

## AGA Community Forum

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### DEALING WITH THE INCREASING PROBLEM OF EARLY-ONSET COLORECTAL CANCER: NEXT STEPS IN THE INTERNATIONAL ARENA.



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This post was drafted in collaboration with Andrea Dwyer and José Perea in response to [this meeting summary](#) in the August issue of Gastro.

It is currently undeniable that the incidence of Colorectal Cancer (CRC) is increasing in individuals younger than 50 years-old, also known as Early-age-onset CRC (EAOCRC). The data are widely documented within the United States population, but is also recently trending on a global scale (1). Some of the most striking evidence shows that an adult born in the 1990s has twice the risk of colon cancer and four times the risk of rectal cancer compared to an adult born in the 1950s (2). Rectal cancer statistics are indeed more astounding and continue to be on the rise. For instance, the incidence of rectal cancers for the young population doubled from 1991 to 2014 according to the Surveillance, Epidemiology and End Results program (SEER) database. This trend is estimated to rise up to 270% by 2030 (3).

This rise in EAOCRC is critical as young adults comprise a significant portion of the U.S population and are most vulnerable to the economic consequences of being sick (4). Further, most EAOCRC cases occur without familial history of colorectal cancer and the disease tends to be diagnosed in more advanced stages due to the absence of symptoms or delayed diagnosis. Because of the importance of this issue, the American Cancer Society (ACS) initiated a recommendation, in mid-2018, to begin screening at 45 years for average-risk adults (5). Other efforts tackling EAOCRC were also promoted by different groups within both the scientific community and patients' advocacy groups.

One of the main community players that has identified EAOCRC as a priority in recent years is Fight Colorectal Cancer (Fight CRC) -- A national advocacy organization actively tracking trends in colorectal cancer diagnoses and prevention. In the August issue of Gastroenterology, a summary of the Fight CRC working meeting held in February 2019 is presented, linking priorities with exploring risk factors and etiology of sporadic EAOCRC (6). This meeting was convened in response to an urgent need to understand EAOCRC and included a gamete of national and international experts focused on this topic.

As starting points in this meeting, apart from developing a description of the epidemiological importance of EAO CRC, a molecular summary was presented discussing the current knowledge to date. The two clearest and most defined points included were that the hereditary component, at least in relation to the susceptibility genes already known, cannot explain more than 20% of EAO CRC cases (7, 8). In addition, from the tumoral-based molecular basis, EAO CRC seems to present differential characteristics when compared to CRC that develops in later ages (Late-onset CRC). Specifically, EAO CRC does not only hold a different molecular basis according to the main carcinogenetic pathways (Microsatellite Instability; CpG Island Methylator Phenotype, Chromosomal Instability) (9, 10), but also a particular epigenetic hallmark (LINE1 hypomethylation) and differential molecular alterations (e.g. altered chromosomal regions) (11, 12).

At the end of the meeting and focusing on the major sporadic component of EAO CRC, major themes were identified as key priority areas related with environmental causes: diet, weight, the microbiome, antibiotic use, and gene-environment interactions. Nevertheless, it was concluded that existing studies alone may not be able to solve or answer all questions regarding the etiology of sporadic EOCRC. Therefore, it's necessary that new approaches be developed to help answer the proposed request.

In addition to the need for study designs to cover important sample sizes and different and diverse geographical areas specifically for sporadic EOCRC, racial disparities have to be accounted for as well (13, 14). Thus, it was apparent during the meeting that there is a need to provide an international dimension on EOCRC research, within different aims. Several months later, in June 2019, we hosted the 1st EOCRC International Symposium in Madrid, Spain. With the intention of continuity, an update was carried out regarding the current knowledge about this type of CRC, but also the importance of developing studies covering different geographical regions, not only on a continental level, but possibly intercontinental as well.

In conclusion, we are only taking the first steps to understand the causes of EOCRC, and therefore the reasons for the increase of incidence and therefore prevention. The planning of the way forward is an essential step in the

achievement of that primordial objective. An international effort developed in multinational and multidisciplinary collaborative groups is crucial.

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