

# Folate and Cancer—Timing Is Everything

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A LARGE NUMBER OF EPIDEMIOLOGICAL STUDIES HAVE shown that a higher intake of folate, as well as higher intakes of vegetables and fruit, is associated with a decreased risk of colorectal polyps and cancer.<sup>1</sup> These results have been corroborated by animal experiments,<sup>2</sup> and biological mechanisms underlying these associations have been proposed<sup>3</sup>: folate functions as a source of carbon moieties in the synthesis of nucleotides that are essential for DNA replication and repair. Folate deficiency leads to mutations and chromosomal damage—effects that are also central to the efficacy of antifolate chemotherapeutic agents (eg, methotrexate). In addition, folate status is important for the provision of *S*-adenosylmethionine, the universal methyl donor, involved in normal and pathological methylation of DNA. Disturbances in DNA methylation are relevant in carcinogenesis<sup>4</sup>; however, the role of folate in these epigenetic changes is not yet understood.

Despite its central function in maintaining DNA integrity, the role of folate in cancer prevention may not be as straightforward as initially conceived. Recent experiments have suggested that the timing of folate administration during cancer progression can modify outcomes.<sup>5,6</sup> Folate administration prior to the existence of preneoplastic lesions can prevent tumor development, whereas provision of folate once early lesions are established appears to increase tumorigenesis. This initially counterintuitive observation may be explained by the function of folate in nucleotide synthesis. Rapidly proliferating tissues, including tumors, have an increased requirement for nucleotides; thus many cancers up-regulate folate receptors, and antifolate drugs are efficacious in cancer treatment.

The overall chemopreventive effectiveness and potentially deleterious consequences of folate supplementation in humans can be established only through randomized controlled trials. In this issue of *JAMA*, Cole and colleagues<sup>7</sup> present results of the first large chemoprevention trial investigating the effects of folate supplementation (at 1 mg/d folic acid, the synthetic form of folate) on the development of colorectal adenomas, established colorectal cancer precursors.

See also p 2351.

Follow-up was performed with 2 colonoscopic surveillance cycles, at 3 years and approximately 3 to 5 years later.

An important eligibility criterion for entry in the Aspirin/Folate Polyp Prevention Study was history of an adenoma. This choice was made because the risk of a metachronous adenoma is high in this group compared with the appearance of new adenomas in previously unaffected individuals, and this criterion allowed a shorter trial and reduced sample size. The study therefore addressed secondary rather than primary prevention of adenoma.

Overall, there was no effect of 1-mg/d supplementation on the development of adenoma, with risk ratios (RRs) of 1.04 (95% confidence interval [CI], 0.90-1.20) at 3 years and 1.13 (95% CI, 0.93-1.37) at the second follow-up. However, at the second follow-up, there was a 67% increased risk of advanced lesions (RR, 1.67; 95% CI, 1.00-2.80), along with a more than 2-fold increased risk of having at least 3 adenomas (RR, 2.32; 95% CI, 1.23-4.35). Of concern, the risk of cancers other than colorectal cancer was significantly increased in the intervention group ( $P=.02$ ), an observation largely attributable to prostate cancer. Moreover, the study showed no evidence that folate supplementation reduced cardiovascular outcomes, an expected benefit because of the homocysteine-lowering effects of folate.<sup>8,9</sup>

How should the unexpected results of this study be interpreted? The most likely explanation for the increased risk of advanced and multiple adenomas in the intervention group is that undetected early precursor lesions were present in the mucosa of these patients (who are at increased adenoma risk), and that folic acid promoted growth of these lesions. This hypothesis is consistent with experimental studies showing increased colorectal neoplasia when folic acid is administered after lesions are present.<sup>2</sup>

Nonetheless, by the nature of the design, the results do not provide information on primary prevention by folic acid (the potential for folic acid to reduce the incidence of first adenomas). The question of efficacy of folate in cancer prevention is not resolved, and animal experiments showing chemopreventive effects of folate, as well as the strong observational epidemiological evidence, speak to the potential of folate as

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a chemopreventive agent, if taken early. Unfortunately, primary prevention trials that start in childhood would be lengthy, expensive, and logistically nearly impossible.

Furthermore, by design, this trial cannot answer another important question. What are the effects of folic acid supplementation among individuals with existing, unresected colorectal polyps? In this study, repeat colonoscopies ensured that no colons contained polyps. However, in the general US population, only approximately 30% of adults older than 50 years have had an endoscopic examination in the previous 5 years,<sup>10</sup> and the prevalence of colorectal polyps among individuals older than 60 years approximates 30%.<sup>11</sup> The question of the effect of folic acid on unresected polyps is particularly concerning, because intakes in the population have increased significantly with folate fortification of food, mandated in the United States since January 1, 1998.<sup>6</sup> At the same time, use of folic acid-containing supplements is high, particularly among the elderly population.<sup>6</sup>

There are several possible explanations for the discrepancy between the results of the trial by Cole et al<sup>7</sup> and the findings from observational studies. First, folate may not be the main bioactive component of fruits and vegetables; other substances may be chemopreventive (eg, fiber, other vitamins, phytochemicals). However, this as an explanation to the exclusion of folate is unlikely, because both animal experimental studies<sup>2</sup> and studies of genetic polymorphisms in folate metabolism<sup>12</sup> suggest a causal role for folate in cancer prevention. Second, the intervention period may have been too short to observe a chemopreventive effect of folate. This explanation is also not convincing, given that increased RRs were observed with longer follow-up.

This leaves the dual role of folate in carcinogenesis as an explanation for the discrepancy. By preventing DNA damage, folate may be efficacious in the primary prevention of colorectal neoplasia. However, this trial tested its efficacy as a secondary prevention agent. The size of these competing effects of folate on carcinogenesis is currently not known. However, if the chemopreventive effects of folate on the development of early lesions are strong overall, the risk reduction with folate would be similar to that observed in epidemiological studies.

Because the timing of folate administration during carcinogenesis matters, the results from this trial do not provide data on primary prevention. However, they certainly provide a definitive answer that, among patients with resected adenoma, folic acid intake of 1 mg/d, which can be achieved with 2 multivitamins plus folic acid from fortified foods, is not beneficial for adenoma prevention. The results also highlight several important research needs on the role of folate in carcinogenesis. First, a better understanding is needed about the dosage, duration, and timing effects of folic acid on the growth of early neoplastic lesions and slow-growing tumors, including, for example, a subset of prostate cancers.

Second, information on the effects of folic acid among individuals with unresected colorectal polyps is critical. As

such studies are unethical in humans, animal experiments, perhaps incorporating mouse endoscopy,<sup>13</sup> can help. Information from these studies may be used to calculate, by using mathematical modeling strategies, the net result of the opposing effects of folic acid on cancer in humans.

Third, research on the effects of folate supplementation among patients with cancer should be a high priority. Patients with cancer tend to consume more supplements than healthy individuals, raising the possibility of adverse effects of folic acid on cancer progression, recurrence, and metastasis. In addition, possible interactions between folate supplement use and drugs targeting folate metabolism are poorly understood.<sup>14</sup>

The results of the clinical trial by Cole et al<sup>7</sup> illustrate, yet again, the principle that chemoprevention with single agents is problematic. Similar to the increased risk of lung cancer observed with beta carotene supplementation, selection of resistant clones is as plausible an outcome of the use of single-agent chemoprevention as it is of single-agent chemotherapy.<sup>15</sup> The data in Figure 2 in the article by Cole et al are particularly illuminating: the excess of advanced polyps was observed only in the group consuming folate but not aspirin. It is time to be as thoughtful about the need for multiagent chemoprevention, not forgetting that diet is one version of this, as about the use of multiagent chemotherapy.

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