Metabolic Risk Factors and Molecular Subtypes of Colorectal Cancer

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Abstract

Background: Colorectal cancer (CRC) is a heterogeneous disease developing from distinct pathways, resulting in tumor subtypes with large differences in clinical and molecular characteristics. Molecular characteristics are increasingly being used clinically to guide therapy. However, whether molecular subtypes of CRC differ in etiology or risk factors is not clear. Clarifying such potential differences may lead to an improved understanding of CRC etiology, with implications for CRC prevention and screening.

Aim: The aim of this thesis was to investigate whether risk factors related to energy metabolism, such as body fatness, and one-carbon metabolism, such as circulating B-vitamin status, were associated with specific subtypes of CRC defined by molecular characteristics of the tumor.

Methods: These prospective studies are based on data and blood samples from cohorts within the population-based Northern Sweden Health and Disease Study (NSHDS). Prospective CRC cases with available archived tumor tissue were analyzed for key molecular features (KRAS and BRAF mutation status, Microsatellite instability (MSI) status, and CpG Island Methylator Phenotype (CIMP) status). Paper I was a cohort study of metabolic factors related to the metabolic syndrome (117 687 participants). Paper II was a nested-case control study on circulating insulin resistance markers and adipokines (1010 cases and 1010 matched controls). Papers III and IV were nested case-control studies of one-carbon metabolism biomarkers and genetic variants (613 cases and 1190 matched controls).

Results: In paper I, we observed associations between metabolic factors, such as BMI, blood pressure, and blood lipids, and CRC risk consistent with previous studies. These associations were similar regardless of tumor KRAS and BRAF mutation status. In paper II, circulating biomarkers of insulin resistance and adipokines were not associated with the risk of CRC or specific molecular subtypes of CRC defined by KRAS and BRAF mutation or MSI status. In paper III, higher circulating levels of metabolites involved in the methionine cycle (namely, betaine and methionine) were associated with a lower CRC risk. In paper IV, we found no support for clear subtype-specific roles of any circulating one-carbon metabolism biomarker or genetic variants in CRC development.

Conclusions: The result of these prospective studies suggests that metabolic factors related to energy metabolism and one-carbon metabolism are generally associated with the risk of CRC, regardless of major subtypes defined by key molecular tumor features. If causal, metabolic risk factors likely influence the risk of colorectal cancer through more than one carcinogenic pathway.

Keywords
Colorectal cancer, risk factors, metabolic syndrome, one-carbon metabolism, molecular subtypes, KRAS, BRAF, MSI, molecular pathological epidemiology