**Supplementary Discussion**

Further complexities regarding this topic deserve comment. In addition to CRC subsites (proximal/distal colon vs. rectum)(1-6), duration of use(7), and statin types (lipophilic statins vs. hydrophilic statins,(8) and individual types(9)), it is still controversial whether the association between statin use and CRC risk may differ by molecular subtypes (KRAS mutation status),(2) genetic variants (in 3-hydroxy-3-methylglutaryl CoA reductase),(10) high-/average- risk groups,(5, 11) age,(5, 12) racial/ethnic background,(5, 13) sex,(14) and dose of use(7, 9). Both inherited genetic susceptibility (e.g., those with preexisting inflammatory bowel disease, polyps, Lynch syndrome, CRC, or family history of CRC) and environmental risk profile should be considered when identifying the risk: benefit profile among subgroups. Moreover, future explorations in well-designed prospective studies or RCTs are warranted to disclose the association of statin use with intermediate end points (e.g., aberrant crypt foci and adenomas).

**References**

1. Lytras T, Nikolopoulos G, Bonovas S. Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. World J Gastroenterol 2014;20:1858-70.

2. Lee JE, Baba Y, Ng K, et al. Statin use and colorectal cancer risk according to molecular subtypes in two large prospective cohort studies. Cancer Prev Res (Phila) 2011;4:1808-15.

3. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184-92.

4. Ibanez-Sanz G, Guino E, Pontes C, et al. Statin use and the risk of colorectal cancer in a population-based electronic health records study. Sci Rep 2019;9:13560.

5. Hachem C, Morgan R, Johnson M, et al. Statins and the risk of colorectal carcinoma: a nested case-control study in veterans with diabetes. Am J Gastroenterol 2009;104:1241-8.

6. Cheung KS, Chen L, Chan EW, et al. Statins reduce the progression of non-advanced adenomas to colorectal cancer: a postcolonoscopy study in 187 897 patients. Gut 2019;68:1979-1985.

7. Broughton T, Sington J, Beales IL. Statin use is associated with a reduced incidence of colorectal cancer: a colonoscopy-controlled case-control study. BMC Gastroenterol 2012;12:36.

8. Liu Y, Tang W, Wang J, et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. Cancer Causes Control 2014;25:237-49.

9. Liu JC, Hao WR, Hsu YP, et al. Statins dose-dependently exert a significant chemopreventive effect on colon cancer in patients with chronic obstructive pulmonary disease: A population-based cohort study. Oncotarget 2016;7:65270-65283.

10. Lipkin SM, Chao EC, Moreno V, et al. Genetic variation in 3-hydroxy-3-methylglutaryl CoA reductase modifies the chemopreventive activity of statins for colorectal cancer. Cancer Prev Res (Phila) 2010;3:597-603.

11. Bertagnolli MM, Hsu M, Hawk ET, et al. Statin use and colorectal adenoma risk: results from the adenoma prevention with celecoxib trial. Cancer Prev Res (Phila) 2010;3:588-96.

12. Sehdev A, Shih YC, Huo D, et al. The role of statins for primary prevention in non-elderly colorectal cancer patients. Anticancer Res 2014;34:5043-50.

13. Davis-Yadley AH, Lipka S, Shen H, et al. Ethnic disparities in the risk of colorectal adenomas associated with aspirin and statin use: a retrospective multiethnic study. J Gastrointest Oncol 2014;5:112-8.

14. Clancy Z, Keith SW, Rabinowitz C, et al. Statins and colorectal cancer risk: a longitudinal study. Cancer Causes Control 2013;24:777-82.