ABSTRACT

BACKGROUND: Folate, a B-vitamin found primarily in fruits and vegetables, especially leafy greens, and other B-vitamins involved in folate metabolism are believed to protect against cancer and cardiovascular disease. Maintaining an adequate folate status ensures availability of methyl groups for DNA synthesis and for all methylation reactions in the body, and prevents the accumulation of homocysteine, a sulphur-containing amino acid that has been linked to cardiovascular disease. The aim of this thesis was to relate factors involved in folate metabolism to the risk of developing colorectal cancer (CRC), prostate cancer (PCa), stroke (ischemic and hemorrhagic), and acute myocardial infarction (AMI).

SUBJECTS AND METHODS: These were nested case-referent studies, with 226 CRC, 254 PCa, 396 stroke (334 ischemic and 62 hemorrhagic), and 571 AMI cases, and double, matched referents from the population-based Northern Sweden Health and Disease Study.

CRC RESULTS: A bell-shaped association was observed between plasma folate concentrations and the risk of CRC [multivariate odds ratio (OR) for the middle versus lowest quintile, 2.00 (95% CI 1.13-3.56)]. Homocysteine was not associated with CRC risk. A reduced risk was observed for the MTHFR 677C>T polymorphism [OR for TT versus CC, 0.41 (95% CI 0.19-0.85), P_trend=0.062] that was independent of plasma folate status. Prediagnostic plasma folate concentrations were higher in cases with promoter hypermethylation in the p16 and/or hMLH1 tumor suppressor genes in CRC tissue compared to cases without promoter hypermethylation in these genes (P=0.025).

PCa RESULTS: Increasing plasma levels of folate and vitamin B12 were associated with increased risk of PCa [OR for the highest versus lowest quartile, 1.60 (95% CI 1.03-2.49), P_trend=0.02 for folate, and 2.63 (95% CI 1.61-4.29), P_trend=0.001 for vitamin B12]. Increasing plasma homocysteine levels were associated with a reduced risk of borderline significance. In multivariate analyses, the risk estimate remained statistically significant only for vitamin B12.

STROKE RESULTS: Plasma folate concentrations were associated with the risk of hemorrhagic stroke in an inverse linear manner after adjustment for conventional risk factors including hypertension [multivariate OR for the highest versus lowest quartile, 0.21 (95% CI 0.06-0.71), P_trend=0.008]. Risk estimates were attenuated by the inclusion of homocysteine in the model [OR 0.34 (95% CI 0.08-1.40), P_trend=0.088]. Similar results were obtained for folate intake. Neither plasma folate levels nor folate intake demonstrated a clear association with the risk of ischemic stroke, and neither plasma nor dietary vitamin B12 was associated with the risk of either type of stroke.

AMI RESULTS: Plasma folate concentrations demonstrated an inverse association with risk of AMI that was independent of other risk factors, including homocysteine [multivariate OR for the highest versus lowest quintile, 0.56 (95% CI 0.34 – 0.90), P_trend=0.080]. For vitamin B12, no clear risk relationships were apparent. None of the risk estimates for dietary intake of folate, vitamin B12, vitamin B6, or vitamin B2 were statistically significant, although the results for folate and vitamin B12 intake were in line with those for the plasma variables.

CONCLUSIONS: The results of these population-based, prospective studies suggest that although a high folate status may be associated with a reduced risk of cardiovascular diseases, the relationship with cancer risk seems to be more complicated. The possibility of a detrimental component to the role of folate and vitamin B12 in carcinogenesis may have implications in the ongoing debate concerning mandatory folate fortification of foods.