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Exploration of Risk Factors for Colorectal Cancer Based on Mendelian Randomization Analysis

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Abstract: ***Colorectal cancer (CRC), encompassing both colon and rectal cancers, is one of the most prevalent cancers in the digestive system. It consistently ranks among the top three cancers in terms of both incidence and mortality, representing a major public health concern. Early prevention of CRC can significantly improve patient survival rates and quality of life. Therefore, identifying its causative factors is of paramount importance. A variety of factors, including diet, lifestyle, and genetics, are closely related to the occurrence of CRC. However, traditional research methods face numerous limitations when exploring the causal relationship between potential risk factors and CRC, resulting in slow progress and unmet expectations. Mendelian Randomization (MR) is an epidemiological technique that utilizes genetic variants as instrumental variables (IVs) to determine causal links between exposures and outcomes. By applying Mendelian inheritance laws, where alleles from parents are randomly assigned to offspring, MR analysis is less affected by environmental and behavioral factors and can effectively reduce confounding biases, thus enhancing the accuracy of causal inference. MR analysis is increasingly playing an important role in identifying CRC risk factors. This article reviews the relationship between potential causative factors and the risk of CRC, as well as the possible underlying mechanisms, and discusses the implications of research in this field for the early prevention, diagnosis, and treatment of CRC.***

Keywords: Colorectal cancer, Mendelian Randomization analysis, Causative factors, Mechanism, Review.

1. Introduction

Colorectal cancer (CRC) is a leading malignant tumor worldwide, with both its incidence and mortality rates increasing each year, representing a significant public health threat. According to data from 2022, it is estimated that there are 20 million new cancer cases and nearly 9.7 million cancer-related deaths worldwide, with CRC accounting for 9.3% of new cancer cases, second only to lung cancer (12.4%) and female breast cancer (11.6%). In terms of cancer-related deaths, CRC also represents 9.3%, again only surpassed by lung cancer (18.7%). For men, CRC has become the third most common cancer and the third leading cause of cancer-related deaths. For women, CRC similarly ranks third in both new cases and cancer-related deaths [1]. The occurrence and development of CRC are closely related to the interaction between environmental and genetic factors. Early prevention is key to reducing the incidence of CRC, and identifying the causative factors of CRC is at the core of early prevention. This knowledge not only has the potential to guide preventive strategies but also plays a crucial role in improving patient prognosis [2]. However, the existing evidence regarding the causal relationship between potential causative factors and CRC risk predominantly comes from observational studies or randomized controlled trials (RCTs). Observational studies are prone to confounding biases and reverse causality, while RCTs face several limitations, including high costs, time consumption, difficulty in controlling complex interventions, and ethical concerns [3]. Therefore, both traditional research methods have certain limitations, highlighting the need for new approaches in research.

Mendelian Randomization (MR) analysis is a powerful causal inference method that has gained attention in recent years, offering a solution to the limitations of traditional research methods. It uses genetic variations, usually single nucleotide polymorphisms (SNPs), as instrumental variables (IVs), which helps reduce confounding biases and the impact of reverse causality [4]. MR's fundamental principle is that genetic variations are randomly distributed during meiosis and fertilization, which means their relationship with disease outcomes is less affected by environmental factors or reverse causality biases. [5]. MR analysis is based on three essential assumptions: (1) There is a strong association between the IV and the exposure; (2) The IV is not associated with any confounding factors between the exposure and the outcome; (3) The IV affects the outcome solely through the exposure and not through other pathways (Figure 1). During the literature search, a total of three systematic reviews were identified that reviewed the association between potential risk factors and CRC risk based on MR studies [6-8]. However, these reviews have certain limitations in scope, with the content summaries being insufficiently comprehensive. Key CRC risk factors, such as pyruvate and non-alcoholic fatty liver disease, have not been adequately addressed. Additionally, some of the data sources are relatively outdated and fail to incorporate the latest research advancements. Therefore, further synthesis and refinement of research in this field are necessary.

This study seeks to provide a comprehensive overview of the causal links between CRC and its associated risk factors. By thoroughly analyzing these associations, the research not only provides scientific evidence for understanding the underlying mechanisms of CRC development but also provides theoretical basis for developing effective prevention strategies. Furthermore, elucidating the impact of key risk factors on CRC prognosis will help optimize clinical interventions, improve patient quality of life and survival rates, and provide important references for the development of public health policies and personalized medical practices.

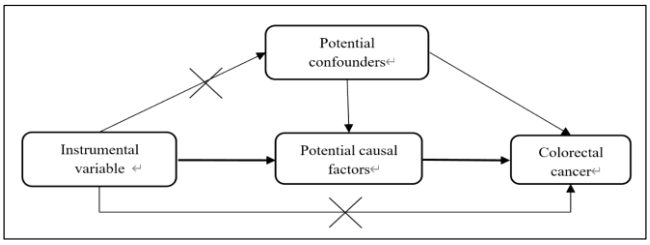

Figure 1: Three main assumptions of Mendelian Randomization

2. Materials and Methods

2.1 Data Sources, Inclusion and Exclusion Criteria

In this study, English search terms "Colorectal Neoplasms" and "Mendelian Randomization Analysis" were used to search the PubMed and Web of Science databases. The search period ranged from database inception to January 2025. The inclusion criteria for the studies were: (1) MR studies with CRC as the outcome and risk factors as exposures; (2) MR studies with CRC as the exposure and other diseases as the outcome. The exclusion criteria included: (1) Duplicate studies; (2) Studies without full-text access; (3) Non-English literature. A total of 93 studies were included based on the aforementioned inclusion and exclusion criteria.

2.2 Quality Assessment

At present, there is no comprehensive method or tool available to evaluate the quality of MR studies. However, MR studies must meet the three key assumptions mentioned earlier. To conduct a systematic review, we created a summary table (see Online Resource 1) and a forest plot (Figure 2) highlighting some of the extracted results, to illustrate the number of studies based on exposure type and the direction of their results. The use of Odds Ratio (OR) to measure the relative risk of an outcome associated with an exposure factor.

Exposure.classification	Exposure	Outcome	Method	OR(95%CI)	P.value
Anthropometric Characteristics (Obesity-Related)	BFP	EOCRC	Inverse variance weighted	1.42(1.20 to 1.67)	2.80e-02
	BMI(Adult)	CRC	Inverse variance weighted	1.39(1.06 to 1.82)	2.80e-02
	WC	EOCRC	Inverse variance weighted	1.42(1.22 to 1.64)	2.80e-02
	BMR	EOCRC	Inverse variance weighted	1.30(1.14 to 1.47)	4.00e-02
	WHR	EOCRC	Inverse variance weighted	1.47(1.26 to 1.71)	4.27e-02
	WHR	CRC	Inverse variance weighted	1.38(1.12 to 1.70)	1.76e-02
	WHR	Colon Ca(Finn)	Inverse variance weighted	1.30(1.00 to 1.68)	2.00e-02
	WHRadjBMI	CRC(Finn)	Inverse variance weighted	1.30(1.08 to 1.56)	1.00e-02
	WHRadjBMI(Woman)	Colon Ca(Finn)	Inverse variance weighted	1.32(1.08 to 1.60)	9.00e-03
	WHR(Woman)	Colon Ca(Finn)	Inverse variance weighted	1.36(1.09 to 1.68)	1.00e-02
	WHRadjBMI	Colon Ca(Finn)	Inverse variance weighted	1.39(1.10 to 1.76)	2.00e-02
	AFR	CRC	Inverse variance weighted	1.50(1.17 to 1.93)	2.00e-03
	ABSI(Man)	Rectal Ca	Inverse variance weighted	1.40(1.10 to 1.77)	2.67e-02
	Adult life body size	CRC	Inverse variance weighted	1.30(1.17 to 1.45)	2.00e-02
	Adult life body size	Colon Ca	Inverse variance weighted	1.32(1.19 to 1.51)	3.00e-02
	Adult life body size	Proximal Colon	Inverse variance weighted	1.42(1.22 to 1.63)	1.00e-02
Diet	Drinks per week	EOCRC	Inverse variance weighted	1.97(1.34 to 2.90)	5.80e-04
	Problematic alcohol use	CRC	Inverse variance weighted	1.53(1.02 to 2.29)	8.30e-03
	Drinks per week	CRC	Inverse variance weighted	1.79(1.23 to 2.61)	1.30e-02
Lifestyle	PA	CRC	Inverse variance weighted	0.66(0.48 to 0.90)	4.00e-02
	PA	CRC	Inverse variance weighted	0.70(0.52 to 0.93)	7.80e-03
	PA	Distal colon	Inverse variance weighted	0.51(0.31 to 0.83)	2.00e-02
	PA(Woman)	CRC	Inverse variance weighted	0.57(0.36 to 0.90)	4.00e-02
	PA	Colon Ca	Inverse variance weighted	0.64(0.44 to 0.94)	9.10e-03
	AMPA	CRC	Inverse variance weighted	0.60(0.41 to 0.88)	2.10e-02
	Hours of television watching	CRC	Inverse variance weighted	1.32(1.16 to 1.49)	4.65e-02
	Smoking per day	CRC	Inverse variance weighted	1.30(1.01 to 1.68)	9.43e-03
	Smoking initiation	CRC	Inverse variance weighted	3.48(1.15 to 10.55)	2.22e-02
	Lifetime amount of smoking	Colon Ca	Inverse variance weighted	1.31(1.11 to 1.55)	2.00e-02
	Lifetime amount of smoking(Man)	CRC	Inverse variance weighted	1.32(1.11 to 1.59)	7.00e-03
	Lifetime amount of smoking	Rectal Ca	Inverse variance weighted	1.36(1.07 to 1.73)	8.00e-03
	Lifetime amount of smoking	Distal colon	Inverse variance weighted	1.50(1.21 to 1.87)	1.49e-02
	Education attainment	EOCRC	Inverse variance weighted	0.09(0.04 to 0.20)	9.00e-03
Immune Mediators	Serum uric acid GCST007725	CRC	Inverse variance weighted	0.23(0.09 to 0.57)	3.43e-03
	Serum uric acid ukb-e-30880_CSA	CRC	Inverse variance weighted	0.55(0.32 to 0.93)	8.84e-03
	PTX3	CRC	Wald radio	0.59(0.40 to 0.88)	3.90e-02
	TNF-R2	CRC	Wald radio	0.68(0.49 to 0.93)	3.80e-03
	ADM	CRC	Inverse variance weighted	1.38(1.08 to 1.77)	7.10e-03
	LOX-1	CRC	Wald radio	1.82(1.18 to 2.80)	2.32e-02
	2-hydroxystearate	CRC	Inverse variance weighted	0.39(0.23 to 0.67)	2.90e-03
	Nonadecanoate (19:0)	CRC	Inverse variance weighted	0.40(0.11 to 0.59)	2.20e-03
	1-linoleoylglyceroph osphoethanolamine	CRC	Inverse variance weighted	0.47(0.30 to 0.75)	2.50e-02
	Pyruvate	CRC	Inverse variance weighted	0.49(0.32 to 0.77)	2.00e-03
	1,6-anhydroglucose	CRC	Inverse variance weighted	1.33(1.11 to 1.59)	9.00e-03
	Gamma-glutamylthreonine	CRC	Inverse variance weighted	2.14(1.02 to 4.50)	9.20e-07
	Serine topyruvate ratio	CRC	Inverse variance weighted	1.33(1.05 to 1.68)	1.00e-03
	Interleukin-2 receptor subunit beta levels	CRC	Inverse variance weighted	1.36(1.02 to 1.81)	1.60e-02
	1-(1-enyl-palmitoyl)-2-oleoyl-gpc(p-16:0/18:1)levels	CRC	Inverse variance weighted	1.40(1.06 to 1.86)	3.00e-03
	1-(1-enyl-palmitoyl)-GPC(p-16:0)levels	CRC	Inverse variance weighted	1.40(1.04 to 1.90)	1.20e-02
	Interferon gamma levels	CRC	Inverse variance weighted	1.44(1.04 to 1.98)	3.70e-02
	Sphingomyelin(d18:2/21:0,d16:2/23:0)levels	CRC	Inverse variance weighted	1.65(1.11 to 2.45)	5.85e-04
	Epiandrosterone sulfatelevels	CRC	Inverse variance weighted	2.07(1.33 to 3.22)	5.00e-03
	IL-16	Rectal Ca	Inverse variance weighted	1.37(1.12 to 1.67)	4.66e-06
	VEGF	Rectal Ca	Inverse variance weighted	1.44(1.15 to 1.80)	2.00e-04
Metabolites	Intestinibacter	CRC	Inverse variance weighted	1.31(1.09 to 1.57)	3.60e-02
Systemic Diseases	Heart failure	CRC	Inverse variance weighted	1.32(1.03 to 1.69)	8.79e-10
	liver volume	CRC	Inverse variance weighted	0.60(0.44 to 0.82)	6.80e-03
	Diverticular disease	CRC	Inverse variance weighted	0.44(0.08 to 0.80)	6.00e-03

P<0.05 was considered statistically significant

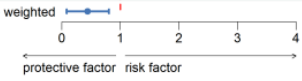

Figure 2: This chart is a forest plot created from data extracted after filtering, used to display key information that aids in the analysis of the results

3. Results

3.1 The Relationship Between Anthropometric Characteristics (Obesity-Related) and CRC

Most observational studies suggest a strong association between high body fat percentage (BFP) and the occurrence of CRC [9], and three MR studies [3,10,11] have also found consistent results, indicating a positive correlation between BFP and CRC risk. Body mass index (BMI) is strongly linked to the development of CRC, although a few studies have suggested that this association may be influenced by age factors [12], and MR analysis results also support this. The MR analysis by Gao [13] demonstrated that higher adult BMI is positively correlated with an increased risk of CRC, while no notable association was found between childhood BMI and CRC risk (OR = 1.2, P = 0.21). Additionally, multiple MR analyses [3,5,10,11,14-17] have consistently confirmed the positive link between BMI and CRC development. Among these, three studies [5,14,17] further analyzed CRC subtypes and gender differences. Two of these results [14,17] were consistent with the overall CRC findings, while one study [5] found that only the results for colon cancer were significant, whereas rectal cancer results were not statistically significant (male OR = 1.09, P = 0.1817; female OR = 1.08, P = 0.2901). Although waist circumference (WC) is positively correlated with BMI, these two indicators are not entirely synonymous, as individuals with normal BMI may still have abdominal obesity or a large waist circumference. Epidemiological data suggest that a larger waist circumference is linked to CRC risk, even among individuals with normal body weight [18]. As a result, WC should be analyzed independently through MR. Three studies [3,10,11] have found a positive association between WC and CRC risk.

The causal relationship between higher basal metabolic rate (BMR) and CRC risk remains uncertain, and MR analysis results provide valuable insights for determining the nature of this relationship. Three MR analyses [3,10,19] found a positive relationship between BMR and CRC risk. One of these studies [19] performed a bidirectional MR analysis using Finnish database data and found no signs of reverse causality. Previous observational studies have indicated that taller adult height (Ht) is linked to an increased risk of CRC [20]. Two MR analyses [3,10] also found similar results (OR = 1.04, P = 0.032; OR = 1.09, P = 0.006). Additionally, one MR analysis [5] indicated that this relationship is more pronounced in women. A prospective survey found an association between waist-to-hip ratio (WHR) and CRC risk [21]and four MR analyses [10,14,22,23] supported this finding, all showing a significant positive correlation between WHR and CRC risk. Two of these studies [14,22] found that this relationship was more significant in women, and one study [22] also demonstrated no reverse causality between WHR and CRC risk. Additionally, some studies [5,22] found that WHR adjusted for body mass index (WHRadjBMI) was positively correlated with CRC risk. One study [22] found this relationship to be more pronounced in women. Another study [5] observed gender differences in the association with colon cancer risk, consistent with previous findings, showing a stronger correlation in women. However, for overall CRC and rectal cancer, the results were the opposite, with men showing a more significant association than women.

The traditional body shape indices mentioned earlier are correlated with BMI. However, BMI adjustments are also influenced by height and weight. Therefore, emerging body shape indices, such as A Body Shape Index (ABSI), Hip Index (HI), and Waist-to-Hip Index (WHI), which are independent of height and weight, provide new references [5]. These factors are linked to CRC risk in traditional observational studies; however, there is a lack of sufficient MR studies on this topic [24]. Among MR analyses, only one study [5] analyzed ABSI, HI, and WHI, and found that ABSI was positively correlated with CRC risk (OR = 1.29, P = 0.0077), with consistent results in subtype and gender analyses. The result for WHI was similar to that of ABSI, while HI did not show statistical significance. Zhang [11]and colleagues performed MR analysis on other obesity-related indicators, and found that only Arm Fat Ratio was associated with CRC risk (OR = 1.50, P = 0.002), while Trunk Fat Ratio and Leg Fat Ratio did not show statistical significance. Although observational studies indicate a link between childhood obesity and an increased CRC risk, it remains unclear whether this association is causal or influenced by obesity in adulthood, and further research is needed. Based on this, one study [25] found that an increase in early body size increases CRC risk (OR = 1.12, P < 0.001), with consistent results in subtype analysis. However, after adjusting for adult body size, most of these associations weakened, and similar conclusions were drawn in gender-specific analysis. This suggests that early body size may not directly affect CRC risk. If an individual maintains a normal weight in adulthood, childhood overweight may not have a significant impact on CRC risk. The result that increased early body size raises CRC risk may be due to individuals who were obese in childhood maintaining obesity into adulthood, leading to this effect.

The risk of CRC is associated with various body measurements in complex ways, which may be driven by multiple biological, metabolic, and environmental factors. Abdominal fat accumulation can increase the secretion of pro-inflammatory factors, leading to chronic inflammation. Obesity also increases insulin and Insulin-like Growth Factor 1(IGF-1) levels, stimulating the proliferation of intestinal epithelial cells and inhibiting cell apoptosis [26]. Obesity may also cause an imbalance in the gut microbiota, generating harmful bacterial populations and their metabolic products [27]. Additionally, obesity and chronic inflammation may alter the expression of oncogenes or tumor suppressor genes through Deoxyribonucleic Acid (DNA) methylation and histone modification [28]. These pathways are potential causes of CRC occurrence and progression.

3.2 The Relationship Between Diet, Lifestyle, and CRC

Studies have indicated [29] that the intake of certain essential trace elements, such as iron, selenium, and zinc, is linked to a higher risk of diseases, particularly CRC. However, different MR analysis results exhibit some discrepancies. A study [3] found a positive relationship between circulating serum iron levels and CRC risk (OR = 1.17, P = 0.049), while higher serum selenium levels were associated with a lower CRC risk (OR = 0.85, P = 0.0078). No causal link was identified between serum zinc levels and CRC. In contrast, another study [30] found no causal associations between serum iron or

selenium and CRC risk, but observed an inverse relationship between serum zinc levels and CRC risk (OR = 0.97, P = 0.02). The differing results may be due to variations in study methodology and data sources. A large number of studies [3,10,31-33] found no causal relationship between vitamin D and CRC risk. There is compelling evidence linking alcohol consumption to CRC incidence [34], and MR studies confirm this. Two studies [10,35] found that weekly alcohol consumption and heavy drinking [35] are risk factors for CRC, while another study [17] also found a link between alcohol consumption history and CRC risk. Two MR studies [3,10] found no significant link between coffee consumption and CRC risk, while one study [36] indicated that coffee consumption is a risk factor for CRC (OR = 1.43, P < 0.001). One MR study [37] found no association between milk intake and CRC risk, while another study [38] found that milk intake is a protective factor for CRC. No significant association was observed between the consumption of fruits, vegetables, meat, candy, and tea and CRC risk [37].

Epidemiological studies consistently show an inverse relationship between physical activity (PA) and CRC risk [39], and three MR studies [11,17,40] also support this conclusion, finding that PA is negatively correlated with CRC risk. A study [41] found that increasing smoking intensity and duration raises CRC risk, while quitting smoking lowers it. Four MR studies [16,17,23,42] found similar results, showing that smoking [16,17], starting smoking, and daily smoking [23], as well as lifetime smoking volume [42], are positively correlated with an increased CRC risk. In subgroup analysis [42], only proximal colon cancer (OR = 1.19, P = 0.09) did not reach statistical significance. Gender-specific analysis showed that lifetime smoking was only positively correlated with CRC risk in men. Moreover, less-studied lifestyle factors, such as educational level [10], were identified as protective factors against CRC risk, while television watching time [43] was a risk factor for CRC (OR = 1.32, P < 0.001). MR results for leisure screen time [10]and leisure computer use time [43] did not show statistical significance. No significant association was found between summer or winter outdoor activity time, sunlight, or the use of sunlight lamps [44]and CRC risk. Morning sleep type [45] was found to be a protective factor for CRC risk, and this factor is associated with a natural morning-type biological clock rather than morning-type behavior (e.g., having sufficient sleep but staying up late and waking up early).

Vitamins may regulate CRC occurrence through various mechanisms, including antioxidant activity, immune modulation, DNA repair, cell proliferation, and apoptosis [46]; acetaldehyde, a byproduct of alcohol metabolism, is a known carcinogen, and alcohol metabolites may directly damage the DNA of intestinal epithelial cells [47], promoting cancer development; smoking increases DNA damage, induces immune suppression, and triggers chronic inflammation [48], which may directly promote CRC development; physical inactivity not only leads to weight gain but also slows down intestinal peristalsis, extending the contact time of carcinogens with the intestinal epithelium [49]. These studies provide evidence that unhealthy diets and lifestyles increase the risk of CRC. Therefore, adopting healthy dietary habits, maintaining appropriate vitamin intake, and changing harmful lifestyle behaviors are important strategies to reduce CRC risk.

3.3 The Relationship Between Immune Mediators and CRC

The relationship between immune mediators and CRC is highly complex. A study [50] found that levels of Programmed Death Ligand 1(PD-L1) (OR = 0.903, P = 0.028), Axis Inhibition Protein 1 (Axin1) (OR = 0.866, P = 0.04), and β-Nerve Growth Factor (β-NGF) (OR = 0.914, P = 0.028) were significantly negatively correlated with CRC risk, and the expression of these factors was also related to CRC's Tumor, Node, Metastasis (TNM) stage and tumor differentiation. Another MR study [51] demonstrated a protective causal association between higher circulating basophil (OR = 0.88, P = 0.04) and eosinophil counts (OR = 0.93, P = 0.01) and CRC risk. Additionally, in multivariable MR analysis, increased lymphocyte counts were also negatively correlated with CRC risk (OR = 0.84, P = 0.007), though no association was found between monocyte or neutrophil counts and CRC risk. A study [52] found that, regardless of whether the data came from the UK Biobank (UKB) or the Finnish database, eosinophil counts and percentages were negatively correlated with CRC risk. Wang [53]'s bidirectional MR study revealed a positive correlation between Tumor Necrosis Factor-α(TNF-α) levels and CRC risk (OR = 1.252, P = 0.047).Zhou [54] found that Interleukin-16 (IL-16), Vascular Endothelial Growth Factor (VEGF), and Monokine Induced by Interferon Gamma (MIG) were positively correlated with rectal cancer risk, while Macrophage Colony-Stimulating Factor (M-CSF) was negatively correlated with colon cancer risk. Zhang [55] confirmed that seven inflammatory protein factors in the tumor microenvironment are causally related to CRC. A study [56]found that IgD+CD24+%B cells (OR = 0.932, P = 0.014), CD14 on CD14+ CD16- monocytes (OR = 0.943, P = 0.014), and IgD-CD38br AC (OR = 0.946, P < 0.001) provided a protective effect against CRC, while SSC-A on B cells (OR = 1.073, P = 0.007), CD8 on CD28- CD8br (OR = 1.054, P = 0.042), and CCR2 on CD62L+ myeloid DC (OR = 1.052, P = 0.023) were identified as risk factors. A study [55] established a causal link between 43 immune cell traits and CRC from a total of 731 immune cell characteristics. Gu's [57] study of 731 immune cell phenotype-specific changes revealed that 31 and 28 immune cell phenotypes were found to be significantly associated with CRC risk in two distinct datasets.

The findings of these studies indicate that the relationship between immune mediators and CRC is exceptionally complex. These immune cell factors may promote CRC development through mechanisms such as inflammation, immune suppression, angiogenesis, and assisting tumor cells in immune evasion [58,59]. Conversely, they may also protect against CRC through immune surveillance, immune killing, and immune modulation [60]. Cytokines such as TNF-α, IL-16, and VEGF are important inflammatory factors that regulate immune responses and influence the gut microenvironment. Chronic inflammation, through activation of relevant signaling pathways, can promote intestinal epithelial cell proliferation, DNA damage, and inhibit apoptosis, thus increasing CRC risk [61]. The increased expression of immune suppressive factors such as PD-L1 and MIG may inhibit T-cell immune responses, leading to

immune evasion and promoting tumor growth and metastasis [62]. Immune cells such as eosinophils, basophils, and lymphocytes play crucial roles in immune surveillance. Increased eosinophils and basophils may protect the host from CRC development by secreting anti-tumor cytokines or regulating immune responses [63]. In conclusion, cytokines, immune cells, and inflammatory protein factors interact through various mechanisms, and these mechanisms not only promote chronic inflammation, immune evasion, and changes in the tumor microenvironment but may also directly influence tumor cell proliferation and metastasis, ultimately affecting CRC occurrence, development, and prognosis.

3.4 The Relationship Between Metabolites and CRC

Studies have shown that metabolic changes are closely associated with the occurrence and progression of CRC [64]. MR studies by Yun [65] provided support for the causal relationship between six circulating metabolites and CRC, revealing that pyruvate, 1,6-dehydroglucose, nonadecanoate (19:0), 1-linoleoylglyceroph osphoethanolamine, 2-hydroxystearate, and gamma-glutamyl threonine were positively correlated with CRC risk. Further Multivariable Mendelian Randomization (MVMR) analysis showed that pyruvate, 1-linoleoylglyceroph osphoethanolamine, and gamma-glutamyl threonine independently influenced CRC occurrence, independent of other metabolites. An MR analysis [66] found a significant association between serum uric acid levels and CRC incidence. Furthermore, strong evidence suggests [67] that omega-3 fatty acids, docosahexaenoic acid (DHA), the ratio of omega-3 fatty acids to total fatty acids, the ratio of DHA to total fatty acids, and the ratio of omega-6 fatty acids to omega-3 fatty acids may influence CRC risk. Cai's [16] MR study identified 23 plasma proteins significantly associated with CRC. Another study [55] established a causal link between 37 serum metabolites and CRC.

Regarding the biological significance of metabolites, elevated pyruvate levels may reflect accelerated glycolysis in cancer cells, which typically utilize glycolysis for energy production and biosynthesis of macromolecules, thereby promoting cell proliferation and growth [68]. Changes in metabolite levels may represent a reprogramming of cellular energy metabolism and biosynthetic pathways, supporting the high proliferative rate and adaptive capabilities of cancer cells [69]. Additionally, alterations in omega-3 fatty acids, DHA, and fatty acid ratios may affect the composition and fluidity of cell membranes, thereby altering signaling processes. Furthermore, the imbalance between omega-3 and omega-6 fatty acids may change local inflammatory responses, as these fatty acids and their metabolites play an essential role in regulating inflammation, which is closely linked to cancer occurrence and progression [70]. The finding of correlations between various metabolites in plasma and urine and CRC risk suggests that cancer development may be associated with systemic metabolic disturbances. These global metabolic changes could influence the tumor microenvironment, modulate immune responses, inflammatory reactions, and cell-to-cell interactions, thereby promoting the carcinogenesis process. These studies offer fresh perspectives on the metabolic mechanisms of CRC and could lead to novel approaches for its early diagnosis, prevention, and treatment.

3.5 The Relationship Between Gut Microbiota and CRC

Growing evidence indicates [71] that the gut microbiota is essential in the development, progression, and metastasis of CRC. Ni [72] found in their study that Blautia genus was causally related to CRC risk in the discovery sample (β = -0.01, P = 0.04), and this relationship was successfully replicated in the validation sample (β = -1.18, P = 0.01). Another study [73] provided initial MR analysis evidence indicating that certain bacteria within the *Bifidobacterium* genus and some uncategorized bacteria from the *Bacteroidetes* phylum might increase the overall and specific site risk of CRC. However, subsequent sensitivity analyses highlighted the complexity of these relationships and their assessment tools, especially the results concerning *Bifidobacterium*, which may not reflect causal relationships. Xiang [74]'s MR analysis results showed that family Porphyromonadaceae (OR = 1.26, P = 0.0267), genera Anaerotruncus (OR = 1.17, P = 0.039), Intestinibacter (OR = 1.31, P = 0.0038), Slackia (OR = 1.24, P = 0.0071), Ruminococcaceae UCG004 (OR = 1.27, P = 0.0232), and species Eubacterium coprostanoligenes group (OR = 1.25, P = 0.0467) were positively correlated with CRC risk.

The gut microbiota may influence immune tolerance and immune surveillance through interactions with the host immune system [75]. It may also promote CRC progression by damaging the gut barrier function and altering the function of intestinal epithelial cells. For example, some microbes may promote intestinal inflammation or increase intestinal permeability, making carcinogens more likely to enter the intestinal wall and cause DNA damage, thereby driving tumorigenesis. In summary, the mechanisms through which the gut microbiota contributes to CRC occurrence, progression, and metastasis may include altering gut immune responses, disrupting the intestinal barrier, triggering chronic inflammation, and influencing gut metabolism, thus directly or indirectly promoting CRC development.

3.6 The Relationship Between Systemic Diseases and CRC

In gastrointestinal diseases, the level of lactase-phlorizin hydrolase [76] has a negative correlation with CRC risk and its subtypes. No causal relationship was found between Helicobacter pylori IgG seropositivity, VacA antibody levels, and CagA antibody levels [77] with CRC, and reverse MR analysis also supported this. Furthermore, no causal relationship was found between constipation [78] and CRC. Primary sclerosing cholangitis [79] was found to be positively associated with the risk of CRC (OR = 1.038, P < 0.001). Although one study [80] found no association between cholecystectomy and CRC risk (OR = 1.543, P = 0.365), gallstone disease may increase the risk of CRC (OR = 1.041, P = 0.009). Further MVMR analysis showed that, after adjusting for cholecystectomy, the genetic susceptibility to gallstones might increase CRC risk (OR = 1.061, P = 0.044). Non-alcoholic fatty liver disease [81] was positively correlated with CRC risk, while liver volume [82] was negatively correlated with CRC risk (OR = 0.60, P = 0.001). In the Finnish database, diverticular disease [83] showed a positive association with CRC risk, while no such correlation was found in the UKB data. Reverse MR analysis showed a slight correlation between CRC and diverticular disease (β =

0.007, P < 0.001).

In cardiovascular diseases, heart failure [84] showed a positive association with CRC risk (OR 1.32, P=0.025). Sterol esters (27:1/14.0) [85] were positively correlated with CRC risk. Mean red blood cell hemoglobin levels [86] were positively correlated with CRC risk. Cardiovascular proteins [87] analysis through cis-Protein Quantitative Trait Loci (cis-pQTLs) showed that Lectin-like Oxidized Low-Density Lipoprotein Receptor-1 (LOX-1), Vascular Endothelial Growth Factor A (VEGF-A), and Osteoprotegerin (OPG) were positively correlated with CRC risk, whereas Pentraxin 3(PTX3), Tumor Necrosis Factor Receptor 2(TNF-R2), and Matrix Metalloproteinase-7(MMP-7) were negatively correlated. Pan-genome Protein Quantitative Trait Loci (Pan-pQTL) analysis showed that Matrix Metalloproteinase-10(MMP-10) was positively correlated with CRC risk, while Adrenomedullin (ADM) (OR = 1.38, P = 0.0091) was negatively correlated. GrimAge acceleration rate [88] was positively associated with CRC risk (OR = 1.12, P = 0.002), with a more significant correlation in colon cancer subtypes (OR = 1.15, P = 0.006), while no such correlation was found for rectal cancer (OR = 1.05, P = 0.24).

In Respiratory, Endocrine, and Urinary System Diseases: Chronic obstructive pulmonary disease [89] increases the risk of CRC incidence and progression (OR: 1.16, P = 0.036). Overall lung cancer [90]is positively correlated with CRC risk (OR = 1.0026, P = 0.0029), with subgroup analysis showing a positive correlation between Squamous cell lung carcinoma and CRC (OR = 1.0017, P = 0.0022), but no such correlation with lung adenocarcinoma (P = 0.4092 > 0.05). No correlation was found between asthma [52]and CRC risk (OR = 0.999, P = 0.095). Type 2 diabetes [91]is a risk factor for CRC (OR = 1.07, P = 0.003), while type 1 diabetes [79] is a protective factor for CRC (OR = 0.965, P = 0.012), and neither showed reverse causality. Proteinuria [92]is a risk factor for CRC, whereas glomerular filtration rate showed no significant association with CRC (OR = 0.98, P = 0.779).

In Other Diseases: A study on autoimmune diseases found that psoriasis (OR = 1.026, P = 0.037) is a risk factor for CRC, with no reverse causality. Systemic lupus erythematosus, juvenile idiopathic arthritis, multiple sclerosis, celiac disease, and rheumatoid arthritis did not show a causal relationship with CRC [79]. However, one MR study [93] demonstrated that rheumatoid arthritis is significantly associated with CRC risk (OR = 1.04, P = 0.005). Uveitis [94] was negatively correlated with CRC risk (OR = 0.97, P = 0.021). No significant link was observed between major depressive disorder [95] and CRC risk.

Overall, the above MR studies clearly demonstrate varying degrees of association between CRC and multiple systemic diseases. These associations may be related to shared genetic characteristics or underlying mechanismsinvolving inflammation, metabolic disturbances, genetic factors, immune regulation, vascular function, and more. Different diseases impact the gut microenvironment, cellular metabolism, and immune function through various pathways, driving the occurrence and progression of CRC. Therefore, considering these interactions in CRC clinical diagnosis and treatment will help improve the scientific and precise nature of clinical decision-making, while also providing valuable insights for future disease prevention and therapeutic strategy optimization.

4. Discussion

This study provides a comprehensive exploration of the multi-dimensional factors influencing colorectal cancer (CRC) incidence, highlighting the complexity of the factors involved while also identifying several limitations in current research. Firstly, although Mendelian Randomization (MR) studies offer the potential for causal inference, differences in research methodologies, sample sources, population characteristics, and control of confounding factors result in disparities in the MR study outcomes. These inconsistencies pose challenges in accurately determining the mechanisms underlying CRC incidence. This variability not only complicates the identification of the most reliable causal relationships but also impacts the development of effective prevention and intervention strategies for CRC. To address this issue, conducting meta-analyses, subgroup analyses, and meta-regression could be effective approaches. These methods can help explore the sources of heterogeneity between studies and allow for a more precise understanding of the relationships between various factors and CRC [96-98]. Secondly, the selection of instrumental variables in MR studies requires special attention. While efforts have been made to screen the instrumental variables, some of them show weak associations with the exposure factors, which may reduce statistical power and introduce potential bias [99].For example, if the F-statistic of an instrumental variable is less than 10, it may not provide sufficient statistical support. Therefore, evaluating the strength of the instrumental variables using F-statistics and other indicators is crucial. For weaker instrumental variables, combining multiple weak variables or using methods like the weighted median approach can enhance power. Additionally, functionally annotating the instrumental variables to ensure their clear association with the exposure factor is an important step to reduce bias [100]. Finally, most MR studies rely heavily on European population samples, with fewer samples from East Asian and other ethnic groups, limiting the generalizability of the findings. Differences in genetic backgrounds, lifestyle, and environmental exposures across ethnic groups may significantly affect the relationships between various factors and CRC. Therefore, future studies should consider expanding the diversity of their samples, particularly by increasing the representation of East Asian and other ethnic groups. This will not only help improve the representativeness of research findings but also offer a more comprehensive understanding of CRC risk factors and mechanisms across different populations. Performing ethnicity-stratified analyses or subgroup analyses will deepen our understanding of the similarities and differences in CRC pathogenesis across ethnicities, ensuring that the research outcomes can be widely applied and disseminated globally.

5. Conclusion

This study summarizes MR research on CRC, providing an in-depth exploration of the factors influencing CRC incidence and its underlying mechanisms from multiple dimensions. It covers well-established, previously underexplored, and

emerging risk factors. However, to improve the reliability and broader applicability of the conclusions, future research should further refine methodologies, expand sample sizes, and increase focus on different ethnic groups. This will provide a more scientific and comprehensive basis for CRC prevention, early diagnosis, and personalized treatment.

References

[1] Global cancer burden growing, amidst mounting need for services. Global cancer burden growing, amidst mounting need for services. SAUDI MED J. 2024; 45(3): 326-327.

[2] Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. TRANSL ONCOL. 2021; 14(10): 101174.

[3] Cornish AJ, Law PJ, Timofeeva M, Palin K, Farrington SM, Palles C et al. Modifiable pathways for colorectal cancer: a mendelian randomisation analysis. The Lancet Gastroenterology & Hepatology. 2020;5(1):55-62.

[4] Jiang F, Zhao J, Sun J, Chen W, Zhao Y, Zhou S et al. Impact of ambient air pollution on colorectal cancer risk and survival: insights from a prospective cohort and epigenetic Mendelian randomization study. EBIOMEDICINE. 2024;103:105126.

[5] Rontogianni MO, Bouras E, Aglago EK, Freisling H, Murphy N, Cotterchio M et al. Allometric versus traditional body-shape indices and risk of colorectal cancer: a Mendelian randomization analysis. INT J OBESITY. 2024;48(5):709-716.

[6] Cornish AJ, Tomlinson IPM, Houlston RS. Mendelian randomisation: A powerful and inexpensive method for identifying and excluding non-genetic risk factors for colorectal cancer. MOL ASPECTS MED. 2019; 69: 41-47.

[7] Zhang X, Gill D, He Y, Yang T, Li X, Monori G et al. Non-genetic biomarkers and colorectal cancer risk: Umbrella review and evidence triangulation. CANCER MED-US. 2020;9(13):4823-4835.

[8] Deng Y, Wang L, Huang J, Ding H, Wong MCS. Associations between potential causal factors and colorectal cancer risk: A systematic review and meta-analysis of Mendelian randomization studies. J DIGEST DIS. 2022;23(8-9):435-445.

[9] Chen Q, Li K, Liu Y, Yu X, Ou F. Association of body composition indicators with colorectal cancer: a hospital-based case-control study. J CANCER RES CLIN. 2024;150(7):344.

[10] Laskar RS, Qu C, Huyghe JR, Harrison T, Hayes RB, Cao Y et al. Genome-wide association studies and Mendelian randomization analyses provide insights into the causes of early-onset colorectal cancer. ANN ONCOL. 2024;35(6):523-536.

[11] Zhang X, Theodoratou E, Li X, Farrington SM, Law PJ, Broderick P et al. Genetically predicted physical activity levels are associated with lower colorectal cancer risk: a Mendelian randomisation study. BRIT J CANCER. 2021;124(7):1330-1338.

[12] Yuan Z, Wang S, Wang Y, Li H, Gao W, Liu X et al. Age- and sex-stratified detection rates and associated factors of colorectal neoplasia in the Tianjin colorectal cancer screening program from 2012 to 2020. BMC GASTROENTEROL. 2023;23(1):435.

[13] Gao C, Patel CJ, Michailidou K, Peters U, Gong J, Schildkraut J et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. INT J EPIDEMIOL. 2016;45(3):896-908.

[14] Bull CJ, Bell JA, Murphy N, Sanderson E, Davey Smith G, Timpson NJ et al. Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. BMC MED. 2020;18(1):396.

[15] Suzuki S, Goto A, Nakatochi M, Narita A, Yamaji T, Sawada N et al. Body mass index and colorectal cancer risk: A Mendelian randomization study. CANCER SCI. 2021;112(4):1579-1588.

[16] Cai Y, Wu Y, Liu J, Pan H, Deng W, Sun W et al. Proteome-wide analysis reveals potential therapeutic targets for Colorectal cancer: a two-sample mendelian randomization study. BMC CANCER. 2023; 23(1): 1188.

[17] Bouras E, Gill D, Zuber V, Murphy N, Dimou N, Aleksandrova K et al. Identification of potential mediators of the relationship between body mass index and colorectal cancer: a Mendelian randomization analysis. INT J EPIDEMIOL. 2024;53(3).

[18] Jung YS, Kim NH, Yang HJ, Park SK, Park JH, Park DI et al. Association between waist circumference and risk of colorectal neoplasia in normal-weight adults. J GASTROEN HEPATOL. 2020;35(1):43-49.

[19] Wu E, Ni J, Tao L, Xie T. A bidirectional Mendelian randomization study supports the causal effects of a high basal metabolic rate on colorectal cancer risk. PLOS ONE. 2022;17(8):e0273452.

[20] Zhou E, Wang L, Santiago CN, Nanavati J, Rifkin S, Spence E et al. Adult-Attained Height and Colorectal Cancer Risk: A Cohort Study, Systematic Review, and Meta-Analysis. CANCER EPIDEM BIOMAR. 2022; 31(4): 783-792.

[21] Kliemann N, Viallon V, Murphy N, Beeken RJ, Rothwell JA, Rinaldi S et al. Metabolic signatures of greater body size and their associations with risk of colorectal and endometrial cancers in the European Prospective Investigation into Cancer and Nutrition. BMC MED. 2021;19(1):101.

[22] Chen X, Yang M, Zhao W, Tu J, Liu Q, Yuan X. Mendelian randomization unraveled: gender-specific insights into obesity-related phenotypes and colorectal cancer susceptibility. FRONT ENDOCRINOL. 2024;15:1322253.

[23] Li X, Chang Z, Wang J, Ding K, Pan S, Hu H et al. Unhealthy lifestyle factors and the risk of colorectal cancer: a Mendelian randomization study. SCI REP-UK. 2024;14(1):13810-13825.

[24] Christakoudi S, Tsilidis KK, Evangelou E, Riboli E. A Body Shape Index (ABSI), hip index, and risk of cancer in the UK Biobank cohort. Cancer medicine (Malden, MA). 2021;10(16):5614-5628.

[25] Papadimitriou N, Bull CJ, Jenab M, Hughes DJ, Bell JA, Sanderson E et al. Separating the effects of early and later life adiposity on colorectal cancer risk: a Mendelian randomization study. BMC MED. 2023;21(1):5.

[26] Miranda BCJ, Tustumi F, Nakamura ET, Shimanoe VH, Kikawa D, Waisberg J. Obesity and Colorectal Cancer: A Narrative Review. Medicina (Kaunas, Lithuania). 2024;60(8):1218.

[27] Wang Z, Dan W, Zhang N, Fang J, Yang Y. Colorectal cancer and gut microbiota studies in China. GUT MICROBES. 2023;15(1):2236364.
[28] Parmar S, Easwaran H. Genetic and epigenetic dependencies in colorectal cancer development. GASTROENTEROL REP. 2022;10:goac035.
[29] Ekmekcioglu C, Wallner P, Kundi M, Weisz U, Haas W, Hutter H. Red meat, diseases, and healthy alternatives: A critical review. CRIT REV FOOD SCI. 2018; 58(2): 247-261.
[30] Tsilidis KK, Papadimitriou N, Dimou N, Gill D, Lewis SJ, Martin RM et al. Genetically predicted circulating concentrations of micronutrients and risk of colorectal cancer among individuals of European descent: a Mendelian randomization study. AM J CLIN NUTR. 2021;113(6):1490-1502.
[31] Cheng W, Wang Z, Shangguan H, Zhu Q, Zhang H. Are vitamins relevant to cancer risks? A Mendelian randomization investigation. NUTRITION. 2020; 78: 110870.
[32] He Y, Zhang X, Timofeeva M, Farrington SM, Li X, Xu W et al. Bidirectional Mendelian randomisation analysis of the relationship between circulating vitamin D concentration and colorectal cancer risk. INT J CANCER. 2022;150(2):303-307.
[33] Katagiri R, Goto A, Nakano S, Nakatochi M, Koyanagi YN, Iwagami M et al. Association of 25-hydroxyvitamin D with risk of overall and colorectal cancer among Japanese using a Mendelian randomization approach. SCI REP-UK. 2023;13(1):2384.
[34] Veettil SK, Wong TY, Loo YS, Playdon MC, Lai NM, Giovannucci EL et al. Role of Diet in Colorectal Cancer Incidence: Umbrella Review of Meta-analyses of Prospective Observational Studies. JAMA NETW OPEN. 2021;4(2):e2037341.
[35] Zhou X, Wang L, Xiao J, Sun J, Yu L, Zhang H et al. Alcohol consumption, DNA methylation and colorectal cancer risk: Results from pooled cohort studies and Mendelian randomization analysis. INT J CANCER. 2022;151(1):83-94.
[36] Ong J, Law MH, An J, Han X, Gharahkhani P, Whiteman DC et al. Association between coffee consumption and overall risk of being diagnosed with or dying from cancer among >300 000 UK Biobank participants in a large-scale Mendelian randomization study. INT J EPIDEMIOL. 2019;48(5):1447-1456.
[37] He M, Huan L, Wang X, Fan Y, Huang J. Nine dietary habits and risk of colorectal cancer: a Mendelian randomization study. BMC MED GENOMICS. 2024; 17(1):21.
[38] Larsson SC, Mason AM, Kar S, Vithayathil M, Carter P, Baron JA et al. Genetically proxied milk consumption and risk of colorectal, bladder, breast, and prostate cancer: a two-sample Mendelian randomization study. BMC MED. 2020;18(1):370.
[39] Morris JS, Bradbury KE, Cross AJ, Gunter MJ, Murphy N. Physical activity, sedentary behaviour and colorectal cancer risk in the UK Biobank. BRIT J CANCER. 2018;118(6):920-929.
[40] Papadimitriou N, Dimou N, Tsilidis KK, Banbury B, Martin RM, Lewis SJ et al. Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis. NAT COMMUN. 2020;11(1):510-597.
[41] Fagunwa IO, Loughrey MB, Coleman HG. Alcohol, smoking and the risk of premalignant and malignant colorectal neoplasms. BEST PRACT RES CL GA. 2017;31(5):561-568.
[42] Dimou N, Yarmolinsky J, Bouras E, Tsilidis KK, Martin RM, Lewis SJ et al. Causal Effects of Lifetime Smoking on Breast and Colorectal Cancer Risk: Mendelian Randomization Study. CANCER EPIDEM BIOMAR. 2021;30(5):953-964.
[43] Papadimitriou N, Kazmi N, Dimou N, Tsilidis KK, Martin RM, Lewis SJ et al. Leisure time television watching, computer use and risks of breast, colorectal and prostate cancer: A Mendelian randomisation analysis. CANCER MED-US. 2024;13(1):e6732.
[44] Lin Y, Wang S, Fan Z, Xie J, Ding G, Liu Y et al. A causal analysis of the relationship between exposure to sunlight and colorectal cancer risk: A Mendelian randomization study. MEDICINE. 2024; 103(18): e37991.
[45] Yuan S, Mason AM, Titova OE, Vithayathil M, Kar S, Chen J et al. Morning chronotype and digestive tract cancers: Mendelian randomization study. INT J CANCER. 2023;152(4):697-704.
[46] Vaughan-Shaw PG, Buijs LF, Blackmur JP, Theodoratou E, Zgaga L, Din FVN et al. The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials. BRIT J CANCER. 2020;123(11):1705-1712.
[47] Bishehsari F, Zhang L, Voigt RM, Maltby N, Semsarieh B, Zorub E et al. Alcohol Effects on Colon Epithelium are Time-Dependent. Alcoholism, clinical and experimental research. 2019;43(9):1898-1908.
[48] Jiang Y, Li H. The effect of smoking on tumor immunoediting: Friend or foe? TOB INDUC DIS. 2024;22(June):1-12.
[49] Friedenreich CM, Ryder Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. MOL ONCOL. 2021;15(3):790-800.
[50] Li H, Li G, Zhang X, Wang Y. [Genetic drivers for inflammatory protein markers in colorectal cancer: a Mendelian randomization approach to clinical prognosis study]. Nan Fang Yi Ke Da Xue Xue Bao. 2024;44(7):1361-1369.
[51] Constantinescu A, Bull CJ, Jones N, Mitchell R, Burrows K, Dimou N et al. Circulating white blood cell traits and colorectal cancer risk: A Mendelian randomisation study. INT J CANCER. 2024; 154(1): 94-103.
[52] Wang Y, Jia Z, Wang Q, Zhu Z. Eosinophils and drugs for eosinophilia are associated with the risk of colorectal cancer: a Mendelian randomization study. Aging (Albany, NY.). 2024;16(16):12050-12062.
[53] Wang Z. Wang Z, Shu Q, Wu J, et al. Evaluating the association between immunological proteins and common intestinal diseases using a bidirectional two-sample Mendelian randomization study. Cytokine. 2024;184:156788.
[54] Zhou H, Yang X, Yang Q, Cai Z, Hu K, Huang T. Exploring causal correlations between inflammatory cytokines and colorectal cancer: A 2-sample Mendelian

randomization study. MEDICINE. 2024; 103(44): e40230.
[55] Zhang J, Chen H, Yang R, Tang J, Yu X, Zeng P et al. Association between immune cell attributes, serum metabolites, inflammatory protein factors, and colorectal cancer: A Mendelian randomization study. MEDICINE. 2024;103(48):e40691.
[56] Yang Q, Duan B, Yue J, Zhang D, Chen X, Shi M et al. Causal effects and metabolites mediators between immune cell and risk of colorectal cancer: a Mendelian randomization study. FRONT IMMUNOL. 2024; 15: 1444222.
[57] Gu X, Zhao S, Xia M, Du S, Song L, Xia T et al. Causal impacts of 731 immunocyte phenotypes on colorectal cancer-evidence from a bidirectional two-sample Mendelian randomization. HUM VACC IMMUNOTHER. 2024;20(1):2432115.
[58] Aristin Revilla S, Kranenburg O, Coffer PJ. Colorectal Cancer-Infiltrating Regulatory T Cells: Functional Heterogeneity, Metabolic Adaptation, and Therapeutic Targeting. FRONT IMMUNOL. 2022;13:903564.
[59] Hou S, Zhao Y, Chen J, Lin Y, Qi X. Tumor-associated macrophages in colorectal cancer metastasis: molecular insights and translational perspectives. J TRANSL MED. 2024;22(1):14-62.
[60] Tang Y, Qian C. Research progress in leveraging biomaterials for enhancing NK cell immunotherapy. Zhejiang da xue xue bao. Journal of Zhejiang University. Medical sciences. Yi xue ban. 2023;52(3):267-278.
[61] De Simone V, Franzè E, Ronchetti G, Colantoni A, Fantini MC, Di Fusco D et al. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. ONCOGENE. 2015;34(27):3493-503.
[62] Bear AS, Vonderheide RH, O'Hara MH. Challenges and Opportunities for Pancreatic Cancer Immunotherapy. CANCER CELL. 2020;38(6):788-802.
[63] Chauhan J, Stavraka C, Grandits M, Palhares LCGF, Josephs DH, Lacy KE et al. Clinical and Translational Significance of Basophils in Patients with Cancer. Cells (Basel, Switzerland). 2022;11(3):438.
[64] La Vecchia S, Sebastián C. Metabolic pathways regulating colorectal cancer initiation and progression. SEMIN CELL DEV BIOL. 2020;98:63-70.
[65] Yun Z, Guo Z, Li X, Shen Y, Nan M, Dong Q et al. Genetically predicted 486 blood metabolites in relation to risk of colorectal cancer: A Mendelian randomization study. Cancer medicine (Malden, MA). 2023; 12(12): 13784-13799.
[66] Lee M, Nam S. The causal relationship of serum uric acid on colorectal cancer: A Mendelian randomization study. MEDICINE. 2024;103(26):e38722.
[67] Bull C, Hazelwood E, Bell JA, Tan V, Constantinescu A, Borges C et al. Identifying metabolic features of colorectal cancer liability using Mendelian randomization. ELIFE. 2023;12.
[68] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science (American Association for the Advancement of Science). 2009;324(5930):1029-1033.
[69] Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. CELL METAB. 2016; 23(1): 27-47.
[70] Beloribi-Djefaflia S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. ONCOGENESIS. 2016;5(1):e189.
[71] Cheng Y, Ling Z, Li L. The Intestinal Microbiota and Colorectal Cancer. FRONT IMMUNOL. 2020; 11: 615056.
[72] Ni J, Li X, Zhang H, Xu Q, Wei X, Feng G et al. Mendelian randomization study of causal link from gut microbiota to colorectal cancer. BMC CANCER. 2022; 22(1):1371.
[73] Hatcher C, Richenberg G, Waterson S, Nguyen LH, Joshi AD, Carreras-Torres R et al. Application of Mendelian randomization to explore the causal role of the human gut microbiome in colorectal cancer. SCI REP-UK. 2023;13(1):5968.
[74] Xiang Y, Zhang C, Wang J, Cheng Y, Wang L, Tong Y et al. Identification of host gene-microbiome associations in colorectal cancer patients using mendelian randomization. J TRANSL MED. 2023; 21(1): 535.
[75] Shanahan F. The colonic microbiota in health and disease. CURR OPIN GASTROEN. 2013;29(1):49-54.
[76] Han S, Yao J, Yamazaki H, Streicher SA, Rao J, Nianogo RA et al. Genetically Determined Circulating Lactase/Phlorizin Hydrolase Concentrations and Risk of Colorectal Cancer: A Two-Sample Mendelian Randomization Study. NUTRIENTS. 2024;16(6).
[77] Luo F, Zhou P, Ran X, Gu M, Zhou S. No evident causal association between Helicobacter pylori infection and colorectal cancer: a bidirectional mendelian randomization study. SCI REP-UK. 2023; 13(1): 18510-18544.
[78] Aierken A, Aizezi Y, Atabieke F, Rehaman M, Aierken M, Li SX. No bidirectional relationship between constipation and colorectal cancer in European and Asian populations: A Mendelian randomization study. MEDICINE. 2024;103(43):e40206.
[79] Chen L, Wang F, Zhang H, Cao B. Exploring potential causal associations between autoimmune diseases and colorectal cancer using bidirectional Mendelian randomization. SCI REP-UK. 2024;14(1):1557.
[80] Chen L, Fan Z, Sun X, Qiu W, Mu W, Chai K et al. Associations of cholecystectomy with the risk of colorectal cancer: a Mendelian randomization study. CHINESE MED J-PEKING. 2023;136(7):840-847.
[81] Yang L. Nonalcoholic fatty liver disease and colorectal cancer: a two-sample bidirectional Mendelian randomization analysis. EUR J GASTROEN HEPAT. 2024;36(12):1447-1452.
[82] Ni Y, Wang W, Liu Y, Jiang Y. Causal associations between liver traits and Colorectal cancer: a Mendelian randomization study. BMC MED GENOMICS. 2023;16(1):316.
[83] Zhang Y, Zhang H, Zhu J, He Y, Wang P, Li D et al. Association between diverticular disease and colorectal cancer: a bidirectional mendelian randomization study. BMC CANCER. 2023;23(1):137.
[84] Han H, Cai X, Liu X. Using multi-omics to explore the genetic causal relationship between colorectal cancer

and heart failure in gastrointestinal tumors. FRONT IMMUNOL. 2024;15:1454021.
[85] Liu C, Xie J, Ye B, Zhong J, Xu X. Unraveling the link between sterol ester and colorectal cancer: a two-sample mendelian randomization study. BMC CANCER. 2024;24(1):1462-1466.
[86] Shen J, Qin X, Zeng X, Xiao H, Lai S. Hemoglobin levels in red blood cells and risk of colorectal cancer: A causal investigation based on Mendelian randomization. MEDICINE. 2024;103(48):e40562.
[87] Tan C, Li Y, Wang K, Lin Y, Chen Y, Zheng X. Causal roles and clinical utility of cardiovascular proteins in colorectal cancer risk: a multi-modal study integrating mendelian randomization, expression profiling, and survival analysis. BMC MED GENOMICS. 2024; 17(1): 138.
[88] Morales BF, McCartney DL, Lu AT, Tsilidis KK, Bouras E, Haycock P et al. Assessing the causal role of epigenetic clocks in the development of multiple cancers: a Mendelian randomization study. ELIFE. 2022;11.
[89] Zhou Y, Lin Z, Xie S, Gao Y, Zhou H, Chen F et al. Interplay of chronic obstructive pulmonary disease and colorectal cancer development: unravelling the mediating role of fatty acids through a comprehensive multi-omics analysis. J TRANSL MED. 2023; 21(1): 1-587.
[90] Xiao Z, Wang Z, Zhang T, Liu Y, Si M. Bidirectional Mendelian randomization analysis of the genetic association between primary lung cancer and colorectal cancer. J TRANSL MED. 2023;21(1):722.
[91] Ke Q, Huang Y, Cheng L, Lin C, Zhao L, Huang W et al. Type 2 diabetes and colorectal cancer: genetic causality explored via Mendelian randomization. Discover. Oncology. 2024;15(1):721-728.
[92] Tang L, Li C, Chen W, Zeng Y, Yang H, Hu Y et al. Causal Association between Chronic Kidney Disease and Risk of 19 Site-Specific Cancers: A Mendelian Randomization Study. Cancer epidemiology, biomarkers & prevention. 2022;31(6):1233-42.
[93] Zhan Z, Huang Z, Lan Q, Luo Y, Li J, Zheng Y et al. Integrated multi-omics analyses revealed the association between rheumatoid arthritis and colorectal cancer: MYO9A as a shared gene signature and an immune-related therapeutic target. BMC CANCER. 2024; 24(1):714-716.
[94] Zhou L, Zhang J. Immune cells mediate the causal relationship between uveitis and colorectal cancer via Mendelian randomization analysis. SCI REP-UK. 2024;14(1):25964.
[95] Wu E, Ni J, Xie T, Tao L. Noncausal effects of genetic predicted depression and colorectal cancer risk: A Mendelian randomization study. MEDICINE. 2022; 101(34):e30177.
[96] Demb J, Kolb JM, Dounel J, Fritz CDL, Advani SM, Cao Y et al. Red Flag Signs and Symptoms for Patients With Early-Onset Colorectal Cancer: A Systematic Review and Meta-Analysis. JAMA NETW OPEN. 2024; 7(5):e2413157.
[97] Howes OD, Chapman GE. Understanding variability: the role of meta-analysis of variance. PSYCHOL MED. 2024;54(12):1-3236.
[98] Montalvan-Sanchez EE, Norwood DA, Dougherty M, Beas R, Guranizo-Ortiz M, Ramirez-Rojas M et al. Colorectal Cancer Screening Programs in Latin America: A Systematic Review and Meta-Analysis. JAMA NETW OPEN. 2024;7(2):e2354256.
[99] Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ (Online). 2018;362:k601.
[100] Davies NM, von Hinke Kessler Scholder S, Farbmacher H, Burgess S, Windmeijer F, Smith GD. The many weak instruments problem and Mendelian randomization. STAT MED. 2015;34(3):454-468.