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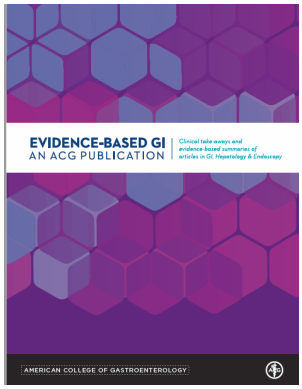

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Increased Risk of Metachronous Neoplasia After Incomplete Polyp Resection – Time to CARE About Polypectomy Technique!

Jeffrey Lee, MD, MPH
Associate Editor

Jeffrey Lee, MD, MPH

Research Scientist and Attending Gastroenterologist, Department of Gastroenterology, Kaiser Permanente San Francisco Medical Center, California.

This article reviews: Pohl H, Anderson JC, Aguilera-Fish A, Calderwood AH, Mackenzie TA, Robertson DJ. Recurrence of Colorectal Neoplastic Polyps After Incomplete Resection. Ann Intern Med. 2021;174(10):1377-1384. https://pubmed.ncbi.nlm.nih.gov/34370514/

Correspondence to Jeffrey Lee, MD, MPH, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does incomplete polyp resection increase your future risk of developing metachronous neoplasia?

Design: Observational cohort study of patients who participated in the Complete Adenoma Resection (CARE) study[1] and received a colonoscopy for colon polyp surveillance. In the CARE study, 233 patients with a total of 349 5-20 mm nonpedunculated polyps were removed by electrocautery ("hot") snare resection. After complete resection, cold forceps biopsies of resection margins were obtained, and polypectomy was defined as incomplete if resection margin biopsies showed adenomatous tissue. Overall, incomplete resection occurred in 10.1% and was significantly higher for large (10-20mm) neoplastic polyps vs small (5-9mm) neoplastic polyps (17.3% vs 6.8%) and for sessile serrated polyps/adenomas vs conventional adenomas (31.0% vs 7.2%). If incomplete resection, the patient was advised to get repeat colonoscopy within 1 year. If complete resection, then repeat colonoscopy recommended per guidelines.

Setting: Two US-based academic medical centers: Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire and VA Medical Center, White River Junction, Vermont.

Patients: Of the 233 original study patients, 166 patients received a follow-up surveillance colonoscopy. The mean age of the study cohort was 62.8 years; 82.5% were men; 19.3% had history of incomplete resection (median time to surveillance colonoscopy of 17 months) and 80.7% had history of complete resection (median time to surveillance colonoscopy of 45 months).
Exposure/Intervention: Surveillance colonoscopy of original CARE study patients, which was performed at 1-year if incomplete resection or performed consistent with guideline recommendations if all polyps were completely resected.
Outcome: Proportion of colon segments with metachronous neoplasia at first surveillance colonoscopy. Colon segments were defined as cecum, ascending colon including hepatic flexure, transverse colon, descending colon including splenic flexure, sigmoid colon, and rectum. "Metachronous neoplasia" means that a conventional adenoma or a sessile serrated polyp/adenoma was found in a specific segment of colon on the surveillance colonoscopy.
Results: Metachronous neoplasia was more frequently detected in colon segments where incomplete resection was previously reported compared to colon segments with complete polyp resection (52% vs 23%; risk difference, 28% [95% Confidence Interval: 9% - 47%, *P*=0.004]). In addition, metachronous advanced neoplasia was more frequently detected in colon segments with prior incomplete polyp resection compared to those with complete polyp resection (18% vs 3%; risk difference 15% [95% Confidence Interval 1% - 29%, *P*=0.034]). Incomplete resection was the strongest independent factor associated with metachronous neoplasia.
Funding: None

COMMENTARY

Why Is This Important?

The prevalence of post-colonoscopy colorectal cancer is estimated to be around 8% (i.e., about 8% of colorectal cancers occur in individuals who had colonoscopy greater than 6 months but less than 3 years before CRC diagnosis).[2] Given this alarming statistic, gastroenterologists have explored potential factors, particularly modifiable, contributing to this devastating diagnosis. Although missed lesions are an important driver of post-colonoscopy colorectal cancer,[3] others have speculated whether the quality of

resection may also be a contributor to this diagnosis. Recent studies have suggested that the quality of resection is variable across experienced gastroenterologists.[1,4] This study expands on prior literature and uses a well-done prospective observational cohort study design to assess the impact of incomplete polyp resection on recurrent neoplasia.[5]

Key Study Findings

Patients with incomplete resection of neoplastic polyps 5-20 mm in size were at higher risk for more metachronous neoplasia (52% vs 23%, *P*=0.004) and advanced neoplasia (18% vs 3%, *P*=0.034) compared to patients who had a complete resection (**Figure 1**). All cases of metachronous advanced neoplasia among patients with incomplete resection were due to polyp size (i.e., 10 mm or greater) and not advanced histologic characteristics. The strongest predictor of metachronous neoplasia on follow-up surveillance was incomplete polyp resection (adjusted odds ratio 3.02; 95% confidence interval 1.12-8.17).

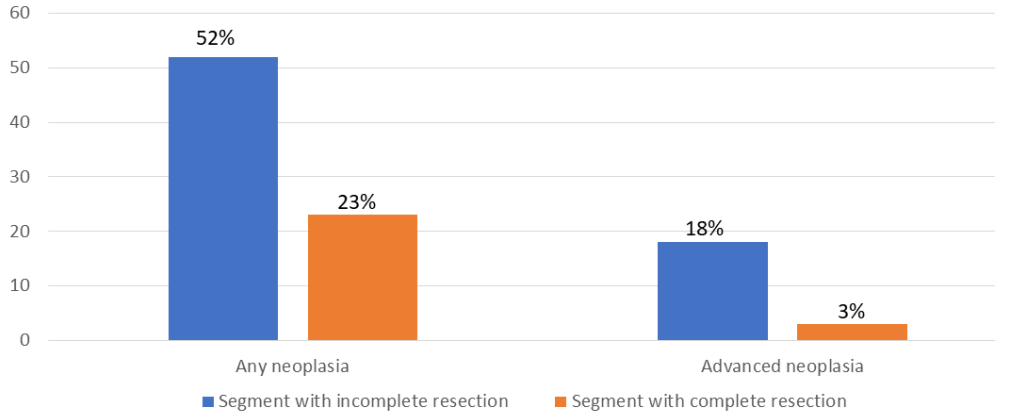

Figure 1. Risk of Metachronous Neoplasia at Surveillance Colonoscopy Following Polypectomy.

Caution

Potential selection bias due to incomplete follow-up of all patients who had incomplete polyp resection. In addition, patients with incomplete polyp resection may have been examined more thoroughly on surveillance compared to patients with complete polyp resection, which may increase the chance of identifying a polyp or an advanced polyp.

My Practice

My approach for the removal of non-pedunculated polyps 5-20 mm varies based on the pathology (diagnosed optically) and size. For all polyps, regardless of its size, I first start with a careful inspection to optically diagnose the lesion and identify any features of deep submucosal invasion. Once I have made the decision to resect the polyp, I ensure that the lesion is at the 5 or 6 o'clock position so that I can have optimal positioning and accurate placement of my instruments. For serrated polyps (e.g., sessile serrated lesions) and conventional adenomas <10 mm in size, I prefer using a dedicated cold snare (e.g., Boston Scientific Captivator Cold, Steris Exacto Cold Snare) for its removal; multiple randomized trials have shown that cold snare polypectomy is superior in terms of complete resection rates compared to cold forceps polypectomy.[6,7] To help ensure complete resection, I like to take a rim of normal tissue when I remove these polyps, which will occasionally give a "sunny-side up" appearance of the resected lesion (**Figure 2**). I think it's essential to remove this rim of normal tissue during cold snare polypectomy to ensure the lesion is completely resected.

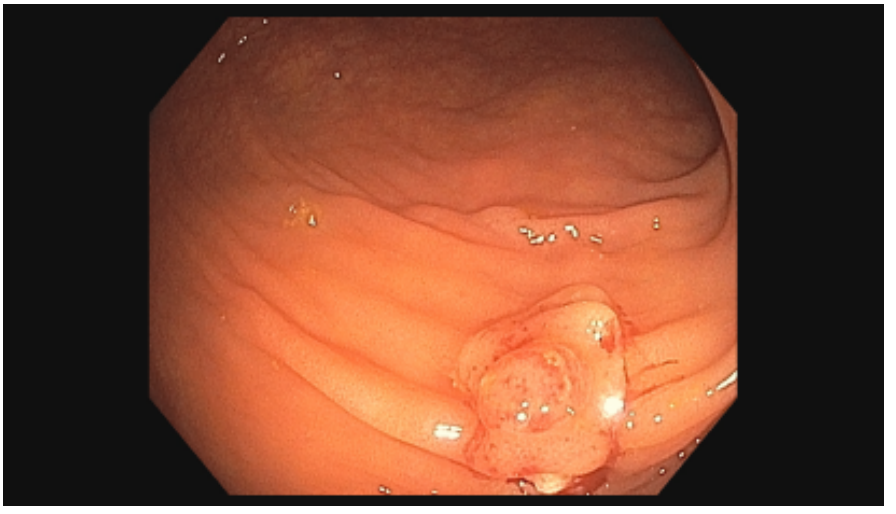

Figure 2. Removal of the rim of normal tissue can lead to a "sunny-side up" appearance.

For serrated polyps and conventional adenomas 10-20 mm in size, I typically use either a conventional or underwater endoscopic mucosal resection (EMR) technique to remove these lesions. For both EMR techniques, I prefer to use a 15-20 mm stiff snare (e.g., Boston Scientific

Captivator II, Olympus Snaremaster) and a cutting current with a microprocessor-controlled current delivery (Erbe VIO 300D EndoCut Q; Erbe, Tübingen, Germany). For conventional EMR, I often use a lifting agent (e.g., hetastarch mixed with a contrast agent) to help delineate the borders and reduce the risk of perforation and thermal injury. Like polyps <10 mm in size, I strive to resect medium sized polyps (10-20 mm) en-bloc while capturing a rim of normal tissue to ensure complete resection. Although, there's limited evidence on the best approach to remove medium sized non-pedunculated polyps, one general rule is to avoid using cold forceps to piecemeal resect these lesions due to the risk of leaving residual neoplastic tissue. In fact, I do not use cold forceps for polypectomy unless the polyp is less than 3 mm in diameter.

For Future Research

More data is needed to determine the impact of improved polypectomy technique on the risk of post-colonoscopy colorectal cancer. In addition, more research is needed to develop and evaluate polypectomy training tools during and following gastroenterology fellowship.

Conflict of Interest

Dr. Lee reports no potential conflicts of interest.

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It's a Bad "Prep" Even Though the Patient Took It Correctly: Consider 15 mg Bisacodyl plus 4-Liter PEG Split Prep Before Next Colonoscopy

Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus)-Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI

Philip Schoenfeld, MD, MSEd, MSc (EPI)
Editor-in-Chief

This article reviews Sey MSL, Von Renteln D, Sultanian R, et al. A Multicenter Randomized Controlled Trial Comparing Bowel Cleansing Regimens for Colonoscopy After Failed Bowel Preparation. Clin Gastroenterol Hepatol 2022; In Press. https://pubmed.ncbi.nlm.nih.gov/34256147/

Correspondence to Philip Schoenfeld, MD, MSEd, MSc (Epi), Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: For individuals who were compliant but failed to get adequate cleansing with prescribed bowel preparation, what is an optimal supratherapeutic bowel purgative regimen to achieve adequate cleansing with repeat colonoscopy?

Design: Randomized, concealed allocation, single-blind (investigator) superiority trial of 15 mg bisacodyl plus 4L + 2L polyethylene glycol (PEG) split-prep vs 15 mg bisacodyl plus 2L + 2L PEG.

Setting: Four Canadian academic medical centers.

Patients: Study included 196 adult outpatients (mean age: 60.7 years, 55.1% men, 32.7% overweight, 36.7% obese, 40.8% with history of constipation or IBS-C) with colon cleansing inadequate to identify polyps >5mm in diameter despite being compliant with prescribed bowel regimen (35.2% 4L PEG, 38.8% 2L PEG + bisacodyl, 12.2% sodium picosulfate). Split-prep used in 64.8% of index colonoscopies, and indication for colonoscopy was screening/surveillance (46.4%), diagnostic (42.3%), or FIT+ (9.7%). Patients were excluded if they were non-compliant with original bowel regimen, used an off-label bowel regimen at index colonoscopy, had a history of colonic surgery, or had an increased risk for electrolyte or fluid disturbances.

Intervention: Patients had 15 mg bisacodyl at 2 PM and PEG 2L between 8-10 PM on the day before the procedure, and 2L PEG started 4-6 hours before the colonoscopy on the day of the procedure (PEG 2 + 2L + bisacodyl) vs 15mg bisacodyl at 2 PM and PEG 4L between 6-10 PM on day before the procedure and 2L PEG started 4-6 hours before the colonoscopy on the day of the procedure (PEG 4 + 2L + bisacodyl). Patients in both arms instructed to consume a low-fiber diet on days 3 and 2 before the procedure, and clear liquids only on day before the procedure.
Outcomes: The primary efficacy endpoint was adequate cleansing defined as Boston Bowel Preparation Scale (BBPS) score of 6 or higher, with a score of 2 or higher in each segment (right, transverse, and left colon). This endpoint was used since lower levels of cleansing on the validated BBPS have been associated with missed adenomas. Secondary efficacy endpoints included the US Multi-Society Task Force on CRC definition of adequate cleansing, which is "adequate to identify polyps > 5mm," bowel preparation tolerability using the Validated Patient Tolerability Questionnaire for Bowel Preparation, adenoma detection rate, and pre-planned secondary analyses based on the history of IBS-C/constipation, type of bowel preparation used at initial colonoscopy, time of study colonoscopy (AM vs PM), and level of compliance with bowel preparation.
Data Analysis: Intention-to-treat analysis and per-protocol analysis
Funding: Lead author was supported by the Academic Medical Organization of Southwestern Ontario Opportunities Award, and research supported by arms-length research grant from Pharmascience, Inc, which was not involved in any aspect of study design, recruitment, or data analysis, etc.
Results: No significant difference in rates of adequate bowel cleansing was observed for 2 + 2L PEG + bisacodyl vs 4 + 2L PEG + bisacodyl regimens (91.2% vs 87.6%, P= 0.44). No significant differences were identified in any secondary analysis (**Table 1**), including history of IBS-C/constipation, type of bowel preparation used at initial colonoscopy, time of study colonoscopy (AM vs PM), or level of compliance. Both regimens were well-tolerated, although patients were more likely to adhere to diet and consume 100% or 80% of prep in the PEG 2 + 2L + bisacodyl arm. The PEG 2 + 2L + bisacodyl was associated with a higher willingness to repeat the bowel preparation (91.2% vs 66.2%, P< 0.01).

Outcome		Split-dose 4L + bisacodyl (n = 97)	Split-dose 6L + bisacodyl (n = 99)	*P*-value
Adequate cleansing	Defined as BBPS ≥ 6	83 (91.2%)	78 (87.6%)	0.44
	Defined as adequate to identify polyps > 5mm	82 (91.1%)	76 (85.4%)	0.24
Secondary endpoints	Cecal intubation rate, n (%)	87 (96.7%)	82 (92.1%)	0.19
	Adenoma detection rate, n (%)	34 (37.4%)	28 (31.5%)	0.41
Adherence	Diet + consumed 100% of prep	67 (81.7%)	53 (68.0%)	0.05
	Diet + consumed 80% of prep	71 (86.6%)	57 (73.1%)	0.03

Table 1. Results

COMMENTARY

Why Is This Important?

It's a frequent question for endoscopists: what prep should I use for patients who have inadequate cleansing despite being compliant with the initial prep? Even though endoscopists face this question daily, there is minimal data, especially for patients who initially used a 4L PEG split-prep. Gimeno-Garcia and colleagues did the only other RCT of 256 patients who had inadequate cleansing.[1,2] Most (74.8%) had initially used a low-volume bowel prep without reporting whether or not the prep was split. For the repeat colonoscopy, all study patients used 10 mg bisacodyl on the day before the procedure and followed a low-residue diet for 3 days pre-procedure. Patients were randomized to 4L PEG-3350 as split-prep vs 2L PEG + ascorbic acid as split-prep. The 4L PEG-3350 was superior for adequate bowel cleansing (81.1% vs 67.4%, $P< 0.01$, ITT analysis). Thus, 4L PEG-3350 split-prep may be helpful for compliant patients who failed a low-volume prep, although the adequate cleansing rate (81.1%) is still lower than the target of 85% of bowel preps with adequate cleansing.[2]

In the absence of other data, endoscopists may recommend a wide variety of inadequately studied regimens, including 2-days of clear liquids prior to colonoscopy and supplementing 4L PEG with magnesium citrate 1-2 days before colonoscopy. Finally, Sey, Barkun, and colleagues with the Canadian Bowel CLEANsing National Initiative have assessed supratherapeutic purgative regimens in a well-designed RCT, and should be congratulated for this effort.

Remember that there are multiple known risk factors for colonic dysmotility and inadequate bowel cleansing even when a patient is compliant, including obesity, current opioid use, diabetes mellitus, history of using constipation treatments, and current use of anticholinergics, including tri-cyclic antidepressants, among others.[2] It appears that most patients in the current trial had one or more of these risk factors: 36.7% obese, 40.8% with history of constipation or IBS-C, approximately 10% using opioids, etc. However, if a patient is not compliant and has poor bowel cleansing (e.g., didn't split the prep properly and drank it all on the previous evening), then additional patient education is likely to be more helpful than prescribing a supratherapeutic regimen.

Key Study Findings

Both supratherapeutic regimens were quite effective with no significant difference in rates of adequate bowel cleansing for 2 + 2L PEG + bisacodyl vs 4 + 2L PEG + bisacodyl regimens (91.2% vs 87.6%, *P*= 0.44). There was no evidence of effect modification in pre-planned secondary analyses based on presence of constipation/IBS-C, type of bowel preparation used initially, etc., although actual rates of adequate cleansing for these secondary analyses were not reported.

Caution

High-doses of bisacodyl (20mg) as part of bowel regimens have been associated with a very small (0.48%) risk of colonic ischemia at the time of colonoscopy.[3] Although this is usually an incidental finding, it contributed to the voluntary withdrawal of Half-Lytely®, a combination of 2L PEG-3350 + 20 mg bisacodyl from the US market in 2010. Subsequently, even bowel preparation kits with 10mg bisacodyl were withdrawn from the US market.

The current trial is too small to identify an increased risk with 15mg bisacodyl. Nevertheless, given the need for a supratherapeutic bowel regimen in these study patients, I think that the risk-benefit ratio favors using this dose of bisacodyl in order to get good cleansing and a thorough exam of the colon.

There were no differences in rates of adequate cleansing regardless of bowel regimen used at index colonoscopy. However, only a minority of patients used a 4L PEG split-prep initially, and it would be interesting to see the actual data for this difficult-to-treat group.

Our Practice

If a patient has been compliant with my standard prep (4L PEG-3350 split-prep) and still has inadequate bowel cleansing, our group prescribes 6L PEG-3350 split-prep with 4L PEG consumed between 6 and 10 PM on night before procedure, and 2L consumed 4-6 hours before colonoscopy. This regimen produced adequate cleansing based on BBPS in 87.7% in an ITT analysis.[4] Furthermore, we proactively prescribe this supratherapeutic regimen for any patient with 2 or more risk factors for inadequate bowel cleansing, and achieve adequate cleansing in 91.5% of these high-risk patients. Given the study findings from Sey, Barkun, and Canadian Bowel CLEANsing National Initiative, our group is planning to trial the 2 + 2L PEG + 15mg bisacodyl as our preferred supratherapeutic regimen and quantify rates of adequate cleansing as part of our ongoing quality improvement initiative.

It's worth re-emphasizing that more and better patient education is the preferred intervention when a patient is clearly non-compliant. For example, I don't use a supratherapeutic regimen when a patient drinks all of their bowel prep on the evening before colonoscopy. My nursing team initially focuses on re-educating the patient on splitting the prep properly and scheduling the patient for a late-morning or early afternoon appointment if the patient is worried about rising early to take the second dose of bowel prep.

For Future Research

Future research should assess supratherapeutic regimens in a larger group of compliant patients who had inadequate cleansing after using 4L PEG-3350 in a split-prep. Also, a future RCT should compare a supratherapeutic regimen vs lower-volume bowel purgative regimen in patients with two or more risk factors for inadequate cleansing.

Conflict of Interest

Dr. Schoenfeld is a consultant, advisory board member and member of the Speaker's Bureau for Salix Pharmaceuticals.

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OBESITY

Effectiveness of Intermittent Fasting for Weight Loss: It's Not Just When You Eat, but What You Eat, Too!

Sonali Paul, MD, MS

Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, University of Chicago Medicine, Center for Liver Disease, Chicago, Illinois

Sonali Paul, MD, MS
Associate Editor

This article reviews: Lowe DA et al. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men with Overweight and Obesity. The TREAT Randomized Clinical Trial. JAMA. 2021; 181(6):883. https://pubmed.ncbi.nlm.nih.gov/32986097/

Correspondence to Sonali Paul, MD, MS, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is time-restricted eating (also known as intermittent fasting) effective to improve weight loss and metabolic parameters in overweight (BMI 25-30) or obese (BMI >30) individuals?

Design: A12 week unblinded randomized clinical trial

Setting: Participants were located in the United States. A subset of 50 patients who lived within 60 miles of the University of California San Francisco were eligible for in person metabolic testing.

Patients: There were 116 participants aged 18 to 64 years old. Mean 46.5 years, M:F ratio of 60:40, mean weight = 218 pounds; mean BMI= 32.7 +/- 4.2 (range: 27 to 43).

Interventions/Exposure: Participants were randomized to consistent meal timing (eating 3 structured meals a day) or time-restricted eating (where participants ate freely from noon until 8:00 PM but stopped completely from 8pm until noon the next day). All participants received multiple daily reminders through a customized phone app to weigh themselves (using an iHealth Lite Bluetooth scale provided to all participants), measure their blood pressure, complete a short daily survey, and to follow their prescribed diet plan.

Outcome: The primary outcome was weight loss. Secondary outcomes included changes in metabolic parameters including fat mass, lean mass, fasting insulin, fasting glucose, hemoglobin A1c levels, estimated energy intake, total energy expenditure, and resting energy expenditure.
Data Analysis: Intention to treat analysis.
Funding: University of California, San Francisco, Cardiology Division's Cardiology Innovations Award Program and the National Institute of Diabetes and Digestive and Kidney Diseases. Weight scales, blood pressure cuffs, and health tracking rings were gifted from iHealth Labs Inc., MOCACuff, and Oura respectively.
Results: There was significant weight loss in the time-restricted eating group loss (-0.94 kg, 1.17%, 95% CI: -1.68 kg to -0.20 kg, P = 0.01) but not in the consistent meal timing group (-0.68 kg, 0.75%, 95% CI: -1.41kg to 0.05 kg, P = 0.07). However, there was no significant difference between the two groups. In the subgroup who underwent in-person metabolic analysis (n = 50), the only additional significant difference was decreased appendicular lean mass index in the time-restricted eating group

COMMENTARY

Why Is This Important?

Overweight and obesity is an epidemic with serious complications and affect a large proportion of the population. Approximately 74% of the population in 2018 was overweight or obese, with estimates thought to rise in the midst of the COVID-19 pandemic.[1] Thus, it is important to find interventions to help with weight loss to mitigate long term chronic disease. While medications (e.g., semaglutide/Wegovy), sleeve gastrectomy, and Rouex-en-Y surgery have demonstrated sustained 15%-20% decreases in weight, these interventions are not covered by some insurance plans. Therefore, identifying and implementing effective lifestyle interventions for weight loss are equally important. Intermittent fasting has recently gained traction for weight loss and patients frequently ask health care providers about its efficacy.

Intermittent fasting is defined as periods of eating alternating with fasting for various periods.[2] Multiple types of intermittent fasting have been studied. Modified alternate-day fasting alternates between days of ad libitum eating and days with total caloric intake of 0-600 kcal for 2-5 days/week. Time-restricted

eating involves fasting for 12-16 hours each day. Both have shown to be favorable for weight loss and improvement in metabolic parameters in mice[3] and humans[4] and is the intervention used in this study.

Key Study Findings

In this randomized controlled trial (RCT), time-restricted eating alone was not more effective for weight loss compared to eating throughout the day. In subgroup analysis, there was reduction in lean mass (vs fat mass) in the time-restricted eating group of about 65% with significant differences in appendicular lean mass. This is important as appendicular lean mass is associated with nutrition and physical status and decreases can lead to frailty and increase the risk of sarcopenia.[5]

Caution

This RCT was fairly small with only 118 participants. In addition, the macronutrient content of each participants diet was not reported, so it is unclear what was consumed in each group. Also, participants were not given any specific guidance about what types of food to eat as part of this trial. It is likely premature to state that time-restricted eating is ineffective, especially since meta-analysis of prior studies demonstrate some benefits.[2,4] However, mean sustained weight loss has only been about 2 kg or less with all types of intermittent fasting.[2] Ultimately, the primary intervention in this trial was a phone application that sent frequent reminders to patients about adhering to their prescribed eating schedule.

My Practice

In my patients with overweight or obesity, I will sometimes use intermittent fasting along with dietary guidance about macronutrient intake as lifestyle interventions to aid in weight loss. I start with a simple 10-hour fast window, where one does not eat during this time (usually sometime in the evening to next morning but water and black tea or coffee are permissible). If weight loss is not achieved, then I increase the fasting window by 1-2 hours but do not exceed 14-16 hours of fasting given the lack of known benefits and increased risk (dehydration, hypoglycemia in those with diabetes, weakness). Our dieticians also counseling patients on eating healthy with a Mediterranean diet (rich in fish and chicken, fruits, vegetables, and whole

grains) with modified carbohydrate intake (not greater than 30 gm/meal). For some motivated individuals, this has been quite effective and useful especially when the patient does not want (or cannot get insurance coverage) for weight loss medications or bariatric surgery.

I do not recommend intermittent fasting in my patients with cirrhosis (even if related to nonalcoholic fatty liver disease) given the importance of nutrition and risk of sarcopenia in this patient population.

For Future Research

Further research is needed prior to uniformly recommending intermittent fasting as a true weight loss tool, specifically as it pertains to changes in lean mass. Additionally, larger trials are needed to identify the most effective protocols (e.g., time-restricted eating, modified alternate day fasting) as well as combining this with dietary counseling on macronutrient intake.

Conflict of Interest

Dr. Paul reports no conflicts of interest related to this study.

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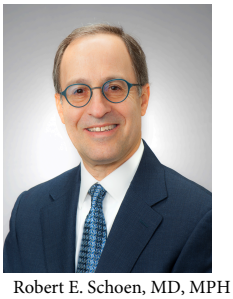
Family Matters: Increased Risk of Colorectal Cancer among Individuals with Family History of Polyps

Ravy K. Vajravelu, MD, MSCE
Associate Editor



Robert E. Schoen, MD, MPH
Guest Contributor

Ravy K. Vajravelu, MD, MSCE[1] and Robert E. Schoen, MD, MPH[2]

[1]*Assistant Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, and Staff Gastroenterologist, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania*

[2]*Professor of Medicine and Epidemiology, Chief, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania*

This article reviews Song M, Emilsson L, Roelstraete, Ludvigsson J. Risk of colorectal cancer in first degree relatives of patients with colorectal polyps: nationwide case-control study in Sweden. BMJ 2021; 373: n877 https://pubmed.ncbi.nlm.nih.gov/33947661/

Correspondence to Ravy K. Vajravelu, MD, MSCE, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is a history of colorectal polyps in a first-degree relative associated with an increased personal risk of colorectal cancer (CRC)?

Design: Retrospective nested case-control study.

Setting: Swedish national health registries.

Patients: Overall, 68,060 adults diagnosed with CRC were considered cases. CRCs were confirmed using a national histopathology registry. These individuals were then matched with 333,753 controls who were never diagnosed with CRC by age, sex, year of birth, and county.

Main exposures of interest: Data from cases and controls were linked to data from their parents and full siblings (first-degree relatives). The main exposure of interest was whether first-degree relatives had a history of colorectal polyps before the date that the case individual was diagnosed with CRC. Polyps were classified as tubular adenomas, tubulovillous adenomas, villous adenomas, and serrated polyps (which included both sessile serrated polyps and hyperplastic polyps). Tubulovillous, villous adenomas, and sessile serrated polyps were considered to be advanced polyps. Of note, because the authors did not have access to data about the size of the polyps, the number of polyps, or the definitive ability to distinguish sessile serrated polyps from hyperplastic

polyps, advanced polyps in this study are not equivalent to the criteria for advanced polyps by the US Multi-society Task Force on Colorectal Cancer.[1]
Data analysis: The authors developed multivariable conditional logistic regression models to calculate the odds ratio (OR) of CRC based on family history of polyps. The authors also adjusted the ORs for sociodemographic factors, medical comorbidities, and family history of CRC. In this study, the OR is approximately equivalent to risk of developing CRC. The authors also performed a subgroup analysis of cases with CRC before age 50 and several secondary analyses assessing the effect of the number of family members with polyps/CRC and the age of family members at the time of polyp/CRC diagnosis.
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Results: After adjusting for family history of CRC and other covariates, having a first-degree relative with any type of polyp increases personal risk of CRC by 40% (OR = 1.40; 95% CI 1.35 – 1.45%). Factors that further increased the risk of CRC included two or more first-degree family members with any type of polyp (OR = 1.70; 95% CI 1.52 – 1.90) and younger age at polyp diagnosis for the family member (e.g. 77% increased risk if a family member was diagnosed with polyps before age 50 [OR = 1.77, 95% CI 1.57-1.99]). In a subgroup analysis, number of family members with polyps and younger age at polyp diagnosis for family members were more strongly associated with CRC diagnosed before age 50 compared to CRC diagnosed at age 50 or older (Figure).

COMMENTARY

Why Is This Important?

Although US gastroenterology societies have recommended earlier CRC screening for individuals with a family history of CRC or advanced polyps since the inaugural guidelines in 1997 (1-3), these recommendations have not been universally emphasized. For example, recent guidelines from the American Cancer Society and US Preventative Services Task Force focus only on average-risk screening, and guidelines from the British Society of Gastroenterology primarily address genetically-determined cancer syndromes such as Lynch Syndrome and Familial Adenomatous Polyposis (4-6). Differences in society recommendations are likely related to a lack of high-quality evidence regarding family history of polyps. For example,

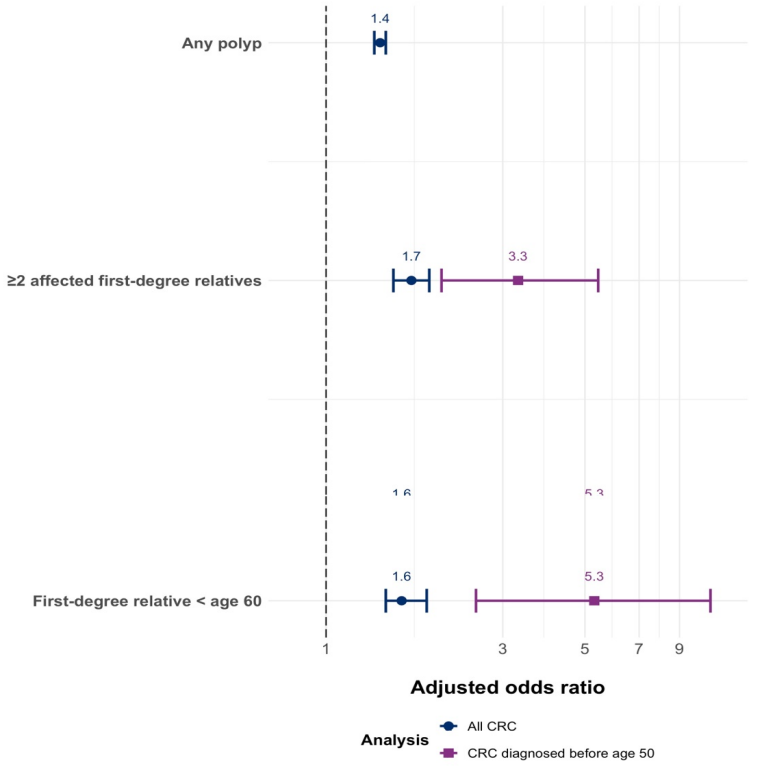

Figure. Adjusted odds ratio of developing CRC based on family history of polyps that preceded the diagnosis of CRC.

Notes: Adapted from M Song et al. BMJ 2021. ORs are adjusted for sociodemographic factors, medical comorbidities, and family history of CRC.

recommendations from the US Multi-society Task Force on CRC are extrapolated from studies assessing the risk of CRC amongst those with a family history of CRC.[7,8] Prior observational studies assessing the risk of CRC based on family history of polyps are limited by methodologic biases.[9,10] For example, a diagnosis of CRC that triggers a colonoscopy in first degree relatives which then identifies adenomas is not equivalent to finding a colorectal adenoma, which is then used to identify a family member at increased risk for CRC. The former is an association; the latter is more suggestive of a causal link because of temporality. This study overcomes this bias by restricting the analysis to polyps in first-degree relatives identified before the diagnosis of CRC. Moreover, these observational data from the Swedish national health registries are among the best available. They are uniquely suited to assess the association between family history of polyps and CRC because of their decades-long follow-up, histopathological confirmation

of CRCs, and access to accurate family linkage. The authors also performed several subgroup and sensitivity analyses to assess the robustness of the results to changes in the statistical methodology. These analyses consistently demonstrated increased risk of CRC among those with a family history of polyps.

Key Study Findings

The main study find was that having a first-degree relative with any type of colorectal polyp increases personal risk of CRC by 40%. The risk was higher if there were more first-degree relatives with polyps or if the first-degree relatives were diagnosed with polyps at younger ages (**Figure**).

Caution

Although this is an exceptionally well-designed research study, there are methodological limitations which may impact interpretation of the results. First, the authors sought to isolate the contribution of family history of polyps from the contribution of family history of CRC through statistical adjustment. Because polyps are precursors to CRC[11], it is unlikely that the effect of family history of CRC could be completely removed from the effect of family history of polyps through statistical methods alone. Therefore, the reported ORs may not accurately reflect the association between family history of polyps and CRC. Second, the definition of advanced polyps in this study is different from the definition used by the US Multi-society Task Force on CRC. This is in part due to lack of data on number of polyps, size of polyps, and difficulty distinguishing sessile serrated polyps from hyperplastic polyps. Inaccuracies in characterizing polyp histology means physicians should take caution when interpreting the reported ORs. Third, the case-control design of this study makes it susceptible to bias. In particular, since there is not universal CRC screening in Sweden, individuals with family history of polyps may seek CRC screening more often than individuals without a family history of polyps. This could artificially increase the OR of the association of family history of polyps with CRC through ascertainment bias. However, the long duration of follow-up mitigates this potential bias.

Our Practice

Guidelines regarding screening in association with a family history of polyps are inconsistently applied in practice, and we continue to lack definitive, prospective data on the yield of screening. Despite the limitations of this study, it addresses a major gap in the literature, particularly by confining the assessment of polyps to those diagnosed before the identification of CRC in the family. Furthermore, the results are consistent with guidelines from the US Multi-Society Task Force on CRC, which we apply in our own practice. Specifically, these guidelines recommend CRC screening at the earlier of age 40 or 10 years before the family member's first diagnosis of advanced adenomas (any polyp greater than 1 centimeter, 3 or more adenomatous polyps in a single colonoscopy, villous histology, tubulovillous histology, traditional serrated adenomas, or high-grade dysplasia). If a patient has a first-degree relative with non-advanced adenomas, then the guidelines recommend CRC screening equivalent to that of average-risk patients: Initiate at age 45 – 50 with repeat screening based on the results of the initial exam. Unfortunately, even when patients know that their family members had polyps, it is often unclear if the polyps were high-risk, non-advanced adenomas, or simply diminutive hyperplastic polyps. Therefore, in our communications to referring physicians, we provide documentation of the details of the findings at_colonoscopy, and, in particular, whether or not advanced adenomas were discovered. We also recommend that patients with advanced adenomas encourage their first-degree relatives to discuss CRC screening with their providers.

For Future Research

The ideal study to assess whether individuals with a family history of colorectal polyps are at higher risk for CRC would be a prospective study in a country with universal CRC screening that is highly utilized. It is unlikely that this study would ever be conducted because it would require follow-up and a very large sample size. However, as the Swedish national health registries and other registries around the world improve with more nuanced polyp data, it may be feasible to address some of the limitations of this study—particularly those related to the definition of advanced polyps.

Conflicts of Interest

Dr. Vajravelu has no disclosures to report. Dr. Schoen reports grant support from Exact Sciences, Freenome, and Immunovia.

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