Mendelian Randomization Study of Body Mass Index and Colorectal Cancer Risk

**Background:** High body mass index (BMI) is consistently linked to increased risk of colorectal cancer for men, whereas the association is less clear for women. As risk estimates from observational studies may be biased and/or confounded, we conducted a Mendelian randomization study to estimate the causal association between BMI and colorectal cancer.

**Methods:** We used data from 10,226 colorectal cancer cases and 10,286 controls of European ancestry. The Mendelian randomization analysis used a weighted genetic risk score, derived from 77 genome-wide association study–identified variants associated with higher BMI, as an instrumental variable (IV). We compared the IV odds ratio (IV-OR) with the OR obtained using a conventional covariate-adjusted analysis. Results: Individuals carrying greater numbers of BMI-increasing alleles had higher colorectal cancer risk [per weighted allele OR, 1.31; 95% confidence interval (CI), 1.10–1.57]. Our IV estimation results support the hypothesis that genetically influenced BMI is directly associated with risk for colorectal cancer (IV-OR per 5 kg/m², 1.50; 95% CI, 1.13–2.01). In the sex-specific IV analyses higher BMI was associated with higher risk of colorectal cancer among women (IV-OR per 5 kg/m², 1.82; 95% CI, 1.26–2.61). For men, genetically influenced BMI was not associated with colorectal cancer (IV-OR per 5 kg/m², 1.18; 95% CI, 0.73–1.92).

**Conclusions:** High BMI was associated with increased colorectal cancer risk for women. Whether abdominal obesity, rather than overall obesity, is a more important risk factor for men requires further investigation. Impact: Overall, conventional epidemiologic and Mendelian randomization studies suggest a strong association between obesity and the risk of colorectal cancer.