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Underexplored Environmental Factors and Gut Microbiome Alterations as a Pathogenic Pathway in Early-Onset Intestinal Cancer: An Analytical Literature Review

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Abstract

Background and Objectives

Early-onset intestinal cancers are rising at an alarming rate, a trend not fully explained by established risk factors alone. This review examines four under-studied environmental factors — antibiotics, pollutants and pesticides, infant formula, and food additives — as potential drivers of early-onset intestinal cancer through gut dysbiosis.

Methods

A systematic search across PubMed, Scopus, Web of Science, and Google Scholar (2015–2026) yielded 67 selected publications spanning randomized controlled trials, cohort studies, case-control designs, experimental models, systematic reviews, and meta-analyses.

Results

Broad-spectrum antibiotics, particularly during childhood, chronically deplete butyrate-producing bacteria while promoting the growth of cancer-associated species such as *Fusobacterium nucleatum*. Environmental toxins disrupt microbial composition through specific pro-inflammatory signaling pathways. Industrial infant formula, lacking human milk oligosaccharides and epithelial growth factors, impair gut immune maturation with effects persisting into adulthood. Food additives including emulsifiers, preservatives, and artificial dyes degrade the mucosal barrier, select for inflammation-promoting bacteria, and activate carcinogenic pathways across multiple generations.

Conclusion

These factors share a common mechanism: the *dysbiogenic exposome*, defined as the multigenerational accumulation of environmental aggressions, progressively degrading the intestinal microbial ecosystem. This interpretive framework suggests that rising early-onset intestinal cancer rates reflect cumulative gut microbiome disruption beginning early in life, rather than isolated exposures. Prospective longitudinal studies incorporating repeated microbiome assessments and early-life exposure data are needed to validate this model and guide primary prevention.

I. Introduction

Intestinal cancer was known to be associated with old age because it mainly affected patients above the age of 50 years. Recently, however, there is a new trend whereby intestinal cancers are increasing in people under the age of 50 with projections exceeding 140% by 2030 [1]. This trend cannot be explained in terms of hereditary syndromes such as Lynch syndrome or familial adenomatous polyposis because they only cause a small percentage of cases [2, 3]. Inflammatory bowel diseases (IBD) contribute less to this trend.

Existing studies have centered mainly on common modifiable risk factors like Western-style diets, obesity, physical inactivity, alcohol intake, and type 2 diabetes to explain this growth [3, 4]. Even though these risk factors are clinically important, they fail to provide an exhaustive explanation for the specific pattern seen in EOCRC. This is because most of these risk factors have been steadily increasing for many decades and among all ages while the increased rate of incidence seen among younger generations indicates that there may be some exposures that are becoming more prevalent in recent times or their effects take time to show [5].

An increasingly large number of studies have identified that gut microbiomes are one of the most critical factors involved in intestinal cancer development. The human gut microbiome consists of trillions of microorganisms with an overwhelming dominance of the phylum Firmicutes and Bacteroidetes; and it has a regulatory function on the intestinal homeostasis in terms of generating SCFA, immunity, and epithelium integrity [6]. Gut dysbiosis, characterized by an imbalance in microbial diversity, is linked to the onset of intestinal inflammation, DNA mutation, and the progression of intestinal cancer [7]. Some bacteria, such as F. nucleatum, enterotoxigenic Bacteroides fragilis, and adherent-invasive E. coli, have been proven to contribute to the induction and development of intestinal cancer [6, 8].

One issue that is yet to be fully explored, however, is the impact that specific environmental exposures have on the health of the individual that has been shown to cause dysbiosis. This analysis focuses on four unexplored environmental factors that include lifetime usage of antibiotics, environmental pollution, pesticide exposure, high prevalence of infant formula feeding, and widespread consumption of artificial food components. While it is uncommon to explore the impact that all these four factors have collectively on human health, it is even less common to analyze their effects in relation to the development of EOCRC [4, 9, 10].

It is suggested that this phenomenon does not occur independently of each other but instead converge to a common pathway, dysbiosis resulting from our modern environment, which can be considered as a new and previously underappreciated potential pathway contributing to the increasing prevalence of EOCRC among young people. The discovery of the pathways mentioned above provides an important and novel addition to our knowledge regarding the causes of early-onset intestinal cancer and paves the way for future preventive research.

II. Methods

This systematic review of existing literature was performed to determine any previously overlooked environmental or behavioral factors capable of causing modifications of the gut microbiota in the onset of intestinal cancer. The literature review process was carried out through searches of the PubMed, Scopus, Web of Science, and Google Scholar databases, in all languages and during the years 2015-2026.

Keywords were used for each of the four environmental factors (antibiotics, environmental toxins/pesticides, infant formula, and industrial food additives) alongside gut microbiota, dysbiosis, intestinal cancer, early onset of intestinal cancer, and intestinal inflammation. The included literature consisted of randomized controlled trials, cohort studies, case-control studies, experimental animal studies, systematic reviews, and meta-analysis providing numerical or mechanistic information regarding the connection between the environmental factor, gut microbiota, and development of intestinal cancer/precancerous states.

Excluded from consideration were studies that concentrated only on the classic risk factors such as overall dietary habits, obesity, and sedentary lifestyle. In all, sixty-seven articles were considered within this paper, categorized into four thematic categories.

III. Results and discussion

a. Antibiotics and the Risk of Early-Onset intestinal Cancer

Epidemiological data. The relationship between antibiotic use and HF susceptibility has been shown to be proven in many large cohort studies, as well as the higher incidence of the disease among young people. Thus, a study conducted in Scotland among about 8,000 patients with intestinal cancer demonstrated that OR (adjusted for potential confounding) for developing intestinal cancer among the EOCRC group is 1.49 compared to 1.09 among the late-onset group, which proves higher sensitivity of younger individuals [5]. Significant OR for quinolones (OR 7.47) and sulfonamides (OR 4.66) were noted concerning proximal colon cancer [11,12].These results are supported by two meta-analyses: one involving 4.1 million individuals reports an increased risk with broad-spectrum antibiotics (OR 1.70; 95% CI: 1.26–2.30) [13], while the other, involving over one million participants, concluded that there was an overall 13% increase in the risk of intestinal tumors among users [7].

It would seem that exposure during the formative years is one of the decisive aspects: in a prospective cohort study conducted in the UK Biobank involving 113,256 patients, early and repetitive use of antibiotics was linked to an elevated

incidence of CRC (OR 1.48) and early adenomas (OR 1.40) in conjunction with a statistically significant gene-finding for FUT2, which controls the microbiome [14]. On the other hand, research using limited exposure during adulthood does not demonstrate any link [15, 16].

Table 1: Summary of Key Studies on the Association Between Antibiotics and intestinal Cancer Risk

Authors	Type	Population	Results	Mechanism
McDowell et al. [5]	Case-control	7,903 CRC (445 <50 years), Scotland	OR 1.49 EOCRC; OR 1.09 LOCRC	↓ Protective anaerobes
Perrott et al. [12]	Case-control	445 EOCRC, Scotland	OR 7.47 quinolones; OR 4.66 sulfonamides	Selective destruction of anaerobes
Jiang et al. [14]	Cohort	113,256, UK Biobank	OR 1.48 EOCRC; OR 1.40 adenomas	Early dysbiosis + FUT2 interaction
Liu et al. [7]	Meta-analysis	1,145,853 participants	+13% colorectal tumor risk	Antibiotic combinations = highest risk
Simin et al. [13]	Dose-response meta-analysis	4.1M individuals	ES 1.70 broad-spectrum	Plateau after 30 days exposure
Song et al. [18]	Nationwide case-control	45,744 polyps, Sweden	OR 1.23 broad-spectrum	↑ Serrated polyps, dose-response
Nguyen et al. [16]	Cohort	54,804 CRC, Sweden	aOR 1.06 (NS)	Insufficient exposure window

Mechanistic evidence. Antibiotics act as carcinogens by selectively targeting beneficial anaerobic microorganisms capable of synthesizing butyrate, specifically Faecalibacterium prausnitzii, Lactobacillus paracasei, and Clostridium tyrobutyricum, in favor of inflammatory microorganisms, including Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis [6, 17]. This results in insufficient butyrate synthesis, which is essential for maintaining epithelial barrier integrity and inhibiting cancerous pathways, alongside chronic NF-$\varkappa$B pathway activation. Treatment of mice with the most frequently prescribed antibiotics in pediatric patients demonstrated that microbial community dysbiosis at a young age led to the development of chronic colitis and enhanced tumor burden after exposure to a colon carcinogen [1]. As the case of metronidazole shows, which decreases the number of F. nucleatum in vitro but increases cancer risk based on observational evidence, the carcinogenic effect depends not on the isolated pathogen but on the entire disruption of the microbial ecosystem.

b. Environmental Pollutants, Pesticides, and Heavy Metals

Disruption mechanisms. There exists a two-way interaction between environmental pollutants and microbiota: while toxins influence the gut microbial community, the latter mitigates the effects of contaminants using five enzyme families involved in the degradation of more than thirty foreign substances [18]. Organophosphates like chlorpyrifos were shown to break down tight junctions in the intestine (claudin-1, ZO-1, occludin), causing persistent inflammation of the colon [19, 20]. Importantly, a combination of ten pesticides at regulatory concentrations resulted in IBD-like damage to the mice intestines that was not predictable from individual tests for each toxin [21], casting doubts on traditional approaches to toxicology. Similarly, heavy metal compounds affect the microbiome in several ways: arsenic reduces NOD2 expression, activates the TNF-α/IL-17 signaling pathways, suppressing APC protein and inducing β-catenin activity, the two hallmarks of carcinogenesis in the colon [22]. Finally, hexavalent chromium promotes colorectal tumorigenesis by decreasing the numbers of butyrate-producing bacteria [23].

Table 2: Summary of Key Studies on Environmental Pollutants, Gut Dysbiosis, and CRC Risk

Authors	Pollutant	Model	Microbiome Effect	CRC/IBD Link
Claus et al. [9]	>30 contaminants	In vitro + animal	5 bacterial enzymatic families affected	Toxicity modulated by microbiome
Tikka et al. [23]	Arsenic (As_2O_3)	Mice (3–6 months)	↓ NOD2, ↑ TNF-α/IL-17	↑ β-catenin, ↓ APC → CRC
Zhang et al. [24]	Chromium Cr(VI)	DMH-CRC model	↓ *Roseburia*, ↓ SCFA producers	CRC facilitation
Ma et al. [22]	Mixture of 10 pesticides (ADI)	ICR mice (17 weeks)	Dysbiosis + ↓ ZO-1/occludin	IBD-like even at regulatory doses

Sharma et al. [20]	OCPs, OPPs, herbicides	Humans + animals	↓ *Bifidobacterium*, ↑ Proteobacteria	Metabolic diseases + colon risk
De Filippis et al. [25]	Dioxins, PCBs, metals	359 subjects, Italy	Xenobiotic genes enriched in CRC	Human CRC molecular signature
Mesnage et al. [26]	Glyphosate, pyrethroids	65 twin pairs, UK	34 pesticides–metabolite associations	Microbial metabolism disruption
Javurek et al. [27]	BPA, ethinylestradiol	California mice	↑ Prevotellaceae, Erysipelotrichaceae	IBD/CRC, transgenerational effects

A metagenomic investigation performed in a severely contaminated area of southern Italy (n = 359) found that participants affected by dioxin and heavy metal contamination displayed an overrepresentation of genes encoding xenobiotic resistance—a pattern that was like the metagenome of the gut of CI patients from twenty-four different populations including 3,769 individuals [25]. Additionally, a study involving monozygotic twin pairs from Britain demonstrated thirty-four relationships between pesticide residues consumed in food and the presence of specific metabolites in feces, demonstrating that dietary pesticide residues cause disruptions in metabolic pathways within the microbiota [26]. Transgenerational effect of bisphenol A exposure on the microbiome, namely increased abundance of microorganisms responsible for the development of IBD and CD in individuals exposed prenatally, constitutes yet another issue relevant to the current research [26].

c. Infant Formula Feeding and Early Microbiome Programming

The impact of breast milk on the infant's gut microbiome is mediated through its oligosaccharides (HMOs). They act as selective substrates for bifidobacteria, which populate the microbiota of exclusively breast-fed babies, create an acidic environment in the infant's gut unfavorable for pathogens, and generate anti-inflammatory compounds [27]. Artificial baby formulas, devoid of HMOs, yield greater microbial diversity, along with an elevated incidence of Proteobacteria, and a heightened level of intestinal inflammation reflected in increased concentrations of proinflammatory cytokines IL-8 and IL-1β already at one month of age in babies on formula feedings [28, 29]. The regulation of the process of gap junctions (GAPs) formation by EGF in the breast milk postpones the activation of immune system in the intestine until proper time. The premature introduction of EGF-free formulas leads to faster exposure of infants' immune system to antigens and affects immunological imprinting of weaning stage with permanent implications on future inflammatory disorders in adults [10].

Table 3: Summary of Key Studies on Neonatal Nutrition, Early Microbiome, and Colorectal Risk

Authors	Type	Population	Comparison	Microbiome Effect	CRC/IBD Link
Laursen et al. [10]	Review	Infants 0–24 months	Breastfeeding vs formula	BF: *Bifidobacterium* dominance; Formula: ↑ pathogens, proteolytic metabolism	Protection against immune diseases
Cioffi et al. [33]	RCT	210 infants	BF vs standard vs innovative formula	Standard formula : ↑ Proteobacteria, ↓ *Bifidobacterium*	↑ Baseline inflammation (calprotectin)
Ames et al. [32]	Mechanistic review	Murine + human models	BF (EGF+) vs formula (EGF−)	Formula: early GAPs → pathological imprinting	Susceptibility to adult colitis/cancer
Cioffi et al. [33]	Case-control	73 children (mean 11 y)	Breastfed vs non-breastfed	↑ Persistent *Bacteroides*	Long-term neonatal diet effect
Yuan et al. [34]	Prospective cohort	158,696 women	Breastfed vs non-breastfed	Not directly measured	CRC HR 1.23; adenomas <50 y OR 1.46

The impact of the feeding modality during neonatal period remains significant at age 11, as demonstrated by the significantly larger number of Bacteroides in the gut microbiota of children not breastfed from an adoption-sibling study that ruled out the influence of genetics [33]. In a prospective study involving 158,696 women, a positive correlation was found between the amount of time breastfeeding and the risk of developing colorectal cancer in adult years (HR 1.23), particularly before age 55 (HR 1.38) [34]. Paradoxically, the increased risk in breastfed individuals during infancy can be

attributed to the confounding social determinants present across the generations under analysis, which suggests that it is not neonatal feeding but its interaction with other factors that affect the risk of developing colorectal cancer later in life.

d. Industrial Food Additives and Intestinal Dysbiosis

Carboxymethylcellulose and polysorbate 80, two of the most common emulsifiers in use today, thin the mucus barrier, facilitate invasion by bacteria through the mucosal layer, and increase levels of LPS and flagellin in the circulation, leading to activation of the TLR4/NF-κB pathway [38]. Exposure to polysorbate 80 in mice results in decreased MUC2 protein expression and increased colonization by colon cancers [38]. Synthetic preservatives (sodium benzoate, sodium nitrite, potassium sorbate) specifically inhibit butyrate-producing bacteria (C. tyrobutyricum, L. paracasei), while leaving inflammatory bacteria (Enterococcus faecalis) untouched [33]. Various studies have suggested artificial sweeteners are involved in gut dysbiosis, decreased butyrate production, and glucose intolerance [33].

Titanium dioxide (E171, which is banned in the EU) decreases the amount of Verrucomicrobia and triggers Th1/Th17 immunity in Peyer's patches, potentially leading to IBD in rodents [32]. Lastly, exposure to bisphenol A in food packaging before conception showed that there was transgenerational inheritance of its impact on the microbiota, with an increase in taxa associated with IBD and IC in future generations [34].

Table 4: Summary of Key Studies on Industrial Food Additives, Gut Microbiome, and Colorectal Risk

Authors	Additive	Model	Microbiome Effect	CRC/IBD Link
Sellem et al. [36]	E471, E407	92,000 adults (NutriNet-Santé)	Not directly measured	HR overall cancer 1.15; no direct CRC association
Zhou et al. [35]	Multi-additives	Review, animal models	↓ Coriobacteriaceae, ↑ *Escherichia-Shigella*, ↓ *Bifidobacterium*	Dysbiosis → IBD/CRC
Rinninella et al. [17]	NAS, emulsifiers, colorants	Review + animals	↑ *Bacteroides*/Enterobacteriaceae, ↓ butyrate	IBS → IBD → CRC
Javurek et al. [27]	BPA (50 mg/kg)	California mice	↑ Prevotellaceae, Erysipelotrichaceae	IBD/CRC, multigenerational effects
Rodriguez-Santiago et al. [37]	BPA, phthalates, PAHs	Humans + animals	↑ Intestinal permeability, dysbiosis	CRC via neuroendocrine inflammation

Cross comparison between the four factors shows surprising mechanistic homogeneity. Despite the heterogeneity of microorganisms and communities in the microbial milieu, the biological effect is the same: reduction in the number of butyrate producers and anti-inflammatory species, increase in pro-inflammatory microorganisms, and chronic NF-κB and TLR4 pathway activation (Table 5). The situation correlates perfectly with the microbial environment necessary for initiating and sustaining intestinal cancer [20, 35].

This similarity proves the validity of introducing the notion of dysbiogenic exposome, defined as the collection of contemporary environmental stressors that can act in concert or separately to induce disturbances in the microbiota composition and function. This hypothesis is confirmed by the evidence that residents from highly polluted environments, just like IC patients, have an identical microbiota biomarker profile characterized by enrichment in genes for xenobiotic resistance [36].

Table 5 — Mechanistic Convergence of Four Environmental Factors Toward Gut Dysbiosis

Factor	Decreased Protective Species	Increased Harmful Species	Inflammatory Pathway	Critical Window	Level of Evidence
Antibiotics	*Faecalibacterium*, *Roseburia*, *Lactobacillus*	*F. nucleatum*, *B. fragilis*	↓ Butyrate → NF-κB	Childhood / adolescence	High
Pollutants / Pesticides	*Lactobacillus*, *Bifidobacterium*, *Roseburia*	Proteobacteria, Prevotellaceae	TLR4 / NF-κB, NLRP3	Chronic exposure	Moderate

Infant formula feeding	*Bifidobacterium* (HMO-dependent)	*Clostridium*, Enterobacteriaceae	↓ EGF → GAPs → inflammation	First 1,000 days	Moderate
Food additives	*C. tyrobutyricum*, *Akkermansia*	*R. gnavus*, Proteobacteria	LPS / Flagellin → TLR4	Daily exposure	Emerging

For each of the four variables, however, the most significant impact occurs in case of exposure during early life stages in agreement with the eight to ten-year latency period required for intestinal carcinogenesis [31, 37]. In this context, it is easy to understand why many scientific papers yield results that seem to contradict the theory, namely, because they study recent exposures or adult exposures that have not been taking place long enough for their impact to manifest itself [16].

The cohorts born after 1970 in industrialized nations become exposed to all these agents simultaneously according to a specific timing pattern, which corresponds to the rise in the incidence of colon cancer in each successive generation [2, 37]. The demonstration that combinations of pesticides even at their permitted levels lead to lesions in the colon that could not be predicted when assessing them individually highlights the need for a new risk assessment paradigm that considers cumulative exposure to reflect the way humans are exposed to chemicals.

A clear connection between these variables and EOCRC is still poorly described in existing epidemiological studies of younger populations. Mechanistic evidence mostly relies on in vivo experiments and/or cell cultures, the extrapolation of which to humans should be established. The lack of microbiome analysis as a mediator variable in most existing epidemiological studies hinders proving the whole causal sequence. Prospective cohort studies with repeated measurements of microbiome composition starting at birth and considering the age-specific effects are key methodological strategies for confirming this interpretative model.

IV. Conclusion

This analysis suggests that the poorly investigated environmental and behavioral determinants—antibiotics, pollutant exposure, pesticide exposure, infant formula feeding, and dietary intake of preservatives—are capable of causing chronic dysbiosis through a similar mechanism, which involves the suppression of beneficial microbes (especially those responsible for butyrate synthesis), the proliferation of inflammatory microbes, and the triggering of NF-$\varkappa$B and TLR4 pathways. This analysis offers an original perspective on the increasing trend of CD among young adults through the interpretation of its underlying pathogenesis.

The originality of this contribution is its departure from the idea that EOCRC risk factors are fragmented in nature to that of an integrated model based on the concept of dysbiogenic exposome defined as "the aggregate of multiple generations' environmental insults leading to gradual disintegration of the intestinal microbiota ecosystem among modern humans." The proposed model is not meant to replace established risk factors, but rather to complement them with an overarching mechanism that acts further upstream, starting from the very beginnings of life. Validating this theoretical framework requires prospective longitudinal studies that incorporate repeated microbiome measurements, data on early-life environmental exposure, and analyses specific to cohorts of people under 50 years of age. These research efforts are essential for developing primary prevention strategies for EOCRC that are tailored to the realities of the modern environment. This framework is particularly relevant for middle-income countries undergoing rapid nutritional and environmental transitions, where simultaneous exposure to all four identified factors is occurring at an unprecedented pace.

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