Adenoma Detection is Increased in the Setting of Melanosis Coli

John W. Blackett, MD, Richard Rosenberg, MD,* Srihari Mahadev, MD,* Peter H.R. Green, MD,* and Benjamin Lebwohl, MD, MS*†*

Goals: To compare the adenoma detection rate (ADR) during colonoscopy in patients with melanosis coli against matched controls without melanosis.

Background: Melanosis coli is a colonoscopic finding in which the colon wall appears darkly pigmented, most often due to extended laxative use, and is considered benign. The pigmentation spares adenomas, which should therefore be more readily detectable in melanosis coli.

Study: We identified all patients with melanosis on colonoscopy at our institution over a 5-year period. We matched each patient with 2 controls by age, gender, and endoscopist. We compared the prevalence of adenomas between groups, and used multivariable analysis, adjusting for procedure indication and bowel preparation quality, to determine the independent association of melanosis with adenoma detection.

Results: At least 1 adenoma was detected in 34.7% of melanosis patients and 26.5% of controls [odds ratio (OR) = 1.52; 95% confidence interval (CI), 1.04-2.24; $P = 0.03$]. On multivariable analysis, the presence of melanosis remained associated with increased adenoma detection (OR = 1.56; 95% CI, 1.05-2.33; $P = 0.03$). Melanosis patients were more likely to have an adenoma ≤ 5 mm (OR = 1.62; 95% CI, 1.04-2.51; $P = 0.03$), but not adenomas 6 to 9 mm or ≥ 10 mm.

Conclusions: Melanosis coli is associated with a significant increase in ADR during colonoscopy compared with controls. The increased visibility of adenomas given their contrast with the pigmented background is a likely explanation. Future efforts to identify bowel preparation agents that can induce a similar effect could improve ADRs during colonoscopy.

Key Words: melanosis coli, adenoma, colonoscopy

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Melanosis coli is a condition characterized by brown or black pigmentation of the colonic mucosa.[1] It results from the presence of lipofuscin granules in macrophages of the colon, rather than melanin as might be expected from the name.[2,3] There is a strong association between melanosis coli and excessive laxative use, in particular anthraquinone laxatives such as senna.[4] It is caused by anthraquinone-induced apoptosis of colonic epithelial cells, followed by phagocytosis of the apoptotic bodies by macrophages.[5,6]

The estimated prevalence of melanosis varies, with 1 study of 200 consecutive autopsies finding melanosis coli in 119 patients, or 59.5%.[7] However, most studies have found much lower prevalence rates, including a series at the Mayo Clinic from 1950 to 1954 that found 750 cases of melanosis out of 91,472 colonoscopies, or 0.82%.[8] Other studies have found prevalence rates of 4.6% and 4.3% during colonoscopy.[9,10]

At least 1 study has raised concern for an association of melanosis with colorectal neoplasms,[11] although more recent studies have shown no association with colorectal cancer.[9,10,12,13] Melanosis has been associated with increased detection of adenomas, however.[9,10] A 1993 analysis of 2277 German colonoscopy patients found an adenoma prevalence of 53.5% for 99 patients with melanosis coli, compared with 25.4% for patients without melanosis.[10] A similar 1997 analysis of 2229 German colonoscopy patients, including 102 with melanosis, found a 24.5% prevalence for tubular adenomas and 9.8% for tubulovillous adenomas in melanosis patients, compared with 13.6% and 4.8%, respectively, among those without melanosis.[9] The higher adenoma detection rate (ADR) was thought to be due to the pigmentation-sparing colorectal adenomas, making them stand out as light lesions on a dark background. The relatively low numbers of melanosis patients in these studies, as well as possible underlying differences between study groups, may have impacted ADRs.

The effect of melanosis coli on adenoma detection bears similarities to chromoendoscopy, a technique in which topical stains or pigments are applied to the gastrointestinal mucosa during endoscopy to improve diagnosis, including the detection of colorectal adenomas. The use of indigo carmine to improve colorectal adenoma detection has had variable outcomes.[14–18] A 2007 meta-analysis of 4 trials showed a significant improvement in neoplastic lesion detection when chromoendoscopy was used, however.[19] Chromoendoscopy may be especially useful for finding small adenomas.[14,15,19] Limitations of chromoendoscopy include an increased average length of colonoscopy and lack of training and familiarity among providers.

We aimed to determine whether the prevalence of adenomas is greater in patients with melanosis than

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From the *Department of Medicine, Division of Digestive and Liver Diseases, Columbia University College of Physicians and Surgeons; and †Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.
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Address correspondence to: Benjamin Lebwohl, MD, MS, Department of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center, 180 Fort Washington Avenue, Suite 936, New York, NY 10032 (e-mail: bl114@columbia.edu).

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matched controls. We hypothesized that melanosis results in improved detection of adenomas due to a chromoendoscopy effect. We therefore matched controls to patients using parameters that can affect the ADR: age, gender, and endoscopist. To our knowledge, this is the only study analyzing the prevalence of adenomas in melanosis coli patients versus matched controls, and the only one in the United States.

MATERIALS AND METHODS

We performed a retrospective cohort study of patients undergoing colonoscopy at Columbia University Medical Center, a university-based medical center in New York City. All data were obtained from the hospital's electronic medical record system. The inclusion criteria consisted of adults (18 y and above) with a diagnosis of melanosis coli on colonoscopy between January 1, 2011 and January 31, 2016. Melanosis coli was diagnosed clinically by gross appearance of the colonic mucosa (Fig. 1). The patients with melanosis coli were each matched to 2 patients without melanosis coli by age (within 5 y), gender, endoscopist, and date of colonoscopy (within 1 y). When >2 control subjects were available for matching, the 2 with the closest age to the melanosis coli subject were selected. In addition to age, gender, and endoscopist, we identified the indication for each colonoscopy, depth of colonoscope insertion, quality of bowel preparation, and neoplastic findings, including the presence, location, size, number, and histology of adenomas. For this analysis, advanced neoplastic lesions were considered to be carcinomas or adenomas ≥ 10 mm in size, or with villous/tubulovillous features or high-grade dysplasia. Adenoma size was recorded as the measurement estimated by the endoscopist in the colonoscopy report. In rare cases when adenoma size was not specified in the colonoscopy report, adenoma size was obtained from the measurement in the pathology report.

The primary outcome was the prevalence of at least 1 adenoma in patients with melanosis coli compared with controls. We used the Cochran-Mantel-Haenszel test to compare rates of adenoma detection among melanosis cases and matched controls.

To identify factors independently associated with adenoma detection, we performed conditional logistic regression, measuring for the association between melanosis and the presence of at least 1 adenoma, adjusting for colonoscopy indication and quality of bowel preparation. Statistical analysis was performed with Stata 13.1 (StataCorp, College Station, TX). All *P*-values are 2-sided. The Institutional Review Board at Columbia University Medical Center approved this study.

RESULTS

We identified 202 patients with melanosis coli observed on colonoscopies during this time period. For each melanosis patient, we identified 2 nonmelanosis controls, resulting in 404 control subjects and a total sample size of 606 patients.

Baseline characteristics of the melanosis patients and controls are displayed in Table 1. The subjects were predominantly (75.2%) women. The mean age was 61.7 years (SD = 11.9; range, 24 to 93 y). The most common indication for colonoscopy was colorectal cancer screening (40.3%) followed by adenoma surveillance (29.9%); the distribution of indications for colonoscopy was not significantly different between the melanosis and control cohorts ($P = 0.4$). Somewhat more patients in the melanosis cohort underwent colonoscopy for constipation (4.0%) compared with the control group (1.2%), as might be expected given the association of melanosis coli with laxative use. There was no significant difference in the proportion of colonoscopies that reached the cecum (98% for melanosis vs. 97.3% for controls, $P = 0.78$), or the proportion of procedures with poor bowel preparation quality (2.5% for melanosis vs. 4.2% for controls, $P = 0.4$).

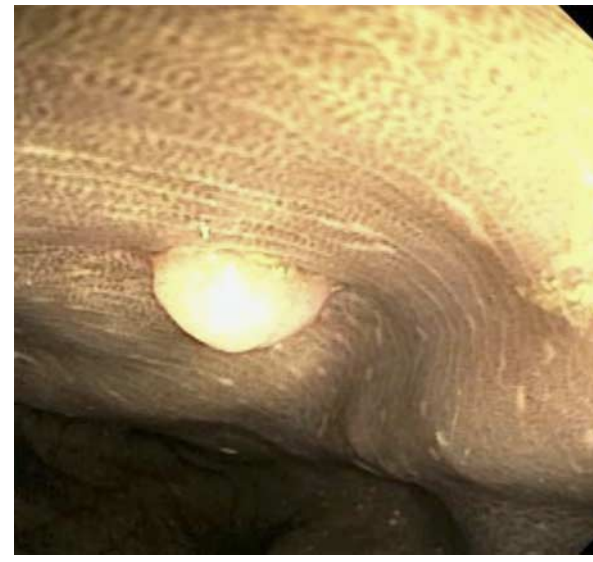

FIGURE 1. Area of melanosis coli containing a tubular adenoma, demonstrating the enhanced ability to detect adenomas in melanosis due to the lack of pigmentation in these lesions. full color online

The neoplastic findings of the melanosis cohort and controls are listed in Table 2. The ADR was 29.2% overall among all patients. The ADR was significantly higher among melanosis coli patients at 34.7%, compared with 26.5% among controls. Using the Cochran-Mantel-Haenszel test to compare melanosis patients against matched controls, there was a significantly higher ADR on univariable analysis for melanosis patients [odds ratio (OR) = 1.52; 95% confidence interval (CI), 1.04-2.24; $P = 0.03$].

The majority of patients with adenomas had only proximal lesions, and there were no significant differences in adenoma location (proximal colon, distal colon, or both) between the melanosis and control groups. However, melanosis patients were significantly more likely to have a single adenoma compared with controls (27.2% of melanosis vs. 17.1% of controls; OR = 1.77; 95% CI, 1.19-2.65; $P = 0.004$). The proportion of patients with 2 or ≥ 3 adenomas was similar between groups. Among patients with at least 1 adenoma, there was no significant difference in the mean number of adenomas per patient (1.4 for melanosis vs. 1.5 for controls, $P = 0.63$).

There was no difference in mean size of the largest adenoma (5.43 mm for melanosis vs. 6.19 mm for controls, $P = 0.35$). However, a significantly higher proportion of the melanosis patients had only small adenomas ≤ 5 mm (24.3% for melanosis vs. 17.1% for controls; OR = 1.62; 95% CI, 1.04-2.51; $P = 0.03$). The proportion of patients

TABLE 1. Baseline Characteristics of the Melanosis Coli Cohort Compared With Controls

Characteristics	All Patients (n = 606)	Melanosis (n = 202)	Controls (n = 404)	*P*
Mean age (y)	61.7 (11.9)	61.8 (11.9)	61.7 (11.9)	0.97
Age [n (%)]				
20-39	18 (3)	6 (3)	12 (3)	0.99
40-49	48 (8)	16 (8)	32 (8)	
50-59	200 (33)	66 (33)	134 (33)	
60-69	168 (28)	58 (29)	110 (27)	
70-79	140 (23)	45 (22)	95 (24)	
≥80	32 (5)	11 (5)	21 (5)	
Gender [n (%)]				
Male	150 (24.8)	50 (24.8)	100 (24.8)	0.92
Female	456 (75.2)	152 (75.2)	304 (75.2)	
Indication [n (%)]				
Screening	244 (40.3)	76 (37.6)	168 (41.6)	0.4
Surveillance	181 (29.9)	64 (31.7)	117 (29)	
Diarrhea	11 (1.8)	1 (0.5)	10 (2.5)	
Constipation	13 (2.1)	8 (4)	5 (1.2)	
Other bowel change	11 (1.8)	3 (1.5)	8 (2)	
Anemia	23 (3.8)	6 (3)	17 (4.2)	
Bleeding	71 (11.7)	28 (13.9)	43 (10.6)	
Other	52 (8.6)	16 (7.9)	34 (8.4)	
Depth of insertion [n (%)]				
Cecum/ileum	588 (97)	198 (98)	393 (97.3)	0.78
Did not reach cecum	18 (3)	4 (2)	11 (2.7)	
Preparation quality [n (%)]				
Poor	22 (3.6)	5 (2.5)	17 (4.2)	0.4
Excellent/good/fair	584 (96.4)	197 (97.5)	387 (95.8)	

with largest adenoma 6 to 9 mm or ≥10 mm was similar between groups. There was also no significant difference in the distribution of histologic diagnoses of adenomas. There was a trend toward more tubular adenomas in the melanosis group (29.7% for melanosis vs. 23.5% for controls; OR = 1.39; $P = 0.09$). An advanced neoplastic lesion was diagnosed in 6.4% of melanosis patients and 5.0% of controls (OR = 1.33; 95% CI, 0.64-2.78; $P = 0.44$).

TABLE 2. Neoplastic Findings in Patients With Melanosis Coli and Controls

Characteristics	Melanosis (n = 202) [n (%)]	Controls (n = 404) [n (%)]	Odds Ratio (95% CI)	*P*
≥1 adenomas	70 (34.7)	107 (26.5)	1.52 (1.04-2.24)	0.028
Location*				
Proximal only	41 (20.3)	62 (15.3)	1.44 (0.91-2.28)	0.11
Distal only	21 (10.4)	28 (6.9)	1.52 (0.85-2.70)	0.15
Proximal and distal	8 (4.0)	17 (4.2)	0.93 (0.38-2.29)	0.88
No. adenomas				
1	55 (27.2)	69 (17.1)	1.77 (1.19-2.65)	0.004
2	9 (4.5)	28 (6.9)	0.62 (0.28-1.35)	0.23
≥3	6 (3.0)	10 (2.5)	1.22 (0.42-3.55)	0.71
Mean number†	1.43	1.5		0.63
Size of largest adenoma				
≤5 mm	49 (24.3)	69 (17.1)	1.62 (1.04-2.51)	0.025
6-9 mm	15 (7.4)	22 (5.4)	1.36 (0.71-2.63)	0.35
≥10 mm	6 (3.0)	16 (4.0)	0.71 (0.26-1.96)	0.52
Mean size of largest adenoma (mm)†	5.43	6.19		0.35
Histology				
Tubular	60 (29.7)	95 (23.5)	1.39 (0.94-2.05)	0.086
Tubulovillous, villous, or high-grade dysplasia	7 (3.5)	6 (1.5)	2.33 (0.78-6.94)	0.12
Sessile serrated adenoma	1 (0.5)	3 (0.8)	0.67 (0.07-6.41)	0.72
Adenocarcinoma	2 (1.0)	3 (0.7)	1.33 (0.22-7.98)	0.75
Advanced neoplastic lesion‡	13 (6.4)	20 (5.0)	1.33 (0.64-2.78)	0.44

*Proximal defined as proximal to the splenic flexure.
†Among patients with at least 1 adenoma.
‡Advanced lesions defined as adenocarcinomas or adenomas ≥10 mm, or with tubulovillous, villous histology or high-grade dysplasia.
CI indicates confidence interval.

On multivariable conditional logistic regression, after adjusting for indication and bowel preparation quality, melanosis coli was independently associated with an increased rate of adenoma detection (OR = 1.56; 95% CI, 1.05-2.33; $P = 0.03$). Indication for colonoscopy was not independently associated with adenoma detection on multivariate analysis, with no significant differences among those undergoing either surveillance (OR = 1.50; 95% CI, 0.85-2.62; $P = 0.16$) or diagnostic (OR = 0.73; 95% CI, 0.39-1.38; $P = 0.33$) colonoscopies compared with screening. There was also no significant difference in adenoma detection among patients with poor compared with adequate preparation quality (OR = 3.56; 95% CI, 0.95-13.29; $P = 0.06$).

We also examined the detection rate of hyperplastic polyps in melanosis patients compared with controls. Hyperplastic polyps were found in 35 of 202 melanosis patients or 17.3%, and 77 of 404 controls or 19.1%. There was no significant difference in hyperplastic polyp detection rate between groups by χ^2 testing ($P = 0.68$).

DISCUSSION

In this analysis of 606 patients undergoing colonoscopy at our institution, we found a significantly higher ADR among melanosis patients compared with controls matched by age, gender, and endoscopist on both univariable and multivariable analysis. The absolute risk difference in ADR was approximately 8% (34.7% for melanosis vs. 26.5% for controls). The reason for this higher detection rate is likely an improved ability to visualize the lighter adenomas on a pigmented background, illustrated in Figure 1. Adenomas themselves are rarely pigmented, although there are reports of melanosis affecting adenomas.[20]

We selected gender, age, and endoscopist for matching because these factors have been significantly associated with ADR. A study of 10,034 colonoscopies performed by 9 gastroenterologists found adenoma prevalence increased from 14.6% at age 30 to 35.2% at age 70.[21] The same study also found that men had more adenomas than women (24.4% vs. 16.6%), and that there was a significantly different rate of adenoma detection between providers, ranging from 15.5% to 41.1%. We therefore chose these variables as matching parameters to minimize the possibility that these were serving as confounders when estimating the association between melanosis and adenoma detection.

Prior research suggests that adenomas are found more frequently in patients with melanosis coli, although these studies have not compared melanosis patients against matched controls. In a retrospective study of 2277 patients undergoing colonoscopy between 1988 and 1991 in Germany, among 4474 colonoscopies performed, Nusko et al[10] found 99 cases (4.3%) of melanosis coli. Adenomas were detected in 53 (53.5%) of these melanosis patients, compared with 25.4% of nonmelanosis patients. The relative risk of adenoma detection in melanosis patients was 2.19 (95% CI, 1.79-2.67). Only 1 (1%) melanosis patient was found to have colorectal carcinoma, compared with 4.7% of the nonmelanosis patients, for a nonsignificant relative risk of 0.22 (95% CI, 0.03-1.53). Compared with this study, we found a similar prevalence of adenomas in the nonmelanosis cohort (26.5% for our study vs. 25.4% for Nusko and colleagues' study). However, Nusko and colleagues found a much higher prevalence of adenomas among the melanosis patients at 53.5%, as compared with 34.7% in our study. Nusko and colleagues did not compare the melanosis patients against matched controls, and did not provide information on the mean age, gender, or colonoscopy indications for the melanosis subset. This raises the possibility that the higher adenoma prevalence in their melanosis patients was due to factors such as older age, predominantly male gender, or higher risk colonoscopy indications.

In a follow-up study published in 1997, Nusko et al[9] analyzed 2229 consecutive colonoscopies at the University of Erlangen and found 102 (4.6%) cases of melanosis coli. Adenomas were found in 441 (19.8%) patients overall, and 35 (34.3%) patients with melanosis, compared with 406 (19.1%) without melanosis. The relative risk was 1.80 (95% CI, 1.26-2.56) for tubular adenoma, and 2.03 (95% CI, 1.09-3.76) for tubulovillous adenoma. Adenomas in the melanosis patients were significantly more likely to be ≤ 5 mm (80.1% vs. 60.0%, $P = 0.0001$). Although the overall prevalence of adenomas in that study was slightly lower than our own (perhaps due to a slightly younger mean age, at 55 y vs. 61.7 y in our study), the adenoma prevalence in the melanosis subset closely matched our own results (34.3% for Nusko and colleagues' study vs. 34.7% in our study). That study compared melanosis patients against unmatched controls. This increases the likelihood that confounders such as age or gender, which are known to be associated with both adenomas and melanosis,[7,8,22,23] could be contributing to increased adenoma detection.

Our study also found that the melanosis cohort had a significantly higher proportion of patients whose largest adenoma was ≤ 5 mm (24.3% vs. 17.1%; OR = 1.62; 95% CI, 1.04-2.51; $P = 0.03$). The melanosis patients were also more likely to have only a single adenoma (27.2% vs. 17.1%; OR = 1.77; 95% CI, 1.19-2.65; $P = 0.004$). The proportion of patients whose largest adenoma was 6 to 9 mm or ≥ 10 mm was similar in melanosis patients and controls. This provides further evidence that melanosis particularly augments the detection of small, difficult-to-identify lesions. Although the mean size of the largest adenoma was smaller in melanosis patients, the difference was small and neither clinically nor statistically significant (5.43 mm for melanosis vs. 6.19 mm for controls, $P = 0.35$).

Our study also examined the prevalence of hyperplastic polyps in melanosis patients and controls. The prevalence was 35 out of 202 or 17.3% among melanosis patients, and 77 out of 404 or 19.1% among controls, with no significant difference between groups ($P = 0.68$). It is possible that hyperplastic polyps were not found more frequently in the melanosis group due to insufficient power to detect a difference. There have also been reports of melanosis in hyperplastic polyps. Coyne[20] describes 10 cases of hyperplastic polyps with melanosis, as well as 2 adenomas with melanosis. Although it seems that melanosis can occur in both adenomas and hyperplastic polyps, it may be more common in hyperplastic polyps, making these lesions less readily visible.

Although it is widely believed that melanosis coli is a benign condition not associated with colorectal cancer, some studies have shown associations of anthraquinone laxatives with mutagenesis in vitro,[24,25] as well as in rats.[26] However, in a prospective case-control study in Germany of 202 patients with colorectal carcinoma, 114 with adenomas, and 238 controls, Nusko et al[13] found no association with anthraquinone laxative use among the carcinoma patients (OR = 1.0; 95% CI, 0.6-1.8) or the adenoma

patients (OR = 1.0; 95% CI, 0.5-1.9). They also found no association between the adenoma patients and endoscopic melanosis coli (OR = 1.5; 95% CI, 0.5-4.9). However, the null association between melanosis and adenomas may have been due to insufficient power, as only 20 patients among all groups were found to have melanosis in that prospective study.

Other than case reports,[27,28] these studies by Nusko et al[9,10,13] are the only ones we are aware of analyzing the relationship between melanosis coli and adenoma detection. Although 2 of these 3 studies showed an increased ADR in melanosis patients, none of the studies compared melanosis patients against matched controls.

Our study has several limitations. It is a single-institution study at a referral center, which may limit its generalizability. The limited sample size of 202 patients with melanosis and 404 controls may have masked a true difference in adenoma size between groups that was not detected due to limited power. Additional variables that could affect ADR, such as colonoscopy withdrawal time and patient race/ethnicity,[29] were not evaluated.

In addition, confounders affecting the prevalence of adenomas are a possibility in a retrospective study, given the modest magnitude of the OR. Whereas we were able to eliminate the most likely confounders for adenoma detection by controlling for age, gender, and endoscopist, other possible factors such as smoking history, family history, obesity, and other comorbidities were not evaluated, as that information was not readily available in the electronic endoscopy database. It is possible that laxative users could be more likely to smoke or be obese. We noted that the melanosis cohort had a higher rate of constipation, which is expected given the association of melanosis with laxative use. Of note, whereas constipation is associated with an increased risk of colorectal cancer, laxative use is not, and may even be associated with a decreased risk.[30,31]

We are also unable to conclusively say whether the increased frequency of adenomas in melanosis patients is due to a true higher prevalence or simply increased detection. As adenomas are lightly colored compared with melanosis, and prior studies have shown no association between melanosis coli and colorectal cancer, we believe improved detection underlies the observed higher frequency. Our results support the hypothesis that melanosis may be functioning as a form of chromoendoscopy, augmenting the ability to detect small lesions that are easily missed. This brings up the possibility that the improvement in ADR could be exploited by inducing a melanosis-like effect in patients before colonoscopy.

The demonstration that differential uptake of dye between healthy colonocytes and adenomas can enhance ADR has potentially important implications. It has been estimated that every 1% increase in ADR leads to a 3% decrease in interval colon cancer and a 5% reduction in colorectal cancer mortality.[32] Although chromoendoscopic sprays such as methylene blue and indigo carmine are available to enhance ADR during colonoscopy, they require specialized equipment, training, and prolong endoscopy, all features that may discourage widespread adoption. A dye that can produce a similar effect by ingestion before or during a bowel preparation could be a powerful tool, with potential to enhance the ADR of many, if not most endoscopists. Identification of an ideal agent could be an attractive target for future research and development efforts.

In conclusion, we found that the presence of melanosis coli was associated with a significant increase in adenoma detection compared with age, gender, and endoscopist matched controls on both univariable and multivariable analysis. Melanosis patients were more likely than controls to have only small, solitary adenomas. To our knowledge, this is the largest study analyzing adenoma prevalence in melanosis coli, as well as the only one to compare melanosis patients against matched controls. Although it would not be advisable to encourage the use of anthraquinone laxatives to induce melanosis coli to improve adenoma detection, providers who measure and monitor colonoscopy quality should be aware that the presence of melanosis coli may be positively affecting adenoma detection. Future efforts to identify bowel preparation agents that induce a similar effect could improve ADRs during colonoscopy.

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