The Rise of Early-Onset Colorectal Cancer: Mini-Review of an Alarming Trend

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Mini Review

Incidence and Scope

The incidence of early-onset colorectal cancer (EOCRC), diagnosed before the age of 50, has been rising alarmingly in recent decades [1-3]. As of the latest data, approximately 10-12% of new colorectal cancer diagnoses are early-onset [4]. Noted initially in the 1980s in adults aged 20-39 years and then in those aged 40-54 years in the mid-1990s, the term "birth cohort effect" was coined [5]. This phenomenon describes a group of individuals carrying forward increased colorectal cancer risk due to various factors including dietary changes, obesity, microbiome changes, and environmental exposures, among others.

In recent years, high-income countries including the United States, Australia, and Canada have experienced increasing EOCRC rates, contrasting with decreasing rates of late-onset colorectal cancer (LOCRC; diagnosed at age >50 years) [6]. Recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program show that colorectal cancer rates, while declining steadily in older Americans [Average Annual Percent Change (AAPC) -2.4% per year, 2012-2021, age > 65 years], are persistently climbing in younger individuals [AAPC +3.2% per year, 2012-2021, age < 50 years] [7].

Clinical Characteristics:

EOCRC may represent a distinct disease process from LOCRC, with EOCRC more often arising in the distal colon and rectum, presenting at advanced oncologic stages, and displaying unfavorable histopathologic features (i.e., poor differentiation, signet ring cell and mucinous morphologies, perineural and vascular invasion) [3]. These tumors have distinct molecular profiles from LOCRCs, with frequent KRAS mutations, TP53 mutations, and LINE-1 hypomethylation but infrequent APC mutations and BRAF mutations [8]. They are predominantly microsatellite stable and chromosomal instable2. Comparative data on survival outcomes are conflicting [3,9].

Hereditary predisposition to colorectal cancer may be identified in up to 30% of EOCRC cases [10]; however, familial cancer syndrome rates have remained stable, suggesting that sporadic cases largely account for the rise in EOCRC.

Risk Factors:

The sporadic nature of EOCRC and its rising incidence in high-income countries point to environmental factors as significant contributors, though the exact cause remains unclear. To address this urgent public health concern, the National Cancer Institute and National Institute of Environmental Health Sciences convened an "Early-Onset Colorectal Cancer Think Tank" meeting in September 2020 to investigate risk factors, mechanisms, and clinical implications [2]. Obesity, sedentary behavior, and Western diet were deemed to be major risk factors [2]. Indeed, several published meta-analyses have identified these among other demographic, clinical, and environmental risk factors [10-14]. To summarize their findings, significant demographic risk factors include male sex and Caucasian race; clinical risk factors include inflammatory bowel disease, hyperlipidemia, diabetes, and obesity; and environmental risk factors include tobacco use, alcohol use, sedentary behavior, and consumption of Western diets or those high in red meat or sugar-sweetened beverages. Other potential contributors include

antibiotics, synthetic dyes, monosodium glutamate, titanium dioxide, and high-fructose corn syrup [8]. Key questions remain about how environmental exposures interact and by which underlying biologic mechanisms their effects are mediated [2].

Proposed Mechanisms:

As EOCRC emerges as a distinct disease process from LOCRC, research into molecular underpinnings has intensified. Multi-omics analyses in search of a molecular signature for EOCRC [15,16] have revealed several unique characteristics including alterations in the oxidative stress response [15] as well as differences in tumor mutation burden, DNA repair features, gene expression, and immunophenotype [16]. Molecular differences may also predict differences in prognosis among patients with EOCRC, with one study identifying a gene signature consisting of 6 different genes that was associated with higher risk for recurrence but better response to adjuvant chemotherapy [17].

With EOCRC's known metabolic (i.e., obesity, red meat, Western diet) and inflammatory (i.e., IBD) risk factors, the intestinal microbiome and the inflammatory response have also become active areas of investigation. Microbiome research has identified specific microbial signatures associated with higher risk of colorectal cancer mutations, but how the microbiome promotes carcinogenesis in this population remains unclear [8]. Links between immune dysregulation and EOCRC have also been identified, including upregulation of the pro-inflammatory TNF-R1 pathway and downregulation of the antioxidant transcription factor NRF2 [18].

Screening Recommendations:

Colorectal cancer screening programs have been effective in reducing the overall cancer burden, particularly in high-resource countries. In addition to detecting cancers at early and more treatable stages, colonoscopic screening prevents cancer development by allowing for the removal of pre-cancerous polyps. However, because screening traditionally began at the age of 50, early-onset cancers were often missed.

Due to the rise in EOCRC, screening recommendations have been updated. In May 2021, the United States Preventative Services Task Force (USPSTF) revised their 2016 position statement, changing the recommended age for initiation of colorectal cancer screening from 50 to 45 [19]. This change is endorsed by the United States Multi-Society Task Force (MSTF) on colorectal cancer, which includes representatives from the American Gastroenterological Association (AGA), the American College of Gastroenterology (ACG), and the American Society for Gastrointestinal Endoscopy (ASGE) [19,20]. The MSTF now recommends screening all average-risk individuals starting at age 45 [19].

Conclusions

Over the past several decades, the incidence of EOCRC has been increasing in the United States and other developed countries at an alarming rate. Early epidemiological studies suggest that EOCRC has unique clinical, pathological, and molecular features that should be considered in screening for, diagnosing, and treating this disease.

Numerous environmental risk factors have been uncovered, many of which are metabolic in nature, but current evidence is only beginning to unravel how such exposures interact with human biology to produce EOCRC. National organizations have started to respond to this problem, recently lowering the recommended age for colonoscopy screening from 50 to 45 years. However, further research is needed to fully understand this growing problem and optimize methods for prevention and early detection.

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