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Systematic Review: Factors Associated with the Incidence of Colorectal Cancer

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Keyword: Colorectal Carcinoma; Risk Factors; Systematic Review; Early-Onset Colorectal Cancer; Cancer Prevention;

Abstract
Introduction: *Colorectal carcinoma (CRC) ranks third in global cancer incidence with an estimated 1.93 million new cases in 2020 and constitutes the second leading cause of cancer-related mortality worldwide. Indonesia documented 34,189 new cases, predominantly diagnosed at advanced stages, underscoring the critical need for comprehensive identification of CRC risk determinants.* ***Objective:*** *To systematically synthesize factors associated with CRC occurrence and analyze the magnitude of their associations to formulate evidence-based prevention recommendations.* ***Methods:*** *A systematic literature review following PRISMA 2020 guidelines was conducted across PubMed, Google Scholar, and ScienceDirect (2015–2024), yielding 30 selected articles from 309 initial records.* ***Results and Discussion:*** *Non-modifiable factors demonstrated the highest associations, including first-degree family history (OR 17.78), precancerous lesions (OR 8.57), and inflammatory bowel disease (OR 7.07). Modifiable factors encompassed physical inactivity (OR 5.69), excessive red meat consumption (OR 4.97), alcohol (OR 4.92), central obesity causally confirmed via Mendelian randomization (OR 1.38), diabetes (HR 2.20), and hypertension (HR 1.99). Gut microbiota dysbiosis actively contributed to carcinogenesis through genotoxicity and chronic inflammation mechanisms.* ***Conclusion:*** *CRC is multifactorial in nature; while non-modifiable factors carry larger absolute effect sizes, modifiable factors offer more strategically actionable intervention targets*

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Introduction

Colorectal carcinoma (CRC) is an epithelial malignancy originating from the malignant transformation of mucosal cells of the colon and rectum, and continues to represent a growing global health burden. According to the Global Cancer Statistics 2020 report, CRC ranks third in incidence with an estimated 1.93 million new cases, while simultaneously occupying the second position as a leading cause of cancer-related mortality, accounting for 935,000 deaths worldwide (Sung et al., 2021). More recent data from the Global Burden of Disease Study 2021 reveal an even more alarming trend, with the number of new CRC cases globally rising from 916,583 in 1990 to 2,194,143 in 2021, with projections estimating a surge to more than 3.2 million new cases and 1.6 million deaths by 2040 (Tian, Wang, & Wei, 2025). In Indonesia, CRC ranks second in incidence within the Southeast Asian region at 24.1%, and is recorded as one of the fifth leading causes of cancer-related mortality nationally, with the majority of patients diagnosed at advanced stages, leaving therapeutic options severely limited (Kementerian Kesehatan RI, 2022).

Etiologically, CRC is a multifactorial disease influenced by the interaction between non-modifiable factors—including advanced age, male sex, history of inflammatory bowel disease (IBD), and genetic predispositions such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC)—and modifiable factors such as excessive red meat consumption, obesity, physical inactivity, smoking, and alcohol consumption (Lewandowska et al., 2022). A systematic review and meta-analysis by Hua et al. (2023) found that obesity increases the risk of early-onset colorectal cancer (EOCRC) with an OR of 1.52, smoking with OR 1.44, alcohol consumption OR 1.41, and a history of IBD up to OR 4.43, affirming that lifestyle modification constitutes the primary pillar of CRC prevention. Pathophysiologically, CRC develops through three main pathways, namely the adenoma-carcinoma sequence, the serrated pathway, and the inflammation-driven pathway, each progressing gradually over many years, thereby presenting a genuine opportunity for early detection through screening programs (Chen et al., 2026). The clinical manifestations of CRC in early stages are generally asymptomatic, with commonly encountered symptoms including rectal bleeding, changes in bowel habits, abdominal pain, and iron deficiency anemia, while the characteristics of symptoms are further determined by tumor location (Duan et al., 2022).

Despite the existence of numerous studies on CRC risk factors, the available literature still harbors several fundamental limitations. The majority of prior studies focused on one or two risk factors in isolation without integrating them into a comprehensive evidence synthesis. Aswan & Hanriko (2023) noted that local research in Indonesia remains highly limited in simultaneously assessing CRC risk factors, despite the fact that the risk profile of Asian populations carries distinct characteristics compared to Western populations. Furthermore, Wu et al. (2022) highlighted that the interaction between genetic and lifestyle factors in determining CRC risk has yet to be examined in depth within the context of developing countries. The novelty of this study lies in its systematic synthesis of various factors associated with CRC incidence through a systematic literature review (SLR) approach, with the aim of generating evidence-based recommendations relevant to the Indonesian public health context.

Based on the foregoing, this study aims to: (1) identify and synthesize factors associated with CRC incidence based on SLR findings; (2) analyze the strength of association between modifiable and non-modifiable risk factors and CRC incidence; and (3) formulate clinical and public health implications of these findings as a basis for

developing prevention strategies in Indonesia. The results of this study are expected to enrich the body of knowledge in the fields of oncology and cancer epidemiology, serve as a reference for clinicians in conducting individual risk assessments, and provide a scientific foundation for policymakers in designing national screening programs and more targeted community-based interventions (Morgan et al., 2023).

Method

This study employed a systematic literature review (SLR) design aimed at synthesizing scientific evidence on factors associated with colorectal carcinoma incidence. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines developed by Page et al., 2021, encompassing a 27-item checklist and an updated study selection flow diagram to ensure transparency and completeness of reporting. A comprehensive literature search was conducted across reputable electronic databases, including PubMed/MEDLINE, Google Scholar, and ScienceDirect, using Boolean AND/OR operators to combine key terms such as "karsinoma kolorektal," "kanker kolorektal," "faktor risiko," "colorectal cancer," "risk factors," and "associated factors." Publications were restricted to those published between 2015 and 2024 to ensure currency and relevance of evidence. All study selection processes were performed independently by two researchers to minimize selection bias.

As presented in the PRISMA flow diagram, the initial identification yielded 309 articles from various databases. Following the removal of 102 duplicate records, 207 articles proceeded to the screening stage, of which 95 were excluded based on irrelevant titles and abstracts, leaving 112 articles for further evaluation. A second screening excluded 56 articles that did not meet methodological criteria, resulting in 56 articles assessed for eligibility. At the eligibility stage, 26 articles were excluded for classified reasons (Reason 1: 14 articles; Reason 2: 12 articles), consistent with the principle of staged selection emphasizing consistent application of inclusion and exclusion criteria at each phase (Putra et al., 2025). Ultimately, 30 articles met all criteria and were included in the final synthesis. Inclusion criteria comprised quantitative studies with cross-sectional, case-control, or cohort designs; participants diagnosed with colorectal carcinoma; full-text accessibility; and publication in Indonesian or English. Exclusion criteria included case reports, narrative reviews without primary data, and articles not reporting odds ratios (OR) or equivalent association measures. Data were extracted systematically using a structured table capturing study identity, research design, population, risk factor variables, and association measures, and were subsequently synthesized narratively

Result and Discussion

1. Result

The study selection process was carried out systematically following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flowchart. During the identification stage, electronic database searching yielded 309 articles. After removing 102 duplicate records, 207 articles entered the screening stage. Screening based on titles and abstracts excluded 95 irrelevant articles, leaving 112 articles for further review. The second screening stage excluded 56 articles for not meeting methodological criteria, resulting in 56 articles evaluated for full eligibility. During the eligibility assessment stage, 26 articles were excluded, with 14 articles excluded based on Reason 1

and 12 articles based on Reason 2. Consequently, 30 articles met all inclusion criteria and were included in the final research synthesis. The complete study selection process is presented visually in Figure 1.

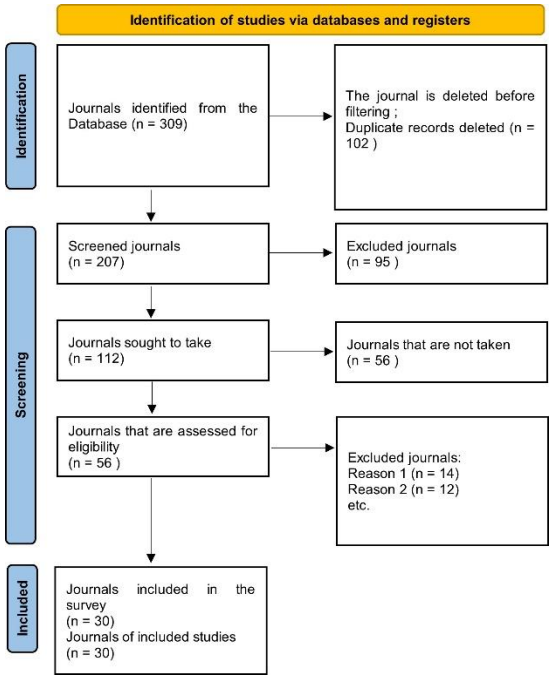

Figure 1. PRISMA Diagram

Table 1
Characteristics of Studies Included in the Review

No	Author	Design and Population	Risk Factors/Exposures Assessed	Refocused Interpretation of Findings
1	(Dite, Wong, Gafni, & Spaeth, 2025)	Population-based cohort study; 395,072 UK Biobank participants aged 40–69 years.	Family history, polygenic risk score (PRS), and clinical factors for 10-year risk prediction.	Family history and PRS demonstrated adequate risk discrimination capacity; the addition of clinical factors significantly improved model performance. These findings are more appropriately used for risk stratification than for single etiological claims.
2	(Kanehara et al., 2024)	Prospective cohort study; 192,651 multiethnic cohort participants with a mean follow-up of 19 years and 4,403 incident CRC cases.	Total sugar intake and sugar food sources, including fructose, glucose, and maltose.	High sugar intake was associated with a relatively small but significant increase in CRC risk (HR highest vs lowest quintile 1.13; 95% CI: 1.01–1.27). The association was stronger in those aged 45–54 years, colon cancer, and Latino ethnicity, indicating heterogeneity by age, tumor location, and ethnicity.
3	(Pan et al., 2023)	Prospective cohort study; 222 EOCRC cases and 87,833 controls aged 30–50 years with a median follow-up of 9.1 years.	BMI, alcohol consumption, fish intake, hypertension, diabetes, and family history of cancer.	Diabetes (HR 2.20), hypertension (HR 1.99), alcohol consumption (HR 1.69), and family history of cancer (HR 1.70) were associated with EOCRC. These results support the role of metabolic comorbidities, but should still be interpreted as observational associations.
4	(Carson et al., 2024)	Case-control study; 11 newly diagnosed female CRC cases and 22 cancer-free controls, matched by age, BMI, and race.	Gut microbiota, diet, stress, and race.	Microbiota variation associated with CRC differed by racial group, and psychological stress was inversely associated with alpha diversity. Given the small sample size, these findings are exploratory in nature and primarily suggest potential biological and social heterogeneity.
5	(Roos et al., 2022)	Prospective pooled multicohort study; 171,063 men and women from seven Finnish health surveys.	Overweight, smoking, and alcohol consumption in pairwise combinations.	Higher risk was observed in overweight male smokers (HR 1.75) and overweight women with alcohol consumption (HR 1.45). No significant pairwise interaction was found, so combined effects should be carefully explained as accumulated associations rather than definitive causal synergy.
6	(Hoang et al., 2023)	Cross-sectional study; 331 post-resection CRC patients at Seoul National University Hospital.	Smoking, alcohol consumption, diabetes, obesity, hypertension, and microbiome variation.	Lifestyle and metabolic diseases were associated with microbiome composition variation in CRC patients. Given the cross-sectional design in patients who already had CRC, this study cannot establish the direction of the relationship between these factors and CRC incidence.

No	Author	Design and Population	Risk Factors/Exposures Assessed	Refocused Interpretation of Findings
7	(Sun et al., 2025)	Real-world data and machine learning-based case-control study; 1,358 colon cancer cases and 560 rectal cancer cases aged <45 years with matched controls.	EHR-derived predictors including immune disorders, digestive disorders, secondary malignancies, underweight status, and blood diseases.	The model demonstrated promising predictive performance for EOCRC, particularly close to diagnosis time. These findings are relevant for detection and risk stratification, but do not constitute etiological causal evidence, as predictors may reflect symptoms, comorbidities, or clinical processes preceding diagnosis.
8	(Puspitaningtyas et al., 2024)	Cross-sectional study based on the Yogyakarta Population-Based Cancer Registry; 1,295 CRC cases from 2008–2019.	Age, sex, cancer location, and early-onset trends.	Women had a relatively higher risk for colon cancer, and those aged 30–39 years showed the highest RR for colon cancer. This study reveals local heterogeneity in Indonesia and reinforces the need for population-based risk factor studies within the country.
9	(Bener et al., 2024)	Comprehensive case-control study; 704 CRC cases and 704 controls in a Turkish population.	Genetic factors, family history, bowel disease, smoking, hookah/nargileh, alcohol, stress, obesity, and red meat consumption.	Various clinical, lifestyle, and dietary factors were associated with CRC. Exposures such as hookah/nargileh highlight an important cultural context, but the potential for recall bias and residual confounding in a case-control design should be considered.
10	(Danial et al., 2022)	Retrospective cohort/database analysis; 13,800 young adults aged 20–50 years with primary CRC.	Family history of CRC, primary breast cancer, IBD, alcohol, smoking, obesity, diabetes, hyperlipidemia, and ethnicity.	Family history of CRC (OR 17.78) and primary breast cancer (OR 16.94) were the strongest predictors of EOCRC; IBD also showed a strong association. Lifestyle and metabolic factors were associated, though interpretation is limited by the retrospective nature of the data and potential differences in clinical documentation.
11	(Shafiee et al., 2023)	Hospital-based case-control study in Malaysia; 99 CRC cases, 73 colon polyp cases, and 141 healthy controls.	Dietary Inflammatory Index (E-DII), obesity, age, smoking status, and anthropometric indices.	Pro-inflammatory diet was associated with CRC risk particularly in obese subjects (OR 1.45; 95% CI: 1.30–1.77). These findings highlight a possible differential effect of diet by obesity status and in the Southeast Asian population context.
12	(Li et al., 2024)	Two-sample Mendelian randomization study; 3,022 CRC cases and 174,006 controls from FinnGen.	Waist-to-hip ratio, smoking, physical activity, and alcohol.	High WHR was associated with increased CRC risk (OR 1.38), while smoking initiation showed a suggestive association. Physical activity and alcohol showed no causal evidence in this analysis. Causal claims remain subject to the validity of MR instrument assumptions and the European population used.

No	Author	Design and Population	Risk Factors/Exposures Assessed	Refocused Interpretation of Findings
13	(El-Moselhy et al., 2025)	Multi-center case-control study in Egypt; 200 CRC cases and 200 controls.	Colorectal precancerous lesions, family history, IBD, type 2 diabetes, red/processed meat, physical inactivity, coffee consumption, alcohol, and other clinical history.	Precancerous lesions, family history, and IBD showed strong associations, while dietary factors, physical activity, and alcohol were also associated. Some clinical variables may be subject to reverse causality or healthcare setting context, requiring prospective validation.

Refocused Summary of Results

Based on the aforementioned primary studies, the non-modifiable factors most consistently associated with CRC are family history, genetic predisposition or polygenic risk scores, IBD, age, sex, and ethnic or population characteristics. In the UK Biobank-based study, the combination of family history and PRS demonstrated adequate predictive capacity for 10-year CRC risk, with clinical factors only incrementally improving model discrimination (Dite et al., 2025). In studies of young adults, family history of CRC and IBD emerged as strong predictors of EOCRC, while ethnic differences indicated that risk is not uniform across population groups (Danial et al., 2022).

For modifiable factors, the most relevant evidence comes from cohort and case-control studies assessing lifestyle, dietary, metabolic, and behavioral exposures. High sugar intake was associated with increased CRC risk in the Multiethnic Cohort Study, though the magnitude of the association was relatively small and varied by age, ethnicity, and tumor location (Kanehara et al., 2024). In a Chinese cohort, diabetes, hypertension, alcohol consumption, BMI, and family history of cancer were associated with EOCRC (Pan et al., 2023). Meanwhile, a multicohort study in Finland found that the combination of overweight, smoking, and alcohol was associated with increased risk, though no statistically significant pairwise interactions were identified (Roos et al., 2022).

Primary case-control studies from Turkey, Malaysia, and Egypt indicated that dietary factors, obesity, physical activity, alcohol, smoking, clinical history, and culturally specific exposures may be associated with CRC (Bener et al., 2024; Shafiee et al., 2023; El-Moselhy et al., 2025). However, as case-control designs are susceptible to recall bias, selection bias, and residual confounding, these findings are more appropriately positioned as a basis for identifying at-risk groups and prioritizing future research, rather than as definitive causal evidence.

Microbiome findings also revealed important variation. A small case-control study in women and a cross-sectional study in post-resection CRC patients indicated that microbiota composition may differ by race, stress, lifestyle, and metabolic disease (Carson et al., 2024; Hoang et al., 2023). Accordingly, the microbiome is best discussed as a potential mechanism and an emerging biomarker, rather than a causally established risk factor across all populations.

One Mendelian randomization study provided stronger support for causal interpretation, particularly for central obesity measured by waist-to-hip ratio (Li et al., 2024). Nevertheless, MR findings remain contingent on the validity of genetic instruments, population structure, and the assumption of no pleiotropy. Therefore, causal claims should be restricted to factors supported by analytical designs that permit causal

inference, and should continue to be compared with observational findings from other populations.

2. Discussion

Emphasis on Primary Study Evidence and Limitations of Causal Inference

This discussion positions primary studies as the primary basis for assessing CRC risk factors. This approach is important because not all articles included in the review carry equal evidentiary weight for explaining etiological relationships. Review studies, modeling studies, epidemiological projections, and clinical guidelines remain useful for providing context, but are not used as primary sources for concluding on risk factors. Accordingly, the findings of this review more appropriately state that certain factors are "associated with," "related to," or "can be used for risk stratification," unless supported by designs that specifically permit causal inference.

The majority of primary studies included in the synthesis employed observational designs, including cohort, case-control, cross-sectional, database analysis, and EHR-based machine learning studies. Such designs are strong for identifying association patterns and at-risk groups, but remain susceptible to confounding, selection bias, recall bias, variability in documentation quality, and reverse causality. Therefore, statements suggesting that obesity, smoking, alcohol, diet, or physical inactivity "directly cause" CRC should be avoided. A more accurate formulation is that these factors are associated with increased CRC risk in certain populations and may serve as prevention targets given their modifiable nature.

Non-Modifiable Factors as the Basis for Risk Stratification

Non-modifiable factors demonstrated relatively consistent evidence, particularly family history of CRC, IBD, genetic predisposition, age, sex, and ethnic or population differences. Danial et al. (2022) reported that family history of CRC carried the highest association measure for EOCRC, while IBD also showed a strong relationship. These findings align with El-Moselhy et al. (2025), which demonstrated that precancerous lesions, family history, and IBD were among the primary medical predictors in an Egyptian population. At the population prediction level, Dite et al. (2025) showed that family history and PRS can provide meaningful risk discrimination.

The interpretation of these findings should be directed toward risk stratification, not biological determinism. Individuals with family history, IBD, or high genetic risk may be prioritized for earlier screening or more intensive surveillance, yet the magnitude of risk remains influenced by age, access to screening, environmental factors, lifestyle, and population characteristics. Non-modifiable factors thus serve as an initial basis for identifying high-risk groups, which must then be complemented by an assessment of modifiable factors.

Modifiable Factors: Important Prevention Targets, but Should Not Be Interpreted as Overly Causal

Modifiable factors such as obesity, smoking, alcohol consumption, physical inactivity, and unhealthy dietary patterns appeared repeatedly across several primary studies. However, the strength and consistency of their associations varied across designs and populations. Kanehara et al. (2024) found that high sugar intake was associated with greater CRC risk, but the effect size was relatively small and differed by age, ethnicity, and tumor location. Pan et al. (2023) reported that diabetes and hypertension were

associated with EOCRC, while Roos et al. (2022) showed increased risk with combinations of overweight, smoking, and alcohol, without evidence of statistically significant interactions. These results indicate that modifiable factors are relevant to prevention, but should not be oversimplified as single causes.

Case-control studies from Turkey, Malaysia, and Egypt extended the evidence that dietary patterns, obesity, physical activity, smoking, alcohol, and certain local exposures are associated with CRC (Bener et al., 2024; Shafiee et al., 2023; El-Moselhy et al., 2025). However, case-control designs often rely on exposure histories collected after diagnosis, meaning recall bias and behavioral changes due to early symptoms may influence results. Therefore, discussion of modifiable factors should emphasize that they represent rational health promotion targets, not evidence that modifying any single factor will always directly reduce CRC risk in all populations.

Li et al. (2024) provided additional perspective through Mendelian randomization, with results supporting an association between central obesity and CRC and a suggestive association for smoking initiation. However, since physical activity and alcohol did not demonstrate causal evidence in that analysis, it would be inaccurate to claim that all lifestyle factors carry the same level of causal evidence. This finding reinforces the need to distinguish between factors that are observationally consistent, factors supported by causal inference, and factors that still require further investigation.

Heterogeneity of Studies, Populations, Exposures, and Outcomes

Heterogeneity is a critical aspect to address, as the synthesized studies differed substantially in design, population, exposure measurement, and outcome definition. In terms of design, cohort studies such as Kanehara et al. (2024), Pan et al. (2023), and Roos et al. (2022) carry temporal advantages over case-control designs, yet remain susceptible to residual confounding. Case-control studies such as Bener et al. (2024), Shafiee et al. (2023), and El-Moselhy et al. (2025) are more efficient for evaluating multiple risk factors, but are prone to selection and recall bias. Cross-sectional studies such as Hoang et al. (2023) and Puspitaningtyas et al. (2024) are useful for describing patterns, but cannot establish the direction of causal relationships.

Population heterogeneity was also highly prominent. Studies were drawn from diverse contexts including the UK Biobank, a multiethnic cohort, China, Finland, Korea, Yogyakarta, Turkey, Malaysia, Egypt, and United States health databases. These differences encompass genetic variation, diet, culture, socioeconomic status, urbanization, access to screening, diagnostic quality, and patterns of health documentation. For example, Kanehara et al. (2024) demonstrated differences in sugar associations by ethnicity and age; Puspitaningtyas et al. (2024) revealed local early-onset patterns in Yogyakarta; while Bener et al. (2024) highlighted the culturally relevant exposure of hookah/nargileh. This indicates that association measures from one country cannot be directly generalized to other populations without local validation.

Outcome heterogeneity also warrants attention. Some studies evaluated CRC broadly, some focused on EOCRC, some distinguished between colon and rectal cancer, while microbiome studies assessed bacterial composition or microbial community variation in patients already diagnosed. Different outcomes may yield different associations. Therefore, synthesis of results should avoid treating all outcomes as a single homogeneous entity, but rather distinguish between incidence risk, diagnostic prediction, incidence patterns, and potential biological mechanisms.

Implications of Findings for CRC Prevention and Control in Indonesia

For Indonesia, these findings point toward the need for risk-based prevention strategies, while exercising caution in adopting association measures derived from other countries. Puspitaningtyas et al. (2024) demonstrated an increase in early-onset colon cancer in Yogyakarta, highlighting the urgency of strengthening local research on dietary risk factors, obesity, physical activity, smoking, diabetes, hypertension, family history, and IBD. Local data are essential, as risk factors that are significant in European, American, Chinese, Turkish, Malaysian, or Egyptian populations may not carry the same effect size in the Indonesian population.

For primary prevention, modifiable factors should continue to be targeted through health promotion efforts, as the interventions involved are relatively feasible and also beneficial for other non-communicable diseases. However, the scientific narrative should emphasize that recommendations such as obesity control, increased physical activity, reduction of smoking and alcohol, and dietary improvement are grounded in an accumulation of risk associations and broad health benefits, rather than on causal claims from any single study. Integration of CRC risk assessment into existing non-communicable disease management programs such as Posbindu and Prolanis represents a realistic step, particularly for individuals with diabetes, hypertension, obesity, family history, or gastrointestinal symptoms requiring referral.

For secondary prevention, a risk stratification-based screening approach remains important. Heisser et al. (2024) demonstrated substantial benefit of screening colonoscopy in reducing mortality, while Issaka et al. (2023) emphasized the importance of stratification based on age, family history, and clinical risk. In the Indonesian context, limited access to colonoscopy should be addressed through a staged approach—for example, symptom education, risk assessment at primary care, use of FIT for appropriate groups, and colonoscopy referral for high-risk individuals. This approach is more realistic than implementing a universal single-model screening program without considering healthcare system capacity.

Overall, this revised discussion positions CRC risk factors more proportionately: non-modifiable factors are used for risk stratification, modifiable factors serve as logical prevention targets without being overclaimed causally, and heterogeneity across studies is acknowledged as a primary limitation in generalizing findings. Future research in Indonesia should prioritize population-based cohort or case-control studies with more standardized exposure measurement, separation of colon and rectal cancer outcomes, and subgroup analyses by age, sex, region, metabolic status, and family history

Conclusion

A systematic review of 30 articles published between 2015 and 2026 reveals that colorectal carcinoma incidence is shaped by complex interactions between non-modifiable and modifiable factors. Non-modifiable factors with the highest association strength include first-degree family history (OR up to 17.78), precancerous colorectal lesions (OR 8.57), and inflammatory bowel disease (OR 4.4–7.07). Consistently associated modifiable factors include physical inactivity (OR 5.69), excessive red meat consumption (OR 4.97), alcohol consumption (OR 4.92), central obesity confirmed causally via Mendelian randomization (OR 1.38), diabetes (HR 2.20), and hypertension (HR 1.99). Gut microbiota dysbiosis further contributes through genotoxicity and chronic inflammation. Although non-modifiable factors carry higher absolute effect sizes,

modifiable factors hold greater strategic relevance as targets for population-based intervention.

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