See corresponding article on page 718.

The rise and fall of blood folate in the United States emphasizes the need to identify all sources of folic acid[1,2]

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Folic acid–containing supplements and fortified foods, including enriched cereal–grain products and ready-to-eat (RTE) cereals, are the primary sources of folic acid intake in the United States (1). Changes in the intake of any of these sources may significantly affect blood folate concentrations. To effectively monitor how changes in folic acid intake are influencing trends in folate status, it is important to characterize the sources of folic acid, as illustrated in the recent publications by Yang et al (1) and Berry et al (2). During the past decade, as blood folate concentrations have first increased and then decreased, the assumption was that the blood folate changes were due solely to changes in folic acid intake from enriched cereal–grain products. A report by Pfeiffer et al (3) in this issue of the Journal provides the first opportunity to evaluate trends in blood folate concentrations in the US population that extend beyond the early postfortification phase (ie, 1999–2000) by encompassing the more recent periods of 2001–2002 and 2003–2004. In these 2 survey periods, serum and RBC folate concentrations declined significantly from those seen in 1999–2000. The observed decreases are of a magnitude much smaller than that of the initial increase that occurred in the wake of fortification. Detailed analysis of the sources of folic acid intake will be necessary before it is possible to ascertain whether the observed changes in blood folate concentrations could be attributed to changes in folic acid intakes from enriched cereal–grain products, folic acid–containing supplements, or RTE cereals.

It is important to consider that changes in the use of folic acid–containing supplements may have affected blood folate concentrations in the years since fortification was implemented. Supplement use in the United States previously was reported to be greater during the first postfortification period (NHANES 1999–2000) than during the prefortification period (NHANES 1988–1994); considerable variation was seen, depending on race-ethnicity (4). The reported use of folic acid–containing supplements in predominantly white women of childbearing age across all time intervals fluctuated from ≈30% of that population before fortification (1995–1998), rising to ≈40% in 2004 and returning to prefortification proportions in 2005 (5). Differences in supplement use should also be considered as a potential explanation for observed differences in blood folate concentrations between different racial-ethnic groups. Yang et al (1) estimated that non-Hispanic white women in the United States obtained ≈48% of their folic acid intake from supplements, whereas non-Hispanic black and Hispanic women obtained only ≈26%, according to data from NHANES 2001–2002. No supplement use data are provided in the report by Pfeiffer et al (3); however, the rank order of blood folate concentrations among racial-ethnic groups—ie, non-Hispanic white > Mexican American > non-Hispanic black—likely is due in part to differences in the proportions of each of these groups who used folic acid–containing supplements (1, 6). Because the blood folate data were not analyzed separately for supplement users and nonusers, it is not possible to estimate the potential influence of supplement use on observed changes in blood folate concentrations (3). In future investigations of trends in blood folate concentrations, it would be of interest to determine whether folate status differs between supplement users and nonusers and whether supplement use is affected by race-ethnicity in each sex and age group.

A potential explanation for the most recent observed decreases in blood folate concentrations may be that industry has reduced the amount of folic acid it adds to enriched cereal–grain products. In an analysis of a number of enriched foods during the early postfortification period (1998–1999), Rader et al (7) found that the total folate content of many of the analyzed foods far exceeded the amount required by federal regulations. Although there has been no systemic examination of changes in folate content of enriched cereal–grain products, 2 research groups have reported data supporting the conclusion that the amount of folic acid added to the food supply has been reduced (8, 9). Johnston and Tamura (8) found that, in 2002 and 2003, the folate content of white breads containing enriched flour was significantly lower than that observed in 2001. Poo-Prieto et al (9) used a new affinity/HPLC method to measure the quantity of folic acid in numerous folic acid–enriched foods. In their study, no evidence was found of folic acid overages in enriched products. An ongoing systematic evaluation of the folic acid content of enriched food products is needed to track changes that may be associated with observed fluctuations in blood folate concentrations in the US population, such as those reported by Pfeiffer et al (3). This evaluation will be a daunting task, considering the fact that there are thousands of food products—including such

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widely used products as flour and pasta—that contain folic acid–enriched cereal-grain components.

Another proposed explanation for the observed decrease in blood folate concentrations from 2001 to 2004 is the reduced consumption of cereal-grain products that resulted from the low-carbohydrate diet trend (5). Before the beginning of the low-carbohydrate diet trend in the early postfortification period (1999–2000), the food category of bread, rolls, and crackers was ranked as the top source of folate in the US diet, exceeding vegetables, which had been the top source before fortification (10). Recent data indicate that the low-carbohydrate trend is diminishing somewhat, which may positively affect blood folate concentrations (5). Whether the current focus in the United States on weight reduction will affect the consumption of folic acid–enriched cereal grain products has yet to be determined.

The early positive effect of the folic acid fortification program—ie, a 26% reduction in the prevalence of neural tube defects (NTDs) in the United States—is well documented (11, 12). It is not known whether the 16% and 8% declines in serum and RBC folate concentrations, respectively, from 1999–2000 to 2003–2004 in women of childbearing age (15–44 y old) affected the incidence of NTDs (13). No data on the prevalence of NTDs during 2003–2004 are available from the National Birth Defects Prevention Network, which prevents a comparison of NTD trends for 1999–2004 with trends in blood folate concentrations in women of childbearing age during that same time period (13). Pfeiffer et al detected no changes in the prevalence of low blood folate concentrations during 1999–2004, when the overall trend was downward, a condition that presumably carries a higher risk of an NTD-affected pregnancy.

Pfeiffer et al addressed the need to increase the folate intake of the target group (ie, women of childbearing age) and yet to guard against "excessive" folate intakes in the population as a whole. No data are available to support any negative effects of folic acid consumed in fortified foods; in contrast, evidence is cited that folic acid fortification is associated with a significant reduction in the rate of death due to strokes (14). These population-based data span more than a decade (1990–2002) and document a significant reduction in stroke mortality after the implementation of folic acid fortification (14). Pfeiffer et al contrasted these findings with data from short-term randomized clinical intervention studies in which supplemental folic acid was not shown to reduce the recurrence of events or mortality due to established vascular disease. Unlike NTDs, chronic vascular and neurologic diseases and cancer evolve over a lifetime, which provides one explanation for why these disease outcomes are not likely to be influenced in short-term secondary intervention studies. When all of the current evidence related to homocysteine and vascular disease risk is considered in the context of study design, varied responses due to folic acid fortification, and statistical power, it is premature to pass judgment on the clinical and public health relevance of these findings (15).

In evaluations of nonrandomized studies in which blood folate concentrations were associated with health outcomes, it is important to recognize that there may be a number of unidentified confounding variables that were not controlled for in the analysis and that could bias the conclusions. An example of such a study is that of Morris et al (16), in which impaired cognition was associated with high serum folate concentrations in a very small subset (42/3707) of persons with low vitamin B-12 status. As is shown in the detailed critique of that study in a letter to the editor by Berry et al (2), subjects in the high serum folate category likely differed from subjects with lower serum folate concentrations because of the former group's supplement use and, potentially, other health-related issues, such as pernicious anemia, that may have negatively affected cognitive function. If future studies identify adverse effects associated with high blood folate concentrations, it will be important to be able to characterize the sources of folic acid intake, including supplements, enriched cereal–grain products, and RTE cereals, that are associated with high blood concentrations, so that appropriate policy decisions can be made.

The report by Pfeiffer et al (3) makes a valuable contribution to our understanding of trends in folate and vitamin B-12 status of the US population before and after the beginning of the folic acid fortification program. The rise and fall in blood folate concentrations in the United States and the potential for these changes to have health-related consequences provide the incentive for further investigations to identify and monitor changes in the specific sources of folic acid intake.

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