Folate and cancer prevention: a closer look at a complex picture\textsuperscript{1–3}

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Folate is thought to play a significant role in cancer prevention. Epidemiologic evidence consistently shows inverse associations between higher intakes of dietary folate (or higher concentrations of respective biomarkers) and a reduced risk of cancer of the colon, of other parts of the gastrointestinal tract, and, more recently, of the pancreas. In addition, genetic polymorphisms in folate metabolism have been associated with these malignancies and, further, with those of the hematopoietic system. These genetic studies have also shown consistently that gene-nutrient interactions exist and that an evaluation of genetics without assessment of dietary intakes or supplement use related to folate-mediated one-carbon metabolism provides only an incomplete picture (1).

Many experimental studies have substantiated the observational findings: folate’s possible cancer-preventive properties have been attributed to its function in the de novo synthesis of thymidylate and purines—nucleotides that are needed for DNA replication and repair. Furthermore, adequate folate status is important for the production of S-adenosylmethionine (SAM), a universal donor of methyl groups for a number of methylation reactions, including DNA methylation (2). DNA methylation is central to gene silencing and probably to the suppression of repetitive DNA of viral origin, which comprises considerable parts of the genome (3). Yet, despite the evident link between the methyl donor SAM and folate metabolism, it is currently not well defined how folate status affects DNA methylation, both at gene promoters and on a genomic level, and what the consequences are for cell biology.

However, the role of folate in carcinogenesis is more complex than was initially thought. Several lines of experimental data suggest that the timing and dose of folate supplementation during carcinogenesis can matter (4, 5). Although increases in folate before the existence of preneoplastic lesions (such as aberrant crypt foci or polyps in the colon) can prevent tumor development, supplementation with synthetic folic acid may enhance progression once preneoplastic lesions are present. Similarly, animal experiments suggest that modest supplementation can reduce carcinogenesis, whereas excessive supplementation may increase tumor growth (6). These opposing effects are thought to be attributable to folate’s function in nucleotide synthesis, which is needed to support rapidly proliferating tissues. Cancers frequently up-regulate folate receptors to meet their elevated need for nucleotides to support DNA synthesis and growth. Folic acid is more bioavailable than is folate and, thus, is probably more potent in fostering growth. Recently, a randomized controlled trial of chemoprevention of polyp recurrence with folic acid (1 mg/d) showed an increased risk of advanced or multiple adenomas after multiple years of intervention (7); these results suggest that the role of folate in fostering the growth of precancerous lesions is a valid concern for humans at intakes that can be achieved with a combination of supplement use and fortification with folic acid (8). The results are particularly relevant because \( \geq 30\% \) of adults aged \( \geq 60 \) y harbor intestinal polyps (9), yet many do not undergo colonoscopic screening for polyp detection and removal.

In this issue of the Journal, the work by Ericson et al (10) adds a new chapter to the evolving story of folate and cancer prevention. Within the Malmö Diet and Cancer cohort of 11 699 women aged \( \geq 50 \) y, they observed strong inverse associations between dietary intakes of folate and invasive breast cancer, with risk reductions of \( \geq 40\% \) in the highest compared with the lowest quintile of intake. These associations are substantially stronger than those reported from previous cohort studies, which have generally shown no relation between folate and breast cancer alone, yet that have noted quite consistently that higher folate intakes or biomarkers thereof were protective in women with a high intake of alcohol. A high consumption of alcohol is an established risk factor for postmenopausal breast cancer, and an interaction with folate is biologically plausible because of the role of alcohol in inhibiting the absorption and metabolism of folate (11).

The question arises as to why much stronger inverse trends were seen in the Swedish cohort than in previous largely United States–based cohort studies. There are several possible explanations for this observation. First, Ericson et al conducted a very thorough assessment of diet and supplement use, which involved the use of a 7-d menu book for major meals, a food-frequency questionnaire, and a complementary interview. It would be helpful to know whether folate intakes estimated with these methods show stronger correlations with biomarkers, such as erythrocyte folate, than do those obtained with the more standard food-frequency questionnaires. Second, the Swedish study population, of which only 19\% are supplement users, had lower intakes...
of folate than did the US populations previously studied. If only a very low folate status increases the risk of invasive breast cancer, then strong associations can be detected only in study populations that include a sufficient number of subjects in the low-folate range (Figure 1).

This finding raises the question of whether intakes that exceed an “adequate” level are still protective against breast cancer risk. Overall, there is little evidence of an additional reduction in risk at above-adequate folate intakes, even though this may be the case for women with high alcohol consumption. Furthermore, recent reports from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) study population suggest that a very high folate status, attributable to excessive supplement use, may generally be harmful rather than beneficial in breast cancer development (12). To illustrate the differences in folate status, the highest quintile in the Swedish cohort (where supplement use was very low) was defined as >349 μg/d, whereas the PLCO cutoff for the highest quintile was more than double, ie, >853 μg/d. Thus, the body of epidemiologic literature on this topic to date suggests that the relation between folate and postmenopausal breast cancer risk may be nonlinear and that one needs to carefully evaluate the nutritional status of the population to draw appropriate conclusions (Figure 1). Whereas an increase in folate intakes may be beneficial in a deficient population, higher intakes may result in no further benefit or could be harmful in women whose folate status is already sufficient. In addition, because of the known gene-nutrient interactions characteristic of folate metabolism, associations with genetic polymorphisms may differ depending on the folate status of the population (1). Thus, the optimal folate intake for breast cancer prevention has not yet been defined and will differ depending on alcohol consumption and genetic susceptibility.

One should be cautious about drawing strong support from the study by Ericson et al for increasing folate intakes in the general population as part of public health measures. Fortification of grain products has been mandated in several countries for the prevention of neural tube defects. The success of this policy is indisputable, given the significant decreases in neural tube defects in the United States, Canada, and Chile since the initiation of fortification (13). Folate status in the US population has increased substantially; ≈40% of the US population has postfortification serum folate concentrations >40 nmol/L—a concentration that has been described as being supraphysiologic (14). At the same time, unmetabolized folic acid is detectable in the circulation of healthy individuals, with unknown physiologic consequences (4). Several European countries are currently considering the introduction of folic acid fortification for the prevention of neural tube defects, perhaps under the assumption that folic acid fortification will also aid in the prevention of cancer and of cardiovascular disease. Yet, as discussed above, there is now increasing evidence from randomized trials that high doses of folic acid can foster the growth of common precancerous lesions. The benefit of reducing a relatively small number of neural tube defects may be outweighed by the possible negative effects on tumor promotion in a substantial fraction of the population. We currently lack good quantitative information on the effects of folic acid on the growth of preneoplastic lesions or on carcinogenic progression. However, even if the extent of these adverse effects was modest, a large number of individuals with cancer precursors would be affected. Thus, a cautionary approach is warranted as we consider whether to recommend an increase in folate status for all.

Folate may play a dual role in cancer development: it may provide protection early in carcinogenesis and in individuals with a low folate status, yet it may promote carcinogenesis if administered later and potentially at very high intakes. We need to evaluate this information carefully when developing public health recommendations and should be mindful that more folate is not better in all circumstances.

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REFERENCES


