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High red blood cell folate levels linked to silenced tumor-suppressors

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People with higher levels of folate in their red blood cells were more likely to have two tumor-suppressing genes shut down by methylation, a chemical off switch for genes, researchers report in the December issue of Cancer Prevention Research.

DNA hypermethylation, notes co-author Jean-Pierre Issa, M.D., professor in MD Anderson's Department of Leukemia, is found in a variety of cancers and diseases of aging, such as heart disease. Methyl groups attach to genes at sites called CpG islands and protrude like tags or book marks from the promoter region, preventing gene expression.

"Our new finding is that having high levels of folate in the blood, as observed in a sensitive measure of red blood cell (RBC) folate, is related to higher levels of DNA methylation," Issa said.

Folate is a naturally occurring B-vitamin that plays a role in DNA creation, repair and function as well as red blood cell production. Pregnant women who have a folate deficiency are at elevated risk of giving birth to a child with neural tube defects, which are caused by the failure of the spinal cord or brain to fully close during development.

Folate is found in leafy vegetables, fruits, dried beans and peas. Since 1998 its synthetic version, folic acid, has been added to breads cereals, flours, pastas, rice and other grain products under order from the U.S. Food and Drug Administration. This has driven down the rate of neural tube defects in the United States, according to the U.S. Centers for

Disease Control and Prevention.

Folate also is taken as a dietary supplement. The recommended daily requirement is 400 micrograms for adult men and women and an additional 400 for women capable of becoming pregnant.

Folate's effect on cancer, once thought to be mainly preventive, has become less clear in recent years, with scientists finding cancer-promoting aspects of folate intake in colorectal, prostate and other cancers.

The research team analyzed the association between folate blood levels and dietary and lifestyle factors on DNA methylation in normal colorectal tissue. They enrolled 781 patients from a parent clinical trial that compared folate to aspirin in the prevention of precancerous colorectal polyps.

They gathered demographic, lifestyle and dietary information and compared methylation of two tumor-suppressing genes between the first colonoscopy and one three years later.

The genes, ERα and SFRP1, are expressed in normal colorectal tissue but silenced by methylation in colon cancer. The two genes also have been found to be methylated in breast, prostate and lung tumors.

Age was strongly associated with increased methylation – a finding that confirmed longstanding research. Methylation levels also varied between the rectum and right colon and among different ethnic groups for each gene.

Neither folate nor aspirin treatment were significantly associated with methylation levels. However, RBC folate was associated with methylation of both genes with significant differences emerging between

the top quarter of patients with the highest RBC folate count and the bottom quarter with the lowest. RBC folate levels closely reflect long-term folate intake.

"These differences were not trivial, they were the equivalent of 10 years of extra aging for those with high RBC folate counts," Issa said.

"Today it's worrisome that taking extra folate over the long term might lead to more DNA methylation, which then might lead to extra diseases including potentially an increased chance of developing cancer and other diseases of aging," Issa said.

"The data for folate supplementation right now are very ambiguous and I personally think people taking folate should think twice about it," Issa said. "Also, these findings, added to other data, should trigger a rethinking of the U.S. position that everyone should be taking extra folate."

Provided by University of Texas M. D. Anderson Cancer Center