

Title:

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Authors:

Yunzhen Lin, Tianhang Li

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The significance of appendectomy in the context of colorectal cancer: impacts on gut microbiota and beyond

Yunzhen Lin¹, Tianhang Li²

¹Department of General Surgery. Nanjing BenQ Medical Center. The Affiliated BenQ Hospital of Nanjing Medical University. Nanjing, Jiangsu Province. China.

²Department of Clinical Medicine. Medical School of Nanjing University. Nanjing University, Nanjing. China

Correspondence: Tianhang Lie

e-mail: DG20350057@smail.nju.edu.cn

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Dear Editor,

A recent study by Shi et al. published in *Oncogene* investigated the association between appendectomy and colorectal cancer (CRC) risk (1). Based on a large population-dependent retrospective study, they found that the history of appendectomy significantly increased the risk of CRC tumorigenesis. Moreover, the results demonstrated that CRC patients that had undergone appendectomy showed a significantly-shifted gut microbiome composition with a dramatical up-regulation of CRC-promoted microbes, such as *Bacteroides vulgatus* and *Villanelle dispar*. Furthermore, the microbiome ecological network as well as the functional characteristics of the gut microbiota were significantly altered following appendectomy, which further verified the impact of appendectomy on gut microbiome composition. *In vivo* experiments in mice verified the tumor-promoting effect of appendectomy on CRC and further demonstrated that this pro-tumor effect

relied on modulation of gut microbiome by depletion of gut microbiome via antibiotic administration.

Despite the lack of a definitive mechanism explanation, this study still gave sufficient proof to verify the clinical significance of the appendectomy-gut microbiome dysbiosis-CRC initiation and functional axis development. A range of implications and guiding conclusions can be derived from this interesting study. Firstly, the utilization and potential risk of appendectomy may need to be re-evaluated. For those patients with higher CRC risks, including old-age, medical history of multiple intestinal polyps, high genetic risk, etc., a strict follow-up with postoperative colonoscopy should be suggested due to the increased risk of CRC. Furthermore, the post-operative probiotics administration for these high-risk patients may be recommended. Secondly, recent studies have verified that the gut microbiome not only participate in the malignant progression of cancers, but also impacts on immunotherapy efficacy (2,3), which indicates that appendectomy may also have specific impacts on the immunotherapy efficacy of CRC as well as other cancers. In the era of immune-checkpoint blockade (ICB), appendectomy history may be another important risk factor for appropriate subgrouping and patient enrollment as well as efficacy prediction.

However, some limitations also exist. Firstly, the gut microbiome composition studied in this research is only limited to bacteria. However, gut fungi, which is another big part of gut microbiota, has also been found to play crucial roles in the pathogenesis of CRC (4,5). How appendectomy may affect the gut fungal species needs to be further investigated. In addition, the definite mechanism of appendix participation in the modulation of the homeostasis of gut microbiome has not been studied, which warrants further investigation for verification.

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