EDITORIAL

Establishing a research agenda for early-onset colorectal cancer

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Background

Colorectal cancer (CRC) incidence and mortality trends have evolved strikingly in recent decades [1,2]. Since the late 1980s, incidence and mortality have declined among older adults (age ≥50 years) in the United States, with particularly dramatic declines in those over the age of 65 years. These improvements are likely due to a combination of screening [3,4], changes in the prevalence of certain CRC risk and protective factors (e.g., smoking, aspirin use) [5,6], and advances in treatment [7]. CRC screening with colonoscopy, sigmoidoscopy, or stool-bases tests facilitates early detection and removal of premalignant lesions (i.e., adenomatous polyps) [8] and is recommended for average-risk persons beginning at age 50 years [9].

In contrast to declines in older populations, the incidence of invasive CRC is increasing in younger adults [10,11]. Starting around 1990, incidence increased in this age group (20–49 years) from 8.6 per 100,000 to 12.5 per 100,000 [12]. The largest absolute increases in incidence have occurred among 40–49-year-olds, from 18.2 per 100,000 in 1992 to 26.5 per 100,000 in 2015. Mortality rates have increased slightly during the same period, ranging from 5.4 to 6.5 per 100,000 among the 40–49-year age group. Similar increases have been reported across the globe [1,13]—from France [14] to Canada [15] to Australia [16,17]. These trends have received research and media attention, with intense speculation for why incidence has increased. As a first step, we outline important considerations for establishing a research agenda to advance our understanding of etiological and diagnostic factors contributing to early-onset CRC.

Increases in early-onset CRC have been primarily driven by higher rates of rectal cancer

Early-onset CRC has not increased uniformly by anatomic sublocation. While rectal cancer incidence in younger adults increased from 3.0 per 100,000 in 1992 to 4.7 per 100,000 in 2015, there were smaller increases in proximal colon cancer during this period [12]. Differences in incidence and distribution of early-onset CRC by sublocation underscore the importance of teasing apart risk factors for colon versus rectal cancer. Generally, risk factors fall into one of three categories: 1) decreased risk of colon cancer but no association with rectal cancer (e.g., dietary intake of folate and calcium); 2) increased risk of colon cancer but no association with rectal cancer (e.g., processed meat, family history); and 3) increased risk of both colon and rectal cancer (e.g., smoking, obesity) [18]. Future etiological studies of early-onset CRC should examine risks separately—or how associations may be modified—by sublocation.
Efforts to understand early-onset CRC must account for increasing use of colonoscopy in younger adults

Early-onset CRC may reflect earlier detection via colonoscopy, prompting discussion on the contribution of diagnostic factors (e.g., screening, case ascertainment, practice patterns) to the observed incidence trends. Increasing incidence with stable mortality rates are often seen when greater use of screening or diagnostic technology detects cancer earlier. Although incidence of early-onset CRC has increased dramatically, corresponding mortality rates have increased only slightly, and in the youngest age groups, mortality has remained stable [12]. Colonoscopy in younger adults increased by 30% from 2001 to 2009, which parallels increases in incidence during the same period [19]. Although it is not clear whether colonoscopy at younger ages represents overuse, symptomatic assessment, or high-risk screening (e.g., for family history), this increase occurred consistently across age groups, sex, and geographic region.

Germline mutations explain only a minority of early-onset CRC cases

Only 15%–20% of patients with early-onset CRC have a germline mutation (e.g., APC, MLH1, MUTHY, STK11, SMAD4, TP53), and of these, about half have Lynch Syndrome [20]. Although the prevalence of hereditary syndromes is higher among patients with early-onset CRC compared to the overall CRC patient population, it raises questions concerning the other 80%–85% without a germline mutation but who may be at increased risk of CRC due to family history or other unknown susceptibility genes. Nearly half of patients with early-onset CRC do not have a known family history of CRC [21], but this may be underreported given limited approaches to systematically collect family history in primary care. Alternatively, the minority of cases attributed to germline mutations and/or familial risk may underscore the role of environmental and lifestyle-related factors involved in early-onset disease.

Persistent racial disparities in early-onset CRC may provide additional insight

CRC disproportionately affects blacks—higher incidence rates and smaller declines in incidence among the screen-eligible population [3]. Although whites have experienced a larger relative increase in incidence of early-onset CRC, absolute incidence rates remain higher among young blacks (14.6 versus 12.4 per 100,000 among blacks and whites, respectively) [12]. Because blacks have higher incidence of early-onset CRC than whites and the age-related acceleration in incidence starts at a younger age, some professional organizations recommend initiating CRC screening at an earlier age, such as 45 years [22]. Racial differences in the distribution of CRC risk factors, such as earlier onset of type 2 diabetes or childhood obesity, may explain some of these disparities and provide additional insight into mechanisms of early-onset CRC.

Birth cohort effects point to exposures during early childhood and adolescence that may increase CRC risk

Early-onset CRC has increased across successive birth cohorts, particularly for those born after 1950 [10]. Birth cohort effects point to early life exposures—or exposures accumulated throughout the life course—that may increase risk of cancer. For example, younger age at smoking initiation and longer duration of smoking increases risk of lung cancer.
Reconsidering the timing and duration of well-established CRC risk factors, such as obesity, may help to identify windows of exposure most susceptible to risk. A growing body of evidence suggests birth weight [23] and childhood obesity [24] increase risk of CRC in adulthood. Others have suggested antibiotic use during infancy or childhood, which increased dramatically during the 1980s [25], may influence microbial diversity [26] and increase risk of cancer in adults [27–29].

Conclusion

In summary, CRC incidence and mortality rates have declined among older adults, in part because of increased screening uptake among persons over the age of 50 years. These declines have not occurred in younger adults, where incidence has increased. Increasing incidence of early-onset CRC has led to enthusiasm for lowering the recommended age to initiate CRC screening. There are clear benefits to screening in older populations [3], and the temptation is to believe that benefits would be similar for younger adults. However, in an era of precision cancer screening [30], recommendations of when to initiate CRC screening should consider individual differences in risk and expected benefits expressed in absolute terms—not solely on temporal trends in incidence [31]. Potential harms, such as cost and colonic perforation or other adverse events [32], should also be considered. Studying population shifts in the distribution of CRC risk factors, as well as diagnostic practices, may advance our understanding of early-onset CRC and its causes. These data are also important to guide precision screening efforts, improve treatment strategies, and identify subgroups (defined by age and risk level) who may be at the highest risk of CRC.

References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017; 66(4):683–91. Epub 2016/01/29. https://doi.org/10.1136/gutjnl-2015-310912 PMID: 26818619.
2. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Can J Clin. 2017; 67(3):177–93. Epub 2017/03/02. https://doi.org/10.3322/caac.21395 PMID: 28248415.
3. Murphy CC, Sandler RS, Sanoff HK, Yang YC, Lund JL, Baron JA. Decrease in Incidence of Colorectal Cancer Among Individuals 50 Years or Older After Recommendations for Population-based Screening. Clin Gastroenterol Hepatol. 2017; 15(6):903–9.e6. Epub 2016/10/25. https://doi.org/10.1016/j.cgh.2016.08.037 PMID: 27609707; PubMed Central PMCID: PMC5337450.
4. Meester RG, Doubeni CA, Lansdorp-Vogelaar I, Goede SL, Levin TR, Quin VP, et al. Colorectal cancer deaths attributable to nonuse of screening in the United States. Annals of epidemiology. 2015; 25(3):208–13.e1. Epub 2015/02/28. https://doi.org/10.1016/j.annepidem.2014.11.011 PMID: 25721748; PubMed Central PMCID: PMC4554530.
5. Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JD, et al. How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. Cancer. 2006; 107(7):1624–33. Epub 2006/08/26. https://doi.org/10.1002/cncr.22115 PMID: 16933324.
6. Cronin KA, Krebs-Smith SM, Feuer EJ, Troiano RP, Ballard-Barbash R. Evaluating the impact of population changes in diet, physical activity, and weight status on population risk for colon cancer (United States). Cancer Cause Control. 2001; 12(4):305–16. Epub 2001/07/18. PMID: 11456226.
7. Edwards BK, Ward E, Kohler BA, Eshemek C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010; 116(3):544–73. Epub 2009/12/10. https://doi.org/10.1002/cncr.24760 PMID: 19998273; PubMed Central PMCID: PMC3619726.
8. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):659–69. Epub 2008/10/08. PMID: 18838717; PubMed Central PMCID: PMC2731975.

9. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Garcia FA, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315(23):2564–75. https://doi.org/10.1001/jama.2016.5989 PMID: 27304597

10. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. J Natl Cancer Inst. 2017;109(8). Epub 2017/04/05. https://doi.org/10.1093/jnci/djw322 PMID: 28376186.

11. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. JAMA Surg. 2015;150(1):17–22. Epub 2014/11/06. https://doi.org/10.1001/jamasurg.2014.1750 PMID: 25372703.

12. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2017 Sub (1992–2015)<Katrina/Rita Population Adjustment>—Linked To County Attributes—Total U.S., 1969–2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

13. Murphy CC, Baron JA. Colorectal Cancer in Older Ages: What's Ahead? Clin Gastroenterol Hepatol. 2017;15(6):901–2. Epub 2017/02/02. https://doi.org/10.1016/j.cgh.2017.01.019 PMID: 28143729.

14. Chauvenet M, Cottet V, Lepage C, Jooste V, Faivre J, Bouvier AM. Trends in colorectal cancer incidence: a period and birth-cohort analysis in a well-defined French population. BMC Cancer. 2011;11:282. Epub 2011/07/02. https://doi.org/10.1186/1471-2407-11-282 PMID: 21718477; PubMed Central PMCID: PMC3149029.

15. Patel P, De P. Trends in colorectal cancer incidence and related lifestyle risk factors in 15-49-year-olds in Canada, 1969–2010. Cancer Epidemiol. 2016;42:90–100. Epub 2016/04/10. https://doi.org/10.1016/j.canep.2016.03.009 PMID: 27060626.

16. Haggar FA, Preen DB, Pereira G, Holman CD, Einarsdottir K. Cancer incidence and mortality trends in Australian adolescents and young adults, 1982–2007. BMC Cancer. 2012;12:151. Epub 2012/04/24. https://doi.org/10.1186/1471-2407-12-151 PMID: 22520938; PubMed Central PMCID: PMC3404933.

17. Young JP, Win AK, Rosty C, Flight I, Roder D, Young GP, et al. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. J Gastroenterol Hepatol. 2015;30(1):6–13. Epub 2014/09/25. https://doi.org/10.1111/jgh.12792 PMID: 25251195.

18. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004; 108(3):433–42. Epub 2003/12/04. https://doi.org/10.1002/ijc.11540 PMID: 14648711; PubMed Central PMCID: PMC2903217.

19. Murphy CC, Lund JL, Sandler RS. Young-Onset Colorectal Cancer: Earlier Diagnoses or Increasing Disease Burden? Gastroenterology. 2015;149(6):1302–4. Epub 2015/08/25. https://doi.org/10.1053/j.gastro.2015.08.033 PMID: 26302487.

20. Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol. 2017;3(4):464–71. Epub 2016/12/16. https://doi.org/10.1001/jamaoncol.2016.5194 PMID: 27978560; PubMed Central PMCID: PMC5564179.

21. Schellner VS, Merkel S, Schumann SC, Schlabakowski A, Fortsch T, Schildberg C, et al. Despite aggressive histopathology survival is not impaired in young patients with colorectal cancer: CRC in patients under 50 years of age. Int J Colorectal Dis. 2012;27(1):71–9. Epub 2011/09/02. https://doi.org/10.1007/s00384-011-1291-8 PMID: 21881876.

22. Kupper SS, Carr RM, Carethers JM. Reducing colorectal cancer risk among African Americans. Gastroenterology. 2015;149(6):1302–4. Epub 2015/08/25. https://doi.org/10.1053/j.gastro.2015.08.033 PMID: 26302487.

23. Smith NR, Jensen BW, Zimmermann E, Gamborg M, Sorensen TI, Baker JL. Associations between birth weight and colon and rectal cancer risk in adulthood. Cancer Epidemiol. 2016;42:181–5. Epub 2016/05/21. https://doi.org/10.1016/j.canep.2016.05.003 PMID: 27203465; PubMed Central PMCID: PMC4911557.

24. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, et al. Early life body fatness and risk of colorectal cancer in u.s. Women and men-results from two large cohort studies. Cancer Epidemiol Biol Markers Prev. 2015;24(4):690–7. Epub 2015/03/18. https://doi.org/10.1158/1055-9965.EPI-14-0909-T PMID: 25777804; PubMed Central PMCID: PMC4412364.
25. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA. 1995; 273(3):214–9. Epub 1995/01/18. PMID: 7807660.

26. Cho I, Yamanishi S, Cox L, Methe BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012; 488(7413):621–6. Epub 2012/08/24. https://doi.org/10.1038/nature11400 PMID: 22914093; PubMed Central PMCID: PMC3553221.

27. Boursi B, Haynes K, Mamtani R, Yang YX. Impact of antibiotic exposure on the risk of colorectal cancer. Pharmacoepidemiol Drug Saf. 2015; 24(5):534–42. Epub 2015/03/27. https://doi.org/10.1002/pds.3765 PMID: 25808540.

28. Cao Y, Wu K, Mehta R, Drew DA, Song M, Lochhead P, et al. Long-term use of antibiotics and risk of colorectal adenoma. Gut. 2018; 67(4):672–8. Epub 2017/04/06. https://doi.org/10.1136/gutjnl-2016-313413 PMID: 28377387; PubMed Central PMCID: PMC5628103.

29. Dik VK, van Oijen MG, Smeets HM, Siersema PD. Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study. Dig Dis Sci. 2016; 61(1):255–64. Epub 2015/08/21. https://doi.org/10.1007/s10620-015-3828-0 PMID: 26289256; PubMed Central PMCID: PMC4700063.

30. Marcus PM, Pashayan N, Church TR, Doria-Rose VP, Gould MK, Hubbard RA, et al. Population-Based Precision Cancer Screening: A Symposium on Evidence, Epidemiology, and Next Steps. Cancer Epidemiol Biomarkers Prev. 2016; 25(11):1449–55. Epub 2016/11/03. https://doi.org/10.1158/1055-9965.EPI-16-0555 PMID: 27507769; PubMed Central PMCID: PMC5165650.

31. Murphy CC, Sanoff HK, Stitzenberg KB, Baron JA, Sandler RS, Yang YC, et al. RE: Colorectal Cancer Incidence Patterns in the United States, 1974–2013. J Natl Cancer Inst. 2017; 109(8). Epub 2017/11/09. https://doi.org/10.1093/jnci/djx104 PMID: 29117391.

32. Warren JL, Klabunde CN, Mariotto AB, Meekins A, Topor M, Brown ML, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med. 2009; 150(12):849–57, w152. Epub 2009/06/17. PMID: 19528563.