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Letter

Comment on "The public health implications of smoking-induced decreased serum and red blood cell folate levels"

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The article "Tobacco smoke exposure and decreased serum and red blood cell folate levels: Data from the Third National Health and Nutrition Examination Survey" by Mannino et al. (this issue) addresses an important question with relevance to the web of causation linking smoking to cancer, ischemic heart disease and other illnesses. A total of 15,564 adults (>17 years of age) enrolled in the Third National Health and Nutrition Examination Study (NHANES III) underwent testing for serum and red blood cell (RBC) folate levels and recorded a 24 hr dietary recall to determine the effects of both active smoking and passive exposure to tobacco smoke on serum and RBC folate levels. Although previously published studies have examined the association between active smoking and folate (Cafolla et al., 2000; Mansoor et al., 1997; Piyathilake, Macaluso, Hine, Richards, & Krumdieck, 1994), NHANES III is the first study to also examine the effects of *passive* smoking on folate. The findings from this study should be considered in terms of their significance for both direct and indirect causal associations.

With regard to the issue of causal inference of a direct relationship between active or passive smoking and folate levels, it should be noted that serum folate levels reflect only very recent dietary intake and do not accurately reflect total body folate stores (Lichtenstein & Mueller, 1996). Rather, erythrocyte (RBC) folate levels are a more robust measure. When adjusted for age, sex, race or ethnicity, socioeconomic status, dietary and vitamin intake, and alcohol intake, the odds ratio for RBC folate deficiency for smokers compared with nonsmokers with low exposure to passive cigarette smoke was 2.4 (95% confidence interval = 2.0, 2.8). The effect size suggests that smokers have a significantly lower serum folate level than do nonsmokers. However, given that smoking was associated with decreased folate intake, it is not entirely clear whether the observation of lower RBC folate levels is due entirely to decreased intake among smokers, whether the decreased folate levels are due to changes in folate metabolism due to smoking, whether decreased folate levels precede smoking initiation in the temporal relationship, or whether the observed reduction in folate is due to a combination of the above.

The investigators used a folate level of less than 340 nmol/l as the criterion for folate deficiency. Although the sensitivity of clinically significant folate deficiency for patients with megaloblastic anemia is uncertain in particular patient populations (e.g., pregnant or alcoholic patients), this is a conservative criterion for the general population (Savage & Lindenbaum, 1986). Folate deficiency impairs the production of tetrahydrofolate, leading to a defect in DNA synthesis, preventing cell division in the bone marrow, and resulting initially in increased RBC mean corpuscular volume (MCV) and eventually in anemia. When adjusting for covariates, these data

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demonstrated a statistically significant increased risk for an MCV of greater than 100 fl for smokers when compared with nonsmokers. The effect sizes for RBC folate among subjects exposed to passive tobacco smoke were small (odds ratio 1.5 for high exposure and 1.3 for low exposure) and demonstrated no significant difference in MCV. Thus, the data among this nationally representative population suggest that *active* but not *passive* smoking increases risk for clinically significant folate deficiency. Even so, the graded increase in effect size from low passive exposure to active smoking provides evidence of a biological gradient or dose–response relationship, further strengthening the argument for a causal relationship between smoking and decreased folate levels (Hill, 1965).

Folate deficiency can result from a wide array of causes including inadequate dietary intake; increased demands from pregnancy, infancy, and diseases associated with rapid cellular proliferation such as exfoliative dermatitis; malabsorption; and biological competition for dietary folate from bacterial overgrowth; or as a result of several classes of medications or alcohol (Savage & Lindenbaum, 1986). Although this study controlled for self-reported dietary folate intake, vitamin use, and alcohol use, it is still possible that the results are confounded by many other potential causes of folate deficiency.

With regard to whether the causal relationship between smoking and cancer, ischemic heart disease, and other illnesses is mediated through folate metabolism (i.e., indirect causation), data is needed. However, one can begin to predict the significance of a causal relationship mediated through folate metabolism through a case in point. One of the best-studied associations is that between use of folate in the prenatal period and neural tube defects (Berry et al., 1999; Bower & Stanley, 1989; Czeizel & Dudas, 1992; Milunsky et al., 1989; MRC Vitamin Study Research Group, 1991; Mulinare, Cordero, Erickson, & Berry, 1988; Shaw, Schaffer, Velie, Morland, & Harris, 1995; Smithells et al., 1980; Werler, Shapiro, & Mitchell, 1993). Approximately 720,000 out of approximately 4 million live births each year in the United States are to women who smoke throughout pregnancy (U.S. Department of Health and Human Services, 2000). Although the risk of neural tube defects among folate-deficient mothers has not been clearly identified, the risk of neural tube defects among mothers who do not take folate supplementation is about 4.8 per thousand live births, compared with about 0.7 per thousand live births among women using folate supplementation. Thus, the population-attributable fraction (the fraction of the incidence rate of neural tube defects in the population attributable to lack of folate supplementation) is about 85%. In view of the data from this study, the absolute risk of folate deficiency among smokers is about 14% compared with about 6% among nonsmokers. Thus, about 98,500 pregnant smokers in the United States could be folate deficient. Folate-deficient mothers are about twice as likely to give birth to babies with neural tube defects compared with mothers who are not folate deficient (Smits & Essed, 2001). In the United States, the prevalence of neural tube defects is about one per thousand live births. Therefore, we would expect more than 1,400 babies with neural tube defects to be born to folate-deficient mothers who smoke and approximately 1,200 excess cases of neural tube defects caused by smoking in the United States each year. Given the potentially profound morbidity of spina bifida and the lethality of anencephaly, these figures are of great concern and underscore the need for the healthcare system to be vigilant in helping women to quit smoking in the preconception and prenatal periods.

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