Folate consumption and cancer risk: a confirmation and some reassurance, but we’re not out of the woods quite yet1–4

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Over the past ~25 years, a body of quite compelling evidence has accrued that indicates that habitually low consumption of folate leads to an increased risk of certain types of cancer. The evidence is most persuasive for cancers of the colorectum, in part because it is in this organ that the greatest number of studies have been done, but also because of the overall consistency of the epidemiologic studies [reviewed in Chen et al (1)] as well as the more mechanistic studies in relevant animal models [reviewed in Kim (2)]. Lesser degrees of evidence exist for cancers of other organs, such as those of the breast, stomach, lung, esophagus, and pancreas (1). Interestingly, in the epidemiologic studies of breast cancer, adequate folate consumption appears to be most consistently protective among those women who are regular consumers of alcohol, an observation that recapitulates some of the observations that have been made with regard to colon cancer [including in the present study by Gibson et al (3)] and which is consistent with the fact that alcohol is a moderately potent inhibitor of folate metabolism (4). It is nevertheless important to point out that, even among studies of the colorectum, there are some notably null observations [eg, in Eussen et al (5)], the explanations for which remain unclear.

Interestingly, folate’s central role as a cofactor in nucleotide synthesis also means that abundant availability of the vitamin can facilitate the proliferation of rapidly dividing cells, and hyperproliferation is a feature of most dysplastic (“precancerous”) and malignant (“cancerous”) neoplasms. Evidence indicative of this effect began to emerge in the 1940s in the context of some small clinical trials, and the effect has since been reproduced in various rodent models of colorectal cancer [eg, in Song et al (6)]. More convincingly, 2 contemporary clinical trials containing large numbers of subjects have observed an acceleration in the development of premalignant adenomas (7) or frank malignancies (8, 9) among those subjects randomly assigned to receive folic acid supplements. Thus, under most circumstances adequate availability of folate appears to assume the role of a cancer protective agent, presumably by enhancing genetic stability and diminishing activation of procarcinogenic cell signaling (10). However, a concern has arisen that in an individual who harbors a neoplasm (or perhaps even a microscopic clone of dysplastic cells), an overly abundant consumption of folate might paradoxically facilitate the proliferation of neoplastic cells, transforming the vitamin into an agent that causes cancer promotion. Many investigators in this field would acknowledge that a cancer-promoting effect of excess folate might genuinely occur under highly select circumstances in animal models and in humans, but the more difficult—and considerably more controversial—question is whether such an effect exists in the general population. In determining whether this indeed is a generalized problem, one also needs to consider that several other folic acid intervention trials [albeit of shorter duration than that of Cole et al (7)] have not observed a cancer-promoting effect [eg, Logan et al (11)] and that a meta-analysis observed only a 5% increase in cancer risk, which was within a 95% CI that included an RR of 1.0 (12).

The issue is a particularly poignant one because many new sources of folate have entered our food stream in the past few decades, largely in the form of supplements and fortified foods. Estimates derived from nationally representative data indicate that ~4.8–5.2% of US adults aged 51–70 y (ie, an age group that is likely to harbor indolent precancerous lesions of the colon and prostate) consume >1000 μg folic acid each day (13), which is the upper limit of safety cited by the Institute of Medicine and the range in which the paradoxical cancer-promoting effect is hypothesized to occur. This translates into ~2.6 million Americans in this age stratum alone (14) who regularly consume an excessively high amount of folic acid.

This brings us to the article by Gibson et al (3), which appears in this issue of the Journal. This study was designed to examine, within the context of a large cohort of AARP members, the question of folate consumption and colorectal cancer risk at both ends of the spectrum. In many respects this is a study in whose results we should place confidence: it has a prospective and population-based design; the study population has a wide range of folate intakes; and the sample size is very large, providing sufficient statistical power for stratified analyses of many relevant effect modifiers. Therefore, the observation by Gibson et al that excess folate consumption is associated with a 5% increase in colorectal cancer risk, which was within a 95% CI that included an RR of 1.0, is a confirmation of some grossly reassuring, but not disquieting, nature.

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that consuming adequate amounts of folate (assessed as either dietary or total folate intake) compared with a low amount of the vitamin is associated with a substantial decrease in the risk of colorectal cancer is a robust confirmation of what has been observed in a number of preceding studies. Of equal interest is the fact that little or no additional protection was conveyed when either total or dietary folate consumption rose above ~500 µg/d. More than those in any preceding study, these observations provide some excellent guidelines as to what levels of folate intake we should target for the purpose of minimizing colorectal cancer risk.

Importantly, these observations also provide some genuine reassurance that the concern raised by myself and others regarding the possibility of cancer promotion due to extraordinarily high amounts of folate intake is not a widespread phenomenon in the general population. The results and conclusions, therefore, concur with those of another large prospective cohort study that was just published a few months ago (15).

So why, then, do some of us continue to feel that we are not yet at a point where we can totally dismiss the concern over a potential cancer-promoting effect of excessively high intakes of folate? The answer, in part, relates to the gravity of the public health ramifications if such an effect exists and is inadvertently overlooked. The weight of evidence used to disprove a potentially harmful phenomenon should be roughly proportional to the severity and extent of damage that could be incurred by the phenomenon. Second, and more importantly, I believe that neither the Gibson et al (3) nor the Stevens et al (15) studies were able to satisfactorily examine that segment of their study populations that would be most susceptible to a cancer-promoting effect of high folate intake. The subgroup in which we would most likely observe a cancer-promoting effect is individuals who harbor an existing adenoma or cancer of the colon. Gibson et al try to address this by performing a secondary analysis of the 9% of individuals who reported a history of polyps in their 1996 questionnaire (see their Discussion). However, it is unlikely that this accurately captured the correct subgroup considering that 1) given the known prevalence of different types of polyps, the majority of that 9% probably had hyperplastic rather than adenomatous polyps (ie, polyps not predictive of cancerous transformation), 2) subjects who are aware that they have had polyps are much more likely to undergo subsequent colonoscopies, thereby removing adenomas and making this a very-low-risk subgroup, and 3) the accepted prevalence of adenomas in this age group in North America is ~35–40%, which suggests that the investigators fell far short of capturing the subgroup at risk. In the case of the Stevens et al study (15), the median intake of the group consuming the most folic acid was only 660 µg/d. Moreover, only 2% of their study population consumed more than 1000 µg/d, suggesting that these investigators lacked sufficient numbers of individuals consuming very high amounts of folate to effectively probe for a cancer-promoting effect.

In summary, it is heartening to have further confirmation about the cancer-protective effect of consuming adequate amounts of folate and quite reassuring that a cancer-promoting effect is not a prevalent phenomenon in the general population. However, I, for one, believe it is still premature to entirely dispel the notion that there might be segments of our aging population that are susceptible to a promoting effect if they consume extraordinarily large amounts of the vitamin. We should remain mindful of this possibility as we move ahead.

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