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Plasma metabolic profiles in association with subsequent risk of colorectal cancer in the UK Biobank cohort

Introduction: Dysregulation of metabolic processes contributes to colorectal cancer (CRC) etiology. We aimed to comprehensively evaluate the prospective associations between pre-diagnostic metabolic biomarkers and CRC risk in 230,420 UK Biobank participants.

Methods: A total of 249 metabolic biomarkers were measured by nuclear magnetic resonance spectroscopy from baseline plasma samples. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of metabolic biomarkers with CRC risk after adjusting for potential confounders. Subgroup analyses were performed by sex and CRC subsites (i.e., proximal colon, distal colon, rectum). We also conducted factor analyses to identify latent factors and examined their associations with CRC risk.

Results: During a median follow-up time of 9.7 years, 2,410 incident primary CRC cases were identified after excluding participants diagnosed with CRC within two years after blood collection. After correcting for multiple testing, 50 metabolic biomarkers, including lipids and lipoproteins, fatty acids, ketone bodies, and inflammation, were significantly associated with incident CRC risk. No statistically significant differences were observed for the biomarker-CRC associations by sex and CRC subsite. In the sensitivity analysis, excluding cholesterol-lowering medication users did not alter the main findings. In factor analyses, we identified a significant association of CRC risk (HR = 1.08; 95% CI = 1.04-1.13; *P*-value = 6.89×10^{-5}) with a metabolite pattern which was positively correlated with triglycerides and inversely correlated with relative concentrations of omega-6 fatty acids and polyunsaturated fatty acids.

Conclusions: We identified multiple metabolic biomarkers and a metabolite pattern associated with CRC risk in a large prospective cohort. These findings suggest lipid metabolism may contribute to carcinogenesis of the colorectum.