

## REVIEW ARTICLE

## OPEN ACCES

## Cite as:

Cruz-Diaz WE, Colomo V, Montenegro P. Role of the gut microbiome in the pathogenesis of early-onset colorectal cancer: evidence and perspectives. *Onkoresearch*. 2025;3(4). doi: 10.69482/onkoresearch.v25i4.98

## Received:

15/11/2025

## Approved:

30/12/2025

## Author's contributions:

WCD: participated in the conception and design of the study, developed the methodology, and prepared the original draft of the manuscript. VC: contributed to the review and editing of the manuscript. PM: provided expert guidance, supervision, and critically reviewed the final version. All authors critically reviewed and provided final approval of the manuscript and were responsible for the decision to submit the manuscript for publication.

## Financing:

None.

## Conflicts of interest:

The authors declare no conflicts of interest.

## Correspondence:

Wagner Cruz-Diaz

E-mail: wagner.cruz@upch.pe

## Role of the gut microbiome in the pathogenesis of early-onset colorectal cancer: evidence and perspectives

### Rol del microbioma intestinal en la patogénesis del cáncer colorrectal de aparición temprana: evidencia y perspectivas

Wagner Eduardo Cruz-Diaz<sup>1a</sup> , Valeria Colomo<sup>2,a</sup> , Paola Montenegro<sup>2,b</sup> 

<sup>1</sup> Instituto Nacional de Enfermedades Neoplásicas. Lima, Peru.

<sup>2</sup> Oncosalud, Auna. Lima, Peru.

<sup>a</sup> MD, <sup>b</sup> MSc

#### ABSTRACT

The incidence of early-onset colorectal cancer (EO-CRC) has risen alarmingly, contrasting with the declining rates of colorectal cancer in older populations. Alterations in the gut microbiome have been implicated in the pathogenesis of this condition. The microbiome comprises a diverse community of microorganisms that inhabit the human body, primarily in the gastrointestinal tract, skin, and other mucosal surfaces. Over time, these microbial populations have developed a symbiotic relationship with their host, contributing to metabolism and immune regulation functions. Environmental factors, including diet, sedentary lifestyle, smoking, and alcohol consumption, influence the composition and function of the gut microbiome. These exposures can induce dysbiosis, which has been associated with an increased risk of EO-CRC. Evidence suggests that genetic ancestry or individual single-nucleotide polymorphisms have minimal influence on the gut microbiome. Instead, environmental exposures appear to be predominant in its shaping. Consequently, the pathogenesis of EO-CRC likely reflects a complex interplay between environmental exposures, lifestyle-related factors, and host susceptibility. This review aims to summarize the current evidence of the role of the gut microbiome in EO-CRC pathogenesis and will explore future perspectives in this rapidly evolving field.

#### Keywords

*Gastrointestinal Microbiome; Colorectal Neoplasms; Dysbiosis; Age of Onset; Environmental Exposure (source: MeSH-NLM).*

#### RESUMEN

La incidencia del cáncer colorrectal de aparición temprana (EO-CRC) ha aumentado de manera alarmante, en contraste con la disminución de las tasas de cáncer colorrectal en poblaciones de mayor edad. Las alteraciones del microbioma intestinal han sido implicadas en la patogénesis de esta entidad. El microbioma comprende una comunidad diversa de microorganismos que habitan el cuerpo humano, principalmente en el tracto gastrointestinal, la piel y otras superficies mucosas. A lo largo del tiempo, estas poblaciones microbianas han desarrollado una relación simbiótica con el huésped, contribuyendo a las funciones metabólicas y a la regulación del sistema inmunológico. Factores ambientales, incluidos la dieta, el sedentarismo, el tabaquismo y el consumo de alcohol, influyen en la composición y la función del microbioma intestinal. Estas exposiciones pueden inducir disbiosis, la cual se ha asociado con un mayor riesgo de EO-CRC. La evidencia sugiere que la ascendencia genética o los polimorfismos de un solo nucleótido individuales ejercen una influencia limitada sobre el microbioma intestinal. En cambio, las exposiciones ambientales parecen desempeñar un papel predominante en su configuración. En consecuencia, la patogénesis del EO-CRC probablemente refleja una interacción compleja entre exposiciones ambientales, factores relacionados con el estilo de vida y la susceptibilidad del huésped. Esta revisión tiene como objetivo resumir la evidencia actual sobre el papel del microbioma intestinal en la patogénesis del EO-CRC y explorar perspectivas futuras en este campo en rápida evolución.

#### Palabras clave

*Microbioma Gastrointestinal; Neoplasias Colorrectales; Disbiosis; Edad de Inicio; Exposición ambiental (fuente: DeCS-BIREME).*

## INTRODUCTION

Colorectal cancer (CRC) ranks as the third most common cancer worldwide, accounting for 9.6% of cases, and represents the second leading cause of cancer-related mortality<sup>(1)</sup>. In recent decades, an alarming increase in the incidence of Early-Onset Colorectal Cancer (EO-CRC), defined as cases diagnosed in individuals younger than 50 years old, has been observed globally, contrasting with the decreasing rate in Average-Onset Colorectal Cancer (AO-CRC). Moreover, projections estimate that, by 2030, 10% of all colon and 22% of all rectal cancers are expected to be diagnosed in patients younger than 50 years old in the United States<sup>(2)</sup>. Key clinicopathological and molecular differences between EO-CRC and AO-CRC are summarized in Table 1.

The gut microbiota comprises a complex and dynamic community of interacting bacteria, archaea, bacteriophages, eukaryotic viruses, and fungi that inhabit the intestinal tract. Most of these microorganisms establish commensal or mutualistic relationships with the host, contributing to homeostatic balance. The gut microbiome refers to the collective genetic content of these microbial communities<sup>(3)</sup>. Factors such as dietary

patterns, obesity, smoking, alcohol consumption, and exposure to environmental agents-including microplastics and pesticides-can disrupt gut microbiome homeostasis, promoting dysbiosis, see Figure 1. Alterations in the composition and function of the gut microbiome have been strongly associated with recent trends in gastrointestinal carcinogenesis<sup>(4)</sup>.

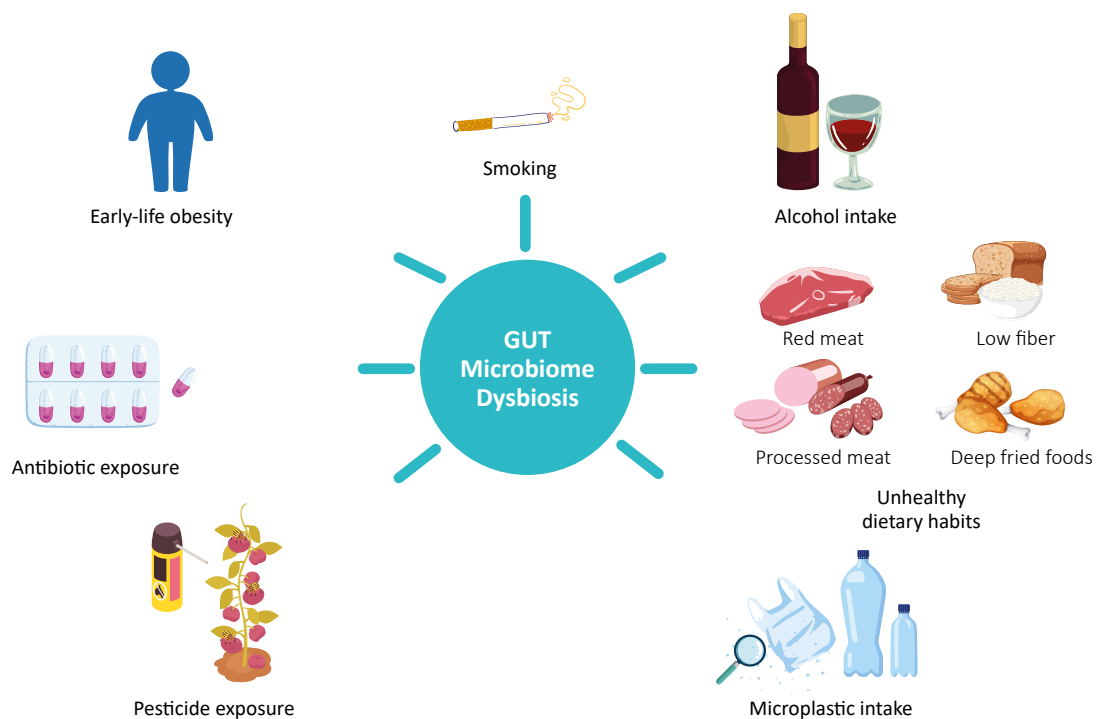
This narrative review summarizes the current evidence on the characteristics of the intestinal microbiome, its role in the pathogenesis of EO-CRC, and its interactions with treatment. Additionally, it discusses future research directions in this rapidly evolving field.

## MATERIALS AND METHODS

A narrative review of the literature was performed using structured searches in the PubMed and Scopus databases. Articles published up to December 2025 were identified through predefined combinations of the following keywords: “early-onset colorectal cancer”, “gut microbiome”, “dysbiosis”, and “environmental exposure”. Original research articles, systematic and narrative reviews, and relevant clinical guidelines published in

**Table 1.** Comparison between Early-Onset and Average-Onset Colorectal Cancer

Category	EO-CRC (<50 years)	AO-CRC (≥50 years)
Epidemiological trend	Rising incidence <sup>(2,4,11,15)</sup>	Stable or declining incidence in regions with established screening programs <sup>(2,4)</sup>
Symptoms	Prolonged symptom duration and delayed diagnosis following symptom onset <sup>(2,11,15)</sup>	Frequently asymptomatic with earlier detection <sup>(11)</sup>
Stage at diagnosis	Higher proportion of advanced-stage disease at diagnosis <sup>(2,11,15)</sup>	Lower proportion of advanced-stage disease at diagnosis <sup>(2,11)</sup>
Histopathology	Higher frequency of poorly differentiated, mucinous, and signet ring histology <sup>(2,11,15)</sup>	Lower frequency of high-grade or adverse histologic features <sup>(11)</sup>
Tumor location	Predominantly left-sided and rectal tumors <sup>(2,11,15)</sup>	More heterogeneous distribution, with increased right-sided tumors <sup>(11)</sup>
Genomic alterations	Higher prevalence of germline pathogenic variants (especially Lynch syndrome); MSI enriched in very young patients; distinct epigenetic and WNT-pathway alterations reported <sup>(11,15)</sup>	Higher prevalence of somatic APC, KRAS, and BRAF mutations <sup>(11)</sup>
Microbiome enrichment taxa (tissue, 16S rRNA)	<i>Akkermansia</i> and <i>Bacteroides</i> <sup>(49)</sup>	<i>Bacillus</i> , <i>Staphylococcus</i> , <i>Listeria</i> , <i>Enterococcus</i> , <i>Pseudomonas</i> , <i>Fusobacterium</i> , and <i>Escherichia/Shigella</i> <sup>(49)</sup>
Microbiome enrichment taxa (stool DNA)	<i>Flavonifractor plauti</i> , <i>Vibrio qinghaiensis</i> , <i>Bacteroides vulgatus</i> , <i>Bacteroides cellulosilyticus</i> , <i>Parabacteroides</i> sp., <i>Odoribacter splanchnicus</i> <sup>(50)</sup>	<i>Fusobacterium nucleatum</i> <i>Bacteroides caccae</i> <sup>(50)</sup>



**Figure 1.** Environmental and lifestyle determinants of gut microbiome dysbiosis.

This figure illustrates key environmental and lifestyle exposures associated with gut microbiome dysbiosis. Early-life obesity, smoking, alcohol intake, unhealthy dietary habits (including high consumption of red and processed meats, low fiber intake, and deep-fried foods), antibiotic use, pesticide exposure, and microplastics contribute to sustained alterations in microbial composition and function.

English were included. Studies were chosen based on their scientific quality, relevance to the topic, and their contribution to the current understanding of biological mechanisms and clinical implications.

### Definition and function of the microbiome

The gut microbiome comprises the collective genomes of the microbial inhabitants of the intestine and exerts essential functions in the host, including immune maturation, nutrient metabolism, regulation of gut endocrine signaling, modulation of neuroimmune communication, drug biotransformation, detoxification, and the production of bioactive metabolites that influence host physiology. Its composition and functional characteristics are shaped during life by multiple factors, including mode of delivery at birth, breastfeeding, early-life feeding practices, lifestyle, diet, medication exposure (antibiotics), and host genetic background <sup>(3)</sup>.

### Interactions with the host's immune system

The intestinal immune system controls bacterial exposure to host tissues, thereby lessening the potential for pathologic

outcomes through stratification and compartmentalization mechanisms. Stratification reduces direct contact between bacteria and the epithelial surface through a mucus layer secreted by goblet cells and IgA. Intestinal dendritic cells, a type of antigen-presenting cell, interact with B and T lymphocytes in Peyer's patches, thereby inducing the production of specific IgA. Intestinal compartmentalization restricts pathogenic bacteria to defined mucosal niches, thereby limiting systemic dissemination <sup>(5)</sup>. Other immune cell populations, such as Group 3 innate lymphoid cells, play a key role in maintaining intestinal homeostasis and influencing disease processes by producing important cytokines-especially IL-22 and IL-17-which are crucial for strengthening epithelial barrier integrity and preventing bacterial translocation <sup>(6)</sup>. Other endogenous factors, like alpha-defensins secreted by Paneth cells, also shape the microbial community and support gut homeostasis <sup>(7)</sup>. Additionally, the gut microbiome is vital for immune system development, particularly in the differentiation and activation of T-cell subsets, including TH1, TH2, TH17, and regulatory T-cells <sup>(8)</sup>.

### Influence of environmental and lifestyle factors

A universally present core set of microbial taxa in healthy individuals has not been definitively identified, as there is a high degree of individual variability in the species observed. Therefore, characterizing a healthy microbiome as an ideal set of specific microbes is not a practical definition. Instead, the current hypothesis focuses on a functionally healthy core. From an ecological perspective, the stability of the microbiome, defined as its capacity to resist changes or return to an equilibrium state following stress, should be considered a hallmark of a healthy microbiome<sup>(9)</sup>. The metabolic functions of the gut microbiome include the degradation of glycosaminoglycans, the production of short-chain fatty acids (SCFAs), the synthesis of specific lipopolysaccharides (LPS), and the biosynthesis of some essential amino acids and vitamins<sup>(3)</sup>.

The environment plays a much more significant role than host genetics in shaping the human gut microbiome, with overall microbiome heritability estimated to range from 1.9% to 8.1%<sup>(10)</sup>. On the other hand, the exposome concept explores cumulative lifetime exposures as contributors to EO-CRC risk. Notably, younger cohorts exhibit higher CRC risks than previous generations at equivalent ages, likely due to cumulative exposures that disrupt microbial homeostasis<sup>(11)</sup>.

Early-life obesity has been directly linked to an increased risk of EO-CRC<sup>(12)</sup>. In a study conducted on 85,256 women, obesity-defined as a body mass index (BMI) of 30 or greater-was associated with a 93% increased risk of EO-CRC compared to women with a BMI of 18.5-22.9<sup>(13)</sup>. Obesity alters the composition of the gut microbiome, increasing the abundance of lipopolysaccharide endotoxin-producing gram-negative bacteria, resulting in the disruption of the mucosal barrier and low-grade chronic inflammation<sup>(14)</sup>.

Dietary patterns have a profound impact on the composition and function of the gut microbiome. A Western diet, characterized by a high intake of red and processed meats and insufficient fiber, disrupts microbial balance, driving inflammation and processes linked to carcinogenesis<sup>(15)</sup>. Moreover, the Western deep-frying cooking style increases the formation of pro-inflammatory and pro-carcinogenic advanced glycation end products (AGEs), which can contribute to dysbiosis and further exacerbate the unhealthy nature of this diet<sup>(16)</sup>.

In the same line, antibiotics use disrupt microbial colonization, reduce diversity, and delay the establishment of commensal bacteria during early life<sup>(17)</sup>. Rasmussen *et al.*<sup>(18)</sup> identified an association between antibiotic exposure and childhood overweight and

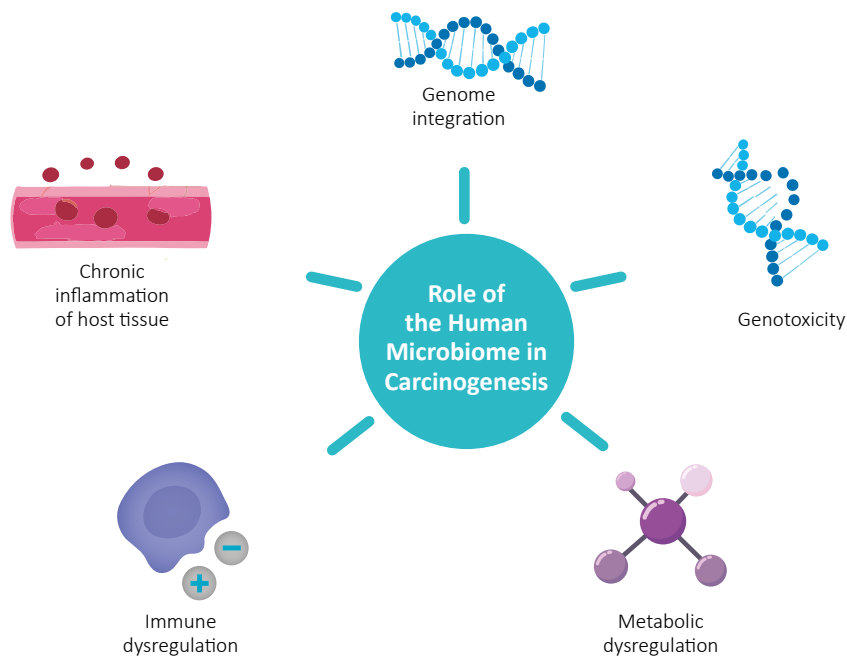
obesity in a systematic review and meta-analysis. Lu *et al.*<sup>(19)</sup> found a robust association between antibiotic use and a higher risk of proximal colon cancer in a population-based study that covered the entire population of Sweden. The impact of antibiotics on CRC development is complex and context dependent. Hattori *et al.*<sup>(20)</sup> reported that antibiotics might suppress tumorigenesis by modulating inflammation-associated gut microbiome and preventing aberrant DNA methylation. Furthermore, Hamoya *et al.*<sup>(21)</sup> found that erythromycin reduced intestinal polyp formation in murine models by attenuating local inflammation, suggesting its potential as a chemopreventive agent. Contradictory data indicate that this field still requires extensive research to clarify the actual role of antibiotics in the genesis of EO-CRC.

Other substances have been implicated in gut microbiome dysbiosis, which may increase the risk of EO-CRC. Low-level chronic dietary pesticide exposure has been shown to impact the gut microbiome<sup>(22)</sup>, and it is associated with an increased risk of CRC in populations with high pesticide exposure<sup>(23)</sup>. In contrast, the link between microplastics and CRC remains less well-established. Bisphenol A (BPA), an industrial chemical used in the production of polycarbonate plastics and epoxy resins, has been found to significantly alter the composition of gut microbiome in various organisms<sup>(24)</sup>, suggesting that BPA may contribute to an increased risk of carcinogenesis<sup>(25)</sup>.

### Microbiome and carcinogenesis: mechanisms, pathogenic interactions, and theoretical models

The proposed mechanisms linking the microbiome to cancer development include genomic integration, genotoxicity, inflammation, and regulation of the immune and metabolic systems<sup>(26)</sup> (Figure 2). A well-established example of genomic integration is seen in high-risk human papillomavirus serotypes, where E6 and E7 oncogenes play a pivotal role in cervical cancer development by integrating viral DNA into the host genome<sup>(27)</sup>. Although genomic integration is a well-established oncogenic mechanism, current evidence does not support a major role for direct microbial genomic integration in EO-CRC. Genotoxicity is another critical mechanism. Cytolethal distending toxin (CTD) is a genotoxin produced by *Escherichia coli* and *Campylobacter jejuni*, which generates DNA damage through its DNase activity. Other genotoxic effects include the production of reactive oxygen species by *Porphyromonas* sp. and the generation of hydrogen sulfide by *Bilophila* and *Fusobacterium*, all of which are associated with CRC<sup>(28)</sup>.

Mechanisms of immune evasion have been identified in *Fusobacterium nucleatum*, which expresses the Fap2 surface protein that interacts with T lymphocytes



**Figure 2.** Role of the human microbiome in carcinogenesis.

This schematic summarizes the major biological mechanisms through which the human microbiome contributes to carcinogenesis. Microbial alterations can induce chronic inflammation of host tissues, promote immune dysregulation, generate genotoxic compounds, disrupt host metabolic pathways, and, in selected contexts, facilitate microbial genome integration into host cells.

and NK cells, effectively inhibiting their antitumor cytotoxicity by binding to the human inhibitory receptor TIGIT<sup>(29)</sup>. Microbial virulence factors induce chronic inflammation of host tissue, stimulating cellular proliferation, failure of apoptosis, and resulting in a malignant phenotype. Activation of the nuclear factor- $\kappa$ B and WNT/ $\beta$ -Catenin pathways are activated by *F. nucleatum* and enterotoxigenic *Bacteroides fragilis*<sup>(30)</sup>. Bacterial metabolic products have been identified as key contributors to the development of cancer. For example, the metabolism of bile acids and proteins can generate aromatic amines and hydrogen sulfide, both of which create a pro-carcinogenic environment. Other microbiome-derived metabolites, such as acetaldehyde, further promote carcinogenesis by inducing DNA damage and genomic instability<sup>(31)</sup>.

Human studies have shown that the CRC microbiome exhibits reduced diversity and an altered microbial composition, including a lower relative abundance of potentially protective species, such as butyrate-producing *Roseburia*, and an increased presence of taxa associated with procarcinogenic properties, including *Fusobacterium*, *Bacteroides*, *Campylobacter*, *Escherichia*,

and *Porphyromonas*<sup>(26)</sup>. Evidence suggests that the development of CRC by these microorganisms depends on the formation of biofilms. These gut microbial biofilms develop within the inner colonic mucus layer and comprise polymicrobial communities. Their presence disrupts E-cadherin redistribution in colonic epithelial cells, increases gut permeability, and compromises the intestinal barrier, all of which contribute to intestinal dysbiosis and promote carcinogenesis<sup>(32)</sup>.

The alpha-bug hypothesis suggests that certain microorganisms possess specific oncogenic virulence factors and can modulate the microbiome profile toward a more pro-oncogenic composition. Among the leading alpha-bug candidates is enterotoxigenic *Bacteroides fragilis*, which induces direct mucosal damage in the colon through toxin production while disrupting immune response mechanisms<sup>(33)</sup>. This theory was later refined into the driver-passenger model, which proposes that specific driver bacteria initiate DNA damage, promoting oncogenesis and creating a favorable environment for opportunistic passenger microorganisms, eventually replacing the driver species<sup>(34)</sup>. Over time, these driver bacteria are gradually replaced by passenger bacteria,

which hold a competitive advantage within the evolving tumor microenvironment. These passenger bacteria include tumor-foraging opportunistic pathogens (such as *Fusobacterium* or *Streptococcus* spp.), commensal or probiotic bacteria (e.g., members of the Coriobacteriaceae family), or other microbial species that thrive within the tumor niche<sup>(34)</sup>. Scott *et al.*<sup>(26)</sup> introduced a comprehensive framework for modeling the role of gut microbiome in cancer development based on the interactome concept. This model views carcinogenesis as the result of complex, multidirectional interactions among the microbiome, environmental factors, and a genetically or epigenetically susceptible host.

### Microbiome influence on cancer therapy and future areas of investigation

A key aspect in oncology is the influence of the gut microbiome on treatment response. With millions of protein-coding genes, gut microbiome can process ingested nutrients and modify drug pharmacokinetics. Pharmacomicrobiomics has been proposed to explain unresolved pharmacogenomic responses, particularly the interaction between the microbiome and the efficacy of chemotherapy, radiotherapy, targeted therapy, and immune checkpoint inhibitors (ICI)<sup>(35)</sup>. An example of microbiome-driven drug metabolism alteration occurs with irinotecan, a widely used chemotherapy for advanced colorectal cancer. Bacterial  $\beta$ -glucuronidase, expressed by *Clostridium* clusters XIVa and IV (*Clostridium*, *Eubacterium*, and *Ruminococcus*), reactivates SN-38G-a detoxified metabolite processed by hepatic uridine diphosphate-glucuronosyltransferase (UGT)-back into its active form, 7-ethyl-10-hydroxycamptothecin (SN-38), within the intestinal mucosa. This reactivation markedly increases irinotecan toxicity and the incidence of chemotherapy-induced diarrhea<sup>(36)</sup>. *F. nucleatum* also promotes chemoresistance to oxaliplatin and 5-FU by inactivating the TLR-4/MYD88-dependent pathway. This inhibition suppresses microRNA activity, shifting CRC cells from apoptosis to autophagy<sup>(37)</sup>.

Studies have demonstrated that the efficacy of immunotherapy is significantly influenced by the composition and function of the gut microbiome<sup>(38)</sup>. Anti-CTLA-4 monoclonal antibodies have been shown to promote the growth of specific bacterial species in the intestinal mucosa, including *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, and *Burkholderia cepacia*. These bacteria produce polysaccharides that stimulate CD11b<sup>+</sup> dendritic cells in the lamina propria, enhancing the IL-12-dependent Th1 immune response in tumor-draining lymph nodes<sup>(39)</sup>. *B. breve* and *B. longum* activate dendritic cells for CD8<sup>+</sup> T-cell priming and infiltration in the tumor microenvironment, thereby enhancing the immunotherapeutic effect of anti-PD-1/PD-L1<sup>(40)</sup>. *B. bifidum*

was found to upregulate IL-10Ra and IL-10 expression in intestinal Treg cells, thereby strengthening their immunosuppressive function and mitigating the immune-related side effects of CTLA-4 blockade in the gut<sup>(41)</sup>.

Probiotic supplementation, primarily with *Lactobacillus* and *Bifidobacterium*, has been explored to modulate gut microbiota. Meta-analyses of randomized trials in colorectal cancer patients demonstrate that probiotics likely decrease the risk and duration of chemotherapy-related diarrhea and alleviate other gastrointestinal symptoms; however, further large-scale studies are needed to refine clinical recommendations and address evidence gaps<sup>(42,43)</sup>. Similarly, in studies on prebiotics, dietary fiber intake, particularly involving fructans and galacto-oligosaccharides, leads to higher fecal abundance of *Bifidobacterium* and *Lactobacillus* spp. but does not affect  $\alpha$ -diversity<sup>(44)</sup>.

Fecal microbiota transplantation (FMT) involves transferring a complete fecal microbial community from a healthy donor to a recipient, including bacteria, viruses, fungi, and metabolites<sup>(45)</sup>. Wang *et al.*<sup>(46)</sup> reported the first use of FMT to treat ICI-induced colitis, demonstrating clinical improvement in corticosteroid-refractory patients, coinciding with an enrichment of beneficial *Bifidobacterium* species. Furthermore, evidence suggests that FMT likely enhances the objective response to ICIs in patients with refractory melanoma<sup>(47)</sup>.

Metagenomic profiling, 16S rRNA gene sequencing, and liquid chromatography-tandem mass spectrometry have provided invaluable insights into the study of the gut microbiome associated with CRC. Metagenomic datasets from gut microbiome research encompass over 22 million non-redundant genes<sup>(48)</sup>. A 16S rRNA amplicon sequencing analysis of 276 fresh-frozen tissue specimens revealed an enrichment of the genera *Akkermansia* and *Bacteroides* in EO-CRC. In contrast, AO-CRC showed a higher abundance of *Bacillus*, *Staphylococcus*, and *Listeria*. Alpha diversity was consistently lower in AO-CRC, suggesting a decline in microbial richness with aging and tumor progression<sup>(49)</sup>. Similarly, metagenomic and metabolomic analyses of 441 individuals by Kong *et al.*<sup>(50)</sup> reported reduced  $\alpha$ -diversity as a standard feature. AO-CRC was characterized by *Fusobacterium nucleatum* enrichment, SCFA depletion, reduced microbial GABA biosynthesis, and a metabolic shift in acetate/ acetaldehyde pathways toward acetyl-CoA production. In EO-CRC, *Flavonifractor plauti*, a species associated with red meat intake and choline metabolism, as well as the KEGG orthology genes *pldB* and *cbh*, were identified as potential tumor stimulators.

EO-CRC represents a growing global health challenge, with its increasing incidence strongly linked

to environmental and lifestyle factors that disrupt the gut microbiome, leading to dysbiosis. Advances in metagenomic and metabolomic technologies have revolutionized the study of the EO-CRC-associated microbiome, positioning it as a potential cornerstone for future research. Multiomics-based investigations are crucial for uncovering the associations between gut microbiome-derived omics signatures and the risk of EO-CRC. These efforts should focus on driving the clinical transformation of microbiome-derived strategies to develop precise screening, diagnostic, and therapeutic approaches, addressing the needs of this increasingly affected population.

### Take-Home Messages

- The rising incidence of EO-CRC contrasts with declining trends in AO-CRC population, underscoring the need to understand age-specific pathogenic mechanisms.
- Environmental and lifestyle factors appear to play a predominant role in shaping the gut microbiome, potentially contributing to dysbiosis associated with the increased risk of EO-CRC.
- The gut microbiome influences EO-CRC carcinogenesis through multiple mechanisms, including genotoxicity, chronic inflammation, immune modulation, metabolic reprogramming, and microbial-host interactions.
- Distinct microbial and metabolic signatures have been identified in EO-CRC compared with AO-CRC, suggesting possible age-specific biological pathways.
- The gut microbiome also modulates cancer therapy response, affecting chemotherapy toxicity and immunotherapy efficacy, highlighting its translational relevance.
- Multi-omics approaches integrating metagenomics, metabolomics, and host factors are essential to advance precision prevention, early detection, and microbiome-targeted therapeutic strategies in EO-CRC.

### Acknowledgments

Artificial intelligence (AI) tools were used solely for language editing, including grammar and punctuation correction. No AI tools were employed in data analysis, interpretation, or in generating the scientific content of this manuscript. The authors take full responsibility for the integrity and originality of the text.

## REFERENCES

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, *et al.* Global Cancer Observatory: Cancer Today [Internet]. Lyon (FR): International Agency for Research on Cancer; 2024 [cited 2025 Feb 11]. Available from: <https://gco.iarc.who.int/today>
2. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol.* 2019;13(2):109-131. doi: 10.1002/1878-0261.12417.
3. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol.* 2021;19(1):55-71. doi: 10.1038/s41579-020-0433-9.
4. Dai R, Kelly BN, Ike A, Berger D, Chan A, Drew DA, *et al.* The Impact of the Gut Microbiome, Environment, and Diet in Early-Onset Colorectal Cancer Development. *Cancers (Basel).* 2024;16(3):676. doi: 10.3390/cancers16030676.
5. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science.* 2012;336(6086):1268-73. doi: 10.1126/science.1223490.
6. Horn V, Sonnenberg GF. Group 3 innate lymphoid cells in intestinal health and disease. *Nat Rev Gastroenterol Hepatol.* 2024;21(6):428-443. doi: 10.1038/s41575-024-00906-3.
7. Schroeder BO, Ehmann D, Precht JC, Castillo PA, Kuchler R, Berger J, *et al.* Paneth cell  $\alpha$ -defensin 6 (HD-6) is an antimicrobial peptide. *Mucosal Immunol.* 2015;8(3):661-71. doi: 10.1038/mi.2014.100.
8. Shim JA, Ryu JH, Jo Y, Hong C. The role of gut microbiota in T cell immunity and immune mediated disorders. *Int J Biol Sci.* 2023;19(4):1178-1191. doi: 10.7150/ijbs.79430.
9. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. *Genome Med.* 2016;8(1):51. doi: 10.1186/s13073-016-0307-y.
10. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, *et al.* Environment dominates over host genetics in shaping human gut microbiota. *Nature.* 2018;555(7695):210-215. doi: 10.1038/nature25973.
11. Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol.* 2022;7(3):262-274. doi: 10.1016/S2468-1253(21)00426-X.
12. Du M, Drew DA, Goncalves MD, Cao Y, Chan AT. Early-onset colorectal cancer as an emerging disease of metabolic dysregulation. *Nat Rev Endocrinol.* 2025;21(11):686-702. doi: 10.1038/s41574-025-01159-z.
13. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, *et al.* Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. *JAMA Oncol.* 2019;5(1):37-44. doi: 10.1001/jamaoncol.2018.4280.
14. Chai W, Morimoto Y, Cooney RV, Franke AA, Shvetsov YB, Le Marchand L, *et al.* Dietary Red and Processed Meat Intake and Markers of Adiposity and Inflammation: The Multiethnic Cohort Study. *J Am Coll Nutr.* 2017;36(5):378-385. doi: 10.1080/07315724.2017.1318317.
15. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, Pena MM, *et al.* Early-onset colorectal cancer: initial clues and current views. *Nat Rev Gastroenterol Hepatol.* 2020;17(6):352-364. doi: 10.1038/s41575-019-0253-4.
16. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, *et al.* Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc.* 2010;110(6):911-16.e12. doi: 10.1016/j.jada.2010.03.018.

17. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic exposure in neonates and early adverse outcomes: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2017;72(7):1858-1870. doi: 10.1093/jac/dkx088.
18. Rasmussen SH, Shrestha S, Bjerregaard LG, Ängquist LH, Baker JL, Jess T, *et al.* Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2018;20(6):1508-1514. doi: 10.1111/dom.13230.
19. Lu SSM, Mohammed Z, Häggström C, Myte R, Lindquist E, Gylfe Å, *et al.* Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study. *J Natl Cancer Inst.* 2022;114(1):38-46. doi: 10.1093/jnci/djab125.
20. Hattori N, Niwa T, Ishida T, Kobayashi K, Imai T, Mori A, *et al.* Antibiotics suppress colon tumorigenesis through inhibition of aberrant DNA methylation in an azoxymethane and dextran sulfate sodium colitis model. *Cancer Sci.* 2019;110(1):147-156. doi: 10.1111/cas.13880.
21. Hamoya T, Miyamoto S, Tomono S, Fujii G, Nakanishi R, Komiya M, *et al.* Chemopreventive effects of a low-side-effect antibiotic drug, erythromycin, on mouse intestinal tumors. *J Clin Biochem Nutr.* 2017;60(3):199-207. doi: 10.3164/jcbn.16-107.
22. Gama J, Neves B, Pereira A. Chronic Effects of Dietary Pesticides on the Gut Microbiome and Neurodevelopment. *Front Microbiol.* 2022;13:931440. doi: 10.3389/fmicb.2022.931440.
23. Soliman AS, Smith MA, Cooper SP, Ismail K, Khaled H, Ismail S, *et al.* Serum organochlorine pesticide levels in patients with colorectal cancer in Egypt. *Arch Environ Health.* 1997;52(6):409-15. doi: 10.1080/00039899709602219.
24. Mao W, Mao L, Zhou F, Shen J, Zhao N, Jin H, *et al.* Influence of Gut Microbiota on Metabolism of Bisphenol A, a Major Component of Polycarbonate Plastics. *Toxics.* 2023;11(4):340. doi: 10.3390/toxics11040340.
25. Chiu K, Warner G, Nowak RA, Flaws JA, Mei W. The Impact of Environmental Chemicals on the Gut Microbiome. *Toxicol Sci.* 2020;176(2):253-284. doi: 10.1093/toxsci/kfaa065.
26. Scott AJ, Alexander JL, Merrifield CA, Cunningham D, Jobin C, Brown R, *et al.* International Cancer Microbiome Consortium consensus statement on the role of the human microbiome in carcinogenesis. *Gut.* 2019;68(9):1624-1632. doi: 10.1136/gutjnl-2019-318556.
27. Zhang Y, Qiu K, Ren J, Zhao Y, Cheng P. Roles of human papillomavirus in cancers: oncogenic mechanisms and clinical use. *Signal Transduct Target Ther.* 2025;10(1):44. doi: 10.1038/s41392-024-02083-w.
28. Lai YR, Chang YF, Ma J, Chiu CH, Kuo ML, Lai CH. From DNA Damage to Cancer Progression: Potential Effects of Cytotoxic Distending Toxin. *Front Immunol.* 2021;12:760451. doi: 10.3389/fimmu.2021.760451.
29. Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, *et al.* Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity.* 2015;42(2):344-355. doi: 10.1016/j.immuni.2015.01.010.
30. Hernández-Luna MA, López-Briones S, Luria-Pérez R. The Four Horsemen in Colon Cancer. *J Oncol.* 2019;2019:5636272. doi: 10.1155/2019/5636272.
31. Gou H, Zeng R, Lau HCH, Yu J. Gut microbial metabolites: Shaping future diagnosis and treatment against gastrointestinal cancer. *Pharmacol Res.* 2024;208:107373. doi: 10.1016/j.phrs.2024.107373.
32. Chew SS, Tan LT, Law JW, Pusparajah P, Goh BH, Ab Mutalib NS, *et al.* Targeting Gut Microbial Biofilms-A Key to Hinder Colon Carcinogenesis? *Cancers (Basel).* 2020;12(8):2272. doi: 10.3390/cancers12082272.
33. Sears CL, Pardoll DM. Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. *J Infect Dis.* 2011;203(3):306-11. doi: 10.1093/jinfdis/jiq061.
34. Tjalsma H, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. *Nat Rev Microbiol.* 2012;10(8):575-82. doi: 10.1038/nrmicro2819.
35. Ting NL, Lau HC, Yu J. Cancer pharmacomicrobiomics: targeting microbiota to optimise cancer therapy outcomes. *Gut.* 2022;71(7):1412-1425. doi: 10.1136/gutjnl-2021-326264.
36. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Keefe DM. Faecal microflora and beta-glucuronidase expression are altered in an irinotecan-induced diarrhea model in rats. *Cancer Biol Ther.* 2008;7(12):1919-25. doi: 10.4161/cbt.7.12.6940.
37. Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, *et al.* *Fusobacterium nucleatum* Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. *Cell.* 2017;170(3):548-563.e16. doi: 10.1016/j.cell.2017.07.008.
38. Elkrief A, Pidgeon R, Maleki Vareki S, Messaoudene M, Castagner B, Routy B. The gut microbiome as a target in cancer immunotherapy: opportunities and challenges for drug development. *Nat Rev Drug Discov.* 2025;24(9):685-704. doi: 10.1038/s41573-025-01211-7.
39. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, *et al.* Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science.* 2015;350(6264):1079-84. doi: 10.1126/science.aad1329.
40. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, *et al.* Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science.* 2015;350(6264):1084-9. doi: 10.1126/science.aac4255.
41. Sun S, Luo L, Liang W, Yin Q, Guo J, Rush AM, *et al.* *Bifidobacterium* alters the gut microbiota and modulates the functional metabolism of T regulatory cells in the context of immune checkpoint blockade. *Proc Natl Acad Sci U S A.* 2020;117(44):27509-27515. doi: 10.1073/pnas.1921223117.
42. Yang M, Wang L, Luo C, Shang J, Zheng X, Qian J, *et al.* Efficacy and safety of probiotics in preventing chemotherapy-related diarrhea in patients with colorectal cancer: A systematic review and meta-analysis based on 18 randomized trials. *Medicine (Baltimore).* 2025;104(27):e43126. doi: 10.1097/MD.00000000000043126.

43. Yao B, Wei W, Zhang H. Efficacy of probiotics or synbiotics supplementation on chemotherapy-induced complications and gut microbiota dysbiosis in gastrointestinal cancer: a systematic review and meta-analysis. *Eur J Clin Nutr.* 2025;79(7):616-626. doi: 10.1038/s41430-024-01542-5.
44. So D, Whelan K, Rossi M, Morrison M, Holtmann G, Kelly JT, *et al.* Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr.* 2018;107(6):965-983. doi: 10.1093/ajcn/nqy041.
45. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nat Rev Gastroenterol Hepatol.* 2011;9(2):88-96. doi: 10.1038/nrgastro.2011.244.
46. Wang Y, Wiesnoski DH, Helmink BA, Gopalakrishnan V, Choi K, DuPont HL, *et al.* Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med.* 2018;24(12):1804-1808. doi: 10.1038/s41591-018-0238-9.
47. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, *et al.* Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science.* 2021;371(6529):595-602. doi: 10.1126/science.abf3363.
48. Tierney BT, Yang Z, Lubber JM, Beaudin M, Wibowo MC, Baek C, *et al.* The Landscape of Genetic Content in the Gut and Oral Human Microbiome. *Cell Host Microbe.* 2019;26(2):283-295.e8. doi: 10.1016/j.chom.2019.07.008.
49. Barot SV, Sangwan N, Nair KG, Schmit SL, Xiang S, Kamath S, *et al.* Distinct intratumoral microbiome of young-onset and average-onset colorectal cancer. *EBioMedicine.* 2024;100:104980. doi: 10.1016/j.ebiom.2024.104980.
50. Kong C, Liang L, Liu G, Du L, Yang Y, Liu J, *et al.* Integrated metagenomic and metabolomic analysis reveals distinct gut-microbiome-derived phenotypes in early-onset colorectal cancer. *Gut.* 2023;72(6):1129-1142. doi: 10.1136/gutjnl-2022-327156.