Mucin 5AC as a Biomarker for Sessile Serrated Lesions: Results From a Systematic Review and Meta-Analysis

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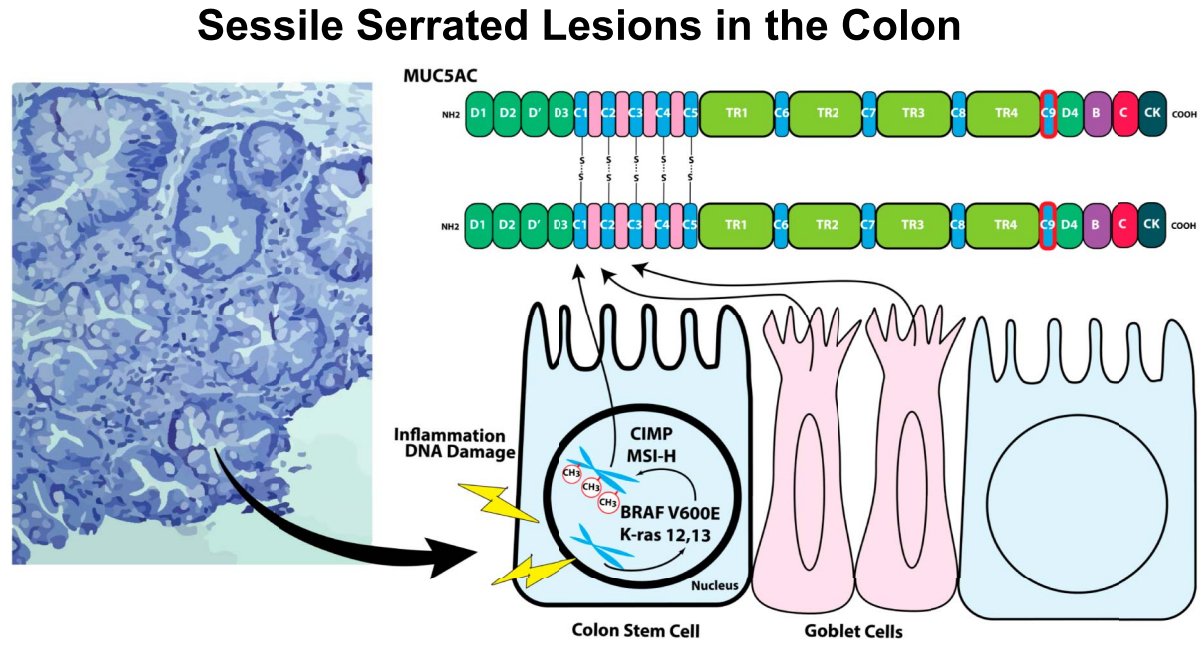
INTRODUCTION: **Sessile serrated lesions (SSLs) are a class of colon polyps challenging to detect through current screening methods but highly associated with colon cancer. To improve detection, we sought a biomarker sensitive for SSLs. Recent endoscopic and histopathologic studies suggest that SSLs are associated with alterations in intestinal mucin expression, but the frequency with which this occurs is not known.**

METHODS: **We performed a meta-analysis of available pathologic studies comparing mucin expression on SSLs to normal colonic mucosa, tubular adenomas, villous adenomas, traditional serrated adenomas (TSAs), and hyperplastic polyps (HPs). We searched Medline, Pubmed, and Embase and found 440 publications in this topic, and 18 total studies met inclusion.**

RESULTS: **We found that MUC5AC expression was more common in SSLs compared to normal colonic mucosa (OR = 82.9, $P < 0.01$), tubular adenoma (OR = 11, $P < 0.01$), and TSAs (OR = 3.6, $P = 0.04$). We found no difference in MUC5AC expression between SSLs versus HPs (OR = 2.1, $P = 0.09$) and no difference in MUC5AC expression between left colon and right colon HPs, with an OR = 1.8, $P = 0.23$.**



Liu et al. *Clin Trans Gastroenterol. 2025*. doi:10.14309/ctg.0000000000000831

Clinical and Translational GASTROENTEROLOGY

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Received August 2, 2024; accepted February 18, 2025; published online March 20, 2025

DISCUSSION: **We found that MUC5AC expression was found commonly on villous adenoma, SSLs, and TSAs while the frequency on colon cancers declined. MUC5AC is also upregulated in inflammatory bowel disease and in response to intestinal infections. MUC5AC expression highlights the potential of mucins as useful biomarkers, though not specific to SSLs. Further research into the clinical utility of MUC5AC as a pathologic or fecal biomarker could enhance SSL detection.**

KEYWORDS: sessile serrated lesions; biomarker discovery; meta-analysis; colon polyps; mucin 5AC

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B291, http://links.lww.com/CTG/B292

Clinical and Translational Gastroenterology 2025;16:e00831. https://doi.org/10.14309/ctg.0000000000000831

INTRODUCTION

In the United States and globally, populations have benefitted greatly from colon cancer screening efforts, with fecal immunochemical testing, colonoscopy, and computed tomographic colonography, the most widely used tests (1). A significant improvement in morbidity and mortality comes from the ability to detect and remove colon polyps (2,3), neoplastic lesions in the colon which are precursors to high-risk dysplasia, or cancer. Colon polyps are defined by histopathology as hyperplastic polyps (HPs), tubular adenomas (TAs), villous adenomas (VAs), or sessile serrated lesions (SSLs) and provide prognostic information on an individual risk of cancer (4).

Detecting colon polyps is a major goal of colonoscopy (5); however, SSLs in particular have evaded currently available screening methods (6). SSLs are thought to account for 15%–25% of colorectal cancers (7) and are thought to arise either from a rapid carcinoma sequence or missed lesions not visualized during colonoscopy (8,9). SSLs are typically right-sided lesions, morphologically flat, with histological features of dilated, mucin-filled, serrated crypts (10). SSLs display reduced expression of mismatch repair proteins MLH1 and are associated with mutations in *BRAF* or *KRAS* (11). SSLs were differentiated pathologically from HPs in 2003, and the World Health Organization criteria for the pathological diagnosis of SSLs was updated recently (4,12).

Previous efforts to improve the detection of SSLs in the colon have included methods to examine methylation patterns in DNA (13–16), chromoendoscopy with narrow band imaging (17), color enhancement (18,19), and novel artificial intelligence approaches (20). Despite these efforts, no single modality has gained acceptance because of cost and modest sensitivity (15). We hypothesized that a biomarker akin to the widely available fecal immunochemical testing, would be a reasonable marker for SSL development. To search for a biomarker of SSLs, we performed a meta-analysis of immunohistochemical studies and found numerous studies examining an altered pattern of mucin expression on the surface of SSLs. Our findings support that the mucin MUC5AC is a potential surface marker of SSLs.

Mucins are glycoproteins expressed on the surface of colon epithelium, secreted either by enterocytes or goblet cells (Figure 1), forming a dual layer of protective proteins for epithelial cells (21). The normal colon secretes mucins MUC1, MUC2, and MUC3 in a membrane-bound or unbound form (22,23). However, endoscopists (24,25) and pathologists (26) have noted abnormalities in the mucin expression pattern on polyps and colon cancers, and this pattern remains a criterion for detection of SSLs. Although MUC5AC is typically expressed on surface and pit epithelia of gastric mucosa (27) as well as airway epithelia (28,29), aberrant mucin expression in the colon is thought to arise from the same genetic alterations, which cause colon cancer (24,30).

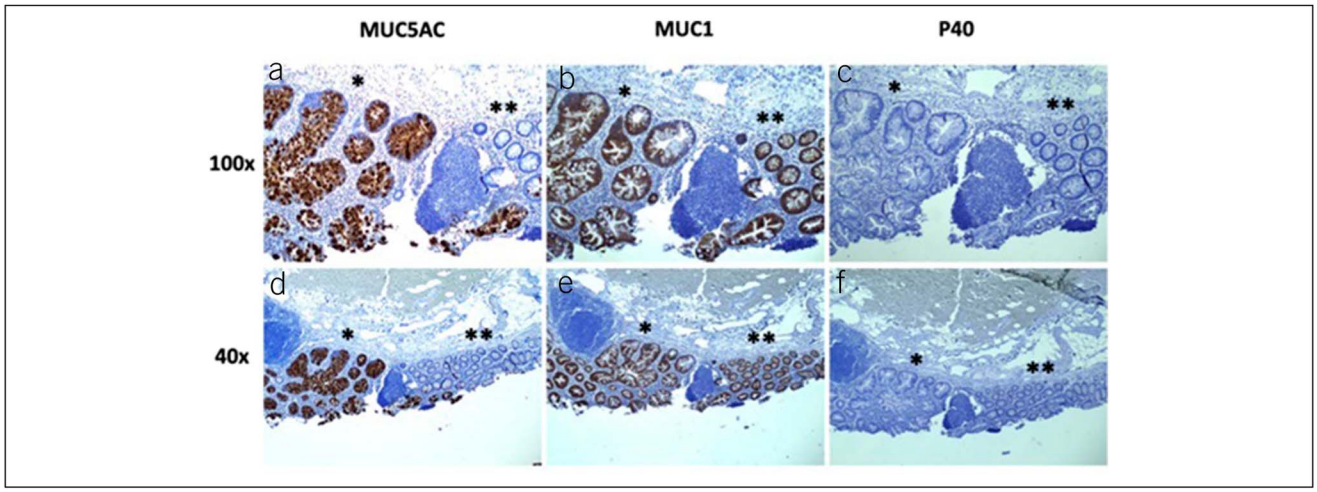

Figure 1. Expression of MUC5AC in a sessile serrated lesion without dysplasia from the ascending colon. The lesion was stained with MUC5AC (**a** and **d**), MUC1 (**b** and **e**), and P40 (**c** and **f**) and photographed at ×100 (**a**, **b**, and **c**) and ×40 (**d**, **e**, and **f**). MUC5AC was expressed in serrated glands (*) but not in nearby normal glands (**) (**a** and **d**). MUC1 was expressed in both serrated glands and normal glands (**b** and **d**). P40 was not expressed in either serrated or normal glands.

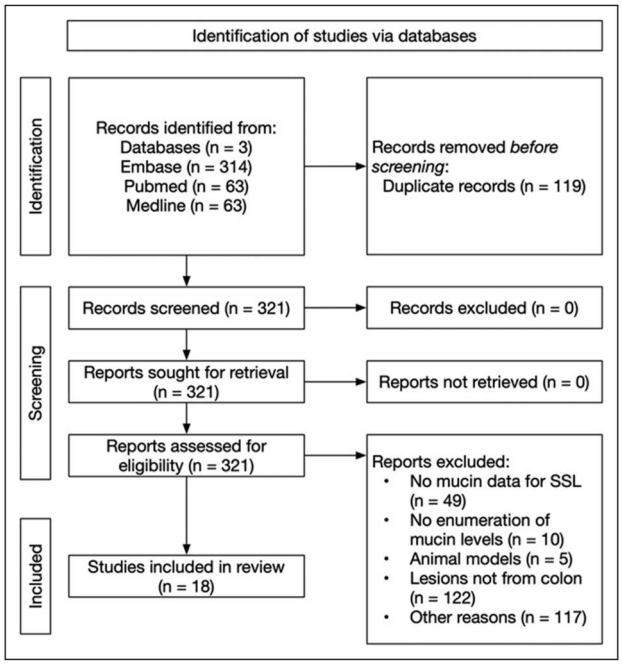

Figure 2. Flowchart of inclusion and exclusion criteria for studies.

In this study, we examined the mucin expression pattern across colon polyps by histopathologic subtype. We find that MUC5AC is a surface marker highly expressed on the surface of SSLs, though it is not specific to serrated pathway lesions.

METHODS

A total of 3 databases including Embase, Pubmed, and Medline were searched from inception to November 2023. A search strategy using the search criteria "mucin" AND "immunohistochemistry" AND "polyp" to identify studies reporting mucin expression in colonic polyps. Peer-reviewed journal articles but not conference abstracts were included in the analysis.

Observational retrospective studies and case series were included for full review if they were human studies that reported at least colonic sessile serrated lesion pathology subtypes and the number of colonic polyps associated with mucin positivity. For a study to be included in a mucin expression comparison group, the authors must report mucin expression in polyp subtypes compared. Other reasons for exclusion were if they were written in a language other than English, were conference abstracts, or reported insufficient data to calculate odds ratios (ORs).

The primary outcome assessed was the expression of mucins on the surface of SSLs compared with normal mucosa, TAs, TSAs, and HPs. Secondary outcomes included the expression of mucins in proximal HPs vs distal HPs. Studies included are listed in Supplementary Table 1 (see Supplementary Digital Content 2, http://links.lww.com/CTG/B292) (31–49).

Full texts were reviewed by 2 study authors (K.L. and M.S.). Data were extracted from the full text by 1 author (either K.L. or M.S.) and confirmed by an alternative author (either K.L. or M.S.). Conflicts were resolved by discussion and consensus, with a senior author (G.Q. or V.P.) serving as the final arbiter if consensus was not achieved.

A random-effects meta-analysis was used because of the initial assumption of heterogeneity among the individual studies.

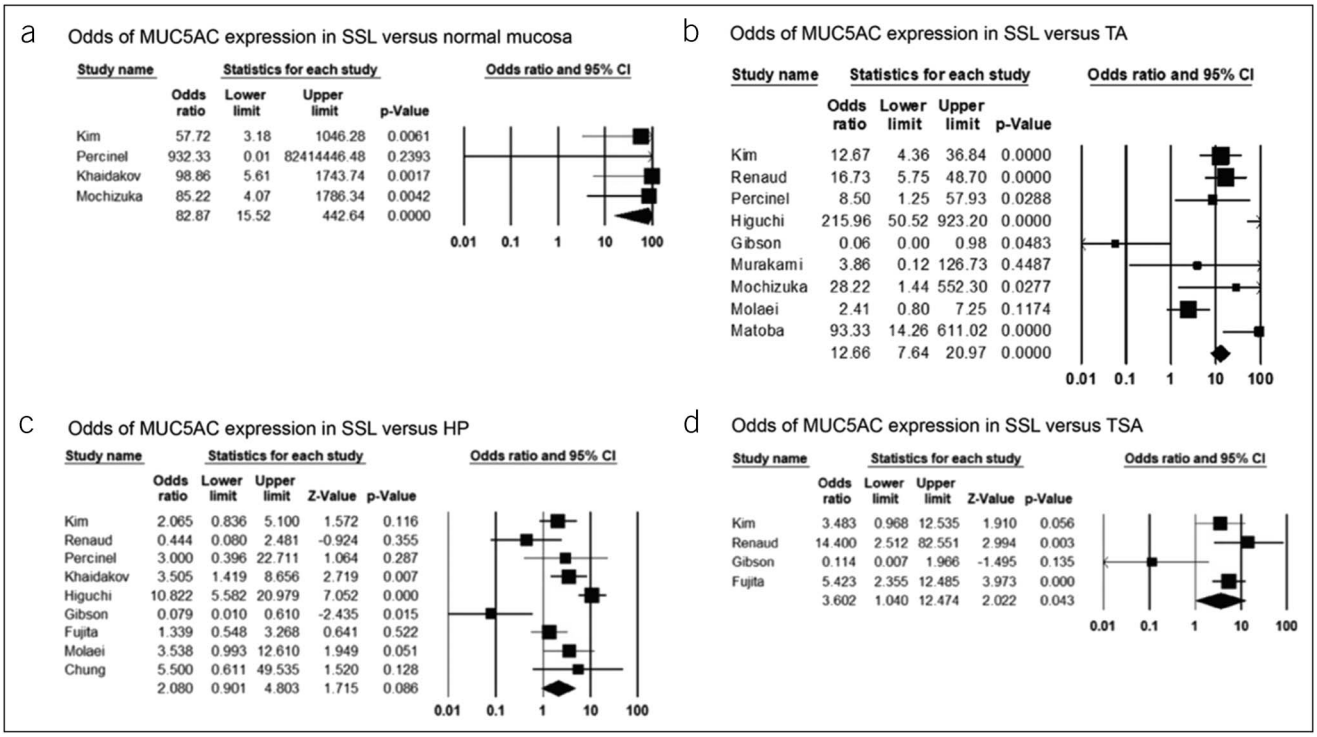

Figure 3. Forest plots of the odds ratios of MUC5AC expression in SSLs vs other histopathologic subtypes. Plots demonstrate the odds of MUC5AC expression on the surface of SSL vs normal mucosa (**a**), TAs (**b**), HPs (**c**), and TSAs (**d**). Studies included in the meta-analysis are shown on the left panel with the cumulative odds ratio and *P* values shown on the last line. HP, hyperplastic polyp; SSL, sessile serrated lesion; TA, tubular adenoma; TSA, traditional serrated adenoma.

Heterogeneity was assessed using the Cochran Q and I^2 statistics, classified as not important (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%) (Higgins and Green, 2011). All analyses were performed using Comprehensive Meta-Analysis Software, version 3.0 (Biostat, Englewood, NJ).

Histopathologic analysis was performed by 1 author (Z.P.), using monoclonal antibodies against MUC1 (SPM533; Novus Biologicals, Centennial, CO), MUC5AC (917 + 45M1; Novus Biologicals), and P40 (a squamous cell marker) used as a negative control.

RESULTS

Of the 440 citations identified, 18 were included in the final analysis (Figure 2). Included studies encompassed 3,554 polyps, of which 32%–75% came from female patients, with an average age ranging from 57 to 67 years. Studies included polyp samples from the United States, Japan, Iran, Korea, France, and Turkey (see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/CTG/B292). For MUC1, MUC2, MUC5AC, and MUC6 expression, there was insufficient data to perform a meta-regression by age and sex.

Of the 18 studies that were included in the final analysis, 14 reported MUC5AC expression in SSLs (see Supplementary Table 2, Supplementary Digital Content 2, http://links.lww.com/CTG/B292). We found that MUC5AC expression was more common in SSLs compared with normal colonic mucosa, with an OR = 82.9, $P < 0.01$ (4 studies, 107 SSLs polyps, 86 normal samples, $I^2 = 0\%$) (Figure 3). This finding is consistent with prior research as MUC5AC is not normally expressed in normal colonic mucosa (22). MUC5AC expression was also found to be higher in adenomatous lesions in comparison with normal mucosa though each study individually was not significant, OR = 5.09, $P < 0.0074$ (n = 4 studies, $I^2 = 0\%$). We found MUC5AC positivity in SSLs to be higher than in TA samples, with an OR = 12.01, $P < 0.001$ (8 studies, 412 SSLs polyps, 1,221 TA polyps, $I^2 = 82\%$), and TSA samples, OR = 3.6, $P = 0.04$ (4 studies, 287 SSLs polyps, 115 TSA polyps). We found no difference in MUC5AC positivity between SSLs vs villous adenomas (OR = 1.92, $P = 0.0924$) though few studies were available for analysis (see Supplementary Figure S1, Supplementary Digital Content 1, http://links.lww.com/CTG/B291). We found no difference in MUC5AC positivity between SSLs vs HP samples, with an OR = 2.08, $P = 0.09$ (9 studies, 443 SSLs polyps, 681 HP polyps), and no difference in MUC5AC positivity between SSLs with and without dysplasia, OR = 0.38, $P = 0.34$ (3 studies, see Supplementary Figure S2, Supplementary Digital Content 1, http://links.lww.com/CTG/B291). TAs were found to express MUC5AC higher than that of normal mucosa, OR = 5.09 $P = 0.0074$ (n = 4 studies, see Supplementary Figure S5, Supplementary Digital Content 1, http://links.lww.com/CTG/B291). Our findings are summarized in Figure 3.

Prior research suggests that a high proportion of proximal HPs show features of SSLs (50) and are classified as SSLs on review (51). As proximal HPs and SSLs share such pathologic similarities, we wanted to assess whether proximal HPs would also express increased MUC5AC in comparison with distal HPs. There was no difference in MUC5AC expression between left colon and right colon HP samples, with an OR = 1.46, $P = 0.46$ (3 studies, 77 right HP polyps, 151 left HP polyps, see Supplementary Figure S3, Supplementary Digital Content 1, http://links.lww.com/CTG/B291).

As the diagnostic criteria for SSLs have changed over time, we reasoned that the likelihood of MUC5AC positivity on SSLs would vary by the year of study. We found a modest inverse relationship in MUC5AC positivity on SSLs in comparison with HPs over time. Thus, SSLs were more likely to be MUC5AC positive in studies published before 2010. The correlation was weak, however, ($R^2 = 0.4071$) with a low correlation coefficient (see Supplementary Table 3, Supplementary Digital Content 2, http://links.lww.com/CTG/B292).

Mucin 6 (MUC6) is another mucin not normally expressed in the colon and could potentially be used as a biomarker of differentiation. MUC6 was studied originally as a selective marker of SSL development (36,40), though subsequently was not found to be specific to SSLs (42). We found that SSLs were more likely to be positive for MUC6 (see Supplementary Figure S4, Supplementary Digital Content 1, http://links.lww.com/CTG/B291) than that of normal mucosa, with an OR = 41.54, $P < 0.0001$ (n = 4 studies), and were more likely to be MUC6 positive than that of TAs, OR = 4.77, $P < 0.0001$ (n = 9 studies), or HPs, OR = 4.73, $P < 0.0002$ (n = 9 studies). TAs also trended toward higher MUC6 expression levels over normal mucosa though this difference was not statistically significant, OR = 4.71, $P = 0.054$ (n = 4 studies).

DISCUSSION

Our search of mucin biomarkers reveals that MUC5AC differentiates serrated lesions of the colon from normal tissue. Furthermore, we found the odds of MUC5AC expression follows SSL > HP > TSA > TA. This suggests that there is a quantitative difference of MUC5AC expression among phenotypes, which may be more specific to SSLs. For example, Mikhaleva and colleagues report that MUC5AC expression is found intensely across the entire length of the crypt, whereas in HPs and TSAs, the expression is focal (52). Differences in MUC5AC expression between SSLs and other polyp types align with previous research on this topic. MUC5AC, MUC6, and MUC17 are consistently upregulated on SSLs based on evidence from transcriptomic, proteomic, and immunohistochemical studies.

Numerous studies have examined MUC5AC expression in the colon in various pathologic states. MUC5AC is absent from the normal intestine past 12 weeks of gestation (53). Forgue-Lafitte et al (54) revealed high MUC5AC expression in ulcerative colitis and to a lesser extent diverticulitis. Mucin-secreting cells in the colon express MUC5AC in response to bacterial and parasitic infections (55) and after perforation of the appendix associated with bacterial invasion (56). In the progression of colon polyps to cancer, Bu (47) and Kocer (44) both demonstrated that most conventional colorectal adenocarcinomas are negative for MUC5AC, but most mucinous cancers are positive. MUC5AC RNA is known to be expressed to very high levels in serrated lesions of the colon (57,58); however, 2 previous studies using differential transcriptomics did not reveal MUC5AC to have high sensitivity or specificity for SSLs (59,60). Therefore, we found that MUC5AC is normally expressed by mucous-secreting cells of the stomach, endocervix, gallbladder, and tracheobronchial tree but can be found in the large intestine in states of chronic inflammation, infection, and specific cancers, in addition to precancerous colon polyps.

Our findings are consistent with the notion that polyp subtypes, through differing carcinogenesis pathways, lead to significant differences in MUC5AC expression. The mechanism by which MUC5AC is upregulated is postulated to be through

promoter hypomethylation and overexpression (34). DNA methylation has been found to be highly associated with serrated pathway lesions (34) and is correlated with *BRAF* mutation, CpG island methylator phenotype, and microsatellite instability-high (MSI-H) chromosomal phenotypes (34,58). In addition to alterations of mucin glycoproteins normally found in the colon, previous immunologic studies have shown that gastric antigens are expressed *de novo* in colonic polyps as well (61–63).

Other biomarkers for SSL development include Annexin A10 (64), Hes1 (65), Trefoil factor 1 (66), and Agrin in the muscularis layer (67); however, few follow-up studies have validated these proteins. Of note, trefoil factors are often associated with mucins (68). Gastric-type mucin MUC6 was previously shown to be a promising biomarker for SSLs (36,40) but in a validation study did not demonstrate specificity (42), supporting the notion that HPs and SSLs lie on a continuum of carcinogenesis (58).

We found that the odds of MUC5AC expression on traditional serrated adenomas (TSAs) was lower than that on SSLs. Although SSLs and TSAs arise from the serrated pathway, SSLs are recognized as a type of precursor lesion with MSI-H phenotype, whereas TSA is likely to progress into CRC with a microsatellite stable phenotype (69). This again suggests that MUC5AC overexpression is a result of a carcinogenic pathway, namely the MSI-H, serrated pathway.

Our study has a few important limitations. Because of the difficulty in distinguishing SSLs from HPs, reported reclassification rates of HPs to SSLs in the 2007–2019 literature range from 2.6% to 85%, which may explain why we found no significant difference in MUC5AC expression between SSLs and HPs. Thus, there is likely pathological overlap between the defined SSLs and HPs in the studies we analyzed. SSLs are likely large HPs, but the studies in our meta-analysis did not correlate mucin level with polyp size. Further studies examining mucin expression level with polyp size and presence of dysplasia will further determine if this biomarker is reliable for high-risk polyps. Technical factors, such as staining protocols and antibodies used; different definitions of thresholds to determine positivity; and possible selection bias regarding the analyzed neoplasms may have caused these discrepancies.

Currently available colon cancer screening methods cannot accurately identify serrated lesions, the vast majority test negative to fecal immunochemical testing, and are difficult to detect endoscopically because of flat morphology (6,25). However, approximately 25% of colon cancers arise from serrated pathway lesions; thus, a significant number of patients go unscreened (7). Given the high odds of SSL association, we hypothesize that MUC5AC could be quantified on the surface of polyps and serve as a marker of SSL carcinogenesis. More broadly, akin to fecal immunochemical testing, in the proper clinical context (i.e., excluding inflammatory bowel diseases and colitis patients), elevation in fecal MUC5AC may serve a role to identify patients with SSL. MUC5AC is known to be shed into the stool of mammals (70), thus may be detected in a noninvasive manner. Our results here indicate that MUC5AC is virtually absent from the normal healthy colon, and thus, detection of this protein holds potential as a sensitive marker for high-risk SSLs. In addition, detection of MUC5AC before colonoscopy may alert endoscopists to presence of SSLs, enhancing inspection of the right colon, and enlisting the use of adjunct techniques such as chromoendoscopy in select cases (17–20). Detection of MUC5AC may extend colon cancer screening to patients with serrated pathway lesions, which current screening methods cannot accurately identify. Further studies comparing the level of MUC5AC protein in stool of patients with SSL, hyperplastic polyps, conventional adenomas, and no polyps are thus needed.

CONFLICTS OF INTEREST

Guarantor the article: Giulio Quarta.

Specific author contributions: Article written by K.L and M.S. Data extraction and analysis performed by K.L. and M.S. Statistical analysis performed by V.P. Immunohistochemical analysis and article editing performed by Z.P. Conceptualization, manuscript editing, analysis performed by G.Q.

Financial support: We gratefully acknowledge support from NYU Grossman School of Medicine's Chairman's Circle Fund through the Department of Medicine to G.Q. and Translational Research Program from the Department of Pathology to Z.P. Funding was also provided from the National Institutes of Health, and National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (KL2TR001446) to G.Q.

Potential competing interests: None to report.

IRB approval: No breach of privacy or anonymity occurred during this study thus IRB approval was not sought.

Study Highlights

WHAT IS KNOWN

- ✓ Sessile serrated lesions contributed to 20% of colon cancers.
- ✓ Currently available screening methods do not detect Sessile serrated lesions with high precision.

WHAT IS NEW HERE

- ✓ A meta-analysis of available immunohistochemical studies reveals that secretory mucin MUC5AC is expressed on the majority of Sessile serrated lesions.
- ✓ MUC5AC is expressed more often on Sessile serrated lesions than on adenomas. MUC5AC may be used as an endoscopic or fecal biomarker of Sessile serrated lesions in the colon.

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