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Association Between Smoking Status and Prevalence of Advanced Outcomes in Patients With and Without Positive Stool Test Prior to Colonoscopy: Data from the New Hampshire Colonoscopy Registry

Joseph C. Anderson^{1,5}, William M. Hisey^{2,3}, Christina M. Robinson^{2,3}, Paul J. Limburg⁴, Bonny L. Kneedler⁴, Lynn F. Butterly^{1,2,3}

¹Geisel School of Medicine at Dartmouth, Hanover, NH, USA

²Department of Medicine, Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

³NH Colonoscopy Registry, Lebanon, NH, USA

⁴Exact Sciences Corporation, Madison, WI, USA

⁵White River Junction VAMC, 163 Veterans Dr, White River Junction, VT 05009, USA

Abstract

Background and Aims: Our goal was to examine the association between smoking status (current, former, and never) and prevalence of advanced findings in patients with colonoscopy after a positive multi-target stool DNA test (mt-sDNA), patients with colonoscopy after a positive Fecal Immunochemical Test (FIT), and patients with colonoscopy only (no prior stool test).

Methods: Our main outcome was prevalence of advanced lesions (any colorectal cancer (CRC), advanced adenoma, or advanced serrated polyp). We also looked at advanced adenomas and advanced serrated polyps separately. We performed logistic regressions comparing findings by smoking status within mt-sDNA + , FIT + , and colonoscopy-only patients, adjusting for age, sex, and CRC risk. We also performed logistic regressions within all current smokers comparing outcome odds between each screening method cohort.

Joseph C. Anderson joseph.c.anderson@dartmouth.edu.

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Declarations

Conflict of interest Dr. Limburg serves as Chief Medical Officer for Screening at Exact Sciences and holds stock in the company. Prior to his direct employment, Dr. Limburg worked with Exact Sciences through a contracted services agreement with Mayo Clinic. Exact Sciences provided funding support for this analysis to the New Hampshire Colonoscopy Registry (staffed by L. Butterly, W. Hisey, and C. Robinson). The funding agreement ensured that the NHCR authors had independence in designing the study, conducting analyses, and writing and publishing the results.

Disclosures P.J.L. serves as Chief Medical Officer for Screening at Exact Sciences through a contracted services agreement with Mayo Clinic. P.J.L. and Mayo Clinic have contractual rights to receive royalties through that agreement. The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government.

Results: Our sample included 967 mt-sDNA + , 498 FIT + , and 58,682 colonoscopy-only patients. Within the FIT + (OR = 2.46; 95%CI 1.16–5.26) and mt-sDNA + (OR = 1.65; 95%CI 1.05–2.59) groups, current smokers had higher odds of advanced serrated polyps than never-smokers (reference). In addition, FIT + current smokers (OR = 1.97; 95%CI 1.11–3.50) or mt-sDNA (OR = 3.27; 95%CI 2.25–4.74) current smokers had higher odds of advanced lesions than colonoscopy-only smokers (reference).

Conclusions: Within stool-test-positive patients, current smokers have higher odds of advanced serrated polyps than never-smokers, reinforcing the heightened importance of a follow-up colonoscopy in smokers with positive stool tests. We also found higher yields of advanced outcomes in FIT + and mt-sDNA + smokers vs. smokers who underwent colonoscopy without a prior stool test. Endoscopists need to be particularly vigilant in detecting advanced serrated polyps in patients who smoke and have a positive stool test.

Keywords

Colonoscopy; Screening; Smoking; Polyps

Introduction

The fecal immunochemical test (FIT) and the multi-target stool DNA (mt-sDNA) test are commonly used stool-based colorectal cancer (CRC) screening tests and have been recommended for screening by several societies [1–3]. Both FIT and mtsDNA tests are recommended for screening in the US; however, in Europe only FIT is recommended. Both tests are associated with increased polyp yield at colonoscopy and enhance CRC screening by identifying patients with higher polyp risk [4–8]. FIT and mt-sDNA tests detect different markers; past research has found differences in serrated and adenomatous polyp detection between the two tests [6, 7, 9, 10].

Differences in patient population risk factors also influence adenoma and serrated polyp yield. In the general colonoscopy screening population, for example, smoking has been linked with an increased risk for serrated polyps [11–14] and higher rates of conventional adenomas [11–16]. It is unknown, however, whether this association persists in a stool-test-positive population. There is no prior research on polyp yield in patients who smoke and have a colonoscopy after a positive stool test. Does smoking confer an additive risk beyond that of a stool-test-positive population, or is the prevalence of advanced findings in stool-test-positive patients unaffected by smoking status? Clarifying this risk could inform endoscopists' expectations of polyp yield in stool-test-positive patients who smoke.

In this analysis, we examined the association between smoking status (current, former, and never) and prevalence of advanced findings (advanced lesions, advanced adenoma, and advanced serrated polyps) in patients with colonoscopy after a positive mt-sDNA test, patients with colonoscopy after a positive FIT, and patients with colonoscopy only, without a prior stool test.

We compared findings between smoking categories within each study cohort (mt-sDNA + , FIT + , and colonoscopy only) and also compared findings between all three study cohorts

in our sub-sample of current smokers. We used data from the New Hampshire Colonoscopy Registry (NHCR), a statewide, population-based registry.

Materials and Methods

Data Collection and Population

The New Hampshire Colonoscopy Registry (NHCR) collects demographic, lifestyle, medical, and family history data from patients undergoing colonoscopies in centers across New Hampshire. Procedure information is collected by endoscopists and endoscopy nurses during or immediately following the exam, including exam indication, completion status, quality of bowel preparation, and polyp information including the location and size for all polyps. Pathology outcomes are abstracted by trained NHCR staff who match data from pathology reports to polyp-level findings recorded by the endoscopist or nurse during the exam.

All data collection and study procedures were approved by the Committee for the Protection of Human Subjects at Dartmouth College (CPHS#00015834) in accordance with the Belmont Report and the US Common Rule.

Study Cohorts

Using an IRB-approved protocol, Exact Sciences Laboratories, LLC (Madison, Wisconsin) provided the NHCR with patient identifiers of all patients with positive mt-sDNA tests within the NHCR catchment area (New Hampshire, Vermont, Maine and Massachusetts) between 2/1/2015 and 12/31/2022. We included all patients with a positive stool test (mt-sDNA or FIT) and a complete colonoscopy with adequate bowel preparation recorded in the NHCR. We also included a reference group of individuals having a complete screening or surveillance colonoscopy with adequate bowel preparation without a previous stool test during the same time period. We excluded exams performed on patients < 50 years old (as per the CRC screening guidelines during the time frame of the study), and also those performed for Inflammatory Bowel Disease (IBD) or a genetic syndrome such as Lynch Syndrome.

Our study cohort included 967 individuals with an mt-sDNA + result and a subsequent colonoscopy in the NHCR database and 498 individuals with positive FIT tests during the same time interval and a subsequent colonoscopy in the NHCR database. All stool tests and colonoscopies were performed as part of usual clinical care. We had a cohort of 58,682 patients who had screening or surveillance colonoscopy without a preceding positive stool test. We also performed a sensitivity analysis using a sub-sample restricted to exams indicated for screening or in average-risk screening-equivalent patients, which included 754 mt-sDNA + patients, 360 FIT + patients, and 31,122 colonoscopy-only patients.

Outcomes

Our outcomes were the prevalence of advanced lesions, advanced adenomas, and advanced serrated polyps. Advanced lesions were defined as any CRC, advanced adenoma, or advanced serrated polyp. Advanced adenomas were defined as any adenomas either ≥ 1

cm, with > 25% villous elements, or with high-grade dysplasia. Advanced serrated polyps were defined as any Hyperplastic Polyp (HP) $\geq$ 1 cm, any Sessile Serrated Polyp (SSP), or any Traditional Serrated Adenoma (TSA).

Exposure Variable

Our exposure variable was the smoking status of the patient. We defined smoking status as current, former, and never.

Other Factors Examined

We also compared patient characteristics, including demographic factors (e.g., age, sex, race), health behaviors (e.g., smoking status, Body Mass Index, overall health status), and history of prior colonoscopy or neoplasia across study cohorts and smoking groups.

Statistical and Analytic Approach

We calculated the prevalence of each polyp outcome (advanced lesions, advanced adenomas, and advanced serrated polyps) across never-smokers, former smokers, and current smokers within the mt-sDNA + , FIT + , and colonoscopy-only cohorts. We then ran logistic regressions within each study cohort comparing the odds of each polyp outcome by smoking status, adjusting for patient age, sex, and CRC risk which is defined as a personal history of polyps and/or personal/family history of CRC. Finally, in order to evaluate whether polyp yield differs within current smokers by stool test status, we restricted our sample to current smokers and ran logistic regressions comparing the odds of each polyp outcome between the colonoscopy-only, FIT + , and mt-sDNA + cohorts, again adjusting for patient age, sex, and CRC risk. We repeated this analysis for a sub-sample restricted to screening or average-risk screening-equivalent exams.

Data Availability

Data were collected by the authors. The non-protected health information data used in the analyses are available upon reasonable request.

Results

Our sample included 967 mt-sDNA + patients, 498 FIT + patients, and 58,682 colonoscopy-only patients. Demographic and behavioral characteristics are shown in Table 1.

Table 2 contains the prevalence (and 95% CI) of each polyp outcome by study cohort and smoking status. We found that mt-sDNA + patients generally had the highest prevalence of advanced lesions and advanced serrated polyps, and that within each study cohort, current smokers generally had the highest prevalence of each polyp outcome. We found less variation in advanced adenoma prevalence by smoking status in mt-sDNA + and FIT + patients in our screening-only sensitivity analysis (Supplemental Table 1).

Table 3 contains adjusted odds ratios and 95% CIs for our within-screening-cohort logistic regressions. In line with prior research demonstrating an association between smoking and an increased risk of CRC, we found that among colonoscopy-only patients, odds of all three

outcomes increased significantly along smoking status categories (from never to former to current). Among positive stool test patients, however, we found no significant differences in the odds of advanced adenomas by smoking status but did find that current smokers had significantly higher odds of advanced serrated polyps compared to never-smokers in mt-sDNA + patients and compared to both never- and former smokers in FIT + patients. We found similar results in our sensitivity analysis except in the case of advanced serrated polyp odds among mt-sDNA + patients, where we did not find any significant relationships with smoking status (Supplemental Table 2).

Table 4 contains adjusted odds ratios and 95% CIs for our logistic regressions comparing polyp odds by study cohort within current smokers. We found that FIT + (OR = 1.97; 95%CI 1.11–3.50) and mt-sDNA + patients (OR = 3.27; 95%CI 2.25–4.74) had higher odds of advanced lesions, as well as of advanced adenomas and advanced serrated lesions, than the colonoscopy-only group. In our sensitivity analysis, we found that mt-sDNA + patients had significantly higher odds of all outcomes compared to colonoscopy-only patients, while FIT + patients had significantly higher odds of advanced serrated polyps only (Supplemental Table 3).

Discussion

Smoking has been shown in many studies to be associated with an increased risk for conventional adenomas as well as serrated polyps [11–16]. Positive stool tests are associated with a higher yield of polyps at the first follow-up colonoscopy performed for the positive stool test compared to colonoscopies with no previous stool tests [4, 5, 7]. Our analysis included patients with a positive fecal immunochemical test (FIT) or multi-target stool DNA test (mt-sDNA). Both tests have an antibody to hemoglobin and thus can detect lesions that bleed, including cancer and large conventional adenomas [17]. The multi-target stool DNA test has additional markers for methylation mutations which are observed in serrated polyps. The goal of our study was to examine outcomes for patients with positive stool tests, as stratified by their smoking status. Patients were stratified into current, former, and never smoking groups.

As expected, we found that polyp odds increased significantly with smoking in the colonoscopy-only cohort, but we found fewer significant differences by smoking status within patients with positive stool tests. In particular, we found no significant difference in advanced adenoma odds by smoking status in either FIT + or mt-sDNA + patients. One possible explanation for this finding is that the baseline level of advanced adenoma risk in stool-test-positive never-smokers is high enough that there is no additional risk for advanced adenomas conferred by smoking status in stool-test-positive patients.

However, we did find that smokers had a higher risk for advanced *serrated polyps* than never-smokers in the FIT + and mt-sDNA + cohorts; the effect for the FIT + cohort persisted in our screening-only sensitivity analysis. The association between smoking and serrated polyp odds appears to persist after a positive stool test. There are several possible explanations for this result. One is that smoking may be more strongly associated with serrated polyp odds, so that smoking still confers additional polyp risk even after a positive

mt-sDNA test. In FIT + patients, the explanation may be simpler. While the mt-sDNA test detects markers associated with serrated polyps, the FIT is designed to detect blood from cancers and large adenomas. The relationship between smoking and serrated polyp odds in FIT + patients therefore could be similar to that found in colonoscopy-only patients, since neither cohort has been meaningfully screened for serrated polyps prior to colonoscopy. One consequence of this relationship is that FIT + current smokers may have a substantially higher risk of advanced serrated polyps than would be typically associated with a positive FIT in a non-smoking population, given the low sensitivity of FIT in detecting serrated polyps.

We also examined the current smokers separately as a subgroup (Table 4) and observed that the odds of all three outcomes were significantly higher in patients with positive stool tests compared to the colonoscopy-only cohort; the mt-sDNA association persisted for all outcomes and the FIT + association persisted for advanced serrated polyps in our screening-only sensitivity analysis. However, we did not find significant differences in outcome odds between the two positive stool test cohorts in this subgroup analysis.

Our results have important implications for practicing physicians. When stool tests are used to screen patients, our data suggest that smokers are at increased risk for advanced serrated polyps even among patients with positive stool tests. In our analysis, 1/3 of all smokers with a positive mt-sDNA test had an advanced serrated polyp. Thus, our data demonstrate the elevated risk for patients who smoke and have positive stool tests. Although all patients with a positive stool should have a colonoscopy as follow-up, these data further underscore the importance of smokers having a colonoscopy after a positive stool test, especially for those who have a positive stool test and are declining a follow-up colonoscopy. This is an important message for frontline physicians or providers who order these tests.

Another implication for practicing endoscopists is that smokers with positive stool tests have a high prevalence of advanced lesions, both conventional adenomas and serrated polyps. Current smokers in both positive stool test cohorts had at least a twofold increase in advanced adenoma and advanced serrated polyp odds relative to current smokers without a prior stool test. We also found that current smokers in every study cohort had a higher risk for advanced serrated polyps than never-smokers. For FIT + patients especially, endoscopists need to be just as vigilant in looking for advanced serrated polyps as they are in detecting the advanced conventional adenomas which are more typically associated with FIT + patients.

An important strength of our analysis is that our data are collected from patients who had received stool tests as part of their usual clinical care. In addition, NHCR data are collected from many community and academic settings, and they may better represent real-world practice than a single institutional trial, and thus be more generalizable. However, our analysis does have certain limitations. We do not have data on time since cessation for former smokers; this population may contain patients at varied levels of risk. Although there are data to support the concept that self-reporting of smoking history can be reliable, we acknowledge that this may be a limitation [18]. Additionally, our positive stool test cohorts have smaller sample sizes than our colonoscopy-only cohort, which may result in less precision in our estimates than would be suggested by our overall sample size.

In summary, we observed that FIT + and mt-sDNA + patients who currently smoke have higher yields of advanced serrated polyps than stool-test-positive patients who never smoked. Furthermore, FIT + and mt-sDNA + patients who currently smoke have higher yields of advanced outcomes than current smokers without a prior stool test. When patients are screened with stool tests, these data underscore the importance of follow-up colonoscopies in patients with positive stool tests, especially for patients who smoke. Endoscopists need to be vigilant in detecting advanced serrated polyps in patients who smoke and have a positive stool test.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

No datasets were generated or analyzed during the current study.

Abbreviations

AA	Advanced adenoma
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
FIT	Fecal immunochemical test
HgB	Hemoglobin
HP	Hyperplastic polyp
IBD	Inflammatory bowel disease
IRB	Institutional review board
OR	Odds ratio
SD	Standard deviation

SP	Serrated polyp
SSP	Sessile serrated polyp
TSA	Traditional serrated adenoma
USMSTF	United States Multi-Society Task Force on Colorectal Cancer
USPSTF	United States Preventive Services Task Force

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Table 1

Patient characteristics by smoking status for each study cohort

Colonoscopy-only patients	Never smoker (N = 33,050; 56.3%)			Former smoker (N = 21,458; 36.6%)			Current smoker (N = 4174; 7.1%)		
	N	Mean	%/SD	N	Mean	%/SD	N	Mean	%/SD
Age (continuous)	60,66		7.8	63,32		8.1	59,07		6.8
Patient sex									
Male	15,630		47.3	10,828		50.5	2098		50.3
Female	17,420		52.7	10,630		49.5	2076		49.7
Increased CRC risk	14,283		43.2	11,286		52.6	1991		47.7
Patient race									
Caucasian	30,576		96.6	19,987		97.2	3802		96.1
Other	1084		3.4	567		2.8	153		3.9
BMI categories									
Non-obese (BMI < 30)	19,246		64.5	11,092		58.3	2314		63.3
Obese (BMI ≥ 30)	10,603		35.5	7932		41.7	1343		36.7
# Cigarettes/day									
10 or fewer	0		0	7287		37.4	1589		40.2
11–20	0		0	7942		40.8	1710		43.2
21–30	0		0	3081		15.8	517		13.1
31 or more	0		0	1172		6.0	139		3.5
FIT + patients	(N = 235; 47.2%)			(N = 211; 42.4%)			(N = 52; 10.4%)		
	N	Mean	%/SD	N	Mean	%/SD	N	Mean	%/SD
Age (continuous)	65.86		9.2	68.28		8.0	61.86		7.5
Patient sex									
Male	108		46.0	109		51.7	31		59.6
Female	127		54.0	102		48.3	21		40.4
Increased CRC risk	59		25.1	66		31.3	13		25.0
Patient race									
Caucasian	224		97.8	184		94.4	51		100.0

Colonoscopy-only patients	Never smoker		Former smoker		Current smoker	
	(N = 33,050; 56.3%)		(N = 21,458; 36.6%)		(N = 4174; 7.1%)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Other	5	2.2	11	5.6	0	0.0
<i>BMI categories</i>						
Non-obese (BMI < 30)	136	63.8	108	57.4	26	57.8
Obese (BMI > = 30)	77	36.2	80	42.6	19	42.2
<i># Cigarettes/day</i>						
10 or fewer	0	0	66	35.3	15	29.4
11–20	0	0	76	40.6	25	49.0
21–30	0	0	41	21.9	9	17.6
31 or more	0	0	4	2.1	2	3.9
mt-sDNA + patients						
	(N = 444; 45.9%)		(N = 403; 41.7%)		(N = 120; 12.4%)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Age (continuous)	66.27	7.9	66.95	7.8	62.45	6.8
<i>Patient sex</i>						
Male	164	36.9	189	46.9	50	41.7
Female	280	63.1	214	53.1	70	58.3
Increased CRC risk	100	22.5	88	21.8	25	20.8
<i>Patient race</i>						
Caucasian	401	96.6	374	97.7	109	97.3
Other	14	3.4	9	2.3	3	2.7
<i>BMI categories</i>						
Non-obese (BMI < 30)	255	65.2	200	55.2	63	63.0
Obese (BMI > = 30)	136	34.8	162	44.8	37	37.0
<i># Cigarettes/day</i>						
10 or fewer	0	0	137	39.5	48	42.9
11–20	0	0	133	38.3	49	43.8
21–30	0	0	59	17.0	9	8.0
31 or more	0	0	18	5.2	6	5.4

Increased CRC Risk: a personal history of polyps and/or a personal/family history of colorectal cancer

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Percent missing: never smoker / former smoker / current smoker: *Colonoscopy only:* Race: 4.2, 4.2, 4.2, 5.2%; BMI: 9.7, 11.3, 12.4%; # cigarettes/ day: 9.2% former smokers, 5.2% current smokers; *FIT +:* Race: 2.6, 7.6, 1.9%; BMI: 9.4, 10.9, 13.5%; # cigarettes/day: 11.4, 1.9%; *mt-sDNA +:* Race: 6.5, 5.0, 6.7%; BMI: 11.9, 10.2, 16.7%; # cigarettes/day: 13.9% former; 6.7% current

Table 2

Prevalence of polyp outcomes by study cohort and smoking status

	mt-sDNA +					FIT +					Colonoscopy only				
	N with outcome	N	% with outcome	95% CI lower	95% CI upper	N with outcome	N	% with outcome	95% CI low	95% CI up	N with outcome	N	% with outcome	95% CI lower	95% CI upper
Advanced lesion	164	444	36.9	32.4	41.6	71	235	30.2	24.4	36.5	3984	33,050	12.1	11.7	12.4
	164	403	40.7	35.9	45.7	45	211	21.3	16.0	27.5	3061	21,458	14.3	13.8	14.7
	58	120	48.3	39.1	57.6	19	52	36.5	23.6	51.0	876	4174	21.0	19.8	22.3
Advanced adenoma	78	444	17.6	14.1	21.4	41	235	17.4	12.8	22.9	1503	33,050	4.5	4.3	4.8
	83	403	20.6	16.8	24.9	26	211	12.3	8.2	17.5	1277	21,458	6.0	5.6	6.3
	24	120	20.0	13.3	28.3	10	52	19.2	9.6	32.5	388	4174	9.3	8.4	10.2
Advanced serrated polyp	97	444	21.8	18.1	26.0	28	235	11.9	8.1	16.8	2645	33,050	8.0	7.7	8.3
	95	403	23.6	19.5	28.0	22	211	10.4	6.7	15.4	1924	21,458	9.0	8.6	9.4
	40	120	33.3	25.0	42.5	13	52	25.0	14.0	38.9	551	4174	13.2	12.2	14.3

Table 3

Adjusted logistic regression results—comparing odds of advanced lesions, advanced adenomas, and advanced serrated lesions between smoking groups within each study cohort

Comparison	Advanced lesions			Advanced adenomas			Advanced serrated		
	OR	95% CI lower bound	95% CI upper bound	OR	95% CI lower bound	95% CI upper bound	OR	95% CI lower bound	95% CI upper bound
<i>Colonoscopy after positive mt-sDNA</i>									
Former smoker vs. never smoker (ref)	1.17	0.89	1.55	1.14	0.80	1.62	1.17	0.85	1.63
Current smoker vs. never smoker (ref)	1.47	0.97	2.22	1.09	0.65	1.83	1.65	1.05	2.59
Current smoker vs. former smoker (ref)	1.25	0.82	1.90	0.95	0.57	1.61	1.41	0.89	2.22
<i>Colonoscopy after positive FIT</i>									
Former smoker vs. never smoker (ref)	0.59	0.38	0.91	0.62	0.36	1.06	0.86	0.47	1.57
Current smoker vs. never smoker (ref)	1.38	0.72	2.62	1.19	0.54	2.60	2.46	1.16	5.26
Current smoker vs. former smoker (ref)	2.34	1.19	4.61	1.92	0.84	4.42	2.86	1.29	6.35
<i>Comparison after colonoscopy only</i>									
Former smoker vs. never smoker (ref)	1.18	1.12	1.24	1.23	1.14	1.33	1.13	1.06	1.20
Current smoker vs. never smoker (ref)	1.93	1.77	2.09	2.17	1.93	2.44	1.72	1.56	1.90
Current smoker vs. former smoker (ref)	1.64	1.50	1.78	1.76	1.56	1.99	1.53	1.38	1.69

Advanced adenomas = high-grade dysplasia or any adenoma > 1 cm or with > 25% villous elements

Any advanced lesion = Colorectal cancer, advanced adenoma, or advanced serrated polyp

Advanced serrated polyp = Sessile Serrated Polyp (SSP), any Traditional Serrated Adenoma (TSA) or Hyperplastic polyps (HP) > 1

Table 4

Adjusted logistic regression results—comparing polyp outcome odds between study cohorts WITHIN current smokers

	OR	95% CI lower bound	95% CI upper bound
<i>Any advanced lesion</i>			
FIT + vs. colonoscopy only (reference)	1.97	1.11	3.50
mt-sDNA + vs. colonoscopy-only (reference)	3.27	2.25	4.74
mt-sDNA + vs. FIT + (reference)	1.66	0.85	3.24
<i>Advanced adenoma</i>			
FIT + vs. colonoscopy only (reference)	2.06	1.02	4.17
mt-sDNA + vs. colonoscopy-only (reference)	2.34	1.46	3.76
mt-sDNA + vs. FIT + (reference)	1.14	0.50	2.61
<i>Advanced serrated polyp</i>			
FIT + vs. colonoscopy only (reference)	2.11	1.11	3.99
mt-sDNA + vs. colonoscopy-only (reference)	3.08	2.07	4.58
mt-sDNA + vs. FIT + (reference)	1.46	0.70	3.04