Biomarkers of One-carbon Metabolism in Colorectal Cancer Risk

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av doktorsexamen framläggs till offentligt försvar i sal Eo4, R-1, Norrlands universitetssjukhus, fredagen den 19 januari, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

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One-carbon metabolism, a network of enzymatic reactions involving the transfer of methyl groups, depends on B-vitamins as cofactors, folate as a methyl group carrier, and amino acids, betaine, and choline as methyl group donors. One-carbon metabolism influences many processes in cancer initiation and development such as DNA synthesis, genome stability, and histone and epigenetic methylation. To study markers of one-carbon metabolism and inflammation in relation to colorectal cancer (CRC) risk, we used prediagnostic plasma samples from over 600 case participants and 1200 matched control participants in the population-based Northern Sweden Health and Disease Study cohort.

This thesis studies CRC risk with respect to the following metabolites measured in pre-diagnostic plasma samples: 1) folate, vitamin B12, and homocysteine; 2) components of one-carbon metabolism (choline, betaine, dimethylglycine, sarcosine, and methionine); and 3) three markers of different aspects of vitamin B6 status. In addition, this thesis examines three homocysteine ratios as determinants of total B-vitamin status and their relation to CRC risk.

In two previous studies, we observed an association between low plasma concentrations of folate and a lower CRC risk, but we found no significant association between plasma concentrations of homocysteine and vitamin B12 with CRC risk. We have replicated these results in a study with a larger sample size and found that low folate can inhibit the growth of established pre-cancerous lesions.

Using the full study cohort of over 1800 participants, we found inverse associations between plasma concentrations of the methionine cycle metabolites betaine and methionine and CRC risk. This risk was especially low for participants with the combination of low folate and high methionine versus the combination of low folate and low methionine. Well-functioning methionine cycle lowers risk, while impaired DNA synthesis partly explains the previous results for folate.

We used the full study cohort to study associations between CRC risk and the most common marker of vitamin B6 status, pyridoxal 5-phosphate (PLP), and two metabolite ratios, PAr (4-pyridoxic acid/(PLP + pyridoxal)) estimating vitamin B6 related inflammatory processes, and the functional vitamin B6 marker 3-hydroxykynurenine to xanthurenic acid (HK:XA). Increased vitamin B6-related inflammation and vitamin B6 deficiency increase CRC risk. Inflammation was not observed to initiate tumorigenesis.

Total B-vitamin status can be estimated by three different recently introduced homocysteine ratios. We used the full study cohort to relate the ratios as determinants of the total B-vitamin score in case and control participants and estimated the CRC risk for each marker. Sufficient B-vitamin status as estimated with homocysteine ratios was associated with a lower CRC risk.

These studies provide a deeper biochemical knowledge of the complexities inherent in the relationship between one-carbon metabolism and colorectal tumorigenesis.

Keywords
Colorectal cancer, one-carbon metabolism, biomarkers, folate, epidemiology

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