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Deciphering the increasing incidence, special characteristics and possible aetiology of early onset colorectal cancer: A European perspective within an international effort

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide (there were an estimated 1.8 million new cases in 2018).[1] Regarding global trends, incidence is decreasing in high-income countries due to, among other things, the establishment of CRC screening strategies mainly based on colonoscopy or faecal occult blood tests.[2] However, there has also been a decline in CRC cases diagnosed in patients older than 50.[3,4] Conversely, cases of CRC appearing at a younger age, also known as early onset CRC (EOCRC), have increased significantly in recent years.[5] Data are widely documented within the US population.[6] Indeed, data show that an adult born in the 1990s has twice the risk of colon cancer and four times the risk of rectal cancer than an adult born in the 1950s.[6] The statistics about rectal cancer are even more alarming: the incidence of rectal cancers for the younger population doubled between 1991 and 2014, and it is estimated to rise by up to 270% by 2030.[5] In Europe, data on CRC incidence among younger adults was lacking until recently. Studies published within 2019 show that even though in most European countries the EOCRC incidence has risen, there is wide spectrum of heterogeneity between countries.[3,4] During the most recent decade of available data, EOCRC incidence rates are uniquely increasing in young adults in Germany, the UK, Denmark, Slovenia and Sweden (countries with a stable or declining trend among adults older than 50), while conversely EOCRC declined in only three countries (Italy, Austria and Lithuania). In Cyprus, the Netherlands and Norway (countries with an increasing trend among adults older than 50), increases in incidence in younger adults were twice as rapid as those in older adults.[4]

Even though the early age of onset of colorectal cancer has been traditionally considered a red flag for hereditary conditions such as Lynch syndrome,[7] recent studies focused on EOCRC using next-generation sequencing have shown that the proportion of hereditary cases in this setting only accounts for up to 20% of cases.[7] Although the prevalence of Lynch syndrome reported ranges between 8% and 13%, the prevalence of other high-penetrance syndromes only accounts for up to 5% of cases. Of note, a meaningful proportion of these cases do not display clinical histories typically associated with the identified syndrome. Accordingly, germline testing with multigene cancer panels should be considered for all EOCRC. However, we should keep in mind that in the majority of EOCRC cases, no predisposing germline mutations are found.

From a molecular point of view, EOCRC presents differential characteristics in comparison with CRC among older adults. Some of the approaches previously carried out have identified not only different distribution according to the main carcinogenetic pathways (e.g. microsatellite instability, CpG island methylator phenotype, chromosomal instability)[8,9] but also particular hallmarks (e.g. LINE1 hypomethylation) or differential molecular alterations (e.g. altered chromosomal regions).[8,10] Taken together, the overall increased incidence of EOCRC, the unique molecular patterns and the small proportion of hereditary syndrome suggest that environmental factors as well as lifestyle exposures are likely involved in the carcinogenesis of EOCRC. These changes include, among others, diet, being overweight, microbiome alterations (dysbiosis), antibiotic use and gene–environment interactions. In this sense, recent data strongly support the contribution of obesity and sedentary lifestyle to the increased risk of EOCRC.[11,12] However, the impact of each of these factors remains elusive.

The growing importance and awareness of EOCRC has given rise to the organisation of different monographic meetings in order not only to draw attention to this clinical problem but also to update on the most recent scientific advances. In this sense, in 2019, two international meetings took place: one in the USA (Fight Colorectal Cancer Workshop about EOCRC) and another in Europe (1st EOCRC International Symposium in Spain). We would like to acknowledge the figure of Professor Thomas K Weber (who sadly passed away a few months ago) as the pioneer in the

call for awareness of the worrisome impact of EOCRC, as well as in the organisation of the Summit on EOCRC, which has been celebrating in New York for the last 5 years.

While waiting for a scientific breakthrough in the understanding of EOCRC, clinicians have an essential role in the fight against this disease, first with the documentation and identification of familial cancer history in all CRC patients that often leads to the diagnosis of hereditary syndromes. Nevertheless, current guidelines recommend performing germline testing in all EOCRC patients, regardless of family history. Second, and more importantly, clinicians should collaborate in decreasing morbidity and mortality from EOCRC with a timely workout of symptoms regardless of the patient's age. Because of the importance of this issue, in 2018, the American Cancer Society initiated a qualified recommendation based on the evidence from predictive models for average-risk adults to begin screening at 45 years.

We are only taking the first steps to understand the causes of EOCRC and the reasons for the increased incidence. Paving the way is an essential step to achieving the primordial objective of preventing this epidemic from growing. An international effort developed in multinational and multidisciplinary collaborative groups is crucial. We are currently developing a European network, with some other international collaborators (e.g. the USA), in order to improve the knowledge of this disease. This team effort will not only facilitate to have a large enough sample size to reach reliable conclusions but at the same time analyse the geographical differences that seem to exist.

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ORCID iDs

José Perea https://orcid.org/0000-0001-5522-8844
Francesc Balaguer https://orcid.org/0000-0002-0206-0539

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José Perea[1,2] and Francesc Balaguer[3]
[1]Department of Surgery, Fundación Jiménez Díaz University Hospital, Madrid, Spain
[2]Fundación Jiménez Díaz University Hospital Health Research Institute, Madrid, Spain
[3]Department of Gastroenterology, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), University of Barcelona, Barcelona, Spain

Corresponding author:
José Perea, Fundacion Jimenez Diaz University Hospital, Avenida de los Reyes Católicos 2, Madrid 28040, Spain.
Email: josepereag@hotmail.com