to enter the circulation and diffuse to different organs via paracellular transit or by being transported in conjunction with chylomicrons. They are involved in supervising and directing the development and function of various immune cells, including innate and adaptive immunity [23]. SCFAs have been identified to stimulate the maturation of naive CD4 T cells into Th1 cells by triggering the mTOR-S6K signaling pathway [23, 24] SCFAs can directly upregulate acetyl-CoA levels of B cells, mitochondrial energy output, fatty acid synthesis, and mTOR-regulated glycolysis, contributing to the differentiation of plasma cells and the production of antibodies [23, 25]. Other research revealed that deoxycholic acid produced by bacteria with 7α-dehydroxylating activity, along with secondary bile acids, is considered to increase the risk of PC [26]. Similarly, butyrate, a metabolite of gut bacteria, can participate in the pathophysiological process of PC and its response rate to treatment *in vitro* and *in vivo* experiment. Additionally, it can mitigate some of the damage associated with the cancer itself or caused by chemotherapy [27].

The tumor microenvironment in PC is highly immunosuppressive, containing numerous immune cells, including T cells, macrophages, DCs, and B cells [28]. The role of B cells in the tumor microenvironment is ambivalent [29]. They can exert antitumor effects by producing antibodies, facilitating antigen presentation, and supporting T-cell responses. However, they can also promote tumor progression by secreting inhibitory cytokines that suppress immune reactions. Studies have proved that B regulatory cells can release cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which will elicit suppression by inhibiting the function of effector T cells and NK cells and promoting growth and activity of regulatory T cells [30]. On the other hand, B cells can serve as antigen-presenting cells or produce antibodies. In the humoral immune response of the host against tumors, the presence of B cells and their subsets within the cancer tissue has certain advantages [31, 32]. Overall, B cells play a complex and diverse role in the occurrence and progression of PC, with different types of subgroups promoting or inhibiting tumor growth through various mechanisms.

About Geminocystis, it is a new genus that was isolated from Synechocystis by Korelusova et al in 2009, and it mainly includes two species: *Geminocystis herdmanii* and *Geminocystis papuanica* [33]. Another potential new species has been identified and named *Geminocystis urbisnovae* [34]. Studies have suggested that Geminocystis is a sister group to the Cyanobacteria in terms of phylogenetic evolution. One study indicated that oral Cyanobacteria may be an independent risk factor for hepatocellular carcinoma [35]. However, research also suggests that multiple cyanobacteria synthesize microcystin-LR, which exhibits cytostatic properties, rendering them potential candidates for further drug design [36]. In a cross-sectional study, there was a negative correlation between Geminocystis and M0 macrophages in the alveolar lavage fluid of smokers [37]. Another study demonstrated that microbiomes in mice can modulate tumor-associated macrophages through Toll-like receptor signaling, thereby promoting immune tolerance [9]. In the tumor microenvironment of PC, memory B cells produce antibodies against tumor antigens, which activate NK cells and macrophage functions [30]. However, it has also been found that lipopolysaccharides (LPS) secreted by microbes can stimulate the secretion of the immunosuppressive factor IL-35 by some B regulatory cells consequently leading to tumor proliferation [38]. To date, no studies have been conducted on the effects of the Geminocystis genus on human health, and this study is the first study to identify a correlation between this genus and PC. However, the exact mechanisms require further investigation in subsequent research.

We confessed several limitations in our study. Firstly, the majority of the study population is of European heritage, which may influence the validity and generalizability of our findings.

Secondly, constraints within the database requiring analysis of GM at the genus level may reduce the level of detail in the results. As a result, certain potential discoveries might be overlooked. Additionally, our threshold for GM IVs is set at $P < 5 \times 10^{-5}$, which aims to achieve more comprehensive results. However, this may lead to false positives or miss important genetic variations associated with immune cell traits and PC. This adjustment may introduce some bias into our conclusions. Meanwhile, there may be other mediators that require further investigation. Finally, it is important to note that the findings of this research have not yet been confirmed through external validation within a clinical setting, which is a limitation to be recognized.

Conclusion

Our study clarified the causal relationships between GM, immune cells, and PC. Geminocystis has been identified to raise the risk of PC, with this effect being mediated by the B-cell AC in the TBNK panel as measured. This study provides insight into the causal contributions of GM in PC, which is beneficial to the prevention and treatment of PC.

Supplementary Material

Suppl 1. STROBE-MR checklist of the study.

Suppl 2. The instruments of gut microbiota/immune cells/pancreatic cancer.

Suppl 3. The bidirectional two-sample Mendelian randomization (MR) analysis results between gut microbiota and pancreatic cancer.

Suppl 4. Pleiotropy and heterogeneity test for the Mendelian randomization (MR) analysis results.

Suppl 5. Mendelian randomization (MR) analysis on the causal effect between immune cells and pancreatic cancer.

Acknowledgments

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Financial Disclosure

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Conflict of Interest

The authors have declared that no competing interest exists.

Informed Consent

Not applicable.

Author Contributions

Wang, Zhang, and Pan designed the study. Wang and Yu collected and analyzed the data. Wang, Zhang and Pan drafted the manuscript. Li and Lei supervised the study and revised the manuscript. All authors discussed the results and contributed to the final manuscript.

Data Availability

The GWAS summary dataset for PC is available through the FinnGen Consortium R10 release (https://r10.finngen.fi/). The GM datasets are derived from the GWAS Catalog (https://www.ebi.ac.uk/gwas/, from GCST90032172 to GCST90032644). The data on immune traits are available through the GWAS Catalog (from GCST0001391 to GCST0002121).

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