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ORIGINAL RESEARCH

Differential Causal Associations of Chronic Gastritis and Ulcerative Colitis with Melanoma Risk: A Mendelian Randomization Study Using Large-Sample GWAS Data

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Purpose: Chronic inflammatory diseases are thought to influence cancer development through systemic inflammation and immune dysregulation. However, the causal relationship between chronic gastrointestinal inflammation and cutaneous melanoma remains unclear. This study employed Mendelian randomization (MR) to investigate the potential causal link between chronic gastrointestinal inflammatory diseases and melanoma risk.

Patients and Methods: Genetic variants associated with chronic gastrointestinal inflammation were derived from large-scale genome-wide association studies (GWAS) on autoimmune hepatitis, chronic gastritis, chronic hepatitis B and C infections, chronic pancreatitis, Crohn's disease, gastroesophageal reflux disease, and ulcerative colitis. Melanoma GWAS data served as the outcome dataset. A two-sample MR analysis was conducted to assess causal relationships, with inverse variance weighting (IVW) as the primary method. Sensitivity analyses, including MR-Egger, MR PRESSO, and Cochran's Q test, were also performed.

Results: The MR analysis revealed a significant inverse causal relationship between chronic gastritis and melanoma risk ($p = 0.023$, OR = 0.630, 95% CI = 0.422–0.939). In contrast, a positive causal association was found for ulcerative colitis, with the IVW method showing a significant increase in melanoma risk ($p = 0.014$, OR = 1.130, 95% CI = 1.025–1.246). No significant causal relationships were observed for other inflammatory diseases, including autoimmune hepatitis, chronic hepatitis B/C, chronic pancreatitis, Crohn's disease, and gastroesophageal reflux disease (all $p > 0.05$). Sensitivity analyses confirmed the robustness of these findings. Cochran's Q test indicated no significant heterogeneity among genetic instruments for chronic gastritis or ulcerative colitis. The MR-Egger intercept test showed no evidence of horizontal pleiotropy, and the MR-PRESSO method identified no outlier SNPs. Leave-one-out analysis further demonstrated that no single SNP disproportionately influenced the results.

Conclusion: This study provides evidence of an inverse causal relationship between chronic gastritis and melanoma risk. In contrast, ulcerative colitis was found to have a positive causal effect on melanoma susceptibility. These findings highlight the distinct roles that gastrointestinal inflammation may play in the pathogenesis of skin cancer, potentially mediated by divergent immune and inflammatory mechanisms.

Keywords: Mendelian randomization, melanoma, chronic gastritis, ulcerative colitis, genetic variants

Introduction

Melanoma is a highly invasive malignant tumor that originates from the malignant transformation of melanocytes, with its incidence steadily increasing in recent years. Data show that the global number of melanoma cases rose from 230,000

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in 2012 to 331,647 in 2022.[1] Among the various subtypes of melanoma, cutaneous melanoma is the most common, accounting for over 90% of all melanoma cases.[2] Although the primary risk factors for cutaneous melanoma, such as ultraviolet radiation, sunburn history, genetic pre-disposition, and skin pigmentation, are well-established, modifiable risk factors have not been sufficiently explore.[3–7] Given the significant burden of this disease, further research should focus on potential modifiable risk factors to inform preventive and therapeutic strategies.

Chronic inflammation is widely recognized as a core feature of cancer initiation and progression,[8,9] with increasing evidence linking chronic inflammation to the development of various types of cancer. As the largest immune organ in the body, the gastrointestinal tract is a common site for inflammatory diseases. These conditions not only lead to localized diseases such as gastritis and colitis, but they may also trigger systemic inflammatory responses, impairing normal immune surveillance and promoting cancer progression. Epidemiological studies have shown a strong correlation between chronic gastrointestinal inflammatory diseases—including chronic gastritis, inflammatory bowel disease (IBD), chronic pancreatitis, and hepatitis—and the incidence of gastrointestinal malignancies. Furthermore, these conditions may also elevate the risk of extra-intestinal cancers, including skin melanoma and non-melanoma skin cancer (NMSC).[10]

As a critical component of the immune system, the gastrointestinal tract forms a unique connection with the skin immune system through the "gut-skin axis", creating an inter-organ immune signaling network. Immune cells (such as Th1/Th17 cells) and cytokines (like IL-17 and IFN-γ) produced by the intestinal mucosal immune system can influence the skin via the circulatory system,[11] while gut microbiota metabolites (such as short-chain fatty acids) can systemically regulate immune surveillance. Dysbiosis has been observed in various skin diseases, including psoriasis, atopic dermatitis, and systemic lupus erythematosus.[12,13] This distinctive connection suggests that chronic gastrointestinal inflammation may influence the skin tumor microenvironment through cross-organ immune signaling.

However, the relationship between gastrointestinal inflammation and skin melanoma remains unclear. Traditional observational studies are often limited by confounding factors and reverse causality, which can affect the reliability of the results. Furthermore, considerable discrepancies exist between different studies. For instance, some research suggests that the increased melanoma risk in patients with inflammatory bowel disease (IBD) may be more closely associated with the use of immunosuppressive therapies (such as thiopurines and anti-TNF drugs) rather than direct gastrointestinal inflammation.[14] Therefore, more rigorous studies are needed to clarify the potential link between gastrointestinal inflammation and melanoma, addressing this knowledge gap.

Mendelian Randomization (MR) is a genetic epidemiological method that uses genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and out-comes.[15] Compared to traditional observational studies, MR analysis effectively minimizes the influence of confounding factors and reverse causality, thereby enhancing the reliability of research findings.[16] This study uses the MR approach to investigate the causal effects of chronic gastrointestinal inflammatory diseases on the risk of cutaneous melanoma. Specifically, we examine chronic gastritis, inflammatory bowel diseases (such as ulcerative colitis and Crohn's disease), chronic pancreatitis, hepatitis (including chronic hepatitis B and C), gastroesophageal reflux disease, and autoimmune hepatitis as exposure variables, and systematically analyze their potential impacts on cutaneous melanoma risk. Through a series of rigorous sensitivity analyses and statistical methods, this study aims to provide new insights into the potential etiological mechanisms of cutaneous melanoma and offer scientific evidence for the development of preventive strategies.

Materials and Methods

Study Design

To explore the potential causal relationship between the digestive system and cutaneous melanoma, this study employed a two-sample Mendelian Randomization (MR) analysis. MR utilizes single nucleotide polymorphisms (SNPs) as instrumental variables to assess the causal relationship between exposure factors and outcomes. By leveraging genetic variations as naturally occurring instrumental variables, MR effectively minimizes confounding factors commonly encountered in observational studies, providing more robust evidence for causal inference.

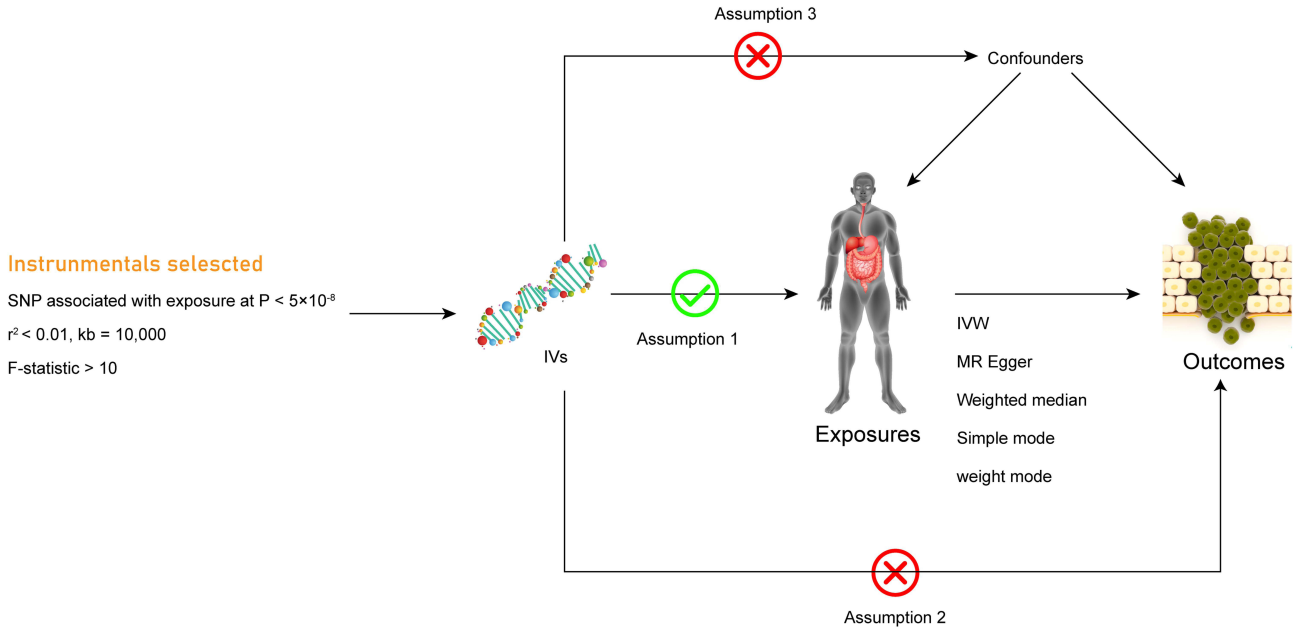


Figure 1 Flowchart illustrating the overall study design.

MR analysis is based on three key assumptions: (1) the relevance assumption, which requires that genetic instrumental variables (SNPs) are significantly associated with the exposure; (2) the exclusion restriction assumption, which posits that genetic instruments influence the outcome only through the exposure, without direct effects; and (3) the independence assumption, which states that genetic instruments must not be associated with confounders affecting either the exposure or the outcome. To investigate the causal relationship between inflammatory digestive diseases and melanoma, this study applied a two-sample MR analysis based on genome-wide association study (GWAS) data. A schematic diagram of the hypothesized causal pathway is presented in Figure 1.

Data Sources and Selection of Genetic Variants

The GWAS data for both exposure and outcome variables were obtained from publicly available databases. Data for inflammatory digestive diseases were sourced from the EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/) and included conditions such as autoimmune hepatitis, chronic gastritis, chronic hepatitis B infection, chronic hepatitis C infection, chronic pancreatitis, Crohn's disease, gastroesophageal reflux disease, and ulcerative colitis:

Autoimmune hepatitis (GWAS ID: ebi-a-GCST90018785): Includes 24,198,482 SNPs from 485,234 Europeans.

Chronic gastritis (GWAS ID: ebi-a-GCST90018825): Includes 24,189,505 SNPs from 445,096 Europeans.

Chronic hepatitis B infection (GWAS ID: ebi-a-GCST90018804): Includes 19,079,722 SNPs from 351,885 Europeans.

Chronic hepatitis C infection (GWAS ID: ebi-a-GCST90018805): Includes 19,074 546 SNPs from 352,013 Europeans.

Chronic pancreatitis (GWAS ID: ebi-a-GCST9001882): Includes 24,195,431 SNPs from 477,528 Europeans.

Crohn's disease (GWAS ID: finn-b-K11_KELACROHN): Includes 16,380,466 SNPs from 217.852 Europeans.

Gastroesophageal reflux disease (GWAS ID: ebi-a-GCST90018848): Includes 24,173,002 SNPs from 467,253 Europeans.

Ulcerative colitis (GWAS ID: ebi-a-GCST90018933): Includes 24,187,301 SNPs from 417,932 Europeans.

The outcome data for cutaneous melanoma were retrieved from the FinnGen study (https://www.finngen.fi/en), with GWAS ID finn-b-C3_MELANOMA_SKIN_EXALLC, comprising 16,380,303 SNPs from 174,104 Europeans. To minimize bias from population stratification, all datasets used in this study were derived from populations of European ancestry. These datasets come from independent cohorts with minimal sample overlap, further reducing the

potential impact of confounding factors and selection bias. However, due to the limitations of currently available high-quality, publicly accessible GWAS data, this study does not include populations of Asian, African, or other ancestries. This limitation may affect the generalizability of the findings to non-European populations. This study is exempt based on national legislation guidelines, such as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

Selection of Genetic Instruments

To ensure the validity and robustness of the genetic instruments, a series of stringent selection criteria were applied. First, a significance threshold of $p < 5\times10^{-6}$ was used to select SNPs strongly associated with the exposure. To minimize the effects of linkage disequilibrium (LD), SNPs were excluded if they had $R^2 \geq 0.01$ or were located within 10,000 kb of each other. Furthermore, the F-statistic for each SNP was calculated, and weak instruments ($F < 10$) were excluded to reduce the potential bias of weak instrument bias in causal inference.[17]

To ensure that the genetic instruments affect the outcome solely through the exposure, we used the PhenoScanner database to filter out SNPs directly associated with melanoma.[18] SNPs associated with potential confounders (such as socioeconomic status and lifestyle factors) were also excluded. Additionally, to maintain the robustness of MR analysis, at least two SNPs were included for each exposure variable.

MR Analysis Methods

Exposure and outcome data were harmonized to ensure alignment of effect alleles, and palindromic SNPs were excluded to avoid potential bias. The primary analytical method used was inverse variance weighted (IVW) regression, which assumes that all genetic instruments are valid and provides the most efficient causal estimates when the assumptions hold. To test the robustness of the results, supplementary analyses were conducted, including MR-Egger regression to detect and adjust for horizontal pleiotropy, the weighted median method for reliable causal estimates when up to 50% of instruments are invalid, and mode-based methods for additional validation.[19–21] Causal effects are reported as odds ratios (ORs) with 95% confidence intervals (CIs), where an $OR > 1$ indicates the exposure is a risk factor, and an $OR < 1$ suggests a protective effect.

Sensitivity Analyses

To ensure the reliability of the causal inferences, a series of sensitivity analyses were conducted. Heterogeneity was assessed using Cochran's Q test, with a p-value < 0.05 indicating significant heterogeneity among the genetic instruments.

Horizontal pleiotropy was evaluated using the MR-Egger intercept test, where a p-value < 0.05 suggests significant pleiotropy. Additionally, the MR-PRESSO method was used to detect and correct for outliers in the genetic instruments, which may arise due to horizontal pleiotropy.

A Leave-One-Out analysis was conducted by systematically removing one SNP at a time and recalculating the causal effect with the remaining instruments. This approach helps to evaluate the influence of individual SNPs on the overall results and further assesses the robustness of the causal estimates. Finally, Funnel plots were generated to visualize potential pleiotropy or bias. These analyses confirmed the reliability and robustness of the MR finding.[22,23]

Statistical Analysis

All statistical analyses were performed using R software (version 4.2.1) with the following R packages: TwoSampleMR (version 0.5.9), MRPRESSO (version 1.0), and ggplot2 (version 3.4.4). A significance level of $P < 0.05$ was used for all analyses.

Results

Selection of Genetic Instruments

To assess the causal relationship between inflammatory diseases of the digestive system and skin melanoma, this study first identified genetic instruments significantly associated with the exposure. SNPs significantly associated with chronic

Table 1 Selection of Instrumental Variables

Outcome	Exposure	id.exposure	SNP (Count)	F-Value Range (Min-Max)
Malignant melanoma of skin (all cancers excluded) (ID: finn-b-C3_MELANOMA_SKIN_EXALLC)	Autoimmune hepatitis	ebi-a-GCST90018785	13	21.39–56.32
	Chronic gastritis	ebi-a-GCST90018825	21	20.89–26.76
	Chronic hepatitis B infection	ebi-a-GCST90018804	19	20.95–192.28
	Chronic hepatitis C infection	ebi-a-GCST90018805	19	21.01–92.99
	Chronic pancreatitis	ebi-a-GCST90018821	21	20.83–32.71
	Crohn's disease	ebi-a-GCST90020071	14	21.07–26.11
	Gastroesophageal reflux disease	ebi-a-GCST90018848	33	20.86–33.60
	Ulcerative colitis	ebi-a-GCST90020072	9	20.92–30.76

Notes: Table 1 shows the outcome (malignant melanoma of skin), exposures (eg, autoimmune hepatitis), their identifiers, SNP counts, and F-value ranges indicating association significance.

inflammatory diseases, including chronic gastritis, autoimmune hepatitis, ulcerative colitis, chronic pancreatitis, chronic hepatitis C, and chronic hepatitis B, were identified as potential genetic instruments.

These selected SNPs exhibited F-statistics ranging from 20.83 to 192.28, well above the threshold for weak instruments ($F > 10$), thereby confirming their robustness and satisfying the relevance assumption for MR analysis. Table 1 provides a detailed summary of the SNP counts and F-value ranges for each exposure variable (Table 1).

MR Analysis Results

The IVW method was used as the primary approach to investigate the causal effects of digestive system inflammatory diseases on skin melanoma risk. The results revealed a statistically significant negative causal relationship between chronic gastritis and skin melanoma ($p = 0.023$, OR = 0.630, 95% CI = 0.422–0.939), suggesting that chronic gastritis may slightly reduce the risk of skin melanoma. Supplementary analyses, including MR-Egger regression ($p = 0.031$, OR = 0.385, 95% CI = 0.173–0.857), Weighted Median ($p = 0.046$, OR = 0.575, 95% CI = 0.334–0.991), Simple Mode ($p = 0.277$, OR = 0.623, 95% CI = 0.272–1.428) and Weighted Mode ($p = 0.068$, OR = 0.578, 95% CI = 0.331–1.007), provided consistent results, supporting the robustness of this finding (Figure 2A and B).

For ulcerative colitis, the IVW method identified a significant positive causal association with melanoma risk ($p = 0.014$, OR = 1.130, 95% CI = 1.025–1.246), indicating a potential increase in melanoma susceptibility. While supplementary analyses including MR-Egger regression ($p = 0.473$, OR = 1.130, 95% CI = 0.838–1.479), simple mode ($p = 0.198$, OR = 1.157, 95% CI = 0.936–1.429), and weighted mode ($p = 0.158$, OR = 1.178, 95% CI = 0.950–1.460) did not reach statistical significance, all methods showed consistent directional effects with the primary IVW result. Notably, the weighted median method trended toward significance ($p = 0.061$, OR = 1.133, 95% CI = 0.994–1.291), further supporting the biological plausibility of the association. The consistency in effect direction across multiple MR approaches, despite variability in statistical significance, underscores the robustness of the positive causal relationship observed in the IVW analysis (Figure 3A and B).

For other conditions, including autoimmune hepatitis, chronic hepatitis B, chronic hepatitis C, chronic pancreatitis, Crohn's disease, and gastroesophageal reflux disease (GERD), no statistically significant causal relationships were observed with melanoma risk (all $p > 0.05$). For example: Autoimmune hepatitis: IVW ($p = 0.345$, OR = 0.872, 95% CI = 0.656–1.158); Chronic hepatitis B: IVW ($p = 0.797$, OR = 0.975, 95% CI = 0.804–1.182); Chronic pancreatitis: IVW ($p = 0.736$, OR = 1.066, 95% CI = 0.736–1.545). These null findings were consistent across supplementary analyses, such as MR-Egger, Weighted Median, Simple Mode, and Weighted Mode (Figure 4).

Sensitivity Analysis Results

To ensure the robustness of the MR findings, sensitivity analyses were performed. Cochran's Q test revealed no significant heterogeneity among genetic instruments for either chronic gastritis ($Q = 19$, $p = 0.89$) or ulcerative colitis ($Q = 7.30$, $p = 0.89$). The MR-Egger intercept test detected no evidence of significant pleiotropy for chronic gastritis

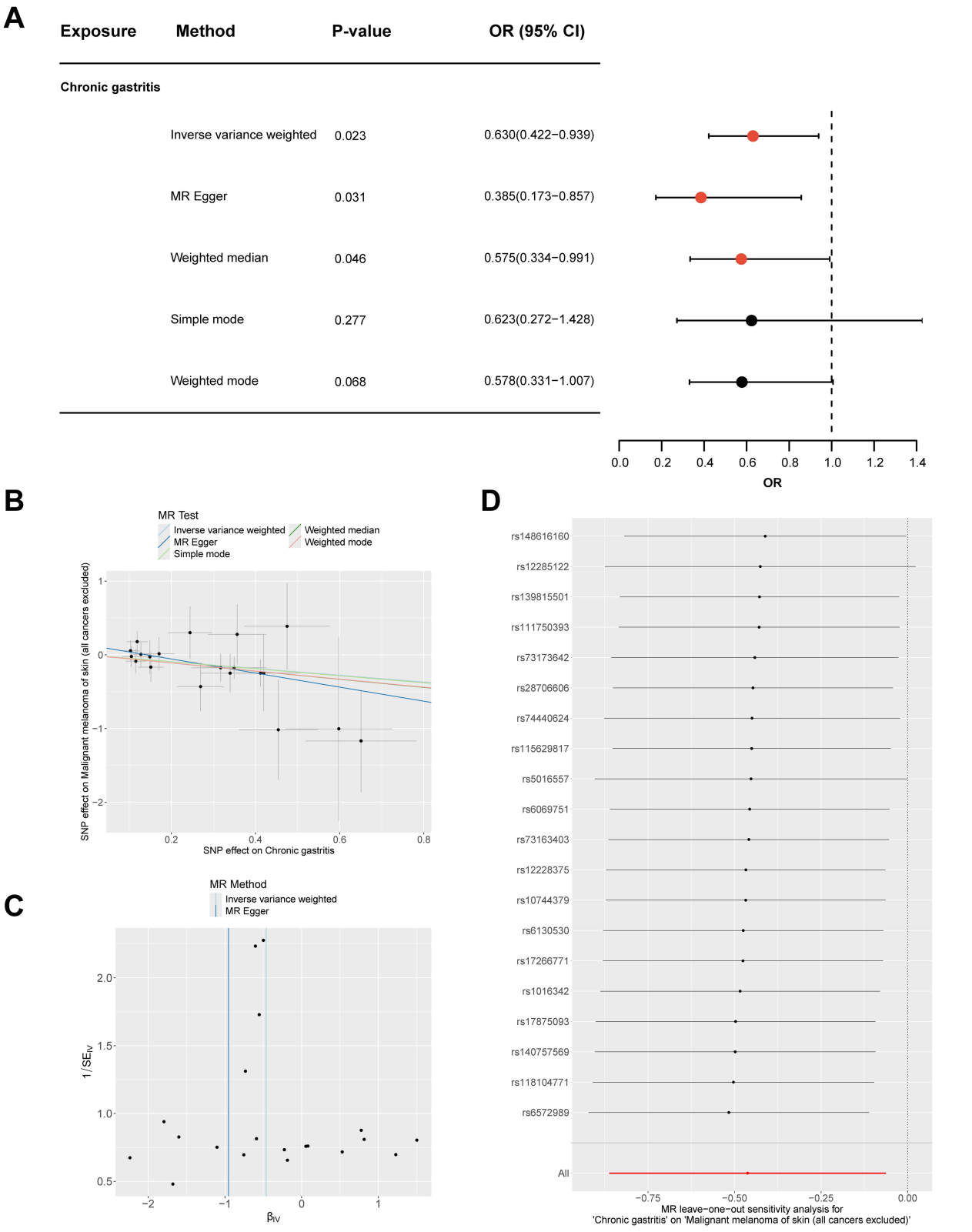
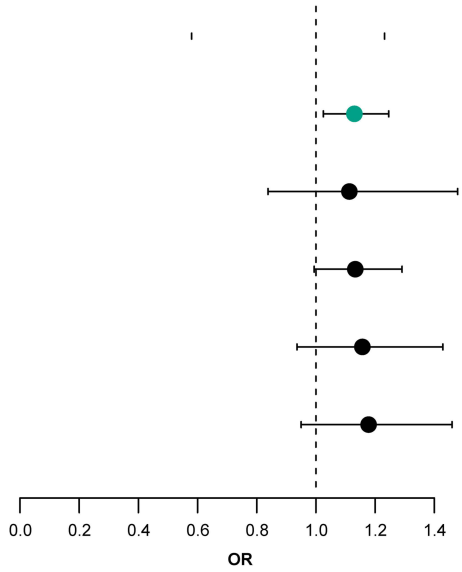


Figure 2 Causal relationship between chronic gastritis and cutaneous malignant melanoma (excluding all other cancers) analyzed using various Mendelian Randomization (MR) methods. (**A**) Forest plot presenting odds ratios (ORs) and confidence intervals (CIs) derived from different MR methods. (**B**) Scatter plot showing the effects of single nucleotide polymorphisms (SNPs) on chronic gastritis and melanoma under various MR methods. (**C**) Funnel plot assessing heterogeneity of SNP effects, indicating consistency among genetic instruments. (**D**) Leave-One-Out analysis revealing the stability of causal estimates by sequentially excluding individual SNPs.

A

Exposure	Method	P-value	OR (95% CI)
Ulcerative colitis			
	Inverse variance weighted	0.014	1.130(1.025−1.246)
	MR Egger	0.473	1.113(0.838−1.479)
	Weighted median	0.061	1.133(0.994−1.291)
	Simple mode	0.198	1.157(0.936−1.429)
	Weighted mode	0.158	1.178(0.950−1.460)



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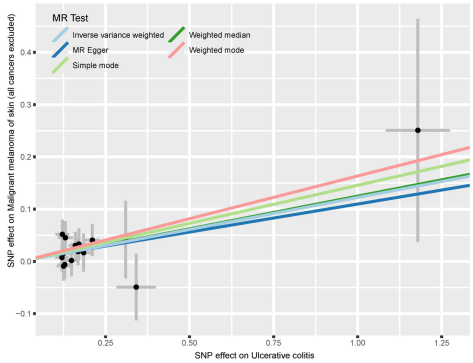

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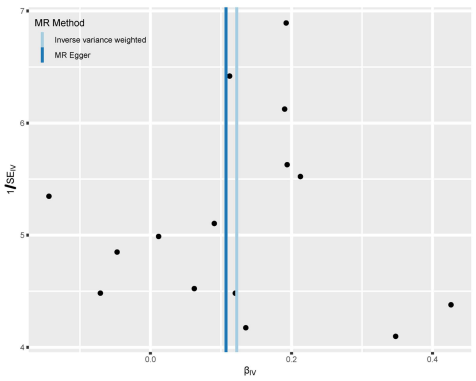

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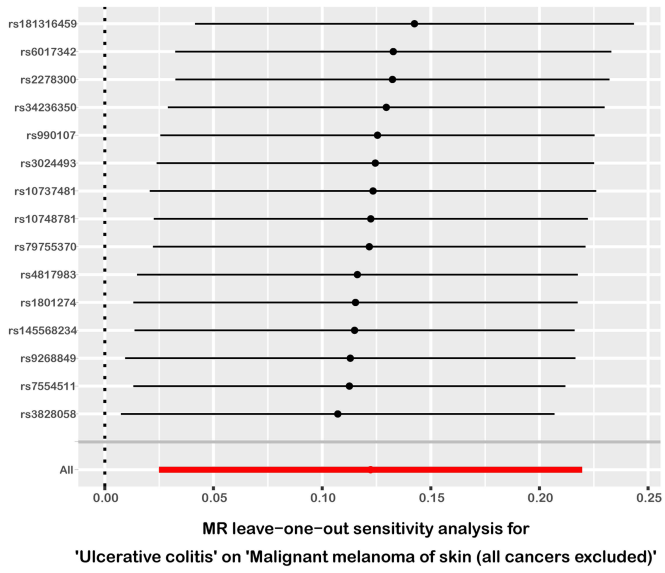

Figure 3 Causal relationship between ulcerative colitis and cutaneous malignant melanoma (excluding all other cancers) analyzed using various MR methods. (**A**) Forest plot summarizing ORs and CIs obtained through different MR methods. (**B**) Scatter plot comparing SNP effects on ulcerative colitis and melanoma. (**C**) Funnel plot evaluating heterogeneity among SNPs, supporting the robustness of the results. (**D**) Leave-One-Out analysis highlighting the influence of individual SNPs on overall causal estimates and confirming the stability of the results.

(Egger intercept = 0.13, p = 0.18) or ulcerative colitis (Egger intercept = 0.0026, p = 0.91), indicating that the genetic instruments influenced the outcome primarily through the exposure pathways. The MR-PRESSO method identified no significant outliers in the genetic instruments, further supporting the validity of the results (Table 2).

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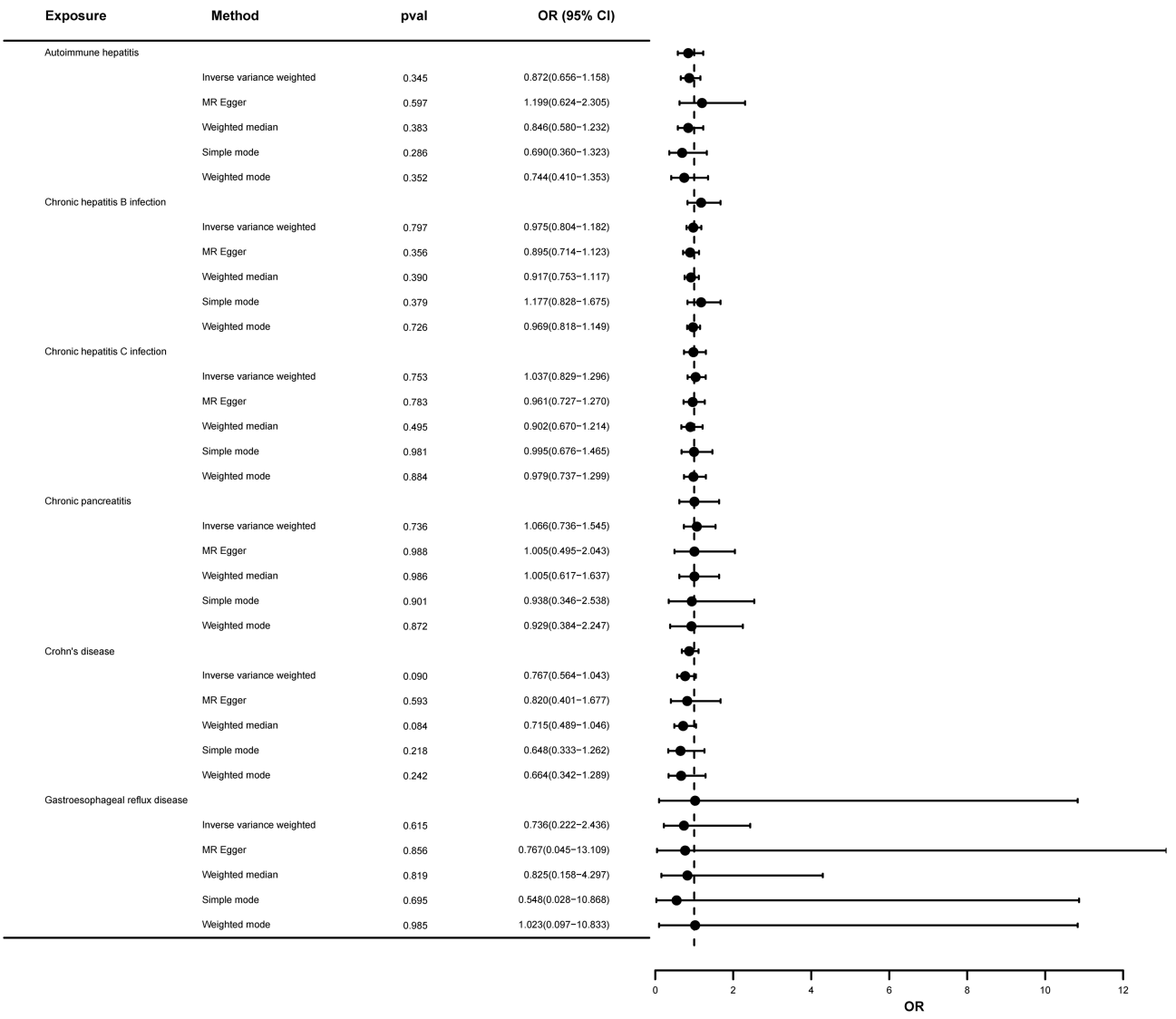

Figure 4 Causal estimates of various inflammatory digestive diseases and cutaneous malignant melanoma (excluding all other cancers). The forest plot presents ORs, CIs, and p-values for each exposure variable obtained through different MR methods. Each estimate demonstrates the robustness and consistency of the null hypothesis results across various methods.

Additionally, Leave-One-Out analysis confirmed that no single SNP disproportionately influenced the causal estimates, underscoring the robustness of the findings. Funnel plots visualized the alignment of SNP effects, demonstrating no substantial bias or pleiotropy in the data (Figure 2C and D; Figure 3C and D).

Discussion

This study employed Mendelian Randomization (MR) to explore the causal relationship between chronic gastrointestinal inflammatory diseases and the risk of skin melanoma. The results indicate a significant negative causal association between chronic gastritis and skin melanoma. In contrast, ulcerative colitis (UC) showed a trend towards increased risk. No significant causal relationship was found between the risk of skin melanoma and other chronic inflammatory diseases, including autoimmune hepatitis, chronic hepatitis B and C, Crohn's disease (CD), chronic pancreatitis, and gastroesophageal reflux disease (GERD).

Our findings suggest that chronic gastritis is inversely associated with the risk of skin melanoma, implying a potential protective role of chronic gastritis. This phenomenon may be linked to systemic immune modulation induced by chronic gastritis. The primary causative agent of chronic gastritis, Helicobacter pylori (H. pylori) infection, may play a crucial

Table 2 Assessment of Mendelian Randomization Robustness

Exposure	Pleiotropy				Heterogeneity	
	MR Egger		MR-PRESSO		Cochran Q	
	Egger_intercept	P	RSSobs	P	Q	P
Chronic gastritis	0.13	0.18	12.51	0.92	19	0.89
Ulcerative colitis	−0.34	0.16	9.59	0.51	7.23	0.51

Notes: Table 2 presents pleiotropy (MR Egger, MR-PRESSO) and heterogeneity (Cochran Q) results for exposures like chronic gastritis and ulcerative colitis. P-values help assess significance of effects and heterogeneity.

Abbreviations: MR, Mendelian randomization; GWAS, genome-wide association studies; IVW, inverse variance weighting; IBD, inflammatory bowel disease; NMSC, non-melanoma skin cancer; TNF, tumor necrosis factor; IVs, instrumental variables; SNPs, single nucleotide polymorphisms; LD, linkage disequilibrium; Ors, odds ratios; Cis, confidence intervals; GERD, gastroesophageal reflux disease.

role by persistently stimulating the host immune system.[24–26] Although H. pylori has evolved various mechanisms to evade immune responses and downregulate host immunity, its infection still induces significant immune activation. For instance, H. pylori infection triggers cytokine signaling in gastric epithelial cells, attracting immune cells such as neutrophils, macrophages, and lymphocytes to infiltrate the gastric mucosa. Immune responses are stronger when infected with CagA-positive strains.[27,28] This initial immune activation, localized in the stomach, may extend systemically, enhancing immune surveillance and potentially aiding in the elimination of malignant cells in distant tissues, including melanoma cells in the skin. Additionally, H. pylori infection activates antigen-presenting cells, such as dendritic cells and macrophages, to enhance adaptive immunity, leading to an upregulation of Th1 responses. Increased interferon-γ (IFN-γ) secretion from Th1 cells and the promotion of specific antibody production by B cells (eg, IgG and IgA) may neutralize pathogens or inhibit their attachment.[29]

Importantly, both animal and human studies have provided preliminary evidence for the immune-modulating effects of H. pylori on systemic and skin immunity. For example, in a mouse model of atopic dermatitis (AD) induced by 2,4-dinitrochlorobenzene (DNCB), H. pylori infection significantly reduced serum Th2 cytokines (such as IL-4 and IL-31) by inhibiting the JAK-STAT signaling pathway, while upregulating the expression of epidermal barrier proteins (keratin and filaggrin), alleviating skin inflammation and restoring barrier function.[30] While this study focused on allergic skin diseases, its findings suggest that the suppression of Th2 immune responses may disrupt the immune escape microenvironment essential for melanoma survival, while enhanced epidermal barrier function may reduce carcinogen penetration and improve local immune surveillance. Furthermore, H. pylori-mediated inhibition of STAT1/STAT3 phosphorylation could directly counteract melanoma cell proliferation and angiogenesis. Human studies also support the link between H. pylori infection and skin immunity. A meta-analysis of 2427 individuals revealed a significantly higher odds ratio for H. pylori infection in patients with psoriasis (a Th1/Th17-driven inflammatory skin disease), indirectly reflecting its role in activating the skin immune system.[31] A prospective study further evaluated the effects of H. pylori eradication therapy on patients with various chronic skin diseases. The study found that H. pylori eradication was effective in treating chronic urticaria, chronic pruritus, and chronic polymorphic eruptions, and was closely related to serum IgE levels and immune responses to specific H. pylori antigens.[32] These results further support the potential link between H. pylori infection and skin immunity, providing evidence for clinical strategies targeting H. pylori infection.

The effects of H. pylori infection on cancer are complex and context-dependent, with strain type and its impact on gastric acid secretion being key factors. For example, CagA-positive strains may reduce gastric acid secretion, potentially offering protection against pancreatic cancer, while CagA-negative strains, by increasing gastric acid secretion, may promote pancreatic cancer development.[33] Moreover, in esophageal adenocarcinoma, H. pylori-induced hypochlorhydria may decrease the incidence of gastroesophageal reflux disease (GERD), indirectly lowering the risk of esophageal adenocarcinoma.[34] However, in contrast to these protective effects, H. pylori infection is a well-established risk factor for gastric cancer. Therefore, careful interpretation of its role in different cancers is essential.[35]

Although our study suggests a protective effect of chronic gastritis against melanoma, the potential for increased gastric cancer risk must also be considered. This dual effect highlights the complex mechanisms of chronic inflammation in various types of cancer: on the one hand, chronic inflammation may inhibit the development of some cancers by enhancing immune surveillance; on the other hand, prolonged inflammation may increase the risk of local carcinogenesis. Thus, further investigation into the mechanisms by which chronic gastritis influences cancer development is crucial. This research will not only help to understand the dual role of chronic inflammation but also provide scientific evidence for personalized cancer prevention and treatment strategies.

Most observational studies indicate that patients with inflammatory bowel disease (IBD), particularly those receiving immunosuppressive therapies (such as thiopurines, anti-TNF drugs), have a significantly increased risk of melanoma. This theory is often attributed to "chronic inflammation or immunosuppression impairing immune surveillance.[10,36] However, patients with Crohn's disease (CD) typically use more immunosuppressive drugs (such as thiopurine, methotrexate, and anti-TNF agents), which may increase cancer risk through mechanisms like interference with nucleotide synthesis, DNA damage, or inhibition of T cell proliferation.[37,38] Traditional studies often fail to distinguish the independent effects of disease-induced inflammation versus the impact of drug metabolism on melanoma risk. Mendelian Randomization (MR) designs, by using single nucleotide polymorphisms (SNPs) associated with genetic susceptibility to disease as instrumental variables, effectively avoid these confounders. The SNPs selected in this study were directly related to genetic susceptibility to ulcerative colitis (UC), and variants related to drug metabolism genes were excluded. Additionally, since genetic variations precede disease diagnosis and drug use, MR can naturally distinguish "disease causal effects" from "treatment secondary effects". While MR designs have inherent advantages in controlling for confounding factors, it is important to note that certain genetic variants may influence both disease susceptibility and drug metabolism (ie, pleiotropy), which could lead to bias. To minimize such bias, we performed MR-Egger intercept tests ($p>0.91$), LD pruning ($R^2<0.01$), and PhenoScanner filtering to ensure that no such effects were present.

Through MR analysis, this study found that genetic susceptibility to UC significantly increased the risk of melanoma (OR=1.13, p=0.014), whereas no significant association was observed between CD and melanoma risk. This discrepancy can be explained by the heterogeneity in immune mechanisms between the two diseases. Crohn's disease is primarily driven by Th1 and Th17 immune responses,[39] with cytokines like IL-12 and IL-23 playing key roles. IFN-γ secreted by Th1 cells can enhance local anti-tumor immune surveillance, while Th17 cells release IL-17 and IL-22, which intensify intestinal inflammation but have a weaker systemic effect.[40–42] Notably, infiltrating cytotoxic T cells (Tc) and natural killer (NK) cells in the intestines of CD patients may exert anti-tumor effects by directly killing abnormal cells, potentially counteracting some of the inflammation-related cancer risks.[43]

Ulcerative colitis, on the other hand, is characterized by a dominant Th2-type immune response, with Th17 responses co-activating.[39,44] IL-13 released by Th2 cells disrupts tight junctions in the intestinal epithelium, leading to increased intestinal permeability and short-chain fatty acid deficiency, impairing regulatory T cell (Treg) function and activating the NF-κB pathway to create a systemic pro-cancer microenvironment.[45–47] Cytokines like IL-5, IL-13, and IL-17 can upregulate VEGF and PD-L1, promoting tumor angiogenesis and inhibiting T cell recognition of melanoma.[48–50] Moreover, anti-neutrophil cytoplasmic antibody (pANCA) in UC patients' sera may activate the complement system, exacerbating systemic oxidative stress and DNA damage.[51] Additionally, the risk genes for UC, such as NOD2 and IL23R, overlap with skin immune cell signaling pathways, possibly enhancing local inflammation through the "gut-skin axis" and indirectly promoting melanoma development.

In conclusion, this study used MR design to effectively eliminate the confounding effects of immunosuppressive drugs and confirmed that UC is an independent risk factor for melanoma, while no significant association was found between CD and melanoma risk. This difference may stem from the distinct immune response patterns (Th1/Th17 vs Th2/Th17), immune cell functions, the extent of inflammation, and genetic susceptibility between the two diseases. Future research should integrate single-cell sequencing and metabolomics to further investigate the dynamic interactions between immune cells and the tumor microenvironment under different inflammatory phenotypes, refining the "inflammation-immune-tumor" causal network and providing more precise prevention and treatment strategies for different patient populations.

Despite the strengths of MR design in controlling confounding bias and reverse causality, key limitations must be acknowledged. First, the population-specific nature of genetic data is a major limitation. The generalizability of these findings to non-European populations (eg, Asian, African) is inherently challenging. Cross-population genetic differences can influence causal inference through dual mechanisms: on the one hand, allele frequencies and functions of disease-related variants (eg, NOD2, HLA) may vary across populations, weakening the association between instrumental variables and exposure phenotypes, violating the MR assumption of "strong instruments";[39,52] on the other hand, genetic associations may differ significantly in allele frequencies and effect sizes across populations,[53] potentially leading to systematic overestimation or underestimation of causal effects (eg, OR=1.13) in non-European populations. Therefore, caution is required when extrapolating the findings to non-European populations, and future studies should validate these conclusions with multi-population data (eg, Japanese biobank, African Genomic Project) to assess the impact of genetic structure differences on the effectiveness of instrumental variables and correct causal effect estimates.

Second, the potential risk of horizontal pleiotropy has not been fully ruled out. Although we conducted MR-Egger intercept tests ($p>0.91$), LD pruning ($R^2<0.01$), and PhenoScanner filtering to exclude known pleiotropic variants, some genetic variations may influence outcomes indirectly through unmeasured intermediate phenotypes (eg, metabolic pathways, microbiome interactions), leading to causal inference bias. With the accumulation of full phenotype association studies (PheWAS) data, future research should further expand the dimensions of pleiotropy testing.

Finally, the molecular mechanisms behind the protective effect remain to be experimentally validated. This study proposes the hypothesis that "chronic gastritis/UC inhibits melanoma through immune surveillance", but the causal pathways (eg, Th1/Th17 cell balance, exosome-mediated inter-organ signaling) lack direct experimental evidence. For instance, whether H. pylori-induced IL-17A in the gastric mucosa can activate skin dendritic cells through the circulatory system remains to be explored using animal models (eg, IL-17A knockout mice) and single-cell sequencing technologies.

Future research should validate these findings in diverse populations and explore the molecular mechanisms linking chronic inflammation to cancer protection. Furthermore, the interactions between genetic susceptibility, environmental factors, and treatment interventions should be investigated to comprehensively understand the complex relationship between chronic inflammation and cancer. Lastly, the potential protective effects of chronic inflammation in other cancer types should be assessed to determine whether these mechanisms are universal.

Conclusion

This study provides new insights into the complex relationship between chronic inflammatory diseases of the digestive system and skin melanoma. We observed a significant negative causal association between chronic gastritis and melanoma, while ulcerative colitis exhibited a positive causal relationship. These findings further support the ongoing discussion in immunology regarding the "double-edged sword effect" of chronic inflammation in cancer development—indicating that inflammation can exert both pro- and anti-cancer effects through heterogeneous mechanisms. By applying Mendelian randomization, this study leveraged the unique design of genetic instrumental variables, effectively circumventing the confounding effects of immunosuppressive treatments (such as anti-TNF drugs and azathioprine) typically encountered in traditional observational studies. This approach successfully distinguished the independent effects of disease-driven inflammation from those of treatment interventions. The results confirm that genetic susceptibility to ulcerative colitis is a positive risk factor for melanoma, while the protective effect of chronic gastritis may be linked to Helicobacter pylori-induced systemic immune activation. This outcome not only aligns with the potential mechanism observed in traditional observational studies—that immunosuppressive treatments may increase cancer risk—but also provides genetic evidence of the direct impact of disease-associated inflammation on melanoma. It should be noted, however, that this study has certain limitations, including potential bias in generalizing the findings from the European cohort and the incomplete understanding of the molecular mechanisms underlying the association between chronic inflammation and melanoma. These aspects warrant further exploration in future research.

Disclosure

The authors declare no potential conflicts of interest in this work.

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