Oral Antibiotics and Risk of New Colorectal Adenomas During Surveillance Follow-up

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ABSTRACT

Background: Antibiotics may increase colorectal neoplasia risk by modifying the gut microbiome. It is unknown whether use is associated with the risk of new colorectal adenomas among individuals with prior adenomas.

Methods: We performed a secondary analysis of four randomized clinical trials for the chemoprevention of colorectal adenomas. Participants self-reported all currently used prescription drugs shortly after an initial colorectal adenoma diagnosis and two or three times a year thereafter over 3 to 5 years of follow-up. We estimated adjusted risk ratios (RR) with 95% confidence intervals (CI) for incident adenomas, analyzing the four trials together.

Results: Cumulatively, the four trials enrolled 5,174 participants (3,491 men and 1,683 women), of whom 4,769 (92%) completed ≥1 follow-up colonoscopy. A total of 763 (15%) participants reported using oral antibiotics on ≥2 occasions. Overall, 39% of those using oral antibiotics at least twice developed new colorectal adenomas compared with 40% of those with no use or a single report of use (RR, 0.99; 95% CI, 0.90–1.10). No statistically significant associations were found in study-specific analyses, and results were similar for high- and low-risk adenoma findings, antibiotic class, anatomic location of adenomas, and analyses excluding those with interim colorectal exams.

Conclusions: Oral antibiotic use during colonoscopic surveillance after an initial adenoma diagnosis was not associated with risk of these polyps.

Impact: Any changes to the gut microbiome as a consequence of oral antibiotic use during surveillance may not affect the development of metachronous colorectal adenomas.

Introduction

Antibiotic use may affect colorectal neoplasia risk by modifying the gut microbiome (1). A meta-analysis of 10 observational studies concluded oral antibiotic use was associated with 17% higher risk of colorectal cancer (2). This association may be stronger for broad-spectrum (2) and anti-aerobic (3) antibiotics, and for neoplasia of the proximal colon (3, 4). One study found early-life oral antibiotic use, but not recent use, was associated with higher risk of colorectal adenomas, the most common precursor lesions for colorectal cancer (4). It is unknown whether oral antibiotic use among those with an initial colorectal adenoma diagnosis is associated with subsequent risk of these polyps.

Materials and Methods

We aggregated individual-level data from the four Polyp Prevention Study trials (5–8). Conducted by a single consortium using similar protocols, each was a multicenter placebo-controlled randomized clinical trial among those recently diagnosed with colorectal adenomas. The Antioxidant trial investigated β-carotene and the combination of ascorbic acid and α-tocopherol among 864 participants enrolled between 1984 and 1988 (5). The Calcium trial investigated calcium among 930 participants enrolled between 1988 and 1992 (6). The Aspirin/Folate trial investigated aspirin at two doses and folic acid among 1,121 participants enrolled between 1994 and 1998 (7). The Vitamin D/Calcium trial investigated cholecalciferol and calcium among 2,259 participants enrolled between 2004 and 2008 (8). These studies were approved by Institutional Review Boards and all participants provided written informed consent.

In each trial, the primary endpoint was the occurrence of colorectal adenomas during the treatment period, planned to end at the time of a follow-up colonoscopy 3 to 5 years after randomization. A review of colorectal biopsies by a single study pathologist distinguished conventional adenomas from non-adenomatous polyps and adenocarcinomas. High-risk adenoma findings were defined as ≥1 advanced adenoma (tubulovillous/villous adenomas, ≥1 cm in diameter, with high-grade dysplasia, or adenocarcinoma) or ≥3 synchronous adenomas. Low-risk adenoma findings were defined as one or two non-advanced adenomas.

At baseline, the Antioxidant, Calcium, and Aspirin/Folate trials asked about current use of prescription drugs including antibiotics, whereas the Vitamin D/Calcium trial asked about use in the past year. Follow-up questionnaires administered every 6 months (4 months in the Aspirin/Folate trial) asked about use since the last questionnaire. Oral antibiotic types were classified by Anatomical Therapeutic Chemical code and grouped by class, narrow- or broad-spectrum, and anti-aerobic or anti-anaerobic.

Risk ratios (RR) with 95% confidence intervals (CI) adjusted for age, sex, clinical center, study, and treatment assignment (placebo vs. active) were estimated using log-linear Poisson regression for adenoma occurrence as a binary outcome with robust variance among those with ≥1 follow-up colonoscopy during the treatment period. Subgroup analyses were performed according to study, antibiotic class, and adenoma location. Adenomas diagnosed during interim colorectal exams before the scheduled end of the surveillance interval were

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Table 1. Baseline characteristics of 5,174 participants of the four Polyp Prevention Study trials.

Baseline characteristics	Total	Oral antibiotic use[a]	
		No	Yes
All four trials, *n*[b]	5,174	4,411	763
Age, years, mean (SD)	59 (8)	59 (8)	58 (9)
Men, *n* (%)	3,491 (67%)	3,061 (69%)	430 (56%)
Antioxidant trial, *n*[b]	864	796	68
Age, years, mean (SD)	61 (8)	61 (8)	61 (10)
Men, *n* (%)	684 (79%)	631 (79%)	53 (78%)
Calcium trial, *n*[b]	930	878	52
Age, years, mean (SD)	61 (9)	61 (9)	62 (9)
Men, *n* (%)	672 (72%)	640 (73%)	32 (62%)
Aspirin/Folate trial, *n*[b]	1,121	773	348
Age, years, mean (SD)	57 (10)	58 (10)	57 (10)
Men, *n* (%)	712 (64%)	517 (67%)	195 (56%)
Vitamin D/Calcium trial, *n*[b]	2,259	1,964	295
Age, years, mean (SD)	58 (7)	58 (7)	58 (7)
Men, *n* (%)	1,423 (63%)	1,273 (65%)	150 (51%)

Abbreviation: SD, standard deviation.
[a]Oral antibiotic use defined as ≥2 reports of use at baseline or during the study treatment period.
[b]Number who underwent randomization.

included, unless <1 year after randomization. In sensitivity analyses, we excluded participants with interim exams. We defined antibiotic use as ≥2 separate reports of use at baseline or follow-up and evaluated total count of reports of antibiotic use as a continuous variable in a secondary analysis. Two-sided $P < 0.05$ was considered statistically significant.

Results

Of 5,174 participants across the four trials, 763 (15%) participants used oral antibiotics at least twice (**Table 1**; Supplementary Table S1). Overall, 4,769 (92%) participants completed ≥1 follow-up colonoscopy. Oral antibiotic use was not associated with colorectal adenoma risk in any trial or the four trials combined (RR, 0.99; 95% CI, 0.90–1.10; **Table 2**; Supplementary Table S2). Results were similar by high- and low-risk status (**Table 2**), drug class (Supplementary Tables S3 and S4), anatomic location (Supplementary Table S5), and after excluding those with interim exams (Supplementary Table S6).

Discussion

Oral antibiotic use during colonoscopic surveillance was not associated with colorectal adenoma risk in a secondary analysis of the four Polyp Prevention Study trials. Our results are inconsistent with a meta-analysis of 10 observational studies of invasive colorectal cancer (2), but consistent with an assessment of recent oral antibiotic use in a case–control study nested within the Nurses' Health Study of colorectal adenomas regardless of prior adenoma history (4).

Our study has limitations. The trials did not collect antibiotic dose or duration. History of antibiotic use before study enrollment

Table 2. Association between oral antibiotic use and colorectal adenoma risk in the four Polyp Prevention Study trials.

Endpoint[a]	No. with endpoint (%)			RR[d] (95% CI)	*P*
	Total[b]	Oral antibiotic use[c]			
		No	Yes		
All four trials	4,769	4,034	735		
Any adenoma	1,853 (40%)	1,578 (40%)	275 (39%)	0.99 (0.90–1.10)	0.91
Low-risk adenoma findings	1,152 (29%)	977 (29%)	175 (29%)	0.99 (0.86–1.14)	0.87
High-risk adenoma findings	628 (18%)	536 (19%)	92 (17%)	1.02 (0.83–1.25)	0.85
Antioxidant trial	751	689	62		
Any adenoma	275 (37%)	255 (38%)	20 (33%)	0.87 (0.60–1.28)	0.49
Low-risk adenoma findings	167 (26%)	156 (27%)	11 (21%)	0.78 (0.45–1.35)	0.38
High-risk adenoma findings	94 (17%)	86 (17%)	8 (16%)	0.90 (0.46–1.76)	0.77
Calcium trial	832	785	47		
Any adenoma	281 (35%)	270 (35%)	11 (26%)	0.80 (0.47–1.36)	0.41
Low-risk adenoma findings	161 (24%)	156 (24%)	5 (14%)	0.61 (0.26–1.40)	0.24
High-risk adenoma findings	100 (16%)	97 (16%)	3 (9%)	0.58 (0.19–1.72)	0.33
Aspirin/Folate trial	1,084	740	344		
Any adenoma	417 (40%)	295 (41%)	122 (37%)	0.94 (0.80–1.11)	0.46
Low-risk adenoma findings	265 (30%)	185 (31%)	80 (28%)	0.95 (0.76–1.18)	0.62
High-risk adenoma findings	137 (18%)	98 (19%)	39 (16%)	0.91 (0.65–1.28)	0.60
Vitamin D/Calcium trial	2,102	1,820	282		
Any adenoma	880 (43%)	758 (42%)	122 (44%)	1.10 (0.96–1.27)	0.18
Low-risk adenoma findings	559 (32%)	480 (32%)	79 (34%)	1.13 (0.93–1.36)	0.22
High-risk adenoma findings	297 (20%)	255 (20%)	42 (22%)	1.21 (0.91–1.62)	0.19

Abbreviations: CI, confidence interval; RR, risk ratio.
[a]High-risk adenoma findings were defined as ≥1 advanced adenoma (tubulovillous/villous adenomas, ≥1 cm in diameter, with high-grade dysplasia, or adenocarcinoma) or ≥3 synchronous adenomas of any size. Low-risk adenoma findings were defined as one or two non-advanced adenomas. In total, 123 participants were missing any adenoma endpoint and 73 participants were missing high- and low-risk adenoma findings status.
[b]Count of participants who completed a follow-up colonoscopy during the study treatment period.
[c]Oral antibiotic use defined as ≥2 reports of use at baseline or during the study treatment period.
[d]RR adjusted for age, sex, clinical center, study, and treatment assignment (placebo, active). Study-specific RRs are not adjusted for study. For each RR, those without the endpoint were participants with no incident colorectal adenomas.

was not ascertained, preventing us from assessing early-life use, previously found to be a risk factor for colorectal adenomas (4). Distinct reports of antibiotic use were separated by several months, and we could not distinguish continuous from discontinuous use. It was not possible to determine whether antibiotic use at baseline was related to symptoms leading to the initial adenoma diagnosis that qualified participants for these studies. Likewise, some participants may have been more likely to use antibiotics shortly before or after unscheduled follow-up exams that identified adenomas, but results were not meaningfully different when considering only those who completed the planned surveillance interval without any interim colorectal evaluations. In conclusion, these data suggest no association between oral antibiotic use, not otherwise specified, during surveillance and the risk of new colorectal adenomas.

Authors' Disclosures

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Authors' Contributions

M.N. Passarelli: Conceptualization, resources, data curation, formal analysis, funding acquisition, writing–original draft, writing–review and editing. **L.A. Mott:** Conceptualization, resources, data curation, software, formal analysis, project administration, writing–review and editing. **E.L. Barry:** Resources, data curation, investigation, writing–review and editing. **J.R. Rees:** Resources, data curation, investigation, writing–review and editing. **J.A. Baron:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, writing–original draft, writing–review and editing.

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