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Inflammation in colorectal cancer risk: The role of nutritional determinants and genetic variation

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Inflammatory processes influence the risk of developing colorectal cancer. Two approaches to study inflammatory pathways in more detail and from an epidemiologic perspective were conducted in the presented thesis. The aim of the presented thesis was to investigate the role of inflammation on the risk of developing colorectal cancer. The question raised was approached with two different strategies.

On one hand, nutritional determinants of inflammatory biomarkers were evaluated, described and placed into the context of colorectal cancer prevention and risk. Although significant advances have been made in recent years to uncover the underlying molecular mechanisms of colorectal carcinogenesis, a more defined understanding is still essential. Furthermore, genetic polymorphisms in the *PLA2G1B* gene were evaluated in the second approach, investigating their effect in colorectal carcinogenesis and effect on population-based risk. The work done in two separate study settings is discussed below in two parts.

Part 1: Associations between biomarkers of nutritional status, the one-carbon metabolism and inflammatory markers were assessed and analyzed to understand their interrelation. Folate-mediated one-carbon metabolism is essential for DNA synthesis, repair, and methylation. Perturbations in the one-carbon metabolism have been implicated in increased risk of colorectal

cancer, and affect inflammatory processes. In a cross-sectional study design of 1,976 women, vitamin B_6, vitamin B_{12}, plasma folate, and red-blood-cell folate were measured as nutritional markers, C-reactive protein and serum amyloid A as biomarkers of inflammation, homocysteine and cysteine as integrated biomarkers of one-carbon metabolism. Vitamin B_6 showed significant correlations with CRP and SAA. Using linear regression, associations between RBC folate or homocysteine with both CRP and SAA were observed. As previously hypothesized, the correlation coefficients were smaller in the post-fortification period. In summary, we showed that biomarkers of inflammation are associated with concentrations of PLP, RBC folate and homocysteine. This possible association between the transsulfuration and inflammatory pathways needs to be further investigated and causality established through experimental designs.

Part 2: Pancreatic phospholipase A_2 catalyzes the release of fatty acids from dietary phospholipids for absorption in the small intestine. The product of pancreatic phospholipase A_2, arachidonic acid, is a precursor of eicosanoid signaling molecules, that are linked to inflammation, cell proliferation and colorectal carcinogenesis. Three identified pancreatic phospholipase A_2 tagSNPs were genotyped in three population-based, case-control studies of colon cancer, rectal cancer and colorectal adenomas. In order to evaluate associations for the entire gene, principal component and haplotype analysis were conducted. Independently, individual SNPs were evaluated in relation to neoplasia risk by logistic-regression. Two *PLA2G1B* variants were statistically significantly associated with reduced risk of rectal cancer across heterozygous and homozygous variant genotypes. Particularly, users of NSAIDs with the *PLA2G1B* rs2070873 variant had a statistically significantly reduced rectal cancer risk. Specific statistically significant associations were observed with colon tumor mutation subtypes (*TP53*/*KRAS2*). The results suggest that genetic polymorphisms in *PLA2G1B* affect susceptibility to rectal cancer and may be relevant for NSAID pharmacogenetics.