

cases are likely to have existed undiagnosed at baseline. Thus, in keeping with the fears of some researchers, synthetic FA supplementation may have increased the proliferation of preexisting CA cells. In contrast, dietary folate intake correlated inversely with risk, albeit non-significantly.

What are clinicians to make of all this? First, whenever FA supplementation is serving little purpose, it should no longer be used gratuitously simply because "it's inexpensive, it's natural, and it's harmless." It's not natural. Under certain circumstances it may not even be harmless.

Preventing neural tube defects should not be considered a gratuitous use, given that some researchers have provided evidence that the current level of grain fortification remains less than optimal. Furthermore, a very high percentage of young pregnant women are likely to be CA-free and therefore immune from possible CA cell-proliferating effects of synthetic FA now feared by some researchers. However, in older adults for whom the risk of undiagnosed CA is much higher, it may now be time for caution until this picture comes into focus. Moreover, until more is known, patients with preexisting CA diagnoses should probably avoid synthetic FA supplementation.

In the end, when we don't know how to proceed, we should step cautiously. A few supplement companies offer natural folates, sometimes listed by structure (e.g., "5-methyl tetrahydrofolate") or by name (e.g., "Metafolin"). If the potential problem with synthetic FA turns out to be a function of a buildup of unmetabolized FA, these natural alternatives should provide the solution. However, beware of labels that contain "folic acid and 5-methyl tetrahydrofolate" but do not quantify the amount of each. Given the cost differential, in the absence of such a quantitative breakdown, it's likely that such supplements are mostly inexpensive synthetic FA.

### **Is Selenium Effective for Cancer Prevention?**

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Selenium functions as an antioxidant and also enhances immune function, effects that might be expected to protect against the development of cancer. Numerous animal studies have shown that selenium has an anticancer effect.<sup>1</sup> Observational studies in humans have also found that better selenium status is associated with a lower incidence of cancer. In some clinical trials, selenium supplementation decreased the risk of developing cancer, but a recent double-blind trial did not find a protective effect. These studies are reviewed below, and possible explanations for the conflicting findings are offered.

In a region of China where the incidence of primary liver cancer is high because of polluted water, aflatoxin exposure, and a high rate of hepatitis B infection, selenium supplementation (200 mcg per day) significantly decreased the incidence of liver cancer compared with placebo. Selenium supplementation also significantly decreased the incidence of liver cancer in Chinese patients with hepatitis B infection.<sup>2</sup> In another study of Chinese patients with mild-to-moderate esophageal squamous dysplasia (a precursor to esophageal cancer), supplementation with 200 mcg per day of selenium (as selenomethionine) for 10 months had a protective effect on disease progression that was of borderline statistical significance. Post hoc analysis demonstrated that the protective effect was significant in patients with mild dysplasia, but not in those with moderate dysplasia.<sup>3</sup>

In a double-blind study conducted in the United States in patients with a history of non-melanoma skin cancer, supplementation with 200 mcg per day of selenium (from high-selenium yeast) for a mean of 4.5 years significantly reduced total cancer mortality, total cancer incidence (excluding skin cancers), and the incidences of lung, colorectal, and prostate cancer, compared with placebo. However, selenium supplementation was associated with a possible increase in recurrences of squamous cell carcinoma.

Some 1,312 patients (mean age, 63 years) with a history of basal cell or squamous cell carcinoma of the skin were randomly assigned to receive, in double-blind fashion, 200 mcg per day of selenium (from 500 mg per day of high-selenium yeast) or placebo. Patients were treated for a mean of 4.5 years, and the mean total follow-up period was 6.4 years. Selenium treatment did not affect the recurrence rate of skin cancers. However, compared with placebo, selenium treatment significantly reduced total cancer mortality by 50%, total cancer incidence (excluding skin cancers) by 37%, and the incidence of lung cancer by 46%, colorectal cancer by 58%, and prostate cancer by 63%. Selenium also decreased all-cause mortality non-significantly by 17%. No cases of selenium toxicity occurred.<sup>4,5</sup> In a longer-term follow-up of this cohort, the recurrence rate of squamous cell carcinoma was significantly higher by 25% in patients who had received selenium than in those who had received placebo.<sup>6</sup> Another follow-up study of this cohort suggested that selenium supplementation reduced the risk of lung cancer in people with low baseline plasma selenium concentrations, but not in people with higher levels.<sup>7</sup>

In contrast to these positive results, another double-blind study conducted in the United States, Canada, and Puerto Rico found that supplementation with 200 mcg

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