Peer Review File

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Reviewer A

Well written article on 2 sample mendelian randomization study designed to analyze the causal relationship between frailty and colon cancer. These are my comments:

Abstract: Well summarized, and methods adequately discussed.

Introduction:

1. Maybe the authors can discuss why it is important to establish if there is a causal effect of frailty on the incidence of colon cancer. This would add weight to the importance of the clinical question under study here and allow the readers to better understand the clinical implication.
Reply: Thanks. We revised the fourth paragraph in the INTRODUCTION section.
Change in the text: Please refer to the manuscript.

2. Spelling/typo error in line 108: whether "t" frailty
Reply: We deleted “t” in line 108. Thanks.
Change in the text: We deleted “t” in line 108. Thanks.

Methods: well described, but like the authors mentioned few SNPs were included and the ability to detect causal correlations was limited.

Discussion:

1. Maybe the authors can discuss the clinical implications of their study findings. Any impact on screening regimes for colon cancer in the frail?
Reply: Thanks. We discussed this in the CONCLUSION section.
Change in the text: Page 9, line 11-13: In conclusion, the results of this study suggest that frailty may not be a risk factor for colon cancer and cannot be used as a predictor. The future study should focus on the predictive value of frailty on the prognosis of patients with colon cancer.

2. Would recommend putting the conclusion below the study limitations.
Reply: Sure. We added a CONCLUSION section in the end of the main text.
Change in the text: Page 9, line 11-13: In conclusion, the results of this study suggest that frailty may not be a risk factor for colon cancer and cannot be used as a predictor. The future study should focus on the predictive value of frailty on the prognosis of patients with colon cancer.

Reviewer B

1. There seems to be no weak instrument bias; thus, the little evidence of causal effect seems to be correct.
Reply: Thank you for your comments.
Change in the text: None.

2. Manuscript needs extensive editing: eg; line 108: "t frailty"
line 213: "patients without cancer (36)"; I believe the authors meant to say without hypertension
Reply: Thanks. We checked thoroughly the whole manuscript and corrected some mistakes.
Change in the text: Please refer to the main text.

3. Are the genetic variants associated with potential confounders?
Reply: No. The 4 SNPs (i.e., rs10891490, rs2071207, rs583514, and rs9275160) were excluded due to confounding factors.
Change in the text: None.

4. Do you provide the data that you used in a supplement to allow others to reproduce your findings?
Reply: Anyone who is interested in this article can get related data by emailing to the corresponding author. Thanks.
Change in the text: None.

5. Can you conduct observational analyses in the same cohorts to see if the results will differ?
Reply: Thank you for your excellent advice. Maybe we can do some research to further confirm the result of this study in the future.
Change in the text: None.

Reviewer C

1. Please check if any reference is missing in this sentence since you've mentioned "A prospective study".

patients without hypertension (36). A prospective study carried out in Europe of 307,318 patients with hypertension with an average follow-up time of 13.7 years reported that hypertension increases the risk of esophageal squamous cell carcinoma, head and neck cancers, skin squamous cell carcinoma, colon cancer, postmenopausal breast cancer and uterine adenocarcinoma, but has no effect on esophageal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, or uterine endometroid cancer. However, research has shown that hypertension might decrease

Reply: We added reference at the end of this sentence.

2. Please also define SNP in Figure 1 legends.
Reply: We defined SNP in Figure 1 legends.