Colorectal cancer screening

JUNE 2019

Folic acid supplementation alters the equation

TO THE EDITOR: In their paper on colorectal cancer screening, Mankaney and colleagues noted the increasing rates of colorectal cancer in young adults in the United States.[1] Recent epidemiologic data demonstrate an increasing incidence of the disease in people ages 40 through 49 since the mid-1990s.[2] Even though screening starting at age 45 is not uniformly accepted,[1] there is evidence supporting earlier screening.

During the mid-1990s, the US government mandated that all enriched flour and uncooked cereal grains were to be fortified with folic acid in order to prevent births complicated by neural tube defects.[3] Subsequently, there was a 2-fold increase in plasma folate concentrations and, disturbingly, a temporally associated significant increase in the incidence of colorectal cancer.[3]

Notably, a US trial[4] testing the efficacy of folic acid 1 mg taken daily for 6 years to prevent colorectal adenomas in those with a history of colorectal adenomas failed to show a reduction in adenoma risk. Instead, participants randomized to folic acid exhibited a significantly increased risk of an advanced adenoma. Another trial,[5] conducted in the Netherlands, where there is no mandatory folic acid fortification, investigated folic acid 400 µg and vitamin B_{12} 500 µg daily over 2 to 3 years for the prevention of osteoporotic fractures. The group randomized to the vitamins had a nearly 2-fold increase in the risk of colorectal cancer.

Folic acid can be a double-edged sword.[3,5] Although folic acid intake may protect against carcinogenesis through increased genetic stability, if precancerous or neoplastic cells are present, excess folic acid may promote cancer by increasing DNA synthesis and cell proliferation. Cancer cells have folic acid receptors.

Since screening colonoscopy is typically done in individuals over 50, advanced adenomas from folic acid exposure in people younger than 50 likely go undiagnosed. Therefore, colorectal cancer screening should start at a younger age in countries where folic acid fortification is mandatory.

MARK R. GOLDSTEIN, MD, FACP
Center for Healthy Living
Naples, FL

LUCA MASCITELLI, MD
Comando Brigata Alpina "Julia"
Multinational Land Force, Medical Service
Udine, Italy

ZAKIA H. RAUF, MD
NCH Academic Internal Medicine Clinic Naples, FL

REFERENCES

1. **Mankaney G, Sutton RA, Burke CA**. Colorectal cancer screening: choosing the right test. Cleve Clin J Med 2019; 86(6):385–392. doi:10.3949/ccjm.86a.17125
2. **Meester RGS, Mannalithara A, Lansdorp-Vogelaar I, Ladabaum U**. Trends in incidence and stage at diagnosis of colorectal cancer in adults aged 40 through 49 years, 1975–2015. JAMA 2019; 321(19):1933–1934. doi:10.1001/jama.2019.3076
3. **Mason JB, Dickstein A, Jacques PF, et al**. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 2007;16(7):1325–1329. doi:10.1158/1055-9965.EPI-07-0329
4. **Cole BF, Baron JA, Sandler RS, et al; POlyp Prevention Study Group**. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007; 297(21):2351–2359. doi:10.1001/jama.297.21.2351
5. **Oliai Araghi S, Kiefte-de Jong JC, van Dijk SC, et al**. Folic acid and vitamin B_{12} supplementation and the risk of cancer: long-term follow-up of the B vitamins for the prevention of osteoporotic fractures (B-PROOF) Trial. Cancer Epidemiol Biomarkers Prev 2019; 28(2):275–282. doi:10.1158/1055-9965.EPI-17-1198

doi:10.3949/ccjm.86c.12001

Colonoscopy has disadvantages

TO THE EDITOR: In the article, "Colorectal cancer screening: Choosing the right test," the authors offer an excellent review, but restrict the discussion to just 2 of the many options. Screening compliance improves when clinicians and patients can select their preferred screening approach, and other noninvasive or minimally invasive approaches also deserve consideration and may well be superior. It is important that both the patient and the healthcare provider be fully aware of the advantages and disadvantages of each method.

The article is overly generous in its description of the accuracy and sensitivity of optical colonoscopy. The statement that colonoscopy visualizes the entire colon in more than 98% of cases is not supported by the biomedical literature or clinical experience. The measure of colonoscopy accuracy is best quantified by a review of

more than 15,000 tandem colonoscopies that showed an average polyp miss rate of 22% using standard colonoscopes, and a 69% polyp miss rate compared with full-spectrum colonoscopes with greater fields of view.[1–3] Between 5% and 10% of colonoscopies are technically incomplete and do not reach the cecum. Only 35% of colonoscopy bowel preps are excellent, and 21% are so poor that the procedure cannot be completed.[4–8] Colorectal cancers are frequently missed at colonoscopy, with a rate of 7% quoted in the literature for interval cancer development.[9–16] Studies of computed tomography colonography (virtual colonoscopy) have confirmed that between 10% and 20% of the colonic mucosa is hidden from view on optical colonoscopy by tall haustral mucosal folds.[17,18] The operator variation measured by adenoma detection rates can exceed a 10-fold differential.

Colonoscopy is an important and valuable diagnostic and therapeutic tool. The disadvantages include significant cancer and polyp miss rates, high discomfort, high expense, potentially life-threatening complications, time- and resource-intensive utilization, high loss of patient work productivity, challenging and frequently inadequate preparation, higher risk of metachronous cancer and polyp spread, and high operator variability of quality.[19–24] Unfortunately, while colonoscopy is an important tool, it does not come anywhere close to a score of 98% and should not be considered the gold standard for colorectal cancer screening.[25]

JOSEPH B. WEISS, MD
University of California San Diego

NANCY S. CETEL, MD
Speaking of Health Inc.
San Diego, CA

DANIELLE E. WEISS, MD
University of California San Diego

■REFERENCES

1. **Zhao S, Wang S, Pan P, et al**. Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systemic review and meta-analysis. Gastroenterology 2019; 156(6):1661–1674. doi:10.1053/j.gastro.2019.01.260
2. **van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E**. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006; 101(2):343–350. doi:10.1111/j.1572-0241.2006.00390.x
3. **Gralnek IM, Siersema PD, Halpern Z, et al**. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicenter, randomised, tandem colonoscopy trial. Lancet Oncol 2014; 15(3):353–360. doi:10.1016/S1470-2045(14)70020-8
4. **Ness RM, Manam R, Hoen H, Chalasani N**. Predictors of inadequate bowel preparation for colonoscopy. Am J Gastroenterol 2001; 96(6):1797–1802. doi:10.1111/j.1572-0241.2001.03874.x
5. **Kluge M, Williams J, Wu C, et al**. Inadequate Boston Bowel Preparation Scale scores predict the risk of missed neoplasia on the next colonoscopy. Gastrointest Endosc 2018; 87(3):744–751. doi:10.1016/j.gie.2017.06.012
6. **Gagneja H, Parekh P, Burleson D, et al**. HyGIeaCare® preparation for colonoscopy – a technical update for success. J Gastrointest Dig Syst 2016; 6:4. doi:10.4172/2161-069X.1000458
7. **Das A, Parekh P, Bekal P, et al**. Bowel preparation for colonoscopy: a comparative cost-effective analysis of traditional per os purgatory prep versus a novel method using high-volume colonic water irrigation. Gastroenterol Hepatol Int J 2017; 2(4):000132.
8. **D'Souza SM, Parekh PJ, Johnson DA**. The dirty side of colonoscopy: predictors of poor bowel preparation and novel approaches to overcome the shortcomings. Br J Gastroenterol 2019: 1:1. https://hygieacare.com/wp-content/uploads/2019/06/The-Dirty-Side-of-Colonoscopy-PDF.pdf. Accessed October 23, 2019.
9. **Mouchli M, Ouk L, Scheitel M**. Colonoscopy surveillance for high risk polyps does not always prevent colorectal cancer. World J Gastroenterol 2018; 24(8):905–916. doi:10.3748/wjg.v24.i8.905
10. **Adler J, Robertson DJ**. Interval colorectal cancer after colonoscopy: exploring explanations and solutions. Am J Gastroenterol 2015; 110(12):1657–1664. doi:10.1038/ajg.2015.365
11. **Robertson DJ, Lieberman DA, Winawer SJ, et al**. Colorectal cancers soon after colonoscopy: a pooled multi-cohort analysis. Gut 2014; 63(6):949–956. doi:10.1136/gutjnl-2012-303796
12. **Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M**. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011; 154(1):22–30. doi:10.7326/0003-4819-154-1-201101040-00004
13. **Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M**. Long-term risk of colorectal cancer after negative colonoscopy. J Clin Oncol 2011; 29(28):3761–3767. doi:10.1200/JCO.2011.35.9307
14. **Pohl H, Robertson DJ**. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol 2010; 8(10):858–864. doi:10.1016/j.cgh.2010.06.028
15. **Singh H, Nugent Z, Demers AA, Bernstein CN**. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. Am J Gastroenterol 2010; 105(12):2588–2596. doi:10.1038/ajg.2010.390
16. **Nishihara R, Wu K, Lochhead P, et al**. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013; 369(12):1095–1105. doi:10.1056/NEJMoa1301969
17. **Thompson A, Jones R, Pou P, et al**. Taller haustral folds in the proximal colon: a potential factor contributing to interval colorectal cancer. J Colon Rectal Cancer 2016; 1(1):45–54. doi:10.14302/issn.2471-7061.jcrc-15-899
18. **Zhu H, Barish M, Pickhardt P, et al**. Haustral fold segmentation with curvature-guided level set evolution. IEEE Trans Biomed Eng 2013; 60(2):321–331. doi:10.1109/TBME.2012.2226242
19. **Chukmaitov A, Bradley CJ, Dahman B, Siangphoe U, Warren JL, Klabunde CN**. Association of polypectomy techniques, endoscopist volume, and facility type with colonoscopy complications. Gastrointest Endosc 2013; 77(3):436–446. doi:10.1016/j.gie.2012.11.012
20. **Reumkens A, Rondagh EJ, Bakker CM, et al**. Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. Am J Gastroenterol 2016; 111(8):1092–1101. doi:10.1038/ajg.2016.234

21. **ASGE Standards of Practice Committee, Fisher DA, Maple JT, Ben-Menachem T, et al**. Complications of colonoscopy. Gastrointest Endosc 2011; 74(4):745–752. doi:10.1016/j.gie.2011.07.025
22. **Warren JL, Klabunde CN, Mariotto AB, et al**. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009; 150(12):849–857. doi:10.7326/0003-4819-150-12-200906160-00008
23. **Whitlock EP, Lin JS, Liles E, et al**. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008; 149(9):638–658. doi:10.7326/0003-4819-149-9-200811040-00245
24. **Backes Y, Seerden T, van Gestel R, et al**. Tumor seeding during colonoscopy as a possible cause for metachronous colorectal cancer. Gastroenterology 2019; Aug 13. pii: S0016-5085(19)41229-8. [Epub ahead of print] doi:10.1053/j.gastro.2019.07.062
25. **Lin JS, Piper MA, Perdue LA, et al**. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016; 315(23):2576–2594. doi:10.1001/jama.2016.3332

doi:10.3949/ccjm.86c.12002

The authors reply

IN REPLY: We thank the readers for their interest in our paper.

Drs. Goldstein, Mascitelli, and Rauf point out the concerning epidemiologic increase in the incidence of colorectal cancer (CRC) among individuals under the age of 50 and suggest folate as a potential cause.[1]

The underlying cause of the rise in incidence is unknown, and many environmental and lifestyle risk factors have been proposed.[2–4] Black men have historically had and continue to have the highest incidence of and stage-adjusted mortality from CRC, but the rise of CRC in the young is a phenomenon in whites.[1] Furthermore, these cancers are left-sided. Other known and proposed risk factors associated with this phenomenon include dietary and lifestyle factors such as alcohol consumption, smoking, obesity, and consumption of processed and red meat.[5–7]

The cohort effect of rising colon and rectal cancer incidence in younger individuals is likely due to changes in the microbiome. Antibiotic exposure is widespread and has been conjectured as a cause, as has folate supplementation, which began in the United States in 1998. Folic acid has been shown to be associated with both protective and harmful effects on colorectal neoplasia.[8,9] While Goldstein et al recommend CRC screening starting at an early age in countries with folate supplementation, countries without folate supplementation have also noted a rise in early-onset CRC. For example, in Azerbaijan, the mean age at diagnosis of CRC in 546 individuals was 55.2 ± 11.5, and 23% had an age lower than 40 years. Nearly 60% presented at an advanced stage, and the majority of lesions were in the rectum.[10]

The impact of the confounding variables and risk factors resulting in the epidemiologic shift in young patients with CRC, along with the biology of the cancers, should be teased out. Once these are known, population screening guidelines can be adjusted. Until then, practitioners should personalize recommendations based on individual risk factors and promptly investigate colonic symptoms, no matter the age of the patient.

We also thank Drs. Joseph Weiss, Nancy Cetel, and Danielle Weiss for their thoughtful analysis of our article. Our intent was to highlight 2 of the most utilized options available for CRC screening and surveillance in the United States. As we pointed out, the choice of test depends on patient preference, family history, and the likelihood of compliance. The goal of any screening program is outreach and adherence, which is optimized when patients are offered a choice of tests.[11–13] **Table 1** from our article shows the options available.[14]

When discussing these options with patients, several factors should be taken into consideration. It is important that patients have an understanding of how tests are performed: stool-based vs imaging, bowel prep vs no prep, and frequency of testing.[15] Any screening test short of colonoscopy that is positive leads to colonoscopy. Also, programmatic noncolonoscopic screening tests require a system of patient navigation for both positive and negative results. An individual may be more likely to complete 1 test such as screening colonoscopy every 10 years vs another test annually.

A common misconception about computed tomography colonography is that it is similar to computed tomography of the abdomen with a focus on the colon. Individuals may still have to undergo a bowel preparation and dietary restrictions before the procedure. Furthermore, a rectal catheter is used to insufflate and distend the colon prior to capturing images, which many patients find uncomfortable.[16] Finally, the incidental discovery of extracolonic lesions may result in unnecessary testing.[17]

The sensitivity and specificity of each test and operator variability in accuracy and quality should

also be highlighted. For example, the sensitivity of a one-time fecal immunochemical test to detect an advanced adenoma may be as low as 25%.[18] All testing modalities are diagnostic, but only colonoscopy is therapeutic.

We agree that clinicians who perform CRC screening have an armamentarium of tests to offer, and the advantages and disadvantages of each should be carefully considered and individualized.

CAROL A. BURKE, MD
Department of Gastroenterology and Hepatology
Cleveland Clinic

GAUTAM MANKANEY, MD
Department of Gastroenterology and Hepatology
Cleveland Clinic

RICHARD ANDREW SUTTON, DO
University of Kansas Medical Center
Kansas City, KS

■REFERENCES

1. **Siegel RL, Fedewa SA, Anderson WF, et al**. Colorectal cancer incidence patterns in the United States, 1974–2013. J Natl Cancer Inst 2017:109(8). doi:10.1093/jnci/djw322
2. **Rosato V, Bosetti C, Levi F, et al**. Risk factors for young-onset colorectal cancer. Cancer Causes Control 2013; 24(2):335–341. doi:10.1007/s10552-012-0119-3
3. **Pearlman R, Frankel WL, Swanson B, et al**. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol 2017; 3(4):464–471. doi:10.1001/jamaoncol.2016.5194
4. **Stoffel EM, Koeppe E, Everett J, et al**. Germline genetic features of young individuals with colorectal cancer. Gastroenterology 2018; 154(4):897–905. doi:10.1053/j.gastro.2017.11.004
5. **Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M**. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer 2009; 125(1):171–180. doi:10.1002/ijc.24343
6. **Yuhara H, Steinmaus C, Cohen SE, et al**. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol 2011; 106(11):1911–1921. doi:10.1038/ajg.2011.301
7. **Chan DS, Lau R, Aune D, et al**. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS ONE 2011; 6(6):e20456. doi:10.1371/journal.pone.0020456.
8. **Lee JE, Willett WC, Fuchs CS, et al**. Folate intake and risk of colorectal cancer and adenoma: modification by time. Am J Clin Nutr 2011; 93(4):817–825. doi:10.3945/ajcn.110.007781
9. **Cole BF, Baron JA, Sandler RS, et al**. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007; 297(21):2351–2359. doi:10.1001/jama.297.21.2351
10. **Mahmodlou R, Mohammadi P, Sepehrvand N**. Colorectal cancer in northwestern Iran. ISRN Gastroenterol 2012; 2012:968560. doi:10.5402/2012/968560
11. **Inadomi JM, Vijan S, Janz NK, et al**. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 2012; 172(7):575–582. doi:10.1001/archinternmed.2012.332
12. **Steinwachs D, Allen JD, Barlow WE, et al**. National Institutes of Health state-of-the-science conference statement: enhancing use and quality of colorectal cancer screening. Ann Intern Med 2010; 152(10):663–667. doi:10.7326/0003-4819-152-10-201005180-00237
13. **Subramanian S, Klosterman M, Amonkar MM, Hunt TL**. Adherence with colorectal cancer screening guidelines: a review. Prev Med 2004; 38(5):536–550. doi:10.1016/j.ypmed.2003.12.011
14. **Mankaney G, Sutton RA, Burke CA**. Colorectal cancer screening: choosing the right test. Cleve Clin J Med 2019; 86(6):385–392. doi:10.3949/ccjm.86a.17125
15. **Tiro JA, Kamineni A, Levin TR, et al**. The colorectal cancer screening process in community settings: a conceptual model for the population-based research optimizing screening through personalized regimens consortium. Cancer Epidemiol Biomarkers Prev 2014; 23(7):1147–1158. doi:10.1158/1055-9965.EPI-13-1217
16. **Plumb A, Ghanouni A, Rees CJ, et al**. Patient experience of CT colonography and colonoscopy after fecal occult blood test in a national screening programme. Eur Radiol 2017; 27(3):1052–1063. doi:10.1007/s00330-016-4428-x
17. **Macari M, Nevsky G, Bonavita J, Kim DC, Megibow AJ, Babb JS**. CT colonography in senior versus nonsenior patients: extracolonic findings, recommendations for additional imaging, and polyp prevalence. Radiology 2011; 259(3):767–774. doi:10.1148/radiol.11102144
18. **Robertson DJ, Lee JK, Boland CR, et al**. Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2017; 85(1):2–21.e3. doi:10.1016/j.gie.2016.09.025

doi:10.3949/ccjm.86c.12003