Original Article

Mendelian randomization study on simvastatin and gastric cancer: exploring the therapeutic potential of statins in oncology

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Background: Gastric cancer ranks as the fifth most prevalent cancer and the third leading cause of cancer-related mortality worldwide, Statins, renowned for their cholesterol-lowering effects, have garnered interest for their potential roles in cancer prevention and treatment due to their pleiotropic effects, such as anti-proliferative, pro-apoptotic, and anti-inflammatory properties. This study aims to investigate the therapeutic potential of simvastatin, a widely prescribed statin, in the context of gastric cancer using Mendelian randomization (MR) to explore a possible causal relationship between simvastatin use and gastric cancer risk.

Methods: We conducted a two-sample MR analysis utilizing summary statistics from genome-wide association studies (GWAS). Data from the Integrative Epidemiology Unit (IEU) Open GWAS project included 462,933 participants and 9,851,867 single nucleotide polymorphisms (SNPs) for simvastatin, and 476,116 participants with 24,188,662 SNPs for gastric cancer. Instrumental variables screening criteria were stringent, resulting in 41 valid SNPs as instrumental variables. The MR analysis was performed using the inverse variance weighting (IVW), supplemented by MR-Egger, weighted median estimator (WME), weighted mode, and simple mode approaches. Heterogeneity and pleiotropy were assessed using IVW, MR-Egger tests, and the MR-PRESSO method.

Results: The IVW and WME analyses indicated a significant protective effect of simvastatin against gastric cancer [IVW: odds ratio (OR) =0.1459, 95% confidence interval (CI): −3.502 to −0.346, P=0.01; WME: OR =0.0347, 95% CI: −3.521 to 0.1610, P=0.03]. There was no significant difference between the results of the two MR analyses before and after the removal of outliers (P=0.76), and the Egger-intercept for horizontal pleiotropy testing was not significant (P=0.38). Leave-one-out sensitivity analysis supported the robustness of our findings.

Conclusions: This MR study provides evidence for a potential protective effect of simvastatin against gastric cancer, suggesting its consideration as an adjunct to traditional cancer therapies.

Keywords: Mendelian randomization (MR); simvastatin; gastric cancer; therapeutic potential; single nucleotide polymorphism (SNP)

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Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death globally, the 5-year survival rate remains at a disheartening 40% (1,2). Despite advancements in surgical techniques and chemotherapy, the overall survival rate has not significantly improved, highlighting the need for novel therapeutic approaches (3,4). Statins, primarily known for their cholesterol-lowering effects, have emerged as potential candidates for cancer prevention and treatment due to their pleiotropic effects, including anti-proliferative, pro-apoptotic, and anti-inflammatory properties (5). Simvastatin, a widely prescribed statin, has been the subject of numerous studies investigating its potential anti-cancer effects. Preclinical studies have demonstrated that simvastatin can inhibit the growth and metastasis of various cancer cells, including gastric cancer cells, through multiple mechanisms (6-8). However, clinical evidence is limited and often conflicting, necessitating further investigation to establish a causal relationship.

Mendelian randomization (MR) is a powerful epidemiological tool that uses single nucleotide polymorphism (SNP) as instrumental variables (IVs) to estimate causal effects of modifiable risk factors on health outcomes (9,10). By leveraging the random allocation of alleles at conception, MR can minimize confounding and provide unbiased estimates of causality (11). This study employs MR to investigate the potential of simvastatin in the treatment of gastric cancer. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-576/rc).

Highlight box

Key findings

- Simvastatin may offer protective effects against gastric cancer, a leading cause of mortality worldwide.

What is known and what is new?

- Gastric cancer poses a significant health threat, with limited improvement in survival rates despite advancements in treatment.
- This study presents simvastatin, a commonly used cholesterol-lowering statin, as a potential therapeutic agent for gastric cancer prevention.

What is the implication, and what should change now?

- The evidence from this Mendelian randomization study supports further investigation into the role of simvastatin in gastric cancer prevention, suggesting a novel application for statins in oncology.

Methods

Data sources

Our investigation is anchored in a two-sample MR analysis, utilizing summary statistics from genome-wide association studies (GWAS) to explore the putative causal nexus between simvastatin and gastric cancer (12). The GWAS data, sourced from the Integrative Epidemiology Unit (IEU) Open GWAS project (https://gwas.mrcieu.ac.uk/), encompassed 462,933 participants and 9,851,867 SNPs for simvastatin, and 476,116 participants with 24,188,662 SNPs for gastric cancer. The datasets were exclusively derived from individuals of European descent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

IV screening criteria

The selection of IVs was based on the following criteria (13,14): (I) SNPs with a significance threshold ($P<5e-8$) within the gene locus were considered as potential IVs; (II) SNPs in linkage disequilibrium ($r^2<0.001$) were excluded; (III) a region width of 10,000 kb was applied to ensure independence among SNPs. The Phosanner tool (http://www.phosanner.medschl.cam.ac.uk/) was instrumental in identifying SNPs with a significant phenotypic effect and in excluding those correlated with the outcome. This meticulous process yielded 41 valid SNPs with a pronounced association with simvastatin, designated as IVs.

MR analysis methods

The inverse variance weighting (IVW) method served as the cornerstone for our MR analysis, tasked with evaluating the causal influence of simvastatin on gastric cancer incidence. Supplementary analyses were conducted using the MR-Egger, weighted median estimator (WME), weighted mode (WM), and simple mode (SM) approaches (15,16). All results were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). The research was primarily conducted using the Two Sample MR package (version 0.5.10) in R software (version 4.2.1), with a significance level α set at 0.05.

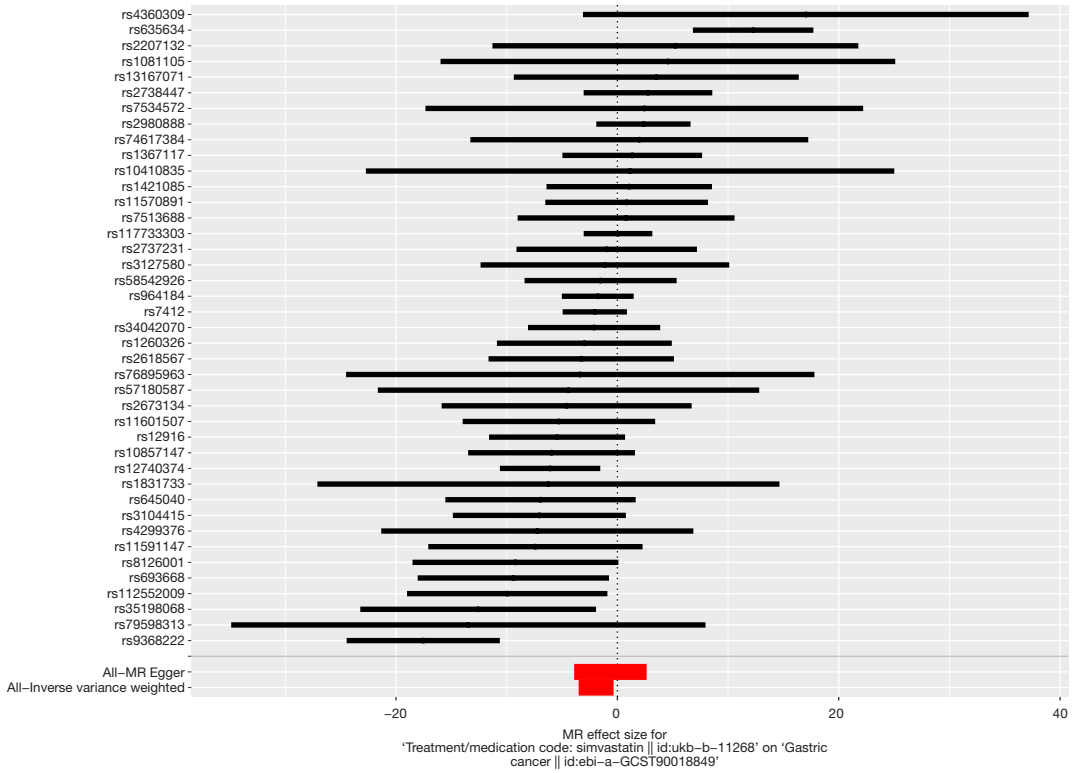

Figure 1 A forest plot shows the ORs and 95% CIs for the effect of simvastatin on gastric cancer using the two-sample Mendelian randomization. MR, Mendelian randomization; OR, odds ratio; CI, confidence interval.

Heterogeneity

Heterogeneity was assessed using IVW and MR-Egger tests, with a P value <0.05 indicating the presence of heterogeneity in the study (17), then, MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to identify and exclude outlier SNPs, followed by a new MR analysis. When the heterogeneity test result P≥0.05, heterogeneity in the causal analysis was considered absent. Funnel plots were constructed to detect heterogeneity, with a symmetric distribution of SNPs indicating the absence of heterogeneity.

Horizontal pleiotropy

The Egger-intercept was used to assess horizontal pleiotropy of the SNPs. If the intercept was not statistically significant compared to 0, it indicated the absence of horizontal pleiotropy (18).

Sensitivity analysis

A leave-one-out approach was used for sensitivity analysis to evaluate the impact of individual SNPs on the MR analysis results (19).

Results

Results of five MR analyses

Our analysis yielded intriguing findings from five distinct MR methods. The IVW analysis suggested a significant protective effect of simvastatin against gastric cancer (OR =0.1459, 95% CI: −3.502 to −0.346, P=0.01), MR-Egger (OR =0.7073, 95% CI: −3.905 to 0.0201, P=0.70), WME (OR =0.0347, 95% CI: −3.521 to 0.1610, P=0.03), SM (OR =0.4507, 95% CI: −4.576 to 0.0102, P=0.45), and WM (OR =0.2282, 95% CI: −3.079 to 0.0460, P=0.22) (*Figure 1*). While the MR-Egger, WM, and SM analyses did not reach conventional levels of statistical significance, the IVW and WME analyses showed statistically significant differences. The direction of the results from the five MR methods was consistent (*Figure 2*), and these findings were in agreement with the forest plot, suggesting that simvastatin may reduce the risk of gastric cancer incidence.

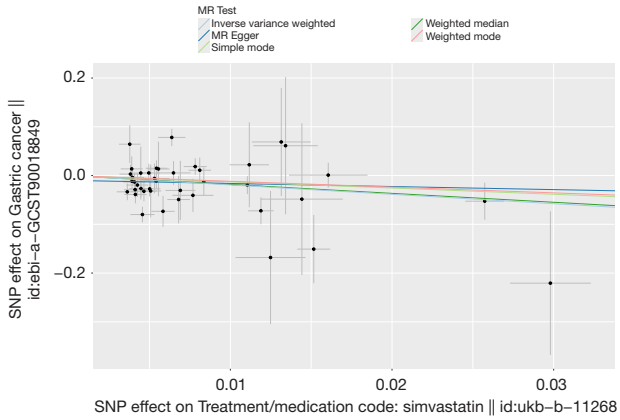

Figure 2 A scatter plot shows the effects of SNPs on gastric cancer. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

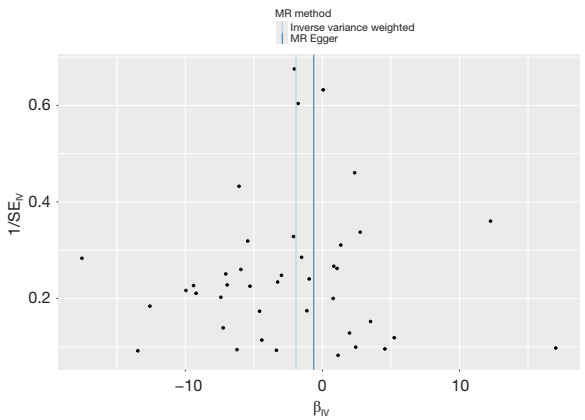

Figure 3 A funnel plot of two-sample MR. MR, Mendelian randomization.

Sensitivity analysis

To assess the robustness of the analysis results, we conducted a comprehensive sensitivity analysis, which revealed that the IVW (Q=86.68, P=2.70e−05) and MR-Egger regression (Q=84.97, P=2.90e−05) indicated the presence of heterogeneity in the analysis results. The results of the MRPresso method showed that two SNPs, rs76895963 (P=0.041) and rs8126001 (P=0.041), were the source of heterogeneity. After removing the outliers, MR analysis was performed again, and the results of the two MR analyses were not significantly different (P=0.76). The Egger-intercept for pleiotropy testing was −0.0098, close to 0, with P=0.38>0.05, not supporting the presence of horizontal pleiotropy.

Furthermore, the funnel plot showed a symmetrical distribution, indicating a lesser likelihood of being influenced by potential biases (*Figure 3*). The leave-one-out sensitivity analysis results demonstrated that, upon sequential removal of each SNP in the exposure, the remaining SNPs did not significantly affect the outcome (*Figure 4*).

Discussion

Simvastatin, a potent HMG-CoA reductase inhibitor, reduces cholesterol biosynthesis by blocking the mevalonate pathway, thereby lowering low-density lipoprotein (LDL) levels (20,21). Beyond its lipid-lowering effects, simvastatin exhibits pleiotropic actions, including anti-inflammatory and anti-proliferative properties (22). It upregulates endothelial nitric oxide synthase, enhances plaque stability, and inhibits smooth muscle cell proliferation, all of which contribute to its cardioprotective effects (23,24). Additionally, simvastatin has been shown to induce cancer cell apoptosis and to impair angiogenesis by downregulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), highlighting its potential as an anti-cancer agent (25-29).

The current study employs MR to investigate the potential causal relationship between simvastatin use and the risk of gastric cancer. Our findings, derived from a robust two-sample MR approach, suggest a protective effect of simvastatin against gastric cancer, with the IVW and WME analyses indicating statistically significant reductions in risk. These results are consistent with preclinical evidence that has shown simvastatin to inhibit cancer cell growth and metastasis through multiple mechanisms, including the modulation of inflammatory pathways and the induction of apoptosis (27,30-32).

The biological plausibility of our findings is supported by the pleiotropic effects of statins, which extend beyond their cholesterol-lowering properties (33,34). Statins have been shown to influence cancer-related processes such as cell cycle regulation, angiogenesis, and immune response. Specifically, simvastatin has been demonstrated to suppress the expression of VEGF, a key factor in tumor angiogenesis, and to inhibit the PI3K/AKT/mTOR signaling pathway (35-37), which is crucial for cancer cell survival and proliferation. The implications of our findings are clinically significant, as they provide evidence for the potential use of simvastatin as a chemopreventive agent for gastric cancer. Given the poor prognosis and limited treatment options for this disease, the identification of a readily available and

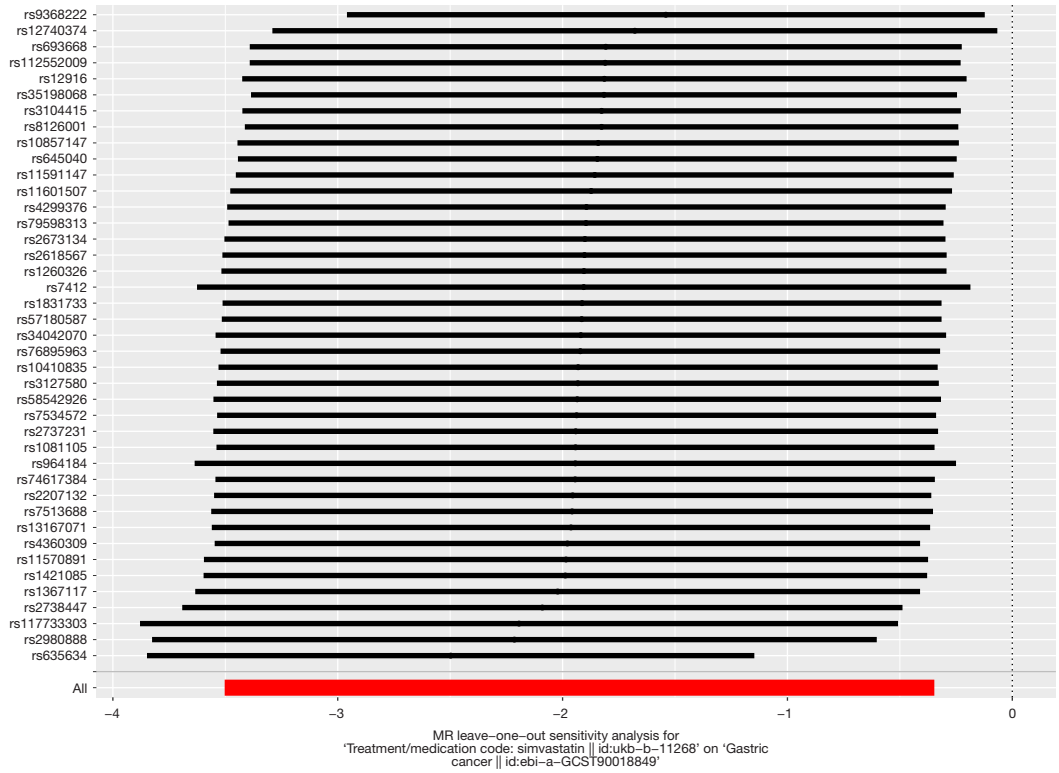

Figure 4 A leave-one-out analysis of the estimations for simvastatin and gastric cancer. MR, Mendelian randomization.

affordable drug with chemopreventive properties could have a substantial impact on public health strategies. However, our findings must be interpreted with caution due to several limitations. The use of GWAS summary statistics limits our ability to assess the impact of unmeasured confounders and the potential for pleiotropy. Additionally, the reliance on European populations may restrict the generalizability of our findings to other ethnic groups, in which the genetic and environmental risk factors for gastric cancer may differ. These limitations underscore the need for further research in diverse populations and using individual-level data to confirm our findings.

In this study, we employed MR to explore the potential causal relationship between the use of simvastatin and the risk of gastric cancer. The MR approach is predicated on several key assumptions: (I) the selected SNPs have a significant genetic association with the exposure (simvastatin in our study); (II) these SNPs are not directly genetically associated with the outcome (gastric cancer) except through the exposure; (III) SNPs are randomly allocated at conception and are not influenced by confounding factors; (IV) there is no pleiotropy, meaning the SNPs' effects on the outcome are solely through their influence on the exposure. In our analysis, we applied stringent criteria for the selection of IVs and utilized multiple MR analysis methods, including IVW, MR-Egger, WME, WM, and SM, to enhance the robustness of our findings. Additionally, we identified and excluded SNPs contributing to heterogeneity using the MR-PRESSO method and performed sensitivity analyses to evaluate the impact of individual SNPs on the MR analysis results.

Conclusions

In conclusion, our MR study provides evidence for a possible protective effect of simvastatin against gastric cancer. Considering simvastatin as an adjunct to traditional cancer therapies may present a novel strategy for enhancing patient outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-576/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-576/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-576/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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