

Genetic Causality of Colorectal and Gastric Cancer Risk: a Mendelian Randomization Analysis

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Abstract:

This study investigated the genetic association between colorectal cancer and gastric cancer using Mendelian Randomization (MR) analysis. Using genome-wide association study (GWAS) data and various statistical methods such as the inverse variance weighting (IVW) method, this study revealed for the first time that colorectal cancer may increase the risk of gastric cancer through genetic mechanisms. The results showed a significant positive correlation between colorectal cancer and the risk of gastric cancer (IVW: OR = 1.196, 95% CI: 1.011–1.414, P = 0.037), which provides an important basis for the prevention and monitoring of subsequent gastric cancer in colorectal cancer patients. The robustness of the results was ensured by multiple sensitivity analyses, such as Egger's intercept test, the leave-one-out method, and funnel plots, and no significant horizontal pleiotropy or potential bias was detected. In addition, the use of an IVW random-effects model further ensured the reliability of the findings, despite Cochran's Q test suggesting heterogeneity of the instrumental variables. The results have important implications for clinical practice, suggesting that early screening for gastric cancer should be enhanced in the follow-up and management of colorectal cancer patients. Meanwhile, future studies should validate these findings in diverse racial populations and further explore the biological mechanisms of genetic variation and cancer development, thus providing a new direction for precision medicine.

Keywords:

Mendelian Randomization, Colorectal Cancer, Gastric Cancer, Causality

1. Introduction

According to the latest statistics, colorectal cancer was estimated to result in 1.9 million new cases and 904,000 deaths in 2022, ranking as the third most prevalent and second most deadly cancer in the world [1]. The high prevalence and seriousness of colorectal cancer pose a significant challenge to public health worldwide. In recent years, with the continuous advancement of medical science and technology, therapeutic approaches for colorectal cancer have been significantly enriched and

enhanced. Traditional treatments like surgical resection, chemotherapy, and radiotherapy have been continuously optimized, while the introduction of novel strategies, such as targeted therapy and immunotherapy, has provided colorectal cancer patients with more therapeutic options [2]. The combined application of these treatments, known as multidisciplinary comprehensive therapy MDT(Multi-Disciplinary Treatment), has become a key approach to enhancing treatment outcomes and prolonging patient survival [3].

Thanks to the promotion of colorectal cancer CRC(Colorectal Cancer) screening programs, advances in diagnostic technology, and improved treatments, the survival rate of CRC patients in China has steadily increased over the past decade[4]. Statistics show that the relative survival rate for CRC reached 56.9% between 2012 and 2015, representing an increase of approximately 10% compared to the period 2003–2005 [5]. However, with prolonged survival comes a new challenge: a rising incidence of second primary tumors [6]. A second primary tumor is a histologically and clonally distinct tumor that develops after the first cancer diagnosis [7]. The survival rate of colorectal cancer patients decreases significantly after the development of a second primary tumor[8]. Among colorectal cancer patients, gastric cancer is a comparatively common second primary tumor [9]. Gastric cancer occurs as a second primary tumor in 1% to 4.2% of colorectal cancer patients[10]. The incidence of gastric cancer after colorectal cancer treatment was 0.93% and 1.4%, respectively, resulting in a combined incidence of 2.4% [11]. In addition, existing observational studies indicate a potential association between colorectal cancer and the development of gastric cancer [12]. However, due to the inherent limitations of these studies, such as confounding factors, the precise genetic association between gastric and colorectal cancer remains uncertain.

Mendelian randomization (MR) is an approach to genetic epidemiology that uses genetic variation as an instrumental variable to explore the causal effect of exposure on disease outcomes, is less prone to confounding, and allows for more accurate causal inferences [13]. In this study, we performed MR analysis based on summary data from genome-wide association studies (GWAS) to investigate the causal relationship between gastric cancer and colorectal cancer, with the aim of providing new insights into the prevention and diagnosis of recurrent gastric cancer after colorectal cancer treatment.

2. Materials and Methods

2.1. Research design

A two-sample Mendelian Randomization (MR) approach was utilized to explore the causal relationship between colorectal cancer and gastric cancer, with colorectal cancer designated as the exposure factor and single nucleotide polymorphisms (SNPs) used as instrumental variables, and gastric cancer as the outcome variable. The validity and accuracy of the MR analysis depend on the following three assumptions: a. There is a significant association between the genetic variation and the exposure factor. b. The genetic variation is independent of confounding factors. c. The genetic variation influences the outcome solely through the exposure factor.

2.2. Data sources

The data for colorectal cancer and gastric cancer were obtained from publicly available GWAS databases. Colorectal cancer data were retrieved from

GWASCatalog (<https://www.ebi.ac.uk/gwas/>), with a sample size of 23,691 and 12,313,483 SNPs analyzed (GWASID: ebi-a-GCST012877). Data for gastric cancer were also retrieved from GWASCatalog (<https://www.ebi.ac.uk/gwas/>), with a sample size of 476,116 and 24,188,662 SNPs analyzed (GWASID: GCST90018849). Detailed information is presented in Table 1. The data used in this study were publicly available summary data, and therefore did not require participant consent or ethical approval.

Table 1. Brief information on the GWAS database in the two-sample MR study.

Project	GWAS ID	Database	Sample size	Number of SNPs	Crowd
Colorectal cancer	ebi-a-GCST012877	GWAS Catalog	23691	12313483	European
Gastric cancer	ebi-a-GCST90018849	GWAS Catalog	476116	24188662	European

2.3. Tool Variable Selection

The selection of instrumental variables must adhere to three main assumptions: a. SNPs must demonstrate a strong association with the exposure factor, colorectal cancer. b. SNPs must be independent of confounding factors. c. SNPs must influence the outcome, gastric cancer, solely through the exposure factor, colorectal cancer [14]. (See Figure 1) Therefore, to satisfy the above assumptions, the following criteria were used to screen SNPs: (1) SNPs with a significance threshold of $P < 5 \times 10^{-8}$ within the locus range were selected as potential SNPs; (2) to prevent linkage disequilibrium, a linkage disequilibrium threshold of $r^2 < 0.001$ was set, with a distance of 10,000 kb; (3) to avoid weak instrumental variables, an F-value > 10 was required, with the F-value calculated using the formula: $F = R^2(n-k-1)/k(1-R^2)$, and R^2 calculated as $R^2 = 2(1-EAF) \times EAF \times \beta^2$. Finally, the selected SNP data were extracted from the outcome variables and searched on the GWAS Catalog website to check whether core assumptions b and c were violated. Outlier SNPs were identified and rejected using the MR-PRESSO outlier test.

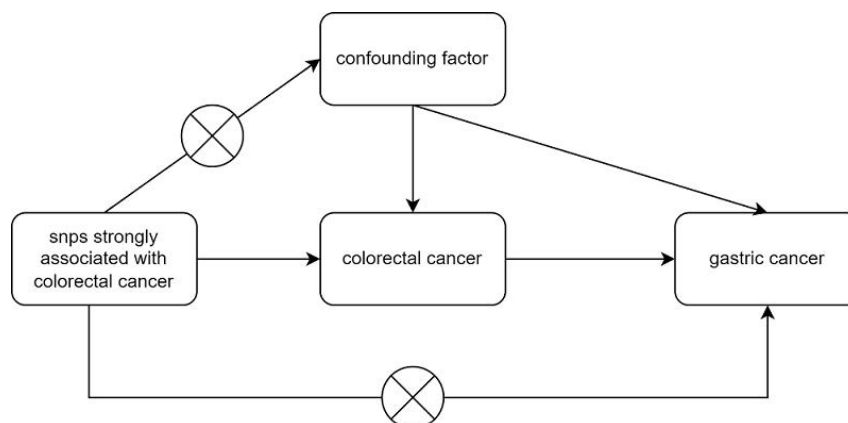


Figure 1. Flowchart of two-sample Mendelian randomized design.

2.4. MR analysis

In this study, various statistical methods were used to explore the causal association between colorectal and gastric cancers, including strategies such as the inverse variance weighting (IVW) method, weighted median (WME), MR-Egger regression analysis, weighted plurality method, and simple model. Among these, the results of the IVW method were used as the primary reference standard, while the other

methods were employed for supplementary validation and further illustration [15]. The results of causal inference were expressed through odds ratios (OR) and their 95% confidence intervals (CI). To assess heterogeneity among instrumental variables, Cochran's Q test was used, with a p-value <0.05 indicating significant heterogeneity. In such cases, correlation analyses were conducted to determine the source of heterogeneity and its impact on the final results. In addition, horizontal pleiotropy was tested using the Egger-intercept test, where an intercept value approaching 0 indicates no significant horizontal pleiotropy. Sensitivity analyses were conducted using the leave-one-out method, while funnel plots were employed to assess potential selectivity bias.

2.5. Statistical methods

In this study, data processing and analysis were performed using version 4.3.1 of R software for two-sample Mendelian randomization (MR) analysis, in conjunction with the TwoSampleMR and MR-PRESSO software packages. The study set a two-sided significance level of $\alpha = 0.05$ to determine statistical significance.

3. Results

3.1. Selection of instrumental variables

SNPs strongly and significantly associated with colorectal cancer were screened using $P < 5 \times 10^{-8}$, and, after removing linkage disequilibrium and conducting an F-test (including instrumental variables with an F-value >10), the initial number of included SNPs was seven. These seven SNPs were also searched on the GWAS Catalog website, and no confounders were found to be associated with them. Ultimately, seven SNPs were included (see Table 2 for details), and the final included SNPs were tested for outliers using MR-PRESSO, which showed that there were no outlier SNPs.

Table 2. Final included SNPs information.

SNPs	chr	E	O	EAF	Colorectal cancer			Gastric cancer			F
					β	SE	p	β	SE	P	
rs11213813	11	T	C	0.689	-0.124	0.021	3.38×10^{-9}	-0.037	0.017	0.030	157.782
rs16892766	8	C	A	0.081	0.221	0.036	5.46×10^{-10}	0.102	0.077	0.183	173.642
rs2427312	20	T	C	0.184	-0.152	0.025	1.43×10^{-9}	0.030	0.031	0.332	165.192
rs34877467	10	T	C	0.316	-0.120	0.021	5.49×10^{-9}	-0.001	0.016	0.938	149.409
rs355528	20	A	G	0.673	-0.122	0.021	3.89×10^{-9}	-0.071	0.023	0.002	155.110
rs4779585	15	T	C	0.794	-0.140	0.024	4.96×10^{-9}	0.001	0.021	0.978	153.637
rs7226855	18	G	A	0.455	-0.171	0.020	2.21×10^{-18}	-0.045	0.019	0.017	349.112

3.2. MR analysis results

In this study, the inverse variance weighted (IVW) method (OR = 1.196, 95% CI: 1.011 to 1.414, P=0.037), the MR-Egger method (OR = 1.263, 95% CI: 0.374 to 4.266, P=0.722), the weighted median method (OR = 1.186, 95% CI: 1.005 to 1.399,

P=0.043), the simple mode method (OR = 1.338, 95% CI: 1.020 to 1.757, P=0.080), and the weighted mode method (OR = 1.195, 95% CI: 0.973 to 1.469, P=0.140) are presented in Figure 2. The IVW and weighted median method results were consistent, indicating a positive causal relationship between the development of colorectal cancer and gastric cancer. Although the results of the MR-Egger and weighted mode methods were opposite to those of the IVW method, the statistical results were still predominantly based on the IVW method, given its highest statistical efficacy. Scatterplot (Figure 3A) and forest plot (Figure 3B) yielded results that were consistent with those of the IVW method.

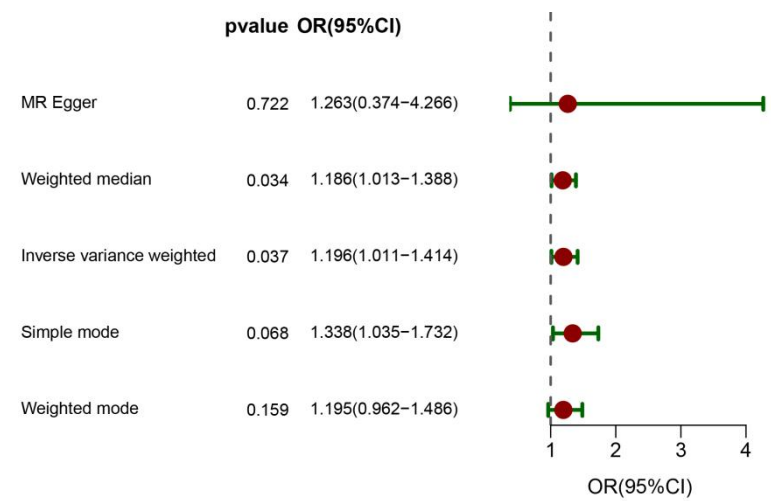


Figure 2. Forest plot of the relationship between colorectal and gastric cancers based on five MR analysis methods, with 95% CI range on the horizontal axis; OR=Odds Ratio.

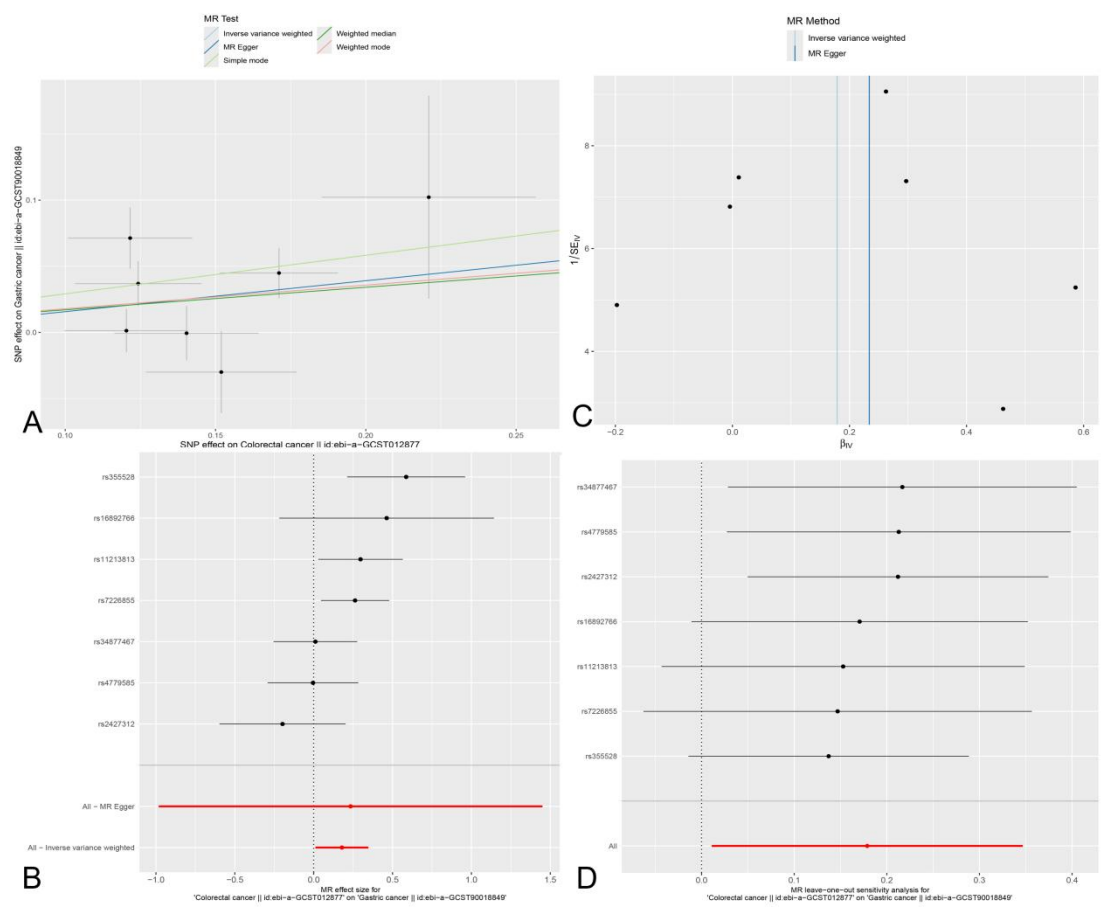


Figure 3. Positive correlations between colorectal cancer and gastric cancer: scatter plot (A), forest plot (B) funnel plot (C), leave-one-out plot (D).

Notes: (A) The scatterplot depicts the association between colorectal cancer and SNPs on the x-axis and gastric cancer and SNPs on the y-axis, and the 95% confidence intervals for each association are shown by horizontal and vertical lines. (B) The x-axis of the forest plot represents the estimated effect of exposure factors on outcome. Each black dot represents the estimated effect of a single genetic variant, red dots represent the combined effect estimate, and horizontal lines represent the Confidence Interval (CI). (C) Funnel plot showing the symmetrical distribution of effect points representing causal relationships, indicating that these effect points are less likely to be affected by potential bias. (D) The black dots of the leave-one-out plot indicate the causality estimates between a specific exposure and the target after removing each SNP in turn. Red dots indicate the overall causal estimates derived from the random effects IVW.

The funnel plot results revealed a more symmetrical distribution of SNPs, suggesting a reduced likelihood of bias influencing the findings (Figure 3C). Sensitivity analysis using the leave-one-out method indicated that the study's results remained stable after the removal of a single SNP, with no significant differences from the original findings (Figure 3D). Cochran's Q test ($Q = 13.045$, $P = 0.042$) indicated the presence of moderate heterogeneity between colorectal cancer and the instrumental variables. The Egger's intercept, being close to zero (intercept = -0.008 , $P = 0.932$), suggests the absence horizontal pleiotropy in this study.

4. Discussion

4.1. Summary and elaboration of the main findings of the study

In this study, we conducted a novel investigation of the causal relationship between colorectal and gastric cancer using the Mendelian randomization (MR) method, drawing from pooled data from a large-scale genome-wide association study (GWAS). The analysis using the inverse variance weighting (IVW) method revealed a significant positive causal association between colorectal cancer and gastric cancer risk (OR=1.196, 95%CI: 1.011–1.414, $P=0.037$). This finding suggests that colorectal cancer may elevate the risk of gastric cancer through genetic pathways, providing new evidence supporting the association between the two cancers. Moreover, the weighted median (WM) method also demonstrated a positive correlation between the two (OR=1.186, 95%CI: 1.005–1.399, $P=0.043$), thus reinforcing the robustness of the findings. However, results from other methods, such as MR-Egger and the weighted plurality method, did not reach statistical significance, indicating some variability across different statistical approaches, but these findings do not undermine the significance of the IVW-derived results in the primary analysis. No significant horizontal pleiotropy or potential bias was detected through various sensitivity analyses, including Egger's intercept, the leave-one-out method, and the funnel plot analysis, ensuring the robustness and reliability of the results. Although Cochran's Q test ($Q=13.045$, $P=0.042$) indicated some heterogeneity between colorectal cancer and the instrumental variables, the heterogeneity observed did not compromise the reliability of the findings due to the use of the IVW random effects model. Overall, the results of this study provide critical genetic insights for the prevention and surveillance of gastric cancer development in colorectal cancer patients.

4.2. Comparison with existing studies

This study provides the first direct genetic evidence of a potential causal association between colorectal and gastric cancers using Mendelian randomization, marking a

significant departure from previous findings that primarily relied on observational studies. Most prior research has suggested an epidemiologic link between colorectal cancer and gastric cancer, typically through case-control or cohort studies. For instance, several cohort studies have observed an increased risk of gastric cancer in patients with colorectal cancer [16,17]. However, these observational studies are heavily influenced by confounding factors, such as dietary habits and environmental exposures, which may compromise the accuracy of the findings and hinder definitive conclusions on causal relationships. In contrast, the Mendelian randomization method, which uses genetic variation as an instrumental variable, can effectively mitigate confounding in traditional observational studies and offers greater potential for robust causal inference [18]. The results of this study, validated through both IVW and weighted median methods, support a positive genetic association between colorectal and gastric cancers, thereby offering novel clinical insights into the shared mechanisms underlying the co-occurrence of these cancers. Moreover, prior genetic epidemiological studies have largely overlooked the genetic relationship between gastric and colorectal cancers, highlighting the novel and distinctive contributions of this study, which opens a new direction for further exploration of the genetic basis of these two malignancies.

4.3. Exploration of potential biological mechanisms

Mendelian randomization analysis uncovered a genetic link between colorectal and gastric cancers, implying that both cancers may share a common biological pathway. First, the shared role of genetic variants in colorectal and gastric cancers warrants further in-depth investigation. For instance, significantly associated SNPs identified in this study, such as rs11213813 and rs7226855, have already been validated in colorectal cancer research [19]. These SNPs might influence the risk of both cancers through the modulation of inflammatory responses, DNA repair mechanisms, or cell proliferation signaling pathways. These mechanisms are aligned with common molecular features of colorectal and gastric cancers, such as the RAS-RAF-MEK-ERK pathway and the PI3K-AKT pathway, indicating their pivotal roles in the pathogenesis of both malignancies [20]. In addition, inflammation and the tumor microenvironment might serve as a shared foundation for the development of both colorectal and gastric cancers. Chronic inflammation has been strongly associated with the development of both gastric and colorectal cancers [21]. Inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor (TNF), and nuclear factor- κ B (NF- κ B) play critical roles in shaping the tumor microenvironment of both cancers [20,21]. This suggests that chronic inflammation, in combination with genetic and environmental factors, might promote the development of colorectal and gastric cancers via genetically regulated pathways. Finally, the role of the microbiota in the pathogenesis of both cancers has garnered considerable attention. *Helicobacter pylori* infection is a known causative factor for gastric cancer, while dysbiosis of the intestinal flora has been strongly linked to colorectal cancer [22]. Future studies should investigate the interplay between the microbiota and specific genetic variants to elucidate their synergistic mechanisms in the pathogenesis of colorectal and gastric cancers.

4.4. Clinical and Public Health Implications

The findings of this study have significant implications for clinical practice and public health policy. First, given the genetic link between colorectal cancer and

gastric cancer, patients with colorectal cancer may have an elevated risk of developing gastric cancer. Therefore, for patients diagnosed with colorectal cancer, especially those at high risk of carrying specific genetic variants, enhanced early screening and surveillance for gastric cancer is recommended during follow-up. This may involve incorporating regular endoscopy or imaging screenings to improve early detection rates and thereby enhance patient prognosis [23]. Second, the findings also underscore the need to thoroughly account for the risk of second primary tumors in cancer patients undergoing multidisciplinary comprehensive therapy (MDT). Patients treated for colorectal cancer may necessitate not only traditional surgery, chemotherapy, and radiotherapy but also personalized preventive strategies tailored to their genetic risk, such as early gastric cancer screening and close follow-up [22]. This opens a novel avenue for precision treatment and long-term management of colorectal cancer patients. From a public health perspective, the results of this study suggest that genetic testing could play a pivotal role in cancer prevention. For individuals with high-risk genetic variants for colorectal cancer, early screening for gastric cancer should be considered as a preventive measure against second primary tumors. In the future, precision medicine interventions based on genetic information could help alleviate the overall cancer burden and contribute to the optimization of cancer prevention and management strategies [24].

4.5. Research limitations

Although this study offered valuable insights into the causal relationship between colorectal and gastric cancers through Mendelian randomization analysis, several limitations remain. First, the study data were primarily derived from genome-wide association studies (GWAS) in European populations; therefore, the generalizability of the results across different racial groups may be limited. Variations in genetic background and cancer incidence across racial groups indicate that future studies should include multiracial cohorts, particularly East Asian populations, given the high incidence of gastric and colorectal cancers in these populations [25]. Second, although we applied stringent screening criteria for single nucleotide polymorphisms (SNPs) to ensure the strength of the instrumental variables, undetected weak instruments may still exist, which could impact the statistical power of the study. Although multiple approaches, including MR-Egger and weighted median methods, were employed to assess the robustness of the instrumental variables, the possibility of minor bias remains. Thus, further refinement of instrumental variable selection criteria is needed [26]. In addition, the Mendelian randomization approach assumes that causality between exposure and outcome is mediated solely by SNPs, but this assumption may not hold entirely in complex multifactorial diseases. There may be interactions between genetic variants and other unconsidered biological factors, potentially complicating causal inference. Therefore, future studies should combine functional genomics and systems biology approaches to elucidate the specific mechanisms by which genetic variation influences cancer co-morbidities. Finally, although this study excluded major horizontal pleiotropy using sensitivity analyses such as Egger's intercept and the leave-one-out method, horizontal pleiotropy may still subtly influence the results due to the complex etiology of gastric and colorectal cancers [27].

4.6. Directions for future research

This study revealed the genetic association between colorectal and gastric cancers, yet many questions remain unanswered, offering multiple avenues for future research.

Although this study identified several key SNPs associated with colorectal and gastric cancers based on large-scale GWAS data, future research should integrate functional genomics approaches to explore the specific roles of these SNPs at the cellular and molecular levels. Investigating how these genetic variants contribute to tumorigenesis through CRISPR/Cas9 gene editing technology or transgenic animal models will enhance our understanding of their underlying molecular mechanisms [21]. Second, the relationship between the microbiota and cancer has garnered increasing attention. Both colorectal and gastric cancers may be influenced by intestinal and gastric microbes, and future studies should further investigate the role of the microbiota in mediating the link between genetic variation and cancer. In particular, the link between *Helicobacter pylori* infection and gastric cancer, and intestinal dysbiosis and colorectal cancer, indicates that microorganisms may modulate genetic variation and host immune responses to influence cancer development [28]. In addition, this study relied on GWAS data from European populations, highlighting the need to expand sample diversity in future studies, particularly by conducting similar research in high-prevalence regions such as Asia and Africa. This would help validate genetic differences across populations and their impact on colorectal and gastric cancers. Cross-ethnic studies will generate more generalizable evidence for the development of cancer prevention and treatment strategies on a global scale.

5. Conclusions

In this study, a potential causal relationship between colorectal and gastric cancers was identified at the genetic level for the first time using the Mendelian randomization (MR) method. This finding not only provides new clues to the mechanisms of comorbidity between these two cancers, but also offers significant insights for clinical practice. The findings suggest that patients with colorectal cancer may face a higher risk of gastric cancer, especially individuals who carry specific high-risk genetic variants. This indicates that clinicians should consider the prevention of second primary cancers, particularly early screening for gastric cancer, in the treatment and follow-up of colorectal cancer patients. The clinical translational potential of this study lies in the future use of genetic information to personalize cancer prevention and management strategies. Identifying high-risk populations through genetic testing could lead to more targeted screening and treatment programs. For example, for colorectal cancer patients with high-risk genetic markers, regular post-treatment screening for gastric cancer is recommended for early detection and intervention. This personalized screening strategy based on genetic information is expected not only to improve patient survival but also to alleviate the public health burden associated with cancer. Additionally, the results of this study provide new directions for future drug development. Given that genetic variants may play a common role in colorectal and gastric cancers, drugs targeting these genetic pathways or preventive interventions, such as immunotherapy or anti-inflammatory drugs, may offer more effective therapeutic options for patients.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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