

## Diet-linked Gut Microbiome Risk Factors in Colorectal Carcinogenesis

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**Abstract:** Colorectal cancer (CRC), the second leading cause of cancer death in the United States, has been linked both to dietary risk factors and to changes in the gut microbiota. Unlike genetic factors, both diet and the human microbiome are modifiable and represent promising future targets for CRC prevention and therapy. However, no studies have yet determined whether specific mechanisms of microbial metabolism in the gut contribute to CRC risk and tumorigenesis in human populations. We thus propose three aims to study of diet-linked gut microbiome risk factors in CRC. First, we will assess the microbiota in the well-characterized Nurses Health Study II, a population with over 20 years of follow-up on diet and CRC outcomes. This will associate dietary components with CRC risk and both microbial community structure (16S rRNA gene sequencing) and function (metagenomic and metatranscriptomic shotgun sequencing). Second, we will validate predicted associations in two independent cohorts of Lynch syndrome patients, a high-risk population in which dietary factors have been epidemiologically associated with tumorigenesis. Third, we will validate the causal molecular mechanisms of CRC progression in the tumor microenvironment using a humanized gnotobiotic mouse model. Our multidisciplinary team includes expertise in gastroenterology, oncology, epidemiology, immunology, microbiology, and bioinformatics, with the goal of surveying the gut microbiome for diet-linked molecular activities in CRC risk, validating these in an independent population, and identifying their mechanisms of action. These aims have the potential to provide concrete, validated, and actionable recommendations for personalized dietary interventions to reduce CRC risk.