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Review Article

Colorectal Cancer in the Era of Early-Onset Disease — A Global Perspective

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Abstract

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, accounting for approximately 1.9 million new cases and more than 900,000 deaths annually [1]. Over the last two decades, population-based screening programs have contributed to a significant decline in both incidence and mortality among individuals older than 50 years [2]. In contrast, a consistent and alarming increase in early-onset colorectal cancer (EOCRC), defined as CRC diagnosed before the age of 50, has been observed across multiple geographic regions [3–5].

This epidemiological divergence reflects a complex interplay of metabolic dysfunction, chronic inflammation, microbiome alterations, environmental exposures, and genetic susceptibility [6–9]. Importantly, EOCRC is increasingly recognized as a biologically and clinically distinct entity rather than simply an earlier manifestation of conventional CRC [10].

This article provides an integrated and expanded overview of EOCRC, linking global epidemiological trends with underlying biological mechanisms and clinical implications. Particular emphasis is placed on how early-life exposures and molecular heterogeneity influence disease development, and how these insights should reshape screening strategies, diagnostic awareness, and precision oncology approaches.

Introduction

Colorectal cancer has traditionally been regarded as a malignancy associated with aging, with the majority of cases occurring after the age of 60. However, this paradigm has shifted significantly. Over the past two decades, multiple large-scale epidemiological studies have documented a steady and reproducible increase in CRC incidence among individuals younger than 50 years [3,11].

This shift is not merely statistical—it has direct clinical consequences. Younger patients often present with more advanced-stage disease, partly due to delayed diagnosis and low clinical suspicion in this age group [12,13]. Symptoms such as rectal bleeding or iron deficiency anemia are frequently misattributed to benign conditions, contributing to diagnostic latency.

These clinical observations correlate with emerging biological data suggesting that EOCRC differs in tumor biology, molecular signatures, and possibly carcinogenic pathways compared to late-onset CRC [10,14]. Therefore, EOCRC should be understood not simply as a temporal variation of CRC, but as a distinct clinicopathological entity shaped by unique environmental and biological exposures.

Building on this premise, the following sections expand on global epidemiological patterns and connect them mechanistically to the biological drivers of disease.

Global Epidemiology

The global burden of colorectal cancer continues to rise, with significant heterogeneity across regions and age groups. While incidence rates have stabilized or declined in older populations due to effective screening and polypectomy [2], EOCRC incidence has increased steadily in North America, Europe, Asia, and parts of Latin America [3–5,15].

This divergence strongly supports the presence of a birth-cohort effect, whereby individuals born after the 1960s exhibit a higher lifetime risk of CRC compared to previous generations [16]. This observation implies that early-life exposures—rather than aging alone—play a central role in disease development.

Dietary patterns characterized by high consumption of ultra-processed foods, red meat, and low fiber intake, combined with rising rates of obesity and sedentary lifestyles, are major contributors [6,17]. Additionally, early exposure to antibiotics and environmental pollutants may disrupt the gut microbiome, further increasing susceptibility [8,18].

Importantly, EOCRC shows a distinct anatomical distribution, with a higher prevalence of distal and rectal tumors, suggesting potential differences in carcinogenic pathways compared to proximal colon cancers [19].

These epidemiological patterns provide the framework for understanding the biological mechanisms discussed in the next section.

Feature	EOCRC (<50)	Late CRC (>50)	Clinical Implication
Tumor location	Distal/rectal predominance	More proximal distribution	Impacts screening modality
Stage at diagnosis	More advanced	Earlier stages	Worse prognosis in EOCRC
Diagnostic delay	Frequent	Less common	Impacts survival outcomes
Molecular features	Distinct patterns	Classic CRC biology	Therapeutic implications

Table 1. Clinical and Epidemiological Differences Between EOCRC and Late-Onset CRC

Biological Mechanisms

The epidemiological trends described above are closely linked to a multifactorial and interconnected biological framework.

Obesity and metabolic syndrome represent central drivers of EOCRC. Hyperinsulinemia and increased insulin-like growth factor-1 (IGF-1) signaling promote cellular proliferation and inhibit apoptosis, creating a pro-tumorigenic environment [6,20]. This metabolic milieu is further amplified by adipokine imbalance, characterized by elevated leptin and reduced adiponectin levels, which enhance inflammatory and proliferative signaling pathways [21].

Chronic low-grade inflammation plays a synergistic role. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) activate oncogenic pathways including STAT3 and NF-κB, facilitating tumor initiation and progression [7,22].

In parallel, oxidative stress leads to DNA damage and genomic instability, providing a substrate for malignant transformation [23]. Bile acid dysregulation, often associated with high-fat diets, contributes to mucosal injury and carcinogenesis [24].

The gut microbiome has emerged as a central regulator in EOCRC pathogenesis. Dysbiosis promotes immune dysregulation, chronic inflammation, and the production of genotoxic metabolites such as colibactin [8,25]. Specific bacterial species, including Fusobacterium nucleatum, have been implicated in tumor progression and immune evasion [26].

Environmental exposures—including antibiotics, endocrine disruptors, and dietary additives—may further alter microbiome composition and host metabolism, reinforcing carcinogenic pathways [18,27].

Although hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis account for a minority of EOCRC cases, most cases arise from complex gene–environment interactions and epigenetic modifications rather than single-gene mutations [9,28].

Thus, the biological mechanisms of EOCRC directly reflect the epidemiological exposures outlined previously, reinforcing the concept of a distinct disease entity.

Mechanism	Pathway	Biological Effect
Hyperinsulinemia	IGF-1 signaling	Enhanced proliferation
Chronic inflammation	IL-6 / TNF-α	Tumor promotion
Microbiome dysbiosis	Bacterial metabolites	DNA damage
Oxidative stress	Reactive oxygen species	Mutagenesis
Adipokine imbalance	Leptin / adiponectin	Pro-tumor signaling

Table 2. Key Biological Pathways in EOCRC

Clinical Implications

The convergence of epidemiological and biological insights has immediate clinical consequences.

Screening strategies have already evolved, with major guidelines recommending initiation at age 45 for average-risk individuals [29]. However, given the continued rise of EOCRC, this threshold may still be insufficient. Risk-adapted screening approaches incorporating family history, metabolic factors, and possibly microbiome profiling should be considered [30].

Diagnostic awareness is critical. The clinical patterns described earlier—particularly advanced stage at presentation—underscore the need for heightened suspicion. Symptoms such as rectal bleeding, unexplained anemia, and changes in bowel habits in younger patients must prompt timely evaluation [12,31].

Precision oncology has become central to CRC management. Molecular profiling—including RAS, BRAF, MSI/dMMR, HER2, and NTRK alterations—guides therapeutic decisions and allows for personalized treatment strategies [32–34]. Notably, EOCRC may exhibit distinct molecular signatures, further supporting tailored approaches.

In addition, survivorship issues are particularly relevant in younger patients, including fertility preservation, long-term toxicity, and psychosocial impact—areas that require dedicated attention.

Thus, clinical management must integrate the epidemiological trends and biological mechanisms previously discussed, translating them into earlier detection and more individualized care.

Conclusion

Early-onset colorectal cancer represents a significant shift in modern oncology. The increasing incidence among younger populations cannot be explained solely by improved detection but reflects deeper changes in environmental exposures, metabolic health, and microbial ecology.

This phenomenon highlights the need for a paradigm shift—from age-based screening alone to a more comprehensive, risk-adapted approach that integrates biological and lifestyle factors.

EOCRC exemplifies the convergence of epidemiology, molecular biology, and clinical medicine. Addressing this challenge requires coordinated efforts across research, clinical practice, and public health, with the ultimate goal of improving early detection, optimizing treatment, and reversing current incidence trends.

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