The impact of weight loss on obesity-related colorectal cancer (CRC) risk is not well defined. Previous studies have suggested that bariatric surgery may have an unexpected adverse impact on CRC risk. This study aimed to investigate the impact of bariatric surgery on biomarkers of CRC risk. Our data suggest that body fatness, and its associated metabolic sequelae, influence miRNA expression in the rectal mucosa and that these factors mediate the impact of obesity on CRC risk. Gene expression analysis showed no increase in inflammation or tumourigenic potential of the rectal mucosa and this, together with the lower proliferation status of the rectal mucosa, suggest that surgically-induced weight loss may reduce CRC risk.