Abstract

Cancer Res. 1997 Mar 15;57(6):1098-102.

Methylenetetrahydrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer.

Ma J, Stampfer MJ, Giovannucci E, Artigas C, Hunter DJ, Fuchs C, Willett WC, Selhub J, Hennekens CH, Rozen R.

Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.

BACKGROUND: Folate derivatives are important in experimental colorectal carcinogenesis; low folate intake, particularly with substantial alcohol intake, is associated with increased risk. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate, required for purine and thymidine syntheses, to 5-methyltetrahydrofolate, the primary circulatory form of folate necessary for methionine synthesis. A common mutation (677C-->T) in MTHFR reduces enzyme activity, leading to lower levels of 5-methyltetrahydrofolate.

OBJECTIVE: To evaluate the role of folate metabolism in human carcinogenesis, we examined the associations of MTHFR mutation, plasma folate levels, and their interaction with risk of colon cancer. We also examined the interaction between genotype and alcohol intake.

METHODS: We used a nested case-control design within the Physicians' Health Study. Participants were ages 40-84 at baseline when alcohol intake was ascertained and blood samples were drawn. During 12 years of follow-up, we identified 202 colorectal cancer cases and matched them to 326 cancer-free controls by age and smoking status. We genotyped for the MTHFR polymorphism and measured plasma folate levels.

RESULTS: Men with the homozygous mutation (15% in controls) had half the risk of colorectal cancer [odds ratio (OR), 0.49; 95% confidence interval (CI), 0.27-0.87] compared with the homozygous normal or heterozygous genotypes. Overall, we observed a marginal significant increased risk of colorectal cancer (OR, 1.78; 95% CI, 0.93-3.42) among those whose plasma folate levels indicated deficiency (<3 ng/ml) compared with men with adequate folate levels. Among men with adequate folate levels, we observed a 3-fold decrease in risk (OR, 0.32; 95% CI, 0.15-0.68) among men with the homozygous mutation compared with those with the homozygous normal or heterozygous genotypes. However, the protection due to the mutation was absent in men with folate deficiency. In men with the homozygous normal genotype who drank little or no alcohol as reference, those with the homozygous mutation who drank little or no alcohol had an 8-fold decrease in risk (OR, 0.12; 95% CI, 0.03-0.57), and for moderate drinkers, a 2-fold decrease in risk (OR, 0.42; 95% CI, 0.15-1.20); no decrease in risk was seen in those drinking 1 or more drinks/day.

CONCLUSIONS: Our findings provide support for an important role of folate metabolism in colon carcinogenesis. In particular, these results suggest that the 677C-->IT mutation in MTHFR reduces colon cancer risk, perhaps by increasing 5,10-methylenetetrahydrofolate levels for DNA synthesis, but that low folate intake or high alcohol consumption may negate some of the protective effect.

PMID: 9067278

FREE FULL TEXT