Pediatric colon cancer - when enemies band together.

Thomas Attard[1]

[1]Children's Mercy Hospitals and Clinics

July 12, 2022

–Title:

Pediatric Colon Cancer - When Enemies Band Together.

–Author affiliation:

Thomas M Attard MD

–Corresponding author:

Thomas M Attard MD

2401 Gillham Rd, Kansas City, MO 64108

Office: (816) 302-8149

Fax: (816) 234-1553

E-mail: tmattard@cmh.edu

–Word Count

770

–The number of Tables, Figures, and Supporting Information files;

0

–A short running title

Pediatric colon cancer

–Three to six keywords to index the content.

Pediatric, colorectal cancer, polyposis

–Abbreviations key.

CRC	Colorectal Cancer
EOCRC	Early-onset colorectal cancer
AYA	Adolescents and young adults
PV	Pathogenic variant
FAP	Familial Adenomatous Polyposis
MAP	*MUTYH*-associated polyposis
JPI	Juvenile Polyposis of Infancy
BMMRD	Biallelic Mismatch Repair Deficiency

The last decades have seen strides made in early detection and effective management of colorectal cancer(CRC). Less encouraging has been an observed increase in CRC in young adults, or early onset colorectal cancer (EOCRC) defined as under 30, 35 or 40 years of age at diagnosis.

In contrast with the observed steady decrease in age adjusted incidence of CRC in individuals over 50 years of age, a 1.3% increase incidence in CRC in individuals 20 – 49 years of age has been observed since 1996. The largest percent increase in incidence is reported among ages 20–29 years, with an increase of 5.2 % in men and 5.6 % in women per year, and largely attributable to left sided and rectal lesions. In the pediatric age range, CRC incidence has remained stable and favors a right sided localization, more common in males between 15 – 17 years of age and from lower socioeconomic background.

The diagnosis of EOCRC in adolescents and young adults (AYA) tends to be delayed for various reasons including under-utilized health care services, and physicians harboring a low index of suspicion. This population is also outside the scope of screening unless individuals are known to have a predisposing syndrome. Younger patients tend to have more advanced stage of disease, less favorable histopathology, and worse prognosis at the time of diagnosis compared with older patients.

Younger patients are more likely to harbor a recognized hereditary, therefore syndromic etiology for CRC. Even then however, only a small minority of individuals harbor pathogenic variants (PV) in the well characterized genetic loci including Familial Adenomatous Polyposis (FAP), Lynch syndrome (LS), MUTYH-associated polyposis (MAP) and the less common hamartomatous polyposis syndromes (Peutz–Jeghers syndrome and juvenile polyposis syndrome).

Phen and colleagues describe 3 patients with CRC diagnosed at 15 years of age, one harbored PV in *MLH1* and *MSH3* , a second with*MSH2* and *APC* risk allele and a third with PV in both*MLH1* and *APC* . This report entails two broad implications. In the context of the increased impact of EOCRC, it offers potentially new insight wherein concurrent pathogenic mutations in Lynch and FAP loci or biallelic Lynch mutations may explain the occurrence of CRC in a subset in adolescents. Conversely, this paper may be an important wake up call on the need for a more aggressive approach to AYA referred for a family history of Lynch Syndrome.

Our current understanding of the molecular pathophysiology of EOCRC, especially during childhood and adolescence is very limited, genetic mechanisms are presumed to dominate over environmental factors. An underlying genetic predisposition is however rarely cited in case reports and, conversely even within the population at risk, for example, Familial Adenomatous Polyposis, CRC is a rare occurrence in the first two decades of life. However, the classic paradigm for a non-syndromic familial predisposition for CRC has included a low-penetrance polygenic inherited predisposition, and the paper by Phen et al. may well be a demonstration of this concept in the adolescent age group. As such, this implies the need for greater awareness of these largely novel, genetic factors. This concept itself is not entirely novel, an aggressive form of juvenile polyposis (Juvenile Polyposis of Infancy; JPI) is associated with contiguous deletion of two tumor suppressor genes, BMPR1A and PTEN. An even closer analogy is biallelic mismatch repair deficiency syndrome (BMMRD) wherein a mismatch repair defect is inherited from each parent with the mean age at diagnosis of CRC being 16 years.

At present, a patient with a family history of Lynch Syndrome will, if a PV is identified in the family, undergo directed genetic testing and, if discovered to be a carrier, will be referred to screening at no earlier than at 20 – 25 years of age. However, in view of the description of EOCRC associated with polygenic etiology, given the decreased cost and availability of comprehensive predisposing gene panel testing, perhaps we should be moving toward more aggressive testing at an early age. This is certainly not a call for indiscriminate testing, genetic testing has far reaching implications; more than just cost, however this and similar observations warrant a discussion reappraising risk, outcomes and testing - bearing in mind the clear impact of presymptomatic endoscopic surveillance.

Pediatric colorectal cancer remains a challenge, often with devastating consequences to patients and families. Delay in diagnosis is a major contributor to adverse outcomes and is, multifactorial but includes our inability,

thus far, to identify the majority of patients at risk. The paper by Phen and colleagues offers a tantalizing opportunity to impact our recognition of some, perhaps a significant proportion, of the individuals at risk and therefore warrants further discussion.

Bibligraphy