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Genetically Assessed Risk Factors of Colorectal Cancer: A Literature Review of Mendelian Randomization Study

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Abstract

***Introduction**: Colorectal cancer (CRC) ranks as the third most common cancer and the second leading cause of cancer-related mortality globally. Despite substantial progress, the causal mechanisms linking various risk factors to CRC remain unclear due to confounding and reverse causality in observational studies. Mendelian Randomization (MR), which utilizes genetic variants as instrumental variables, offers a robust alternative for inferring causal relationships.*
***Method**: This narrative literature review evaluates MR studies published in the last decade that investigated genetically predicted risk factors associated with CRC. Articles were selected through systematic searches using PubMed and Cochrane databases. Inclusion criteria comprised relevance to CRC, MR methodology, full-text availability, and publication in peer-reviewed journals.*
***Discussion**: A total of seven MR studies were analyzed. The findings indicated that higher levels of total bilirubin, epigenetic clock GrimAge acceleration, insulin-like growth factor-1 (IGF-1), alcohol consumption, air pollutants (PM2.5), and specific gut microbiota (e.g., Porphyromonadaceae, Anaerotruncus, Intestinibacter) were causally associated with increased CRC risk. Conversely, Gammaproteobacteria and Enterobacteriaceae appeared protective. While MR reduces confounding and reverse causality, limitations such as horizontal pleiotropy and ancestry-specific biases (primarily European and East Asian populations) may affect generalizability, particularly to Southeast Asian populations.*
***Conclusion**: Genetically predicted exposures including biochemical markers, microbiota, and environmental factors demonstrate significant causal associations with CRC. However, future MR studies involving Southeast Asian populations, especially Indonesians, are needed to validate these findings within different genetic and environmental contexts.*

Keywords: Colorectal cancer, Mendelian randomization, risk factors

1. INTRODUCTION

Colorectal cancer (CRC) ranks as the third most common cancer globally, accounting for approximately 10% of all cancer cases[1]. Additionally, it is the second leading cause of cancer-

related deaths worldwide[2]. In 2022, Indonesia reported 35,676 new cases of colorectal cancer, making it the fourth most prevalent cancer in the country, with 19,255 deaths[3]. By 2030, over 2.2 million new cases and 1.1 million deaths due to CRC are projected, contributing to a 60% increase in the global burden of this disease[4]. This trend exacerbates public health challenges, imposing significant economic strain[5].

The socio-economic impact of CRC is substantial[5]. The high costs associated with treatments, including surgery, chemotherapy, and long- term care, place a significant burden on healthcare systems[5]. In addition, patients' quality of life is severely affected by symptoms such as pain, digestive issues, and chronic fatigue, which take a toll on both their physical and mental well-being[5].

Given the high morbidity and mortality associated with CRC, it is crucial to understand and address the modifiable risk factors to prevent the disease[6]. Early identification of risks such as overweight and obesity, lack of physical activity, smoking, alcohol consumption, and unhealthy dietary patterns, combined with an understanding of the genetic underpinnings, offers an important opportunity for targeted preventive interventions[7].

Despite extensive epidemiological research identifying numerous behavioral, metabolic, environmental, and biological risk factors, the causal nature of many of these associations remains uncertain. Most existing evidence is derived from observational studies, which are inherently susceptible to confounding, reverse causation, and measurement bias[8]. As a result, translating these associations into effective prevention and intervention strategies remains challenging.

Randomized controlled trials (RCTs) provide the highest level of causal evidence but are often impractical or unethical when evaluating long-term exposures such as alcohol consumption, environmental pollution, or endogenous biomarkers[9,10]. Mendelian randomization (MR) offers a complementary approach by using genetic variants as instrumental variables to infer causality between exposures and disease outcomes[11]. Because genetic variants are randomly allocated at conception, MR reduces confounding and reverse causation, thereby strengthening causal inference[12].

This review aims to critically synthesize evidence from MR studies evaluating genetically predicted risk factors for CRC. By focusing on causal inference rather than disease burden alone, this review addresses key knowledge gaps regarding the etiological role of metabolic, epigenetic, microbial, and environmental factors in colorectal carcinogenesis.

2. METHODS

2.1 Literature Search Strategy

This literature review employed a narrative approach with a structured and transparent methodology. A systematic literature search was conducted using the PubMed and Cochrane

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databases to identify MR studies evaluating genetically predicted risk factors for CRC The search included publications from January 2014 to December 2024 and used combinations of the keywords colorectal cancer, Mendelian randomization, genetically predicted, and risk factors.

2.2 Inclusion and Exclusion Criteria

Studies were included if they applied an MR design, evaluated genetically predicted exposures in relation to CRC risk, reported CRC as the primary outcome, and were published as full-text articles in peer-reviewed journals. Reviews, editorials, conference abstracts, and studies that did not employ MR methodology or did not specifically assess CRC outcomes were excluded. Duplicate records were removed, and titles and abstracts were screened for relevance prior to full-text assessment.

2.3 Data Extraction

Data extraction was performed manually by the authors. The extracted information included author and year of publication, type of genetically predicted exposure, number of cases and controls, ancestry of the outcome population, effect estimates (odds ratios or beta coefficients with 95% confidence intervals), and reported p-values, as summarized in the **Table 1**.

2.4 Data Synthesis

Data synthesis was conducted qualitatively due to heterogeneity in exposure variables, genetic instruments, and analytical methods across the included studies. A narrative synthesis was used to summarize and critically interpret the findings. All genetically evaluated risk factors reported in the included MR studies were considered, regardless of statistical significance, in order to minimize selective reporting bias and to provide a comprehensive overview of the current evidence.

3. DISCUSSION

3.1 Overview of Studies Included

This review included seven Mendelian randomization studies evaluating genetically predicted risk factors for CRC, as summarized in **Table 1**. The investigated exposures encompassed metabolic biomarkers (total bilirubin and insulin-like growth factor-1), epigenetic aging indicators (GrimAge acceleration), lifestyle-related factors (alcohol consumption), environmental exposures (fine particulate matter, PM2.5), and gut microbiota composition. Most studies were conducted in populations of European ancestry, while only one study involved East Asian populations, indicating limited ancestral diversity in the current MR literature.

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Table 1. Overview of Studies on Exposures and Colorectal Cancer Risk

Study	Exposure	Control	Case	Ancestry of Outcome	OR (95%CI)	*p-value*
Seyed Khoei et al., 2020	Total bilirubin levels (man)	45,94	52,775	European	1.07(1.02–1.12)	0.006
Berstein et al., 2022	Epigenetic clock GrimAge	613369	66810	European	1.12(1.04–1.2)	0.002
Li, Wanxin et al., 2023	*Gammaproteobacteria*	26,328	16,871	European	0.027(0.017–0.037)	$7.06x10^{-8}$
Li Wanxin et al., 2023	*Enterobacteriaceae*	26328	16,871	European	0.023(0.013–0.034)	$1.29x10^{-5}$
Xiang et al., 2023	*Porphyromonadaceae*	27278	6692	East Asian	1.26(1.03–1.55)	0.0267
	Anaerotruncus				1.17(1.01–1.36)	0.0390
	Intestinibacter				1.31(1.09–1.57)	0.0038
	Slackia				1.24(1.06–1.45)	0.0071
	Ruminococcaceae UCG004				1.27(1.03–1.57)	0.023220
	Eubacterium coprostanoligenes				1.25(1.00–1.56])	0.0467
Zhou et al., 2022	Alcohol	22,661	20,049	European	1.79(1.23,2.61)	0.003
Jiang et al., 2024	Air pollutants: PM2.5	26,328	16,871	European	1.19(1.12,1.27)	<0.05
Murphy et al., 2020	Insulin-like growth factor-1	46,287	52,865	European	1.08(1.03–1.12)	$3.3x10^{-4}$

3.2 Total Bilirubin Levels and Colorectal Cancer Risk

Seyed Khoei et al. (2020) identified a causal association between genetically predicted unconjugated bilirubin (UCB) levels and colorectal cancer risk in men. Elevated UCB levels predicted by the UGT1A1 single nucleotide polymorphism (rs6431625) were associated with an increased risk of CRC (OR [95% CI] = 1.07 [1.02–1.12]) 13. The potential influence of horizontal pleiotropy could not be fully excluded, particularly due to the absence of baseline liver enzyme data that would allow direct assessment of hepatic function[13]. Genetic variants may therefore influence CRC risk through pathways unrelated to bilirubin metabolism.

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Bilirubin is widely recognized for its antioxidant properties and has been hypothesized to exert cancer-protective effects[14]. At elevated concentrations, bilirubin may act as a pro-oxidant by promoting the generation of reactive oxygen species and inducing oxidative stress, which can increase cancer risk[14]. Observational studies have reported inconsistent findings. A retrospective case–control study involving 174 cases reported a higher CRC risk associated with lower total bilirubin levels, whereas a prospective National Health and Nutrition Examination Survey (NHANES I) study found no association between UCB levels and CRC incidence [15]. Differences in study design, sample size, timing of sample collection, and analytical sensitivity may contribute to these discrepancies. In this context, MR provides complementary evidence supporting a potential causal role of bilirubin in CRC development.

3.3 Epigenetic Clock GrimAge and Colorectal Cancer

Berstein et al. (2022) demonstrated that genetically predicted acceleration of the epigenetic clock GrimAge was significantly associated with an increased risk of colorectal cancer (OR [95% CI] = 1.12 [1.04–1.20]. These findings indicate that colorectal carcinogenesis is influenced not only by genetic mutations but also by epigenetic aging processes. The study relied on a weighted mode analysis based on four single nucleotide polymorphisms, which may limit the stability of the estimates and introduce uncertainty[16].

Observational evidence partially supports these findings. Dugue et al. (2021) reported a 4% increase in CRC risk for each additional year of GrimAge acceleration (RR = 1.04, 95% CI 1.01–1.07)[17]. Hillary et al. (2020) reported no significant association between GrimAge acceleration and CRC risk, which may be attributed to the small sample size of 63 patients[18]. GrimAge reflects biological aging through DNA methylation at 5′-C-phosphate-G-3′ (CpG) sites[19]. Increased methylation at these sites can suppress tumor suppressor gene expression, leading to dysregulation of cell proliferation and enhanced tumorigenesis[19]. The MR findings strengthen evidence for a causal role of biological aging in colorectal cancer development.

3.4 Gut Microbiota and Colorectal Cancer Risk

Xiang et al. (2023) reported significant causal associations between specific gut microbiota taxa and increased CRC risk in East Asian populations[20]. Six taxa were identified, including *Porphyromonadaceae*, *Anaerotruncus*, *Intestinibacter*, *Slackia*, *Ruminococcaceae UCG004*, and *Eubacterium coprostanoligenes*[20]. The strongest associations were observed for *Porphyromonadaceae* (OR 95% CI] = 1.26 [1.03–1.55]) and *Intestinibacter* (OR [95% CI] = 1.31 [1.09–1.57]).

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Observational studies provide supporting evidence for these findings. Yang et al. (2019) reported increased abundance of *Porphyromonadaceae* in CRC patients using next-generation sequencing[21]. Loke et al. demonstrated that *Anaerotruncus* influences steroid biosynthesis in tumor tissue, increasing levels of tumor-associated metabolites such as S-adenosylmethionine and S-adenosylhomocysteine[22].

These microbial taxa may promote carcinogenesis through modulation of inflammatory pathways, production of carcinogenic metabolites, and disruption of gut barrier integrity[20].

3.5 Protective Role of Specific Gut Microbiota

Li et al. (2023) identified *Gammaproteobacteria* (β [95% CI] = 0.027 [0.017–0.037]) and *Enterobacteriaceae* (β [95% CI] = 0.023 [0.013–0.034]) as having protective associations against colorectal cancer[23]. Observational studies have reported increased abundance of these taxa in adenoma tissues compared with normal mucosa[24–26]. These findings suggest that gut microbiota may exert differential effects at various stages of colorectal tumorigenesis and highlight the complexity of host–microbiome interactions.

3.6 Insulin-Like Growth Factor-1 (IGF-1)

Murphy et al. (2020) demonstrated Murphy et al. (2020) demonstrated that genetically predicted higher IGF-1 levels were associated with increased CRC risk (OR [95% CI] = 1.08 [1.03–1.12]). Epidemiological studies have reported inconsistent associations, although the biological role of IGF-1 in tumorigenesis is well established[27]. IGF-1 promotes cell proliferation and survival through activation of the MAPK and PI3K signaling pathways. Overexpression of IGF-1 receptors in colorectal neoplastic cells further supports its role in CRC development[27]. Residual horizontal pleiotropy remains a potential limitation of MR analyses evaluating this pathway.

3.7 Air Pollution

Jiang et al. (2024) demonstrated a significant causal association between exposure to fine particulate matter (PM2.5) and colorectal cancer risk (OR [95% CI] = 1.19 [1.12–1.27])[28]. Prolonged PM2.5 exposure induces systemic inflammation and oxidative stress, leading to DNA damage and epigenetic alterations[29]. DNA methylation changes at CpG sites associated with genes such as CXCR5 and TMBIM1 have been linked to increased CRC risk[30–32]. PM2.5 exposure may also disrupt gut microbiota composition and impair intestinal barrier function, creating a pro-inflammatory environment conducive to colorectal carcinogenesis[33]. The use of blood-derived DNA methylation data rather than colorectal tissue samples represents a key limitation of the included MR study[28].

3.8 Alcohol Consumption

Zhou et al. (2022) reported a significant causal association between alcohol consumption and colorectal cancer risk (OR = 1.79, 95% CI 1.23–2.61)[34]. These findings are supported by observational evidence demonstrating a dose-dependent relationship between alcohol intake and CRC risk, particularly among individuals consuming more than 50 g/day of alcohol[35]. Alcohol metabolism produces acetaldehyde, a toxic compound that induces DNA damage, disrupts DNA repair mechanisms, and promotes chronic inflammation[36,37]. Epigenetic dysregulation at CpG sites associated with COLCA1 and COLCA2 further contributes to colorectal tumorgenesis[36,37].

The generalizability of these findings remains limited by the predominance of European ancestry populations. Genetic variants affecting alcohol metabolism, such as ALDH2 rs671, which are common in East Asian populations, were not accounted for and may modify CRC risk[34].

3.9. Limitations

Several limitations of this narrative review should be acknowledged. This review was based on previously published Mendelian randomization studies, and therefore reflects the methodological choices, data sources, and analytical strategies of the original investigations. Differences in genetic instruments, exposure definitions, and statistical approaches across studies may contribute to variability in effect estimates, although all included studies applied established MR frameworks.

Most of the available evidence was derived from populations of European ancestry, with additional data from East Asian populations. This distribution reflects the current landscape of MR research in colorectal cancer rather than a selective focus of this review. While such evidence provides valuable insights, caution is warranted when extrapolating the findings to other populations, including Southeast Asian populations, where genetic and environmental contexts may differ.

Mendelian randomization offers advantages in reducing confounding and reverse causality; however, the presence of horizontal pleiotropy cannot be completely excluded. Several included studies conducted sensitivity analyses to address this issue, although the specific methods and depth of pleiotropy assessment varied. This variability may influence the interpretation of causal estimates but does not negate the overall contribution of the findings.

Certain exposures were instrumented using a limited number of genetic variants, which may affect statistical precision. In addition, population stratification remains an inherent consideration in genetic studies, particularly when exposure and outcome datasets are derived from different cohorts. These factors should be considered

when interpreting the magnitude of reported associations.

This review aimed to provide a qualitative synthesis of the available MR evidence. As a result, formal assessment of publication bias was not performed. The possibility that studies with null findings are underrepresented in the literature should be considered, although the inclusion of both significant and non-significant results in this review was intended to reduce selective interpretation.

4. CONCLUSION

It can be concluded that in this study, data has been collected and presented that can be used to confirm that the risk factors are high total bilirubin levels, acceleration of the Epigenetic clock GrimAge, Increased levels of Insulin growth like factor-1(IGF-1), alcohol consumption, air pollutant, specific type of microbes in gut including *Porphyromonadaceae*, *Anaerotruncus*, *Intestinibacter*, *Slackia*, *Ruminococcaceae*, and *Eubacterium coprostanoligenes* group demonstrated a causal association with colorectal cancer risk.

However, the data collected in this study came from research that used samples from European and East Asian communities which have geographical differences from Southeast Asian communities including Indonesia, which could produce different results with the same exposure.

In the future, it is hoped that research can be carried out in the same field using research data using samples from Southeast Asian society, especially Indonesia.

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