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Clinical take-aways and evidence-based summaries of articles in GI, Hepatology & Endoscopy

AMERICAN COLLEGE OF GASTROENTEROLOGY

EVIDENCE-BASED GI

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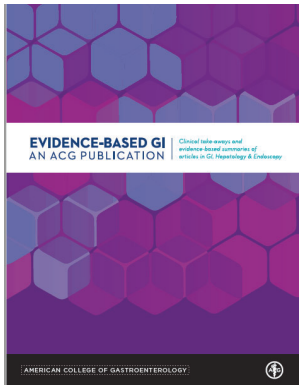

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EBGI **Volume 4, Issue 3**

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IBSRELA®
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INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.

CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

Reference: IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.; 2022.

Please see Brief Summary of full Prescribing Information on the following page.

ardelyx

IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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March 2024 Colorectal Cancer Awareness—A Year in Review

Dr Philip Schoenfeld
Editor-in-Chief

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EDITORIAL

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Per our annual tradition, this month's issue of *Evidence-Based GI: An ACG Publication* is dedicated to clinical research about colorectal cancer (CRC) screening and prevention in honor of CRC Awareness Month. Through increased CRC screening and the performance of high-quality colonoscopy, we should be gratified by the continued decline in CRC incidence (about 3%-5% per year) among average-risk individuals ≥50 years old.[1] Unfortunately, we've also witnessed an alarming rise in the incidence of early-onset CRC (CRC diagnosed in average-risk individuals <50 years old), which is associated with rising rates of obesity and increased consumption of ultra-processed foods and sugar-sweetened beverages.

Our goal is to provide you with concise and thoughtful summaries of the latest and most important clinical research from general medical journals, European gastroenterology journals, and the ACG's flagship journal, *The American Journal of Gastroenterology*, so you can optimize the care of your patients.

In this issue, we've summarized the seminal randomized controlled trial comparing endoscopic submucosal dissection (ESD) with endoscopic mucosal resection (EMR) for large, non-pedunculated polyps. Although adenoma recurrence rates were significantly higher at 6-month follow-up colonoscopy with EMR (5.1% vs 0.6%), the rate of serious complications was quite a bit higher with ESD. The commentary

from our Associate Editor, Jeffrey Lee, MD, MPH, provides context for when to refer patients for ESD (e.g., large rectal polyps with signs of superficial submucosal invasion that benefits from en bloc resection) despite the additional time, increased complications, and the need for advanced training and equipment.

I examine and summarize a groundbreaking Nurses' Health Study and Health Professionals Follow-Up Study research which demonstrated that increased consumption of ultra-processed foods (e.g., "fast foods" from chain restaurants or "junk foods" from convenience stores) is associated with an increased risk of distal CRC, at least in men. Ultimately, "we are what we eat."

A summary from our veteran Associate Editor, Philip Okafor, MD, MPH, demonstrates that performing screening colonoscopy in adults > 75 years old with short life expectancies (< 5 years) is quite common in the US. However, the risk of procedural complications rises in older adults with multiple comorbidities. There can be too much of a good thing, and this summary reminds us to appropriately educate patients when additional screening may not be worthwhile.

Finally, our new Associate Editor, Timothy Yen, MD, summarizes the classic multi-center, European prospective cohort study of serrated polyposis syndrome patients, which demonstrated that colonoscopy surveillance can be extended from annually to bi-annually among patients without advanced neoplasia during clearing colonoscopies.

For our new readers, previous summaries are archived on the *EBGI website*. In the past 12 months, the CRC Screening and Endoscopy categories include summaries about post-colonoscopy CRC and the importance of taking a second look in the rectum,[2] the efficacy of aspirin as chemoprophylaxis for CRC in Lynch syndrome patients,[3] simplifying adenoma detection rate calculations,[4] the pitfalls of the recent American College of Physicians Guidance on CRC Screening,[5] concerns about recommending repeat colonoscopy for colon polyp surveillance despite limited life expectancy[6] or frequently recommending repeat colonoscopy earlier than needed for colon polyp surveillance[7] or frequently performing screening colonoscopy in elderly adults with very limited life expectancy,[8] and how to interpret the variable findings from research about computer-aided detection of polyps during colonoscopy.[9]

Yet, there is still so much more that we could have summarized! Although rising obesity rates may increase CRC risk, GLP-1 receptor agonists are very effective for weight reduction and have been associated with decreased CRC risk in patients with Type 2 diabetes.[10] It's gratifying that many community-based practices emphasize high-quality

colonoscopy and have demonstrated rising trends in adenoma detection rate and sessile serrated lesion detection rate,[11] which should lead to fewer post-colonoscopy CRCs. Artificial intelligence and computer-aided detection of polyps may not be a replacement for the standard tools of high-quality colonoscopy, but rapid software advances continue with improved polyp detection systems[12] and new virtual scales [13-14] produce precise endoscopic measurements of polyp size. The future looks bright for endoscopic technology and medical interventions. Nevertheless, our efforts must continue to further reduce the toll of CRC. We should focus on screening the newly eligible 45–49-year-olds and older individuals who have never been screened and overcome obstacles to care.

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ESD vs EMR for Large Nonpedunculated Colon Polyps: Fewer Recurrences but More Complications

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This summary reviews Jacques J, Schaefer M, Wallenhorst T, et al. Endoscopic en bloc versus piecemeal resection of large nonpedunculated colonic adenomas: A randomized comparative trial. Ann Intern Med 2024; 177: 29-38.

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

Keywords: colonoscopy, polypectomy, endoscopic submucosal dissection, adenomas

STRUCTURED ABSTRACT

Question: Does endoscopic submucosal dissection (ESD) decrease incomplete polyp resection/polyp recurrence of large (≥25 mm) colon polyps with similar rates of adverse events compared to conventional piecemeal endoscopic mucosal resection (EMR)?

Design: Multi-center, prospective, randomized, comparative trial (RESECT-COLON trial).

Setting: Six French referral centers from November 2019 through February 2021, with colonoscopies performed by 13 experienced endoscopists.

Patients: Adults ≥18 years old referred for endoscopic resection of large (≥25

mm) colon polyps consistent with laterally spreading tumors (LST) that were >15 mm from anal verge (i.e., excluded rectal lesions) and with no endoscopic features of deep submucosal invasion. LST and Paris classification used to categorize polyp characteristics.

Interventions: Patients were randomly assigned (1:1 ratio) to EMR or ESD with stratification for center and polyp location. For all colonoscopies, patients had general anesthesia with intubation, had the procedure performed as an inpatient and were hospitalized for 1 night after the procedure, which is the French standard. Submucosal fluid injection was performed prior to all polypectomies. The choice of endoscope, injection fluid and specific ESD/EMR devices were at the discretion of the endoscopist. ESD included dissection around and underneath the lesion to achieve en bloc resection while EMR was performed with piecemeal polypectomies with snare-tip thermal ablation at polypectomy margins. Clip closure of resection site was performed at the discretion of the endoscopist.

Outcomes: Primary outcome was neoplastic recurrence at polypectomy site found during 6-month follow-up colonoscopy. All polypectomy scars were biopsied. Secondary endpoints included frequency of adverse events and procedure time among others.

Data Analysis: Intention-to-Treat and per-protocol analyses were reported. Sample size was calculated assuming 10% recurrence rate in EMR and 2% recurrence with ESD.

Funding: French Ministry of Health.

Results: Among 360 randomized patients, mean age was 69-71 years old, 39%-47% were female, right colon location in 77%, and 85% were Paris Classification 0-IIa. Failure to compete procedure rates were low for ESD and EMR (3.4% and 1.6%, respectively), and en bloc resection rate was significantly higher with ESD vs EMR (96.6% vs 10.4%, respectively). Recurrence rate was significantly lower with ESD (1/161, or 0.6%) vs EMR (8/157, or 5.1%) **(Figure 1).** ESD required significantly more time to complete compared to EMR: 47 minutes vs 14.5 minutes, respectively. Among patients treated with EMR with recurrent neoplasia at 6 months, complete endoscopic resection of residual neoplasia was achieved in all patients.

Adverse events were significantly higher with ESD vs EMR: 35.6% vs 24.5%, respectively; relative risk (RR) 1.40; 95% confidence interval (CI): 1.0-2.0. Specifically, frequency of post-polypectomy syndrome was significantly higher with ESD (11.8% vs 5.5%, respectively; RR 2.2; 95% CI: 1.1-4.5) and were numerically higher with ESD for periprocedural perforation (5.6% vs 2.2%), clinically significant post-procedural bleeding (7.9% vs 5.5%), and surgery for complications (1.1% vs 0%).

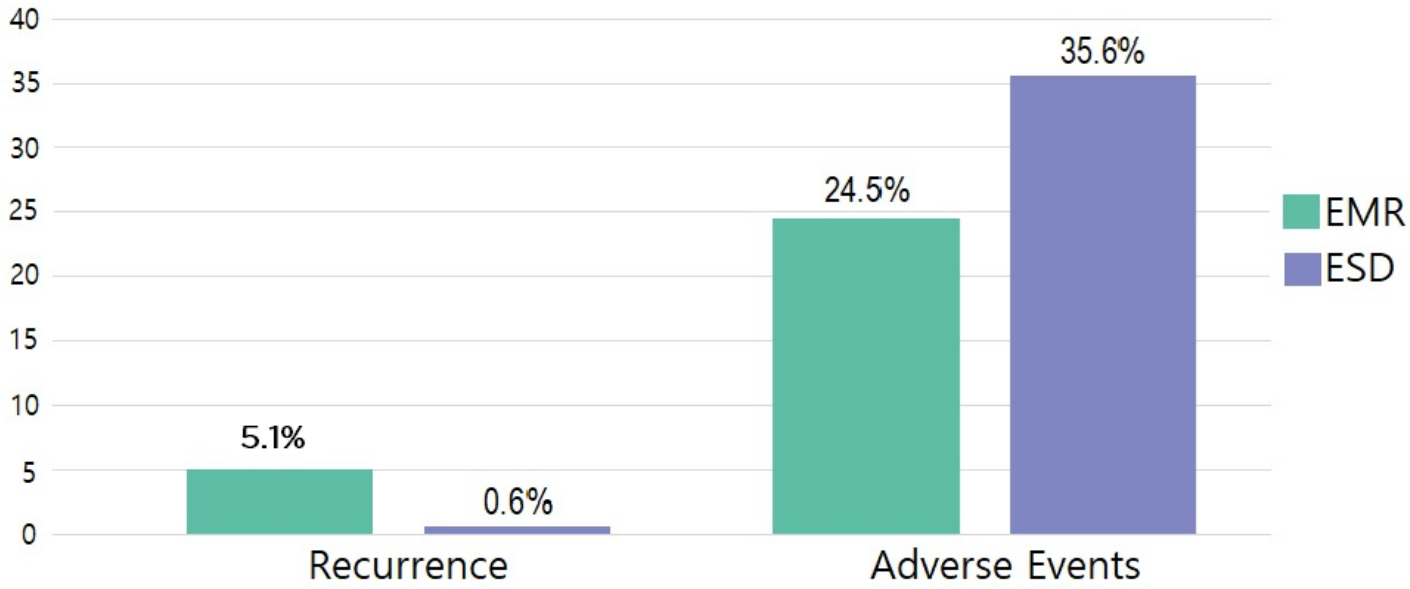

Figure 1. Recurrence rates and adverse events. P <0.05 for both comparisons.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

COMMENTARY

Why Is This Important?

Endoscopic resection is the preferred approach for the management of large non-pedunculated colorectal polyps ≥20 mm. Current guidelines recommend expert endoscopic assessment of all large, non-pedunculated colorectal polyps before surgical consideration.[1,2] In the United States and other Western countries, EMR, frequently performed with submucosal injection, has been the preferred endoscopic technique for the management of large, non-pedunculated colorectal polyps ≥20 mm due to its efficiency, low recurrence rates (5%-20%), and favorable safety profile,[1,3] although en bloc resection of large polyps may not be feasible for all large polyps, leading to the performance of multiple smaller or piecemeal resections with recurrence of neoplasia minimized by using snare-tip soft coagulation of polypectomy margins.

ESD is a newer endoscopic technique that was developed in the East and is now gaining wider adoption in the West. The advantage of ESD is that it provides

the ability to remove all large, non-pedunculated colorectal polyps en bloc, which allows for complete staging and the potential cure of superficial submucosal invasive cancer (i.e., malignant invasion limited to the upper third of the submucosa). In order to do this, ESD usually includes submucosal injection, followed by pre-cutting the mucosa surrounding the polyp, and then dissecting the connective tissue of the submucosa beneath the polyp using specialized cutting tools. In addition to facilitating en bloc resection, ESD produces lower recurrence rate (<2%). However, ESD is technically complex. It may be taught during an advanced endoscopy fellowship or could be learned with observation, proctoring with a skilled endoscopist, and training on animal models prior to independent performance. ESD also has a higher adverse event rate (e.g., perforation)[1] and requires substantially more time to perform compared to EMR.

Given these differences between EMR and ESD, it remains unclear which endoscopic technique is preferable for the management of large, non-pedunculated colorectal polyps, and the authors should be congratulated for conducting a well-designed randomized controlled trial (RCT) to address this important issue. This is the definitive RCT to compare the safety and effectiveness of EMR and ESD for large colonic adenomas

Key Study Findings

Although the recurrence rate was significantly lower with ESD vs EMR (0.6% vs 5.1%, respectively), endoscopic resection of residual neoplasia during 6-month follow-up colonoscopy was achieved in all EMR patients. However, ESD produced significantly more adverse events than EMR (35.6% vs 24.5%, respectively), including post-polypectomy syndrome as well as numeric increases in periprocedural perforation and clinically significant post-procedural bleeding.

Also, ESD required significantly more time than ESD than EMR (47 minutes vs 14.5 minutes).

Caution

This study was conducted among experts in ESD and EMR who have years of experience and their recurrence rates and adverse event rates may not be generalizable in other settings. In addition, the study included sessile serrated lesions, which may not be the ideal lesion for ESD given its low risk of harboring any low-risk submucosal invasive cancer (SMIC) and ease of resection with more safer and effective methods (e.g., piecemeal cold EMR). Also, patients with rectal lesions were excluded. Although the rationale for this was not detailed in the publication, it's probably because ESD is considered the optimal technique for large rectal adenomas, especially if there is evidence of low-risk, superficial submucosal invasive cancer.[4]

My Practice

When I encounter a large (i.e., ≥20 mm) or complex polyp during a screening or

diagnostic examination, the first question I ask is whether it has any deep submucosal invasive features by examining the lesion on high-definition white light (HDWL) and image enhanced endoscopy (e.g., narrow band imaging (NBI), bioluminescence imaging, i-scan, etc.) and using my polyp classification schemes (Paris classification, NBI International Colorectal Endoscopic [NICE], and Japan NBI Expert Team). If there's overt signs of deep submucosal invasive disease (e.g., NICE Type III, Paris III, excavation or ulceration), I would biopsy the lesion to confirm and refer this lesion to surgery. If there's uncertainty regarding any features of deep submucosal invasive, it is reasonable to call a colleague for a second opinion or refer the lesion to an expert advanced resection center. If there is no evidence of any deep submucosal invasive features on HDWL or NBI, then the next question is whether there are any high-risk features of superficial submucosal invasive (e.g., increasing laterally spreading tumor (LST) size, rectal location, LST non-granular appearance, Paris IIc morphology, etc.). If so, these lesions should be resected en bloc using either ESD or EMR, depending on the size. If there's no high-risk features or evidence of superficial or deep submucosal invasion, EMR (either en bloc or piecemeal) is an efficient, safe, and effective approach to remove large, non-pedunculated colorectal polyps.

Although I did not complete an advanced endoscopy fellowship, I learned ESD techniques after appropriate observation, proctoring with hands-on training, and practice on animal models. I limit my practice to performing ESD on large rectal lesions, especially if there is evidence of superficial submucosal invasion since it's important to achieve en bloc resection in these patients. Given the thickness of the rectal wall, the risk of perforation is lower and performance of ESD allows the patient to forego rectal surgery, which is more likely to lead to colostomy and usually has a greater impact on quality of life compared to segmental resection in other sections of the colon.

For Future Research

Additional studies are needed to determine the most safe and effective endoscopic resection method for large, non-pedunculated polyps in the rectum.

Conflict of Interest

Dr. Lee reports no conflicts of interest.

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CRC SCREENING

In Case You Missed It
Eating "Healthy" to Minimize Colon Cancer

Dr Philip Schoenfeld
Editor-in-Chief

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This summary reviews Wang L, Du M, Wang K, et al. Association of ultra-processed food consumption with colorectal cancer risk among men and women. BMJ 2022; 378:e068921.

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Keywords: colorectal cancer, processed food, food frequency questionnaire, NOVA classification

STRUCTURED ABSTRACT

Question: Does high consumption of ultra-processed foods increase the risk of colorectal cancer (CRC)?

Design: Prospective cohort study of male clinicians from Health Professionals Follow-Up Study (1986-2014), and female nurses from Nurses' Health Study I (1986-2014), and Nurses' Health Study II (1991-2015).

Setting: The Health Professionals Follow-Up Study was established in 1986 with 51,529 male clinicians (physicians, optometrists, podiatrists, etc.) aged 40-75. The Nurses' Health Study I was established in 1976 with 121,071 registered nurses, aged 30-55, in the 11 most populous US states. The Nurses' Health Study II enrolled 116,429 female nurses in 1989, aged 25-42. All groups completed bi-annual questionnaires about demographics, lifestyle factors, medical history, and disease outcomes.

Patients: Men from Health Professionals Follow-Up Study and women from Nurses' Health Study I and II with complete dietary intake measurement and no cancer diagnosis at baseline.

Interventions/Exposure: Assessment of ultra-processed food consumption using the Food Frequency Questionnaire (FFQ), which is a validated, semiquantitative instrument assessing intake of 130 food items and was administered to study participants every 4 years.

Using the NOVA classification, individual foods were classified as unprocessed or minimally processed, processed, or ultra-processed foods **(Figure 1)**. Ultra-processed foods are generally defined as ready-to-eat or ready-to-heat formulations that contain little whole foods and commonly contain artificial sweeteners, food preservatives, and contaminants that migrate from the packaging.

Outcome: CRC, defined as proximal CRC if it occurred proximal to splenic flexure, distal CRC encompassing sigmoid and descending colon, and rectal encompassing rectum and recto-sigmoid junction. CRC diagnosis was confirmed by review of medical records and pathology reports.

Data Analysis: Hazard ratios (HR) calculated using Cox proportional hazards model after adjusting for age, sex, smoking, family history of cancer, history of endoscopy, physical activity, aspirin use, menopause status, and total caloric intake. Additional sensitivity analysis also accounted for body mass index (BMI) to differentiate impact of obesity from high ultra-processed food consumption. Based on FFQ data, individuals were categorized into 5 quintiles for ultra-processed food consumption with the lowest quintile used as the reference standard.

Funding: The National Institute of Health.

Results: Valid dietary data was available for 46,341 men (mean age 55, 91% White, mean BMI of 25, 10% current smokers) and 159,907 women (mean age 53, 98% White, mean BMI of 25, 21% current smokers) from the 3 cohorts. During 24 -28 years of follow-up in the 3 cohorts, 1,294 cases of CRC were diagnosed in men and 1,922 cases were diagnosed in women.

In multivariate analysis, men who consumed the most ultra-processed foods (highest quintile or highest fifth) were 29% more likely to develop CRC compared to men who were in the lowest quintile (or lowest fifth): adjusted HR (aHR) 1.29 (95% confidence interval [CI] 1.08-1.53). When stratified by proximal vs distal CRC, this association was limited to distal CRC: aHR 1.72; 95% CI 1.24-2.37. Among sub-groups of ultra-processed foods, high intake of sugar-sweetened beverages (aHR 1.21; 95% CI 1.01-1.44) and high intake of ready-to-eat meat/poultry/fish products (aHR 1.44; 95% CI 1.20-1.73) was associated with an increased risk of CRC.

No overall association was identified between high consumption of ultra-processed foods and CRC in women, although high consumption of ready-to-eat/heat-mixed dishes was associated with an increased CRC risk in women: aHR 1.17; 95% CI 1.01-1.36.

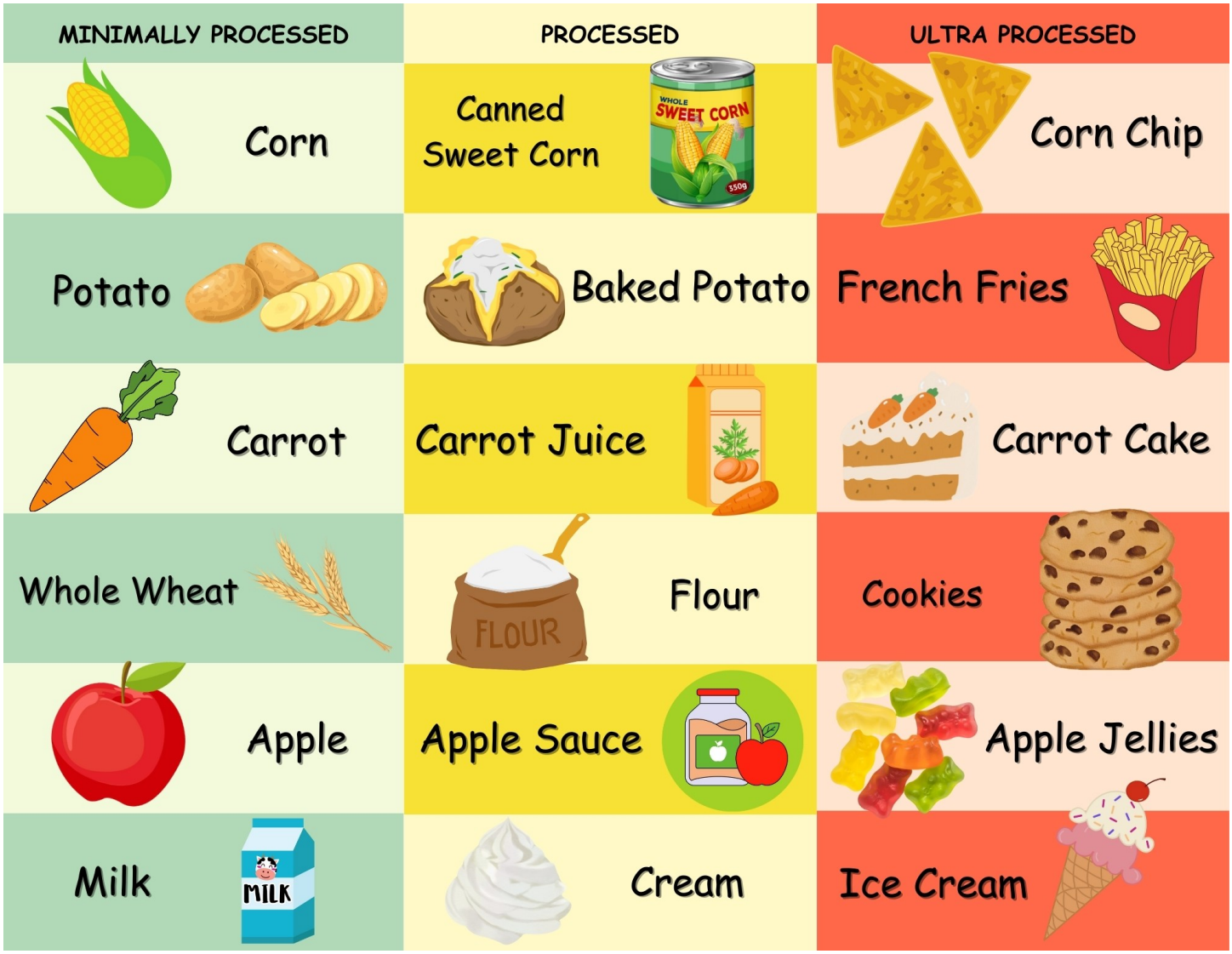

Figure 1. Processed food chart

COMMENTARY

Why Is This Important?

Screening with colonoscopy and stool-based tests has led to significant decreases in CRC in the average-risk population. Still, when I speak briefly with patients after their colonoscopy, they frequently ask me if diet changes may minimize their risk of CRC. I usually emphasize that the most important intervention is to stay up to date with their CRC screening tests, but I note that eating more fresh fruits and vegetables and whole grains is beneficial,[1] while intake of well-cooked red meat should be minimized. With this study, and other research[2-3] based on the Nurses' Health Study and Health Professionals Follow-Up Study, we can better educate patients that ultra-processed foods (e.g., ready-to-eat or ready-to-heat formulations that contain little whole foods and commonly contain artificial sweeteners, food preservatives, and contaminants that migrate from the packaging) should be avoided.

These types of data may be particularly helpful when addressing the rapid rise of CRC incidence in adults <50 years old,[4] which is commonly defined as early-onset CRC. Excessive intake of sugar-sweetened beverages in adolescence and early adulthood as well as developing obesity in early adulthood are associated with an increased risk of early onset-CRC in women,[2-3] while the use of GLP-1 receptor agonists,[5] which have been incredibly effective at treating obesity and type II diabetes mellitus, has been associated with decreased risk of CRC. It seems likely that efforts to reduce early-onset CRC incidence will continue to explore diet interventions, lifestyle changes, and maintenance of a healthy BMI, as well as studying food additives that may have a pro-inflammatory impact on the gut microbiome or be carcinogens.

Key Study Findings

Men who consumed the most ultra-processed foods (highest quintile or highest fifth) were 29% more likely to develop CRC compared to men who were in the lowest quintile (or lowest fifth): aHR 1.29; 95% CI 1.08-1.53.

This finding was confirmed in sensitivity analysis after adjusting for obesity in the patient population, suggesting that high intake of ultra-processed foods was not simply a marker for obesity, which is a known risk factor for CRC.

Caution

Although the Nurses' Health Study and the Health Professionals Follow-Up Study are among the best designed prospective cohort studies from the US, the vast majority of participants are White nurses and physicians, which limits generalizability. Also, although the Food Frequency Questionnaire is

validated, it was only given to study participants every 4 years and may have limited accuracy to quantify intake of different foods.

My Practice

When my patients ask me what they can do to reduce their risk of CRC, the answers are rather straightforward. Get more aerobic exercise, eat a diet high in unprocessed or minimally processed foods with plenty of fresh fruits and vegetables, don't smoke cigarettes, only drink alcohol occasionally, if at all, and maintain a healthy weight (i.e., don't be obese or overweight based on BMI).[1] Easier said than done! Nevertheless, these lifestyle factors minimize the risk of cancer, cardiovascular disease, and many other disorders.

This study provides excellent data to reinforce specific diet changes that may minimize the risk of CRC, independent of obesity or overweight status. Although the widespread availability of ultra-processed foods, including "junk foods" in convenience stores and "fast food" from chain restaurants, may be tempting, these foods should be consumed in moderation while emphasizing consumption of fresh fruits, vegetables, and whole grains.

For Future Research

Additional studies in women are needed to assess the interaction between menopause, hormonal changes, diet, and their impact on CRC risk. Also, more research into dietary risk factors, obesity, and other potential risk factors for early onset CRC need to be explored as well as the impact of dietary factors on CRC risk at specific anatomic sites.

Conflict of Interest

Dr. Schoenfeld reports no relevant conflicts of interest.

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CRC SCREENING

When to Discontinue CRC Screening in Older Adults: Chronological Age or Life Expectancy?

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This summary reviews Liu PH, Singal AG, Murphy CC. Colorectal cancer screening receipt does not differ by 10-year mortality risk among older adults. Am J Gastroenterol 2024;119: 353-363.

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Keywords: colon cancer, screening, geriatrics, colonoscopy, life expectancy

STRUCTURED ABSTRACT

Question: Among older adults (65-84 years) in the US, how often is colorectal cancer (CRC) screening performed in relation to 10-year mortality risk?

Design: Retrospective cross-sectional study using data from the National Health Interview Survey (NHIS) conducted by the National Center for Health Statistics.

Setting: Community-dwelling adults in the US.

Participants: Adult respondents of the National Health Interview Survey aged 65 to 84 years who were not up to date on CRC screening. Individuals residing in long-term care facilities, living abroad, or incarcerated were excluded from the study. Participants with missing information on CRC screening and those

who were up to date with CRC screening were also excluded.

Intervention/Exposure: Completion of CRC screening (colonoscopy, sigmoidoscopy, or stool-based tests).

Outcomes: The primary outcome was the prevalence of CRC screening in the preceding 12 months, regardless of indication, among individuals who were not up to date with CRC screening, stratified by 10-year mortality risk. Other outcomes included the proportion of CRC screening performed among adults with a life expectancy <10 years (i.e., 10-year mortality risk ≥50%) and the association between quintile of mortality index and receipt of past year screening. This was reported as odds ratios (OR) and confidence intervals (CI).

Data Analysis: Ten-year mortality risk was estimated using the Schonberg mortality index developed via NHIS data linked with the National Death Index. This was then used to estimate 10-year life expectancy. The prevalence of past-year CRC screening was assessed by quintiles of mortality risk (quintile 1 = lowest risk, quintile 5 = highest risk) and age group. The association between mortality risk and past-year screening was evaluated using logistic regression after controlling for potential confounders. Other exploratory analyses included the prevalence of past-year screening by combinations of 5-year age group, mortality risk quintile, type of CRC screening modality, and the proportion of screening performed in adults with less than 10 years of life expectancy.

Funding: National Institutes of Health

Results: Among the entire cohort of 25,888 adults, the proportion of individuals who were not up to date with CRC screening was highest in the 65–69-year age group (35.8%) and lowest in the 80-84-year age group (13.3%). The prevalence of past-year screening in the entire cohort was 38.5%. According to mortality risk quintiles, the prevalence of past-year screening ranged from 39.5% in the lowest quintile to 35.4% in the highest quintile (**Figure 1**). Receipt of CRC in the past year was not associated with the mortality index quintile (OR 1.05, 95% CI 0.93-1.2). Interestingly, within some 5-year age groups, such as the 65–69-year age group, the prevalence of past-year screening was similar by quintile of mortality risk. However, within other groups like the 75–79-year age group, the prevalence of past-year screening increased with increasing or higher mortality risk (P=0.02). About 28% of past-year screening was performed in adults with a life expectancy

<10 years. This increased from 13.7% in the 65–69-year age group, to 65.6% in the 80–84 year age group (**Table 1**).

Age (years)	Life expectancy ≥10 years	Life expectancy <10 years	CRC screening in adults with life expectancy < 10 years* (%)
65-69 (n=3,405)	2,915	490	13.7 (12.3 - 15.1)
70-74 (n=2,835)	2,253	582	21.0 (19.0 - 23.0)
75-79 (n=1,997)	1,169	828	42.5 (39.9 - 45.0)
80-84 (n=1,153)	400	753	65.6 (62.2 - 69.1)

Table 1. Colorectal cancer screening rates in older adults based on life expectancy from the National Health Interview Survey (2000-2018)

*Weighted percentage and 95% confidence intervals

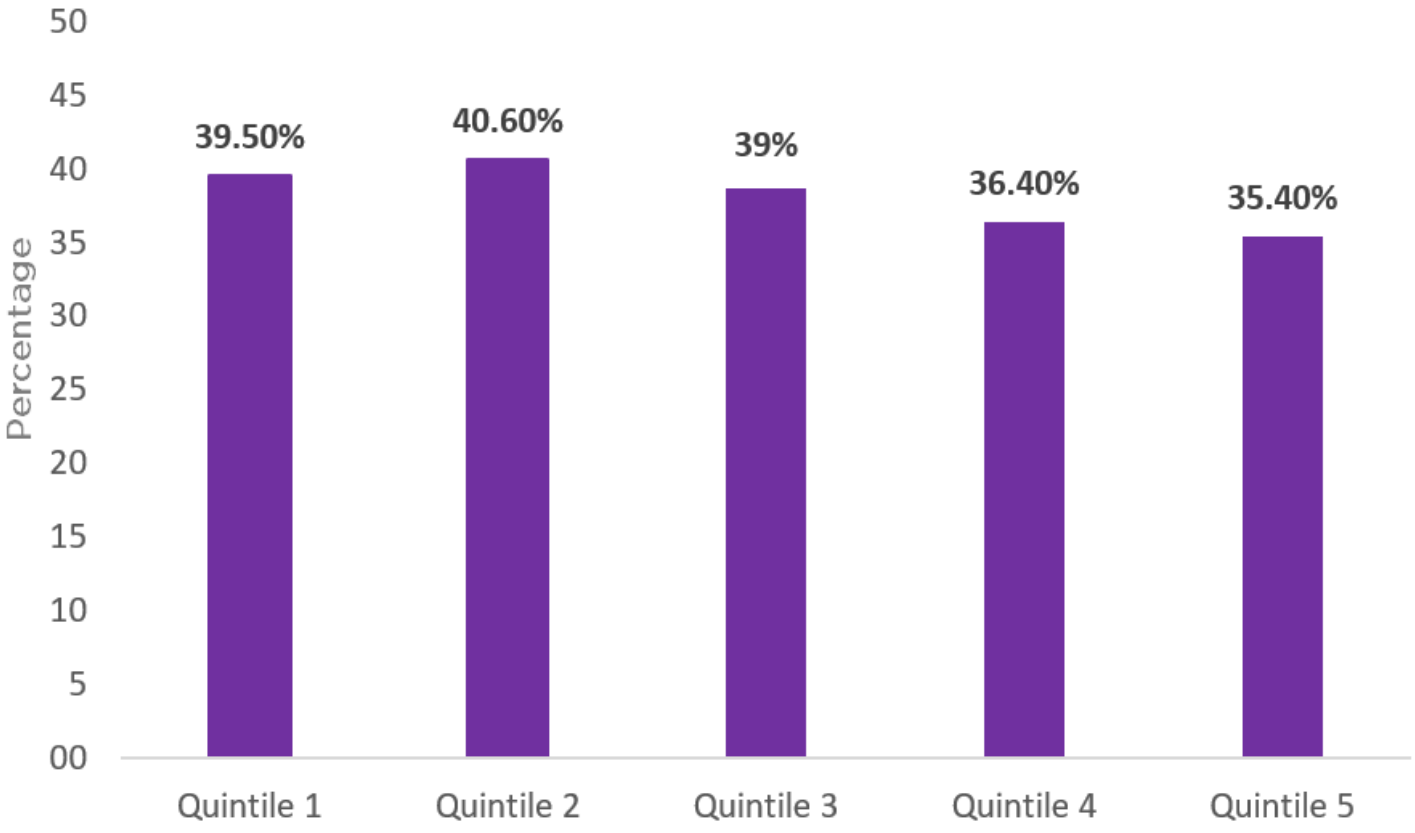

Figure 1. Prevalence of colorectal cancer screening by 10-year mortality risk quintile.
Quintile 1= lowest 10-year mortality risk; Quintile 5= highest 10-year mortality risk

COMMENTARY

Why Is This Important?

Older Americans are estimated to make up 21% of the entire population by 2030.[1] By 2060, nearly 1 in 4 Americans will be 65 years or older.[1] As such, more adults than ever will be faced with deciding when to stop CRC screening. At present, the latest United States Preventative Services Task Force recommendations suggest clinicians selectively offer CRC screening in adults 76 to 85 years old because evidence indicates that the net benefit is small.[2] They also recommend consideration of overall health, prior screening history, and patient preferences.[2] As a result, many providers use the chronological age of 75 years as the major consideration in discontinuing CRC screening. However, recent studies have suggested that we may be over screening patients for CRC.[3,4] Conversely, we may also be underscreening some patients over 75 years with longer life expectancy.

In this study, Liu et al make the case for a shift in the way the decision to stop CRC screening is approached, suggesting we move away from using only the chronological age. Instead, they recommend that life expectancy and overall health status should play a more important role in the decision to stop CRC screening. They show that CRC screening is being performed among patients with a life expectancy of fewer than 10 years, comparable with the findings of Calderwood et al who also showed significant rates of CRC screening among patients with a life expectancy of less than 5 years in New Hampshire.[3] The results of Liu et al become more compelling when you consider recent evidence that the rates of invasive CRC among patients screened over the age of 75 years is very low and that these patients are more likely to have complications than younger patients.[4] Also, even among older adults diagnosed with CRC, only a small proportion will choose to receive treatment for malignancy.[4]

Key Study Findings

The study suggests that life expectancy and overall health status are not always considered by healthcare providers when recommending CRC screening in adult patients.

Importantly, 28% of older adults who received CRC screening in the preceding year had a life expectancy of less than 10 years. Among adults aged 70-79 years, the use of invasive CRC screening modalities increased among those with lower life expectancy.

Caution

While the NHIS is a nationally representative sample, participant responses are self-reported and as such, not validated by the investigators. In addition, given the nature of the NHIS, the authors were also unable to reliably ascertain if the CRC screening modality was truly done for screening pur-

poses vs surveillance or diagnostic indications. The authors also allude to the fact that the reported mortality index used for the study shows good discrimination at the population level but may not be as precise at the individual level.

My Practice

In the US, most recommendations for CRC screening come from primary care. As such, most screening colonoscopies I perform are from open-access referrals. When I do see an elderly patient in the clinic who requests a screening colonoscopy, I try to carry out shared decision-making, emphasizing the risks vs benefits of invasive CRC screening and the prevalence of CRC in previously screened individuals of a similar age profile. I also discuss their thoughts on treatment if a malignancy was found during CRC screening. I often find these conversations challenging because of the sensitive nature of life expectancy and mortality risk. While online resources to estimate mortality risk exist, they are not routinely used in clinical practice, and many providers are not trained on how to incorporate life expectancy discussions into the decision-making process for continued CRC screening. Importantly, I do find that when I emphasize that CRC screening or surveillance is no longer beneficial in the endoscopy report, it goes a long way in reassuring patients and primary care providers.

For Future Research

More efforts are needed to train providers on the incorporation of online tools for estimating mortality risk in the CRC screening decision-making process. Health systems should encourage quality improvement projects that can incorporate these tools into real-time cancer screening calculators. The impact of these tools on the prevalence of CRC screening among the elderly needs to be studied. Providers need to be trained on the proper way to have conversations regarding discontinuing CRC screening via shared decision-making. Audit and feedback for clinicians on their patients' CRC screening rates in relation to life expectancy is deserving of further study. Finally, the perspectives of patients receiving these CRC screening recommendations that incorporate mortality risk and life expectancy need to be investigated qualitatively.

Conflict of Interest

Dr. Philip Okafor reported no potential conflicts of interest.

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

@docamitgs

Amit Singal

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CRC SCREENING

In Case You Missed It

How Frequently Should We Perform Colonoscopy in Patients With Serrated Polyposis Syndrome?

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This summary reviews Bleijenberg AG, IJspeert JE, van Herwaarden YJ et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. Gut 2020;69(1):112-121.

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Keywords: colonoscopy, serrated polyposis syndrome, polyp, colorectal cancer, surveillance

Question: Among patients with serrated polyposis syndrome (SPS), can we increase colonoscopy intervals from annually to every 2 years based upon patient specific factors?

Study Design: Prospective cohort.

Setting: Nine international centers from Spain (33%) and Netherlands (66%).

Participants: All patients fulfilling 2010 World Health Organization (WHO) SPS criteria I and/or III[1] who underwent endoscopic surveillance between January 2013 and April 2018 after initial polyp clearing colonoscopies (removal of all polyps ≥5 mm and those with an optical adenomatous or serrated appearance). Surveillance was started either before or during study period. Those with proctocolectomy, subtotal colectomy, inflammatory bowel disease or known

colorectal cancer (CRC)-related germline genetic variants were excluded.

2010 WHO SPS type I criteria was defined as ≥5 serrated lesions/polyps (SSLs) proximal to the sigmoid colon, with at least 2 lesions/polyps ≥10 mm in size and type III was defined as ≥20 SSLs of any size distributed throughout the colon. Serrated polyps were defined as hyperplastic polyp ≥5 mm, SSL with or without dysplasia, or traditional serrated adenoma. Advanced adenomas were defined as adenomas ≥10 mm, with villous structure and/or with high-grade dysplasia (HGD). Advanced SSLs were defined as traditional serrated adenoma, any SSL ≥10 mm and/or with presence of dysplasia. Advanced neoplasia (AN) was defined as CRC, advanced adenoma, or advanced SSL.

Intervention: Annual surveillance colonoscopy was performed in those with ≥1 advanced adenoma/SSL, ≥5 adenomas/SSLs or if colorectal surgery was performed. All other SPS patients received surveillance colonoscopy every 2 years. Surveillance colonoscopies were done with the goal of removing of all polyps ≥5 mm and those with an optical adenomatous or serrated appearance.

Outcomes: Primary outcome was 5-year cumulative incidence of CRC and AN. Secondary outcomes were frequency of 1- vs 2-year surveillance interval recommendation, incidence of colorectal surgery during surveillance and incidence of AN among 1- vs 2-year surveillance intervals.

Data Analysis: Kaplan-Meier analysis.

Funding: Grants from the Dutch Cancer Society (KWF) and the Instituto de Salud Carlos III (PI16/00766). Co-funded by the European Regional Development Fund (ERDF). CIBEREHD is funded by the Instituto de Salud Carlos III.

Results: Overall, 271 eligible patients were followed for a median of 3.6 years, with a mean age of 60 years old at the start of surveillance. Ninety-nine (36.5%) patients met SPS type I criteria, 99 (36.5%) met type III, and 73 (27%) met both type I & III. Sixty-seven (25%) patients had CRC prior to surveillance. At first surveillance, 131 (52%) received a 2-year follow-up recommendation and 140 (48%) received a 1-year recommendation. Among those with a 1-year follow-up, 50% remained on a 1-year program at second and third surveillance and 50% were transitioned to a 2-year follow-up. Most patients who were recommended a 2-year inter-

val remained with this recommendation after the second (64%) and third (71%) surveillance.

The 5-year cumulative incidence of CRC was 1.3% (95% Confidence Interval [CI] 0-3.2%), which consisted of 2 cases both of whom had prior CRC/AN. The 5-year cumulative incidence of advanced neoplasia was 44% (95% CI 37%-52%). AN incidence was lower for SPS type III (26%) than type I (53%): hazard ratio = 0.38 (95% CI 0.22-0.63, $P<0.001$) adjusted for age, smoking status, and gender. There were no other significant risk factors for AN identified. There was no statistically significant difference in AN incidence between a 1- or 2-year surveillance interval. Surgery was only required for CRC or bowel adhesions in 3 patients during surveillance.

COMMENTARY

Why is this important?

SPS is one of the most common CRC-predisposition polyposis syndromes. The prevalence is approximately 1:111 among individuals ≥ 50 years old with positive fecal immunochemical tests.[2] The National Comprehensive Cancer Network (NCCN) guidelines recommend a 1-3 year interval range,[3] while 2012 USMSTF guidelines recommend annual surveillance colonoscopy for SPS patients.[4] While close colonoscopic surveillance is effective and safe,[5] minimizing overuse of surveillance colonoscopy can alleviate system- and patient-level procedural burden. This study is one of the largest prospective cohorts of SPS patients undergoing colonoscopic surveillance and identifies SPS patients who can safely extend their surveillance interval to every 2 years.

In 2019 (after this study was completed), the WHO criteria for SPS were updated, most notably eliminating the former type II criteria in which any number of serrated polyps proximal to the sigmoid colon in an individual with a first-degree relative with SPS would themselves meet criteria for SPS (**Figure 1**). Given how prevalent serrated lesions are in the general population, this criteria had poor specificity for true SPS.[1] Type I criteria was updated to include serrated lesions in the sigmoid colon due to evidence showing that up to 50% of CRCs in SPS occur in the rectosigmoid colon, but with a minimum size of 5 mm. Type III criteria were renamed as the new type II criteria and now requires at least 5 SSLs proximal to the rectum.

Key Study Findings

Extension of surveillance interval from 1 to 2 years among SPS patients at lower neoplasia risk (<5 polyps and no AN) appears appropriate. The 5-year

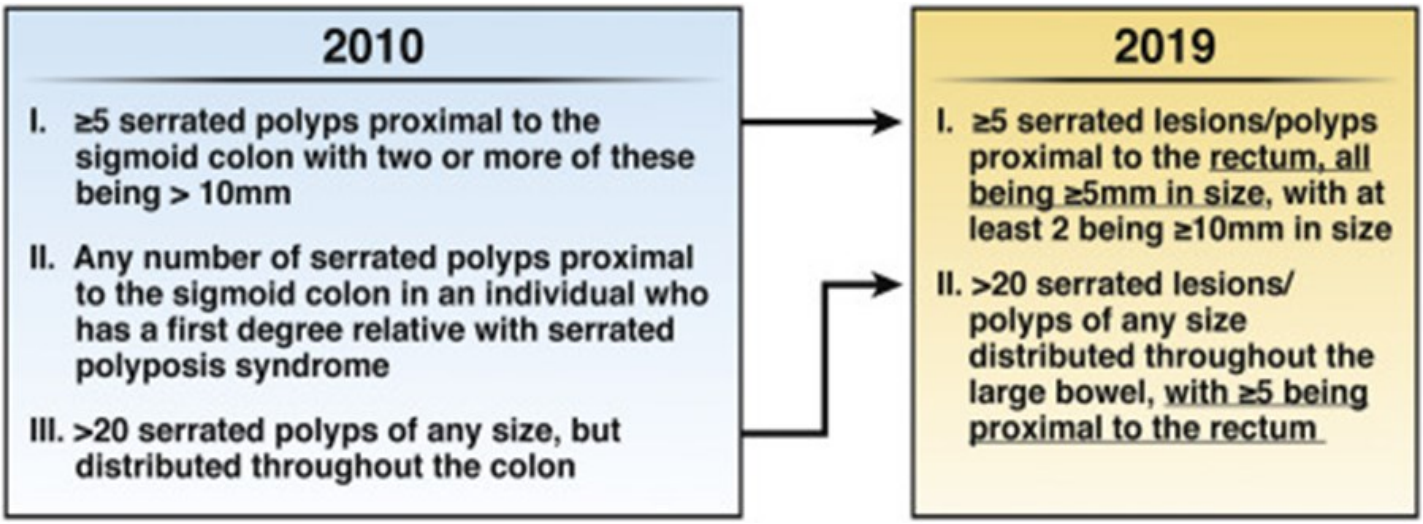

Figure 1. Changes in the World Health Organization's 2010 and 2019 criteria for serrated polyposis syndrome diagnosis. Changes in 2010 I and II criterion are marked with underlining in 2019 criterion. Note that 2010 criterion II was not included with the 2019 criterion. Reused with permission from *Gastroenterology*.[1]

cumulative incidence of CRC is very low (1.3%) and occurred only in patients with prior CRC/AN.

Many SPS patients had AN during surveillance (cumulative incidence 44%), particularly among those with SPS type I, but those with a 2-year follow-up colonoscopy did not have significantly more frequent AN.

Caution

This surveillance study was conducted after all patients underwent clearing of all polyps ≥5 mm and <5 mm with optical appearance of an adenoma or serrated lesion with successful cecal intubation, adequate bowel preparation, and repeat colonoscopies within 6 months as necessary to complete polyp clearing. Virtual chromoendoscopy or distal attachment devices were also not standard practice in this study.

My Practice

After identifying a patient with SPS, I schedule the initial clearing colonoscopy within 3 months and then repeat every 3-6 months until there are <5 small/large polyps and no AN.[6] In order to minimize missed polyps, I usually perform retroflexion in the right colon and use virtual chromoendoscopy (if excellent bowel prep) and a distal attachment device and cleanse residual stool to achieve excellent bowel cleansing. Thereafter, I transition to annual colonoscopies for 2-3 years before relaxing to a biannual interval, while taking into account colonoscopy quality and patient preference. I also recommend early screening of first-degree family members at age 40 (or earlier if early-onset CRC or AN) with repeat every 5 years if no polyps are found[3] at multiple points of patient contact (clinic, colonoscopy report, pathology result letter).

Although SPS often has a familial component, SPS is typically not associated with a pathogenic genetic variant (rare cases can be caused by variants in RNF43). I do offer genetic testing based on patient preference or if there are concomitant adenomatous polyps, which raises the likelihood of mixed polyposis syndromes such as MUTYH-associated polyposis.[3]

It is important to remember that SSLs are sporadic in most patients in the absence of SPS, and SSLs with any dysplasia are thought to be comparable to adenomas with high-grade dysplasia in terms of CRC risk.[7] However, as discussed in a previous EBGI summary, these polyps tend to be flat, subtle in appearance, and easily missed particularly in the proximal colon.[8] There is recent data showing an inverse association between sessile serrated detection rates (SSLDR) and post-colonoscopy CRC risk,[9] raising the question whether SSLDR should be considered a colonoscopy quality metric.[10]

For Future Research

In order to prevent CRC due to SPS, we must improve recognition of SPS patients, especially since the diagnosis is based upon lifetime total number of serrated polyps removed. In addition to improving provider knowledge, a flaw of our current healthcare system is the lack of a centralized longitudinal endoscopic record and cumulative polyp counter. Many patients obtain colonoscopies over time at a variety of clinical locations, and diagnosis of polyposis is often made either in the patient with a peculiar number of polyps during a single colonoscopy, or by an astute clinician paying particular attention to total number of serrated polyps removed during past colonoscopies.

Conflict of Interest

Dr. Yen reports no conflicts of interest.

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