Digestive Diseases and Sciences (2020) 65:1590–1592
https://doi.org/10.1007/s10620-020-06083-y

EDITORIAL

# Inverted Yield Curve: The Alarming Rising Incidence of CRC in Young People

**Samuel B. Ho[1] · Shroque Zaher[1]**

Published online: 5 February 2020


Previous studies have documented changing trends in CRC incidence over time in the USA [1]. The studies indicate that although the incidence of CRC cases is decreasing in both men and women aged ≥ 50 years, since the 1970's, the incidence of CRC is increasing in the cohort that is currently aged 20–54. Adults born in 1990 have double the risk of colon cancer and quadruple the risk of rectal cancer compared with adults born in 1950. Predictive modeling indicates that by 2030, 10.9% of all colon and 22.9% of rectal cancers will be diagnosed in patients under the currently recommended screening age of 50, compared to the respective 2010 rates of 4.8 and 9.5% [2].

In this issue of *Digestive Diseases and Sciences*, Ohri et al. update prior studies examining the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI) for changes in CRC incidence in different segments of the population of the USA over the years 2000–2014 [3]. The SEER database collects cancer incidence and survival data from geographically diverse population-based cancer registries covering approximately 34.6% of the US population, an effort that has been funded by the NCI since 1973 and has uniform standards for all of the registries in an effort to promote data uniformity and to support data pooling. Ohri et al. report the annual CRC incidence by age group stratified by sex, race, and ethnicity and presented as the annual incidence per 100,000 persons, standardized to the US population in the year 2000. The overall rate in 2000–2014 in individuals aged 60–69 was 163.9, declining to 108.1 in 2014, whereas in the 40–49 age group the incidence rate increased from 20.9 to 25.1. Increasing rates in younger age groups were documented in all race/ethnic groups for males and females. Importantly, they report that African-Americans have the highest incidence in all groups aged > 40. Furthermore, although Asians and Hispanics have an overall incidence significantly lower than African-Americans and non-Hispanic whites, CRC incidence increased by 21.9% in the 50–59 age group for Hispanics. Overall, the major burden of CRC is seen in individuals 60 and above, contributing to 70% of all new cases, with individuals < 50 accounting for 10% of all cases.

The strengths of the study include data gathered from geographically diverse cancer registries over 29 years, representing a large segment of the US population. Weaknesses of this study, as with most registry studies, include less than complete representation of the population, and possible misclassification/miscoding/incomplete reporting when entering data into the cancer registry. In addition, it does not take into account context, e.g., absence of information regarding important contributing factors such as adherence to screening programs (especially for ethnic minorities), the extent of management of precancerous lesions, and factors related to CRC risk such as body mass index, family history, medications, and substance use.

Taken together, the accumulating evidence of increasing cancer rates in young people are certainly disturbing—in general, cancer usually affects older people, and modern medicine is most likely responsible for the reverse trend in the older age groups. What is going on here? Three questions come to mind: is this unique to the USA or is it being observed in other countries? What is causing this increase after a phase where CRC incidence was decreasing? And lastly, what are the implications for practice?

First, recent data indicate that this trend for CRC in younger people is being observed worldwide. Siegel et al., in a recent analysis of an international database of population-based annual incidence data for CRC diagnosed through 2012 found that in the most recent decade, incidence in adults < 50 years old was stable in 14 of 36 countries; declined in Austria, Italy, and Lithuania, and increased in 19 countries, nine of which had stable or declining trends in older adults, similar to the trends observed in the USA

✉ Samuel B. Ho
Samuel.Ho@mbru.ac.ae

[1] College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE

[4]. These data are more significant for countries in which young people comprise a high percentage of the population: for example, in the UAE, we see a relatively high percentage of young people (< 50) diagnosed with CRC. Much of this may stem from the fact that 67% of the population are age 25–55, 5.3% are 55–64, and only 1.3% are > 65 years old [5]. The population is 74% male in those aged > 25, and 89% of people are from other countries representing about 200 different nationalities (approximately 54% Indian subcontinent, 8% Asia, 9% Middle East region, and 18% Western or other). Cases of CRC reported to the national registry have increased from 220 cases in 2011 to 373 cases in 2015, 36% of which occurred in patients < 50 years old [6]. Clearly, any increase in rates in the younger age groups in countries with high populations of young people such as this will be quite noticeable.

Second, what is causing this increase? Among patients with early onset CRC, approximately 30% of patients have tumors with mutations associated with hereditary cancer predisposing syndromes, 20% have familial CRC, and the remaining 50% have neither hereditary syndromes nor familial CRC [7]. Since genetic cancer syndromes characteristically manifest at young ages and since genetic factors change slowly over time, the rapid increase of CRC incidence in younger cohorts is attributable to the 50% with no known genetic predisposition, pointing to environmental factors. Many cohort and case control studies have identified modifiable CRC risks, such as obesity and lifestyle factors related to smoking, alcohol, physical inactivity, and diet related to meat intake and low fiber [8]. The increasing trends in most of these risk factors for CRC occurring in the USA and in most parts of the world over the last few decades are well known, particularly related to obesity, diet quality, and physical activity [9, 10]. Recent data have indicated that the projected increase in obesity in the USA will particularly affect some minorities and those with low incomes [11]. Some of the described pathophysiologic factors associated with a pro-inflammatory state in the colon include alterations in diet and the gut microbiome and with obesity [12]. Furthermore, the growing impact of these risk factors is being observed for many other lifestyle- or obesity-related cancers in younger age groups, such as multiple myeloma, and cancer of the uterine corpus, gallbladder, kidney, and pancreas [13]. The interactions between these risk factors that could boost CRC risk further have been studied in several cohort and case–control studies. Of note is a recent study by Carr et al. of a large population-based case study of 4092 cases of CRC compared with 3032 matched healthy controls [14]. The five modifiable lifestyle factors of diet quality, lifetime smoking exposure, lifetime alcohol use, exercise, and body mass index were prospectively collected. Furthermore, a subgroup of patients was analyzed for 53 genetic risk variants linked to CRC risk. The authors found that compared with cases with adherence to 0 or 1 healthy lifestyle factors, cases with increasing adherence to 2, 3, 4, or 5 healthy lifestyle factors had progressively decreasing risks for CRC, significant in patients regardless of known modifiers such as genetic risk, family history of CRC, prior colonoscopy, use of NSAIDs, cancer stage, or age. They found that overall, 45% of cases could be attributed to nonadherence to all 5 healthy lifestyle behaviors. These data support the concept that the cumulative temporal trends in these lifestyle factors are important in explaining the observed trends in CRC in younger age groups.

Third, what are the implications? Should screening start at a younger age? Decreasing the population-wide recommended age for screening is controversial since although the relative rates are increasing, the absolute numbers remain low, leading to the need for careful cost-effectiveness studies of this approach and consideration of the healthcare resources available in different systems. [15, 16]. We agree with Ohri et al., who advocate for identification of high risk groups within the younger age groups in order to better target screening efforts [3]. Ratings based on combining established risk factors such as family history and genetic risk alleles with a lifestyle factor score as in the study by Carr et al. would be a start to more accurately risk-stratify younger patients [14]. Ideally, further metabolic and perhaps gut microbial biomarkers could be added in an effort to refine population stratification by identified risk factors.

The data by Ohri et al. add to a growing body of literature documenting the worrisome trends in CRC in younger age groups worldwide [7] and point to the potential interplay of multiple lifestyle factors that warrant further research. Importantly, taken together, this growing body of evidence strongly points to the need for vigorous private and public health interventions to change health risk behaviors for all individuals beginning at young ages.

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