

May 14, 2013



Dear Editor and Reviewers,

Thank you very much for your time and expertise involved in critically reviewing our submission and for your valuable suggestions. Thank you for considering it worthy of publication in your journal and for allowing us the opportunity to edit our manuscript for consideration of publishing in your prestigious journal. We appreciate most of the reviewers acknowledging our study as interesting, novel, and well-written. We truly believe that all the comments and suggestions provided by the reviewers were excellent and have helped us to greatly improve the focus, accuracy and quality of our research manuscript. We have revised our manuscript and have made all the possible changes requested by the reviewers in order to satisfactorily address all of the reviewers' concerns.

We look forward to your favorable response, and to have our manuscript published in the "**World Journal of Gastroenterology**".

Please find enclosed the edited manuscript in Word format (file name: 2854-edited_REVISED-001.doc). Please find the specific response to reviewers comments below.

Title: Sessile serrated adenomas in the proximal colon are likely to be flat, large and occur in smokers

Author: Tarun Rustagi, Priya Rangasamy, Matthew Myers, Melinda Sanders, Haleh Vaziri, George Wu, John W. Birk, Petr Protiva, Joseph C. Anderson

Name of Journal: *World Journal of Gastroenterology*

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Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Always seeking your advice and wisdom,

Sincerely yours,

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Response to reviewer's comments

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 References and typesetting were corrected

Reviewer #1: In this manuscript, Dr. Rustagi et al. showed the results of retrospective case-control study that sessile serrated polyps in the proximal colon were more associated with smoking compared to tubular adenoma in the proximal colon. However, authors should provide information regarding that study participants include cases of their previous study. What do authors think the difference from previous study? In addition, recent study showed different results regarding risk factors by anatomical site (Burnett-Hartman AN et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. *Am J Epidemiol*, 2013 Mar 3. [Epub ahead of print]). Discussion is needed.

Author response: We greatly appreciate reviewer's comments to provide information regarding the study participants included in the previous study. We have provided information that 90 of the 120 cases were part of the earlier study that focused on risk factors for (all) sessile serrated adenoma. We have also mentioned the time period for study participants included in the earlier study and time period during which additional 30 patients were enrolled in the results section of the paper (page # 6-7) and have also provided reference to the earlier study (reference # 10). Regarding the differences from our previous study with 90 patients, this current study with 120 patients focuses on differentiation of epidemiology (risk factors) and morphological differences between proximal and distal sessile serrated adenomas. Previous study identified several risk factors for SSAs including age, obesity, smoking and diabetes. Current study shows that age, obesity and diabetes are not different for proximal vs. distal lesions, whereas smoking and interestingly family history of CRC is much stronger risk factor and strongly associated with proximal SSAs compared to distal SSAs. We have included these differences and comparisons with the previous study to bring out the new points several places in the manuscript.

We sincerely thank the reviewer for mentioning the findings of the recent case control study by Burnett-Hartman et al evaluating the differences in risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. We have included this study as one of the references (# 29) and appreciate reviewers input to expand on the discussion on this conflicting topic. We have discussed the findings of this study in relation to our study and current existing literature with several studies in the discussion section (page # 8-9). Smoking has been linked with both distal and proximal CRC, but strongly with proximally CRC. Relationship with serrated polyps is complex, as many studies including study by Burnett-Hartman mentioned by the reviewers does not subdivide serrated lesions into SSA and hyperplastic lesions when doing analysis based on anatomical sites. Hyperplastic polyps (NOT SSAs) which are commonly seen in distal colon/rectum are strongly linked with smoking. Lieberman et al observed that smoking was the only risk for hyperplastic lesions in male veterans (Lieberman DA, Prindiville S, Weiss DG, Willett W. Risk factors for advanced colonic

neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 2003 Dec 10; 290(22): 2959-2967). Burnett-Hartman et al themselves in their paper acknowledge the conflicting results compared the existing literature. We have included several other references (# 15, 16, 17, 18, 36, 37, 38, 39)to further strengthen our findings and discuss this topic in detail as suggested by the reviewer.

Reviewer # 2: Nice well written retrospective case-control study. However, this paper may be acceptable for publication after major revisions. According to the authors, sessile serrated adenomas are often flat and proximally located. A recent study has shown smoking to be strongly associated with sessile serrated adenomas of all sizes, including the clinically important large lesions. 2. The title " Sessile serrated adenomas in the proximal colon are likely to be flat, large and occur in smokers " is compatible to the prior literatures.

Author response: We would like to thank reviewer for appreciating our study as **nice, well-written** case-control study acceptable for publication. The recent study is our previous study (Anderson et al Journal Clin Gastro) evaluating risk factors for all sessile serrated adenomas, any size, any location. Current study has more patients (120pts vs.90) and is focused on differentiating association of risk factors based on anatomical location of these SSAs. Our current study focuses on proximal SSAs which may be more important given a recent expert panel's recommendation regarding management of these lesions and their role in serrated adenoma carcinoma pathway and interval cancers. Proximal SSAs are much more important and relevant in colorectal screening and hence identifying risk factors and morphology in comparison to distal SSAs is important and our study provides this valuable data to existing knowledge about SSAs. Difference in association with family history of CRC has never been shown before. Smoking, linked with all SSA, was shown to have stronger relationship with proximal SSAs.

Reviewer #3: You have conducted a retrospective study to identify patients with SSA using a pathology database query from 01/2007-04/2011. Have you analyzed this database or a part of the database for SSA as a part of any previous studies? How is this different from previous studies and there are no substantial overlap from previous studies

Author response: We thank reviewer's comments to provide information regarding the study participants included in the previous study. We have analyzed part of the database for SSA as part of previous study and as mentioned in response to reviewer # 1 comments, we have included this in our manuscript and have mentioned the differences from previous studies. This study has no overlap from the previously published study. We have provided information that 90 of the 120 cases were part of the earlier study that focused on risk factors for (all) sessile serrated adenoma. We have also mentioned the time period for study participants included in the earlier study and time period during which additional 30 patients were enrolled in the results section of the paper (page # 6-7) and have also provided reference to the earlier study (reference # 10). Regarding the differences from our previous study with 90 patients, this current study with 120 patients focuses on differentiation of epidemiology (risk factors) and morphological differences between proximal and distal sessile serrated adenomas. Previous study identified several risk factors for SSAs including age, obesity, smoking and diabetes. Current study shows that age, obesity and diabetes are not different for proximal vs. distal lesions, whereas smoking and interestingly family history of CRC is much

stronger risk factor and strongly associated with proximal SSAs compared to distal SSAs. We have included these differences and comparisons with the previous study to bring out the new points several places in the manuscript (page # 6, 7, 8, 9, 10). Previous study (Anderson et al, JCG) did not find family history of colorectal cancer to be a risk factor for sessile serrated adenomas compared to controls, however, this study found proximal SSAs but not distal SSAs to have association with family history of CRC.