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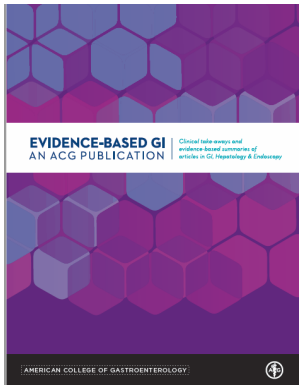

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Special Issue Introduction
March Colorectal Cancer Awareness Month

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This month's issue of *Evidence-Based GI: An ACG Publication* (EBGI) is dedicated to clinical research about colorectal cancer (CRC) screening and prevention in honor of Colorectal Cancer Awareness Month. Generally, CRC Awareness Month activities focus on educating individuals about CRC prevention through screening and reaching out to underserved communities to improve adherence to screening. However, as gastroenterologists, our primarily role is to prevent CRC through the performance of high-quality colonoscopy, which has been a focus of EBGI since its inception!

In this issue, we summarize that most post-colonoscopy CRCs (PCCRC) occur within 4 years of an index colonoscopy and are due to missed polyps. Conversely, as long as a high-quality and complete colonoscopy is performed by an endoscopist with an acceptable adenoma detection rate (ADR), then repeat screening colonoscopy at 10+ years demonstrate very low rates of advanced adenomas. High-quality colonoscopy also emphasizes complete polyp resection with low adverse events. Another summary from this issue reviews the first randomized controlled trial to demonstrate that cold snare polypectomy of small polyps decreases severe post-polypectomy bleeding versus hot snare polypectomy. Finally, endoscopists should

strive to identify under-diagnosed Lynch Syndrome and ensure that all CRCs are tested for deficient mismatch repair proteins with immunohistochemistry.

Ultimately, the first 18 months of EBGI highlight multiple clinical research studies about high-quality colonoscopy for CRC screening. Screening colonoscopy is not beneficial in individuals >75 years old if they have concurrent cardiovascular disease or multiple co-morbidities[1], and intervals for surveillance colonoscopy should be extended to 7-10 years if only 1-2 small adenomas are found.[2] Adenoma detection rates up to 40% are associated with lower rates of PCCRC[3] and even higher ADRs lower PCCRC in fecal immunochemical test-positive (FIT+) patients.[4] Endoscopists should strive to achieve higher ADRs through multiple interventions, including computer-aided detection systems (e.g., GI Genius)[5] and extending withdrawal times to 9 minutes[6], but this process starts with the audit and feedback of endoscopists.[7] These aspirational increases in ADR are appropriate even as we screen 45-49 year olds[8], and don't forget that proximal serrated polyp detection rates are also inversely associated with PCCRCs.[9] Optimizing polypectomy technique is crucial to high-quality colonoscopy since incomplete polyp resection contributes to PCCRCs.[10] A 1-2 mm rim of normal mucosa should be obtained when performing cold snare polypectomy[10], but it's okay to use jumbo forceps for resection of "tiny", 1-2 mm polyps when their position is not amenable to cold snare polypectomy.[11] As discussed above, cold snare polypectomy reduces severe delayed post-polypectomy bleeding in small polyps while also being suitable for piecemeal polypectomy of larger polyps.[12] By following these practices, gastroenterologists optimize the value of colonoscopy for CRC screening and provide the evidence-based practices needed to allay concerns about its efficacy.[13]

REFERENCES:

1. Lee J. Screening Colonoscopy Decreases CRC Incidence and CRC-Related Mortality in Patients > 75 Years Old… As Long As They are HEALTHY! Evidence-Based GI October 21, 2021. https://gi.org/journals-publications/ebgi/screening-colonoscopy-decreases-colorectal-cancer-incidence-and-related-mortality-in-healthy-patients-over-75/ Accessed March 12, 2023.
2. Patel S. Wait 7-10 Years for Repeat Colonoscopy If You Only Find 1-2 Small Adenomas. It's Not Too Long! Evidence-Based GI May 19, 2022. https://gi.org/journals-publications/ebgi/patel_may/ Accessed March 12, 2023.
3. Lee J. Time to Increase Adenoma Detection Rate Benchmarks for Screening Colonoscopies. Evidence-Based GI

September 21, 2022. https://gi.org/journals-publications/ebgi/lee_september_2022/. Accessed date March 12, 2023.

4. Sleiman J, Schoenfeld P. High Adenoma Detection Rate Decreases Post-Colonoscopy CRC in FIT-Based Screening Program: Quality Matters! Evidence-Based GI October 18, 2022.https://gi.org/journals-publications/ebgi/sleiman_october2022/. Accessed March 12, 2023.

5. Kumar S, Raju G. Computer-aided Detection Systems Increase Detection of non-advanced adenomas, but is it ready for prime-time? Evidence-Based GI December 10, 2021. https://gi.org/journals-publications/ebgi/computer-aided-detection-systems-increase-detection-of-non-advanced-adenomas-but-is-it-ready-for-prime-time/. Access March 12, 2023.

6. Kolb J, Shaukat A. Slow Down to Speed Up Quality: Longer Withdrawal Time of 9 Versus 6 Minutes Increases Adenoma Detection Rate. Evidence-Based GI January 13, 2022. https://gi.org/journals-publications/ebgi/withdrawaltime_adenoma_january2022nger-withdrawal-time-of-9-versus-6-minutes-increases-adenoma-detection-rate/. Accessed March 12, 2023.

7. Okafor P, Ladabaum U. The Pursuit of Excellence in Colonoscopy: Audit and Feedback Improves Polyp Detection in Low-Performers. Evidence-Based GI April 1, 2022. https://gi.org/journals-publications/ebgi/april_okafor/. Accessed March 12, 2023.

8. Okafor P. Adenoma Detection Rate in 45-49 Year Olds is Lower Compared to 50-54 Year Olds, but Still Higher than 25% Benchmark. Evidence-Based GI July 18, 2022. https://gi.org/journals-publications/ebgi/okafor_july2022/. Accessed March 12, 2023.

9. Patel S. ADR Isn't the Only Game in Town: Proximal Serrated Lesion Detection Rates Predicts Interval Cancer Risk. Evidence-Based GI August 11, 2022. https://gi.org/journals-publications/ebgi/patel_august_2022/ Accessed March 12, 2023.

10. Lee J. Increased Risk of Metachronous Neoplasia After Incomplete Polyp Resection-Time to CARE about Polypectomy Technique. Evidence-Based GI March 2, 2022. https://gi.org/journals-publications/ebgi/lee_february2022/. Accessed March 12, 2023.

11. Kumar S. Tiny Polyps-It's OK to Remove Polyps ≤3mm with Large or Jumbo Biopsy Forceps! Evidence-Based GI August 11, 2022. https://gi.org/journals-publications/ebgi/kumar_august_2022/. Accessed March 12, 2023.

12. Patel S. Piecemeal Cold Snare Polypectomy of Large Sessile Serrated Polyps is Safe and Effective: Cold is the New Hot! Evidence-Based GI October 22, 2021. https://gi.org/journals-publications/ebgi/piecemeal-cold-snare-polypectomy-of-large-ssp-cold-is-the-new-hot/ Accessed March 12, 2023.

13. Patel S. Colonoscopy Reduces CRC Incidence and CRC-Related Mortality...If You Get It! Evidence-Based GI October 18, 2022. https://gi.org/journals-publications/ebgi/patel_october2022/ Accessed March 12, 2023.

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CRC SCREENING

What are the Causes of Post-Colonoscopy Colorectal Cancer?

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This summary reviews Leung LJ, Lee JK, Merchant SA, Jensen CD, Alam A, Corley DA. Post-Colonoscopy Colorectal Cancer Etiologies in a Large Integrated US Health Care Setting. Gastroenterology 2023;164(3):470-72.

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STRUCTURED ABSTRACT

Question: What are the causes of post-colonoscopy colorectal cancer (PCCRC)?

Design: Retrospective cross-sectional study.

Setting: Community-based integrated healthcare setting in the United States (Kaiser Permanente Northern California).

Patients: A random sample of 533 PCCRCs were identified from January 1, 2006 to December 31, 2018. Among these PCCRC cases, 46.1% were female, 70% were non-Hispanic White, 7.1% had a family history of colorectal cancer (CRC) in a first-degree relative, 54.1% had diverticular disease, 41.5% had a prior adenoma diagnosis, 12.4% had a prior CRC diagnosis, and 7.8% had inflammatory bowel disease diagnosis.

Interventions/Exposure: For each PCCRC case, defined as a CRC occurring >6 months to 10 years after a negative colonoscopy (i.e., no evidence of CRC

on examination), manual chart review was performed to determine the most plausible cause of the PCCRC using the World Endoscopy Organization (WEO) consensus recommendations.

Outcome: Each PCCRC case was categorized as the following: 1) likely new cancer; 2) possible missed lesion, prior examination adequate (i.e., cecum was reached, and the bowel preparation was adequate); 3) possible missed lesion, prior examination inadequate; 4) detected lesion, not resected; or 5) likely incomplete resection of previously identified lesion.

Results: Of the 533 PCCRCs, 197 (37.0%) were likely new cancers, which were diagnosed more than 4 years after a negative colonoscopy. For the remaining 336 PCCRCs diagnosed within 4 years of the negative colonoscopy, the most plausible explanation for these PCCRCs were as follows: 70.2% (236 of 336) were classified as possible missed lesion with adequate prior examination; 15.5% (52 of 336) were classified as possible missed lesion but the prior examination was inadequate; 11% (37 of 336) were classified as likely incomplete resection of a previously identified lesion; and 3.3% (11 of 336) were classified as detected lesion that was not resected (**Figure 1**).

Funding: This study was funded by the National Cancer Institute/National Institutes of Health.

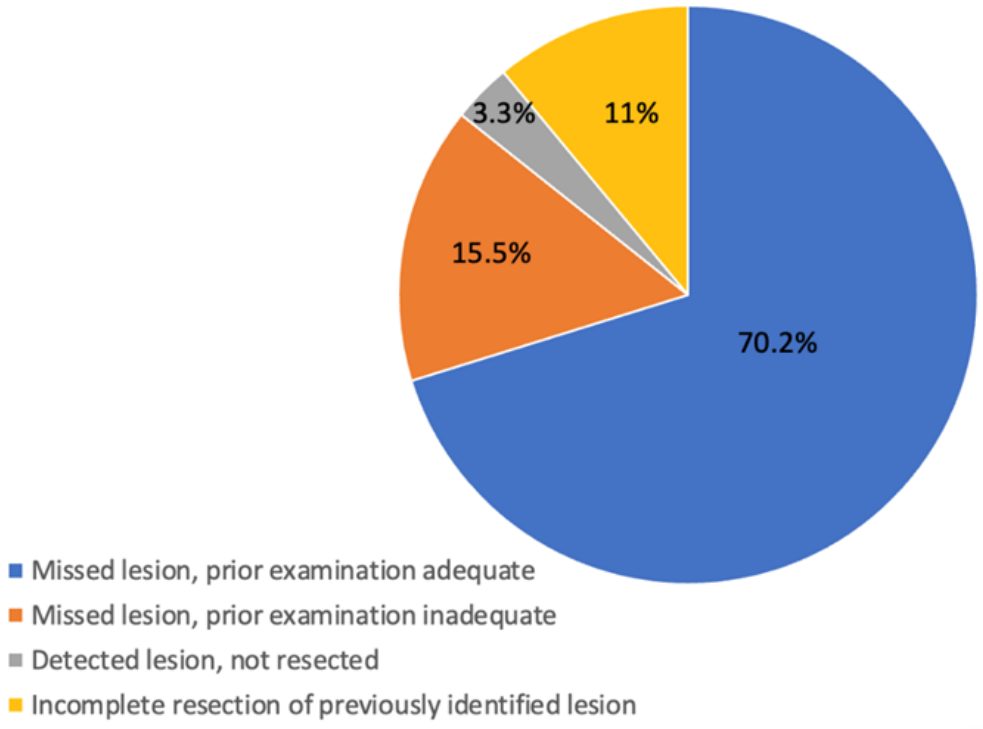

Figure 1. Causes of PCCRC within 4 years of negative colonoscopy (n=336).

COMMENTARY

Why Is This Important?

Multiple studies have shown that colonoscopy reduces CRC incidence and mortality.[1,2] In the US, colonoscopy is the most common screening test for CRC and is the primary diagnostic procedure for follow-up after a positive fecal-based screening test and for evaluating signs and symptoms related to CRC.[1,2] Unfortunately, colonoscopy is not perfect, and cancers can be diagnosed after a negative colonoscopy, which did not detect cancer—termed PCCRC.[3] Although several studies have identified risk factors for PCCRC,[4-7] few have provided the detail required to understand exactly what led to the PCCRC.[3] Recently, the WEO developed a consensus statement and methodology to better classify PCCRCs into their most plausible explanations.[3] However, only a few studies have utilized this methodology, which were all from Europe with small sample sizes (~40-100 PCCRC cases).[8-10] To address these limitations, the authors performed a root cause analysis for 516 PCCRC cases diagnosed within a large and diverse community-based population in the United States using the WEO consensus recommendations and methodology.

Key Study Findings

Among the 533 PCCRC cases, nearly 40% were classified as new cancers per the WEO methodology because they were diagnosed >4 years after the negative colonoscopy. The remaining cases (62.2%) were diagnosed within 48 months of a negative colonoscopy that did not identify a cancer; of these, 72.6% were classified as possible missed lesion with a prior adequate examination; 12.5% were classified as possible missed lesion but prior examination was inadequate; 11.5% were due to incomplete resection of a previously identified lesion; and 3.4% were due to a detected lesion that was not resected (**Figure 1**).

Therefore, among PCCRC cases diagnosed within 4 years after a colonoscopy, 85% are likely due to a missed lesion while the remaining 15% are due to incompletely resected polyps.

This supports targets for reducing the frequency of PCCRCs, including increasing adenoma detection rates and reducing incomplete polyp resection.

Caution

Older cases did not have photodocumentation to ensure adequacy of the examination (e.g., photos of the cecum, ileocecal valve). The WEO criteria also have limitations. Some of the "new cancers" that were diagnosed >4 years after negative colonoscopy developed from missed polyps at the index exam. Also, a small portion of the CRCs that occurred within 48 months of the index exam were most

likely tumors with mismatch repair mutations (i.e., Lynch Syndrome) and grew rapidly as opposed to arising from missed lesions. Notably, Kaiser-Permanente instituted universal screening of CRCs for mismatch repair mutations in 2013.

My Practice

As seen in this study, missed lesion is the most common explanation for PCCRCs diagnosed within 48 months after a clearing or negative colonoscopy. This finding highlights the need for careful inspection of the colon during withdrawal. There are several tools and techniques that I use to optimize lesion detection during withdrawal. First, it is critical to use a high-definition colonoscope with image enhancement (e.g., narrow band imaging) capabilities to help detect and evaluate subtle lesions. Second, it is important to have a mindset for detecting flat polyps since these lesions are often missed. Third, I maximize mucosal exposure by "working the folds" (i.e., deflecting the tip of the colonoscope into the inner-haustral valley and exposing the proximal sides of each haustral folds), cleaning and suctioning any stool debris, and distending the lumen adequately. Fourth, I perform 2 or 3 passes in the right colon since adenomas are often missed in this location. Lastly, when available, I often use a distal attachment device such as a clear translucent cap to help expose the proximal sides of each haustral fold and improve mucosal exposure.

In addition to missed lesions, incomplete resection of a colorectal lesion is another common explanation for PCCRCs diagnosed within 48 months after a negative colonoscopy. There are several tips and techniques that I share with my fellows to ensure complete polyp resection. First, never tackle a polyp you cannot finish during your assigned time slot. Second, consider referral of any complex polyp to a colleague or referral center that specializes in advanced tissue resection. Third, depending on the size of the lesion, aim to remove the polyp *en bloc* rather than in a piecemeal fashion. Fourth, embrace the cold snare over cold forceps for polyps 10 mm or less. Fifth, I recommend using snare tip soft coagulation after endoscopic mucosal resection (EMR) of large non-pedunculated polyps $\geq$20 mm in size. Sixth, carefully inspect the piecemeal EMR defect and remove any residual or visible islands using hot forceps avulsion. Lastly, I recommend close surveillance (i.e., 6 months) for all patients after a piecemeal EMR or an ESD.

For Future Research

Larger studies evaluating the root cause of PCCRC cases are needed, particularly PCCRC cases diagnosed after 4 years following a negative colonoscopy. In addition, future studies should focus on whether patient- or system-related failures (e.g., patient refusal to follow-up for a surveillance colonoscopy) are contributing to PCCRC cases.

Also, future studies should also assess the frequency of mismatch repair mutations, which can produce rapidly growing CRC, among PCCRCs.

Conflict of Interest

Dr. Lee was a co-author and investigator of this study.

Note: The authors of the article published in *Gastroenterology* are active on social media. Tag the to discuss their work and this EBGI summary.

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REFERENCES

1. 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;316:545.

2. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:2564-2575.

3. Rutter MD, Beintaris I, Valori R, et al. World Endoscopy Organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. Gastroenterology. 2018;155:909-925.

4. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370 (14):1298-1306.

5. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362 (19):1795-1803.

6. Shaukat A, Rector TS, Church TR, Lederle FA, Kim AS, Rank JM, Allen JI. Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy. Gastroenterology 2015 Oct;149 (4):952-7.

7. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015;81(1):31-53.

8. Anderson R, Burr NE, Valori R. Causes of post-colonoscopy colorectal cancers based on World Endoscopy Organization system of analysis. Gastroenterology 2020;158:1287-1299.

9. Beaton D, Beintaris I, Rutter MD. Utilization and reproducibility of World Endoscopy Organization post-colonoscopy colorectal cancer algorithms: retrospective analysis. Endoscopy 2022 Mar;54(3):270-277.

10. Aerts R, Severi C, Van Roey G, Harlet R, T'Syen M, Claessens C, Van Gool S, Croonen C, Janssens J. A single-centre analysis of post-colonoscopy colorectal cancer. Acta Gastroenterol Belg 2021 Jul-Sep;84(3):401-405.

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CRC SCREENING

Tumor-based screening for Lynch Syndrome: Check Every Colorectal Cancer

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This summary reviews Stone JK, Winter R, Khan D, et al. A Canadian Provincial Screening Program for Lynch Syndrome. American Journal of Gastroenterology 2023;118:345-53.

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STRUCTURED ABSTRACT

Question: What is the adherence to a universal colorectal cancer (CRC) tumor screening program for Lynch Syndrome and what are factors associated with non-adherence?

Study Design: Retrospective population-based cohort.

Setting: Manitoba, Canada.

Participants: Individuals aged 18-70 diagnosed with colorectal adenocarcinoma based on pathology records between March 2018 and December 2020.

Intervention: Manitoba implemented a universal tumor screening program in 2013, and as of December 2017, the program recommends that the primary diagnostic pathologist order immunohistochemistry (IHC) for mismatch repair (MMR) proteins in all patients diagnosed with colorectal

adenocarcinoma under age 70. These specimens are interpreted by 8 trained pathologists who are responsible for interpreting results and placing referrals for patients that have deficient MMR (dMMR) to the Program of Genetics and Metabolism. Genetic testing through this program is funded by universal health care plan. For those diagnosed with LS, genetic testing for at-risk family members living in Manitoba is offered at no cost to the family member.

Outcomes: The proportion of all CRCs that had appropriate IHC, the proportion of dMMR patients who were referred to the Program of Genetics and Metabolism, the proportion who completed germline genetic testing and the number of family members who completed genetic testing.

Results: Of the 1,692 unique patients diagnosed with colorectal adenocarcinoma during the study period (57% male, mean age 69), 936 were <70 and eligible for IHC screening. Eighty-eight percent of eligible specimens were screened (48% via biopsy specimen, 35% via surgical specimen and 5% via both) and 43 (5%) patients <70 were dMMR. Of the 58 dMMR patients in the entire cohort (all ages), 53% were referred to genetics by the pathologist and an additional 22% were referred by another physician (total referral rate of 75%, n=44). Of those referred, 84% accepted the appointment and of those who accepted the appointment, 87% (n=32) accepted genetic testing. Thirteen of these patients (40%) had a pathogenic or likely pathogenic germline variant in a Lynch Syndrome gene, 5 (16%) had a variant of uncertain significance. Among those with a pathogenic or likely pathogenic variant, 38 at-risk first-degree relatives living in Manitoba were identified and 21% (n=8) completed genetic testing. Individual pathologist (odds ratio 17.51, 95% confidence interval (CI) 6.05-50.67) and age <54 (odds ratio 0.53, 95% CI 0.30-0.97) were independently associated with completion of IHC for MMR proteins.

Funding: Supported by the Health Sciences Center Medical Staff Fellowship Fund Research Award and an infrastructure grant from CancerCare Manitoba Foundation.

COMMENTARY

Why Is This Important?

Lynch syndrome is the most common hereditary cancer syndrome with an estimated prevalence of 1/279 individuals,[1] accounting for 3-5% of all colorectal cancers. It also increases risk of multiple other cancers. There are effective cancer risk reduction strategies for Lynch Syndrome patients, including more intensive endoscopic surveillance, chemoprevention and risk reduction surgery that can significantly decrease the burden of cancer in these patients and their family members.[2] Unfortunately, Lynch Syndrome is grossly underdiagnosed with less than 10% of Lynch Syndrome patients being aware of their diagnosis in the United States.[3] An approach to improving identification of these patients is to screen all CRC patients for dMMR or microsatellite instability (MSI), the hallmarks of Lynch. Though this has been recommended by multiple professional societies, a minority of health systems in the US have successful universal screening programs.[4-7] Successful population-based implementation of a LS screening program can be an example to other health systems.

Key Study Findings

This study demonstrates that a protocolized universal tumor screening program where there is clear designation of who is responsible for ordering, performing, interpreting and conducting follow up on testing results in high adherence to tumor-based screening for Lynch Syndrome where 88% of eligible specimens are screened.

Unfortunately, there is successive drop off in appropriate referral to genetics, patient acceptance of referral, and patient acceptance of genetic testing, such that only 55% of patients who qualify for genetic testing based on tumor screening complete germline testing. Even when offered as a covered benefit, only 21% of family members of those with newly diagnosed syndromes complete germline genetic testing. The individual pathologist responsible for ordering the tumor-based IHC screening was the strongest predictor of whether the screening was completed.

Caution

Though health systems can use the results of this study to model programs within their systems, it is important to acknowledge several limitations to tumor-based screening. It requires multiple steps: (1) ordering/completing dMMR or MSI testing, (2) conducting any follow up tests (for instance *braf* or hypermethylation testing to exclude sporadic cancers in those with absence of *MLH1*/*PMS2* on IHC0, (3) interpreting results, (4) placing referral to genetics, (5) completion of genetic testing, and (6) disclosure of results to patients and clinical providers. Even when there is clear designation of who is responsible for completing, interpreting and following up on the testing, there is drop off at each level. This study also reinforced how these programs are still vulnerable to variabilities in practice among individual clinicians. Furthermore, the tumor testing approach does not screen for other hereditary syndromes, which account for 50% of all pathogenic/likely pathogenic variants among CRC patients,[8] and can even miss patients with Lynch Syndrome[9] . Thus, to try to simplify the process and optimize yield, there is movement in the field towards offering all CRC patients direct multigene panel germline genetic testing with the National Comprehensive Cancer Network asking clinicians to consider this approach for the first time in 2022.

My Practice

I recommend all CRC patients undergo hereditary risk assessment with three simple steps. First, we should be thinking about a possible hereditary syndrome in all patients we diagnose with CRC, regardless of age at diagnosis, family history or tumor characteristics. Second, I recommend ensuring that our pathology colleagues are performing tumor-based screening for dMMR on our CRC biopsy specimens instead of waiting until resection, since surgical management can change based on presence of a hereditary syndrome. Third, and finally, I recommend all patients with CRC be referred to a genetic counselor who can interpret tumor-based testing, collect multi-generation cancer family history and review the indications, benefits and expected yield of multi-gene panel testing for all CRC patients. I always

emphasize the importance of communicating genetic testing results to all family members so they may benefit from relevant cancer risk reduction interventions.

For Future Research

As we move towards direct germline genetic testing in CRC patients, more research will need to be done to determine exactly which genes should be included on a panel and how best to ensure equitable access to genetic testing and appropriate follow up care for newly diagnosed patients and their family members.

Conflict of Interest

Dr. Patel has no disclosures.

REFERENCES

1. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev 2017;26:404-412.
2. NCCN. Genetic/Familial High-Risk Assessment: Colorectal. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/default.aspx, 2021.
3. Hampel H, de la Chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means? Cancer Prev Res (Phila) 2011;4:1-5.
4. Mittal C, Dang D, Stoffel E, et al. Underutilization of Lynch Syndrome Screening at Two Large Veterans Affairs Medical Centers. Dig Dis Sci 2020.
5. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. J Clin Oncol 2012;30:1058-63.
6. Cross DS, Rahm AK, Kauffman TL, et al. Underutilization of Lynch syndrome screening in a multisite study of patients with colorectal cancer. Genet Med 2013;15:933-40.
7. Karlitz JJ, Hsieh MC, Liu Y, et al. Population-Based Lynch Syndrome Screening by Microsatellite Instability in Patients </=50: Prevalence, Testing Determinants, and Result Availability Prior to Colon Surgery. Am J Gastroenterol 2015;110:948-55.
8. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol 2017;35:1086-95.
9. Pearlman R, Frankel WL, Swanson BJ, et al. Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. JCO Precis Oncol 2021;5.

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CRC SCREENING

10-Year Intervals After Normal Screening Colonoscopy: It's Not Too Long with High-Quality Colonoscopy

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Associate Editor

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This summary reviews Heisser T, Kretschmann J, Hagen B et al. Prevalence of Colorectal Neoplasia 10 or More Years After a Negative Screening Colonoscopy in 120,000 Repeated Screening Colonoscopies. JAMA Intern Med 2023; 183: 183-90.

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STRUCTURED ABSTRACT

Question: Is a 10-year interval after a negative screening colonoscopy adequate, and could screening intervals be further extended beyond 10 years?

Setting: This was a cross-sectional study using screening colonoscopy data between January 1, 2013, and December 31, 2019, reported to the German screening colonoscopy registry. Certification for performing screening colonoscopy in Germany is tightly regulated and requires performance of at least 200 colonoscopies per year with the quality and completeness demonstrated by photo or video documentation.

Participants: The analyses were conducted on aggregated data obtained from repeat screening colonoscopies offered to the German general population 65 years and older. In Germany, eligibility for initial screening colonoscopy was lowered for men from 55 years to 50 years in April 2019. For women, eligibility for initial screening starts at 55 years. Per

protocol, individuals in screening colonoscopy registry are average-risk and asymptomatic.

Intervention/Exposure: The investigators identified a subgroup of individuals (65 years or older) with repeat colonoscopies performed 10 or more years after an initial screening colonoscopy. The results of the repeat screening colonoscopies were compared with "all" screening colonoscopies conducted at 65 years or older during the study period, which were mostly first screening colonoscopies. Diagnostic colonoscopies were excluded.

Outcomes: The main outcomes were prevalence of colorectal cancer (CRC), any colorectal neoplasia (any adenoma or CRC), or advanced colorectal neoplasia (any adenoma > 1cm, villous adenoma, or CRC) on repeat screening colonoscopy after having a negative initial screening colonoscopy ≥ 10 years ago.

Data Analysis: The outcomes of interest were stratified by participant age and sex. The observed number of advanced colorectal neoplasia and CRCs in repeat screening colonoscopies were compared with the number of cases expected if the same prevalence rates were observed in this group as in all screening colonoscopy participants and reported as standardized prevalence ratios (also by age and sex) along with 95% confidence intervals.

Funding: German Federal Ministry of Education and Research.

Results: Of the 565,864 men and 688,264 women screened in the study period, an analysis cohort of 120,298 individuals with a repeat screening colonoscopy was created, consisting of 47,949 (39.9%) men and 72,349 (60.1%) women. In this cohort, 49% (n=58,978) had their second screening at 10 years, 28.9% (n=34,762) at 11 years, 12% (n=14,427) at 12 years, and about 10% at 13 years or more.

Among patients who had undergone a repeat screening colonoscopy, the prevalence of advanced colonic neoplasia ranged from 5.2-6.6% in men, much lower than rates in all screening colonoscopy users (11.6%) (**Figure 1).** Advanced colorectal neoplasia prevalence rates were even lower (3.6-4.9%) among women undergoing repeat screening colonoscopies compared to all women undergoing screening colonoscopies (7.1%) **(Figure 1)**. By comparing observed rates of CRC in the repeat screening patients to expected rates in

all screening patients, the authors reported 62-74% lower rates of CRC among women and 77-82% lower rates among men with screening intervals of more than 10 years. They also showed 38-39% lower rates of advanced colorectal neoplasia among women and 44-50% lower rates in men with screening intervals of more than 10 years compared to all screenings.

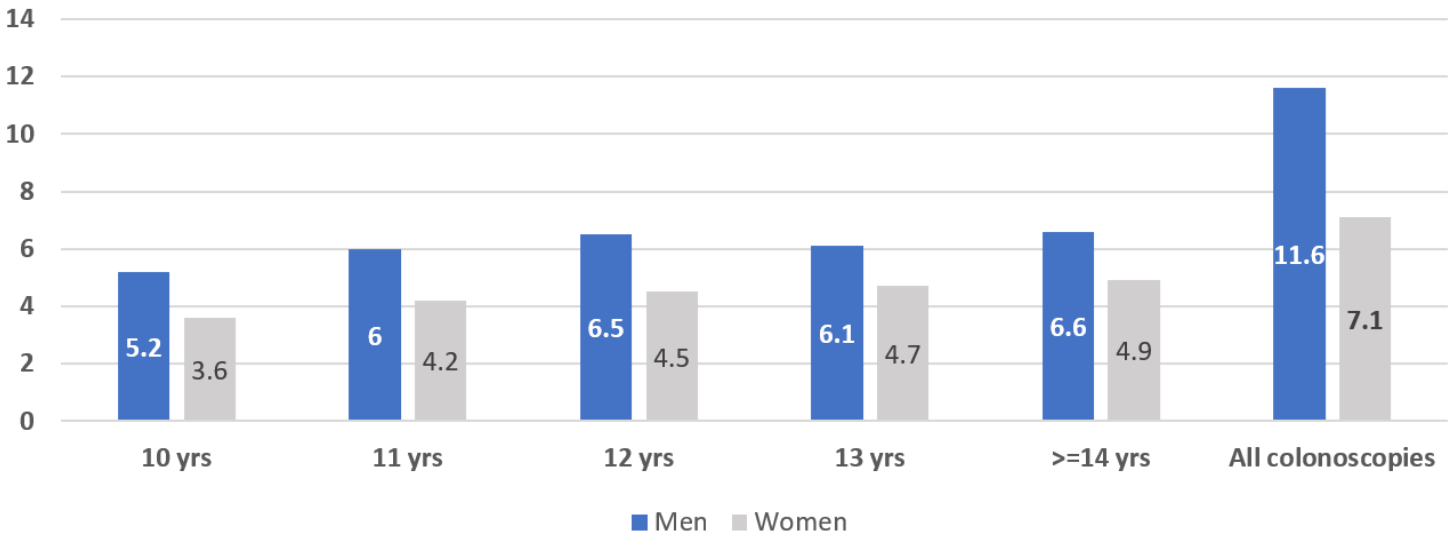

Figure 1. Prevalence of any advanced colorectal neoplasia at repeat screening colonoscopies (%)

COMMENTARY

Why Is This Important?

Following the widespread uptake of CRC screening, a 10-year interval after a negative screening colonoscopy (in average-risk individuals) was recommended by major guidelines based on extrapolations from colonoscopy sensitivity studies and inferences from the adenoma-carcinoma sequence. However, long-term prospective studies and large registry studies were not available to support this recommendation and US endoscopists frequently recommend shorter intervals for repeat screening colonoscopy based on multiple studies.[1] This study by Heisser et al is among the largest and methodologically robust data to support 10-year intervals after a negative screening colonoscopy.

Observational studies outside the United States have suggested that a reduction in CRC incidence and mortality may exist up to 17 years after a negative screening colonoscopy.[2] Extending the screening interval without compromising outcomes could increase primary care providers' choice of colonoscopy as a screening tool and could also have significant healthcare cost savings from a payer and societal perspective.[3] These data from Heisser et al suggest that intervals ≥14 years may be acceptable following a negative screening colonoscopy.

Key Study Findings

The prevalence of advanced colonic neoplasia on 10-year repeat screening colonoscopy was significantly lower vs prevalence in all screening colonoscopies (5.2%-6.6% vs 11.6% in men and 3.6-4.9% vs 7.1% in women).

They uniquely report low prevalence rates at 11 years, 12 years, 13 years, and beyond 14 years, which makes a compelling case that extending repeat screening colonoscopy intervals in low-risk individuals could be possible after high-quality index colonoscopy.

Caution

Data on the race/ethnicity of participants was not reported, which may limit generalizability to a more ethnically diverse country like the United States. All patients that had a screening colonoscopy served as the comparator group raising the possibility of healthy participant bias as patients who did not get a repeat screening colonoscopy were not included in the comparator group. Also, they could not exclude participants who might have gotten diagnostic colonoscopies within the screening interval or ascertain interval CRC.

My Practice

The study provides reassurance that existing screening colonoscopy intervals are safe for our patients *as long as a high-quality colonoscopy to the cecum is performed after adequate bowel cleansing by an endoscopist with an acceptable adenoma detection rate!* This is the crucial caveat. The German screening colonoscopy registry does require participating endoscopists to perform at least 200 screening colonoscopies per year and demonstrate appropriate cecal intubation rates confirmed by photo or video documentation. Although a minimum ADR has not been required previously[4], the average ADR of their endoscopists is appropriate and continues to increase.

Ultimately, these data can also be used to encourage patients to choose colonoscopy over other CRC screening modalities. Colonoscopy is the only CRC prevention tool as well as requiring repeat colonoscopy only every 10 years if no adenomas (or 1-2 small adenomas) are found at initial colonoscopy.

For Future Research

More studies are needed to explore the impact of risk-stratified screening intervals based on sex and age especially the potential benefit of reducing healthcare costs. Similar studies in a more diverse US population would be helpful.

Conflict of Interest

Dr. Philip Okafor reported no potential conflicts of interest.

REFERENCES

1. Rex DK, Schoenfeld P, Cohen J, et al. Quality Indicators for Colonoscopy. Am J Gastroenterol 2015; 110: 72-90.
2. Pilonis ND, et al. Long-Term Colorectal Cancer Incidence and Mortality After a Single Negative Screening Colonoscopy. Ann Intern Med 2020; 173: 81-91.
3. Rex DK, et al. Impact of Expanding Screening Colonoscopy Interval on Providers Choice of Prescribing Colonoscopy for Colorectal Cancer Screening. J Clin Gastroenterol 2022; 56: 781-83.
4. Brenner H, Altenhofen L, Kretschmann J, et al. Trends in adenoma detection rates during the first 10 years of the German screening colonoscopy program. Gastroenterology 2015; 149: 356-66.

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ENDOSCOPY

Cold Snare Decreases Post-Polypectomy Bleeding Vs Hot Snare for Small (≤ 10 mm) Polyps

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This summary reviews Chang LC, Chang CY, Chen CY, et al. Cold versus hot snare polypectomy for small colorectal polyps: A pragmatic randomized controlled trial. Annals Intern Med 2023; In Press.

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STRUCTURED ABSTRACT

Question: Does cold snare polypectomy (CSP) decrease post-polypectomy bleeding compared to hot snare polypectomy (HSP) for small polyps (4-10 mm)?

Design: Multi-center, unblinded, randomized controlled trial (RCT) with concealed allocation and 1:1 randomization without stratification at the time small polyps were identified.

Setting: Six sites in Taiwan

Patients: Inclusion criteria were: (a) individual ≥40 years old; (b) colonoscopy performed for screening or colon polyp surveillance, and (c) polyps 4-10 mm in diameter. Exclusion criteria included inadequate bowel preparation. Individuals who continued on antiplatelet or anticoagulant therapy during colonoscopy were also enrolled.

Interventions/Exposure: CSP vs HSP with electrocautery. Hemoclips could be placed post-polypectomy at discretion of the endoscopist if vessel was exposed

or bleeding developed immediately postpolypectomy.

Outcome: The primary endpoint was delayed bleeding, which was defined as rectal bleeding within 14 days of leaving the endoscopy unit. Rectal bleeding with spontaneous cessation was defined as mild bleeding and severe delayed bleeding was defined as rectal bleeding with a decrease in hemoglobin of ≥20g/l, blood transfusion required, or repeat colonoscopic hemostasis. Multiple secondary outcomes were assessed including mean polypectomy time (measured from appearance of snare on the monitor to time endoscope was withdrawn from the lesion), mean procedure time, *en bloc* resection, and complete histologic resection. Each study participant was interviewed by phone at 2- and 14-days post-colonoscopy to assess study outcomes.

Data Analysis: Intention-to-treat analysis to assess superiority of CSP vs HSP to reduce delayed bleeding. Kaplan-Meier plots and log-rank test were used to assess differences in the primary outcomes. Generalized estimating equations with binomial distribution were used to explore impact of polypectomy technique on secondary outcomes. Planned risk factor analysis was not performed because there were so few bleeding events.

Funding: Partial funding from Boston Scientific Corporation, who had no role in study design, data analysis, or manuscript preparation.

Results: Overall, 4,270 individuals with small polyps were randomized (mean age: 62 years old; 60-61% male; colonoscopy complete to cecum: 99%; anticoagulant use: 2% with >75% discontinuing prior to colonoscopy; antiplatelet use: 11% with >85% discontinuing prior to colonoscopy). Post-polypectomy hemoclips were applied more frequently after HSP vs CSP (27.6% vs 18.9, $P< 0.01$). Delayed post-polypectomy bleeding (any type), mild bleeding characterized as rectal bleeding with spontaneous cessation, and severe delayed bleeding characterized by hemoglobin decrease of ≥20 g/l, need for blood transfusion, or need for repeat colonoscopy with hemostasis were all more frequent with HSP vs CSP (**Table 1**), although overall bleeding rates were low. Specifically, severe delayed bleeding only occurred in 1 patient in the CSP group (0.05%) and 8 patients (0.4%) in the HSP group. No differences in successful *en bloc* resection rates or complete histologic resection rates occurred, although mean polypectomy time and mean procedure time were both shorter with CSP vs HSP (**Table 1**).

Outcome	Cold Snare (n=2137)	Hot Snare (n= 2133)	Risk Difference (95% CI)
Delayed Post-Polypectomy Bleeding-Total	0.4%	1.5%	-1.1% (-1.7 to -0.5)
Mild Delayed Bleeding-Rectal Bleeding with Spontaneous Cessation	0.3%	1.1%	-0.8% (-1.3 to -0.3)
Severe Delayed Bleeding-Decrease in Hgb ≥20 g/L, required blood transfusion, or repeat colonoscopy with hemostasis	0.05%	0.4%	-0.3% (-0.6 to -0.05)
En bloc resection	96.8%	97.2%	Not significant
Complete Histologic Resection	86.5%	85.9%	Not significant
Mean Polypectomy Time (seconds)	119	163	-44 sec (-53 to -35)
Mean Total Procedure Time (minutes)	16.9	18.3	-1.3 min (-1.9 to -0.8)

Table 1. Primary and secondary study outcomes. CI, confidence interval.

COMMENTARY

Why Is This Important?

CSP produces shallower resection depth in the submucosa compared to HSP where electrocautery may produce more severe and deeper submucosal injury, including in the muscularis propria, which could be expected to produce increased arterial damage and delayed post-polypectomy bleeding. However, no prior RCT has demonstrated a significant decrease in severe delayed post-polypectomy bleeding with CSP vs HSP, which is probably due to insufficient sample size since the rate of this adverse event is quite small.[1] This well-designed RCT of over 4,000 patients with small adenomas finally confirms that CSP reduces this severe adverse event compared to HSP.

This is important since European guidelines[2] do not strongly recommend CSP for small polyps. While US multi-society guidelines[3] do strongly recommend CSP for small polyps, they also note wide variability in polypectomy practices in the US. Thus, this important RCT conducted by Dr. Li-Chun Chang and colleagues at 6 Taiwanese medical centers provides further support that CSP is not only as effective as HSP but also is safer too! Our goal moving forward should be to educate and advocate for endoscopists to minimize use of HSP for small

polyps while eliminating use of hot biopsy forceps, which is inefficient as well as associated with deep tissue injury.

Key Study Findings

Severe delayed post-polypectomy bleeding was more frequent after HSP vs CSP (0.4% vs 0.05%; risk difference: -0.3%; 95% confidence interval [CI]: -0.6% to -0.05%) while CSP produced shorter mean polypectomy time (risk difference: -44 seconds; 95% CI: -53 to -35) and shorter total procedure time (16.9 minutes vs 18.3 minutes; risk difference: -1.3 minutes; 95% CI: -1.9 to -0.8).

Caution

The post-polypectomy bleeding rates were quite low in this study and may reflect the liberal use of hemoclips after polypectomy, which was significantly greater with HSP vs CSP (27.6% vs 18.9%, $P< 0.01$). The frequent use of hemoclips after HSP probably decreased post-polypectomy bleeding in this group and minimized the difference vs CSP. Although it is impossible to blind endoscopists to use of CSP vs HSP, it seems that endoscopist knowledge that they were performing HSP may have disproportionately increased their use with HSP. Nevertheless, using hemoclips in >25% of small polyp resections would not be standard of care in the US.

My Practice

Per the US Multi-Society Task Force on Colorectal Cancer Recommendations on Endoscopic Removal of Colorectal Lesions[3], I routinely perform CSP on all polyps ≤10 mm because it's faster than performing HSP. Although indirect evidence suggested that CSP would reduce severe delayed post-polypectomy bleeding, this RCT confirms this, which confirms the importance of emphasizing CSP. I never use hot biopsy forceps, although I'm anecdotally aware of surgical colleagues who continue to use this. I generally reserve HSP for pedunculated polyps > 10 mm, although I use CSP for piecemeal polypectomy of large sessile polyps.[4]

When using CSP for polyps 4-10 mm, I strive to obtain a 2 mm margin of normal colonic mucosa at the resection site to ensure complete resection and should produce the sunny side egg up appearance.[5] I also use jumbo forceps to remove tiny polyps 1-3 mm depending on the position of the polyp in the colon. [6]

For Future Research

Larger studies about the safety of CSP among high-risk patients who cannot discontinue antiplatelet or anticoagulants may be helpful. However, research to identify endoscopists with high-volume of HSP (or even

hot biopsy forceps resection) followed by implementation research to increase CSP use could be more beneficial for our patients.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest.

REFERENCES

1. de Benito Sanz M, Hernandes L, Garcia Martinez MI, et al. Efficacy and safety of cold versus hot snare polypectomy for small (5-9 mm) colorectal polyps: a multicenter randomized controlled trial. Endoscopy 2022; 54: 35-44.
2. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMPR): European Society of Gastrointestinal Endoscopy clinical guideline. Endoscopy 2017; 49: 270-297.
3. Kaltenbach T, Anderson JC, Burke CA, et l. Endoscopic removal of colorectal lesions-recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020: 91: 486-519.
4. Lee J. Increased risk of metachronous neoplasia after incomplete polyp resection—time to CARE about polypectomy technique. Evidence-Based GI Feb 2022.
5. Patel S. Piecemeal cold snare polypectomy of large sessile serrated polyps is safe and effective: cold is the new hot! Evidence-Based GI Oct 202.
6. Kumar S. Tiny polyps—it's OK to remove polyps ≤3 mm with large or jumbo biopsy forceps. Evidence -Based GI Aug 2022.

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CORRECTION

In the February 2023 issue of *Evidence-Based GI*, the title of the article on dupilumab incorrectly referred to it as "an anti-interleukin-4/12 monoclonal antibody," and not an anti-interleukin-4/13 monoclonal antibody. The article title has been corrected in the published article to: "Dupilumab, an IgG4 Monoclonal Antibody for Eosinophilic Esophagitis: Revising the Treatment Paradigm."

Please use the below citation when referencing the article:

Kamal A, Schoenfeld P. Dupilumab, an IgG4 monoclonal antibody for eosinophilic esophagitis: Revising the treatment paradigm. Evidence-Based GI. Published February 21, 2023. https://gi.org/journals-publications/ebgi/schoenfeld_kamal_feb2023/. Updated March 14, 2023.

The authors apologize for this error.