Department of Internal Medicine
University of Medicine and Pharmacy at Ho Chi Minh City
217 Hong Bang Street, District 5, Ho Chi Minh City, Vietnam

Monday 25th, 2023

Dear Editor,

We would like to thank you very much for your kindness in allowing us to revise our manuscript entitled "**Prevalence, risk factors, and BRAF mutation of colorectal sessile serrated lesions among Vietnamese patients"**. Furthermore, we thank the reviewer for the positive comments and helpful suggestions. We would like to respond to your comments as follows. The manuscript has been carefully revised according to these comments, and the revised sections in the resubmitted manuscript have been highlighted.

Comment

As a possible risk factors you extracted male sex, age and some comorbidities, among which also diabetes mellitus. As chronic hyperglycemia and hyperinsulinemia are known risk factors for malignant transformation and growth of many cells it would be of interest to show the data on diabetes duration, and moreover, therapy used (according to literature agents such as metformin might have a preventive role in CRC and precancerous lesions, while insulin on the other hand could potentiate cancer cell growth). I think this could further help in assessing the population in risk for colorectal sessile serrated lesions development and aid clinical decision making in when and how often to do the endoscopy in such patients.

Reply:

Thank you very much for your valuable comment. We completely agree with you on this issue. However, we apologize that the data about diabetes duration and therapy used on patients with diabetes mellitus were not available in our data collection. Therefore, we cannot analyze these data in our manuscript. We highly appreciate your comments. In

the revised manuscript, we have added the information about the role of metformin and insulin therapy on colorectal cancer in the Discussion section of the revised manuscript, as you kindly pointed out (lines 337-345). In addition, we also mentioned this issue as one of the limitations of this study in the limitation section of the revised manuscript (lines 384-386). We think that this would be an important research question for our group's coming studies.

The following paragraphs have been added to our revised manuscript:

"In addition, there is a correlation between the usage of diabetes drugs and CRC. Metformin use has been shown in recent meta-analyses to significantly reduce the incidence of CRC, and improve CRC outcomes [41] [42]. Conversely, hyperinsulinemia is hypothesized to stimulate the development and proliferation of cells [43]. The relationship between insulin therapy and cancer growth is biologically connected via hyperinsulinemia. One meta-analysis of observational studies suggested that insulin therapy might increase the risk of CRC [44]. However, additional prospective cohort studies with extended follow-up periods are necessary to validate this correlation."

"Fourth, the available data about diabetes duration and therapy used in the patients with diabetes mellitus in our study are insufficient and constrained. Therefore, we could not analyze these data in our manuscript."

Once again, we would like to thank you for your time, and we greatly appreciate your insights that helped us refine the manuscript.

With the warmest regards,

On behalf of the authors

Duc Trong Quach, MD; PhD

Department of Internal Medicine, University of Medicine and Pharmacy at Hochiminh City

217 Hong Bang Street, District 5, Ho Chi Minh City, Vietnam

Tel: +84-91-808-025

Email: drquachtd@gmail.com