Folate: Effects on Carcinogenesis and the Potential For Cancer Chemoprevention

Drs. Mason and Levesque thoroughly review data from intervention trials and epidemiologic studies that suggest a role for folate in preventing cancer of the colorectum and, to a lesser degree, cancers of the uterine cervix, lung, esophagus, and stomach. The authors also provide a comprehensive discussion of the possible mechanisms by which folate may prevent cancer, in particular, the relationship between folate status and DNA methylation.

The article begins with a historical perspective that relates the development of megaloblastosis and possibly dysplasia resulting from folate deficiency. Perhaps the most interesting of the early accounts linking folate deficiency to megaloblastic anemia is the experiment by Herbert, in which he deprived himself of dietary folate.[1] However, as Mason and Levesque indicate, the observations linking megaloblastosis to dysplasia are a priori evidence. Although there is a strong link between folate deficiency and hypomethylation and a link between hypomethylation of specific genes and cancer, the connection between folate-deficient diets and dysplasia is circumstantial.

The notion that folate deficiency functions as a cocarcinogen is supported by the observation that an increase in cervical cancer was evident only in folate-deficient patients who had a concurrent human papilloma virus-16 (HPV-16) infection. If this notion is accurate and folate deficiency is manifested as dysplasia only when specific organisms are present or in the context of a specific biochemical environment, there is a very definite need to conduct studies to determine the exact nature of these corequirements for cancer.

How Much Folate? Is More Better?

The authors correctly state that results from epidemiologic studies do not establish a cause-and-effect relationship between folate status and cancer. To take this one step further, results from studies that depend on dietary recall or that do not standardize food preparation do not take into account the fact that food preparation and cooking substantially influence the amount of folate actually ingested.[2]

The authors describe the results of two rat studies coauthored by Dr. Mason (one of which is in press) that support the contention that increased dietary folate intake decreases the incidence of colorectal cancer. To our knowledge, these are the only studies in which the relationship between colorectal cancer and folate status has been examined in animals. In rats, a folate-deficient diet decreases the incidence of mammary cancer, but results from an older study suggests that folate causes regression of mammary tumors in mice.[3,4]

As alluded to by the authors, the cancer chemopreventive effect of folate may be specific to certain organs, but one cannot dismiss the possibility that increasing dietary consumption of folate may have less beneficial or perhaps even harmful effects in some tissues or organs. It seems irrefutable that other dietary components will interact with folate to influence the development of dysplasia and that this interaction may also be organ-specific.

A particularly interesting point made by the authors is that lower red blood cell (RBC) folate levels that are within the conventional normal range are associated with a higher incidence of colorectal and uterine cancer than are higher folate levels. As discussed by McNulty, the currently recommended dietary allowances of folate in both the United Kingdom and the United States have been lowered, presumably in response to a lack of evidence that a higher intake is necessary or beneficial.[2] In view of the aforementioned results, further study is required to determine whether a reevaluation of the current dietary allowances may be needed.

With regard to gender, race, and socioeconomic status, it would be informative to know whether...
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Folate or its metabolites have different effects depending on the indicator. For example, American whites consume significantly more folate than do African-Americans, but it is not known to what extent, if any, this accounts for the observed racial differences in the incidence of various cancers.

Alcohol, Tobacco, and Folates
The interaction among alcohol, tobacco, and folate as it influences colorectal cancer is an area in which there are more questions than answers. As the authors note, high alcohol consumption coupled with a low folate diet translates into a fourfold higher incidence of colorectal cancer. Collectively, the data supporting an association between alcohol and colorectal cancer are unconvincing and are most compelling with regard to beer drinking and rectal cancer. Interestingly, beer accounts for 10% of the total folate intake by adults in the United Kingdom. Given that a small decrease in RBC folate levels appears to result in a higher incidence of colorectal cancer, encouraging temperance, at least with regard to beer, would lower folate levels, producing a net effect that would not necessarily be beneficial!

As mentioned earlier, perhaps folate deficiency functions as a cocarcinogen with alcohol in the colon. In one study, a methyl-deficient (low-methionine, low-folate) diet in conjunction with high alcohol intake has been associated with a higher risk of human colorectal cancer.[5] In this study, smoking was not a confounding factor, and the most recent report focusing on tobacco and colorectal cancer does not support a correlation between the two.[6] Although the data are conflicting, the consensus appears to be that if smoking does increase the risk of colorectal cancer, it does so only in those who smoke for more than 35 years, and the risk is relatively greater for the rectum.

The authors state that chronic use of tobacco is associated with decreased blood folate levels. Thus, owing to the association between cancer incidence and folate concentration, it would stand to reason that chronic smokers would have a higher incidence of colorectal cancer. This has not been observed, however. A host of confounding issues enter into this equation, most of which are just beginning to be approached experimentally or in clinical studies.

DNA Methylation
The authors detail various potential mechanisms by which folate may prevent cancer. The role of folate in altering DNA methylation status is discussed most thoroughly. DNA methylation results from transfer of a methyl group from S-adenosylmethionine to deoxycytidine located primarily in CpG islands. The primary dietary sources of these methyl groups are folate, methionine, and choline. In general, methylation is a mechanism for regulating gene activity.[7] DNA hypomethylation is recognized as a very early event in adenoma formation, specifically in adenomas 0.5 cm or less.[8] It is not certain how methylation influences carcinogenesis, but it is thought that a change in chromatin packing enhances the accessibility of carcinogens to DNA. Alternatively, hypomethylation may lead to global genomic instability and, consequently, aberrant chromosome pairing and dysjunction during mitosis.

Interestingly, hypermethylation can also influence tumorigenesis by downregulating expression of important genes. Both hypomethylation and hypermethylation may be regional and may greatly influence the activation state of important oncogenes or tumor-suppressor genes.[9] The methylation status of specific genes may thereby determine the outcome of subsequent mutational events. It would appear that DNA methylation greatly influences tumor formation, and an important body of work indicates that diet greatly influences methylation status. This is a highly pertinent area of study that will continue to generate considerable interest.

There is a growing consensus that chemoprevention will be most successful through the use of multiple micronutrients. Unfortunately, as noted by Dr. Frank Meyskens at the most recent AACR meeting, we currently lack good intermediate biomarkers to assess the efficacy of dietary interventions in preventing cancer.[10] DNA methylation status may be a good biomarker, but considerable work remains to be done to establish its utility in chemoprevention studies.

References:

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