to be much lower than in convenience stores and corner groceries, which are more prevalent in low-income communities (5–7). The reasons underlying the suboptimal intake of fruits and vegetables in the United States are likely to be varied and complex and require much further investigation.

I agree that food price influences food choice and that energy cost is inversely related to energy density. However, it does not necessarily follow that energy cost is the specific food price measure that determines purchasing decisions, nor that price and/or energy content are the only considerations. Future research should not rely on the use of energy cost until it is validated as an appropriate measure of food price.

The author had no conflicts of interest to declare.

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On the gene-nutrient analyses of Cahill et al

Dear Sir:

I read with great interest the article by Cahill et al (1) on gene-diet interaction in serum vitamin C deficiency. The report deserves broad attention for its clinical and biochemical perspectives. But I have concerns regarding their several arguments and would like to provide other insights.

First, the authors did not provide measures of validity or reliability of serum vitamin C and estimates of vitamin C intake from food-frequency questionnaires (FFQs). This information is critical to retrieve unbiased quantitative information. The authors argued that their measurement errors were nondifferential and only attenuated true associations toward the null. This is true for their point estimates. However, because the population average of serum vitamin C concentrations was above the cutoff and the lower tail of the distribution became wider than the true distribution, prevalence of serum vitamin C deficiency may have been underestimated by nondifferential random error (2). The overestimation of prevalence may pose bias in odds ratios, given the prevalence of vitamin C deficiency of >10% (3). That is, the odds ratio could not approximate the risk ratio in addition, overestimation of overall prevalence spuriously increases power, and therefore statistical inference and 95% CIs may have been biased in favor of statistical significance (3). Readers need to be cautious of interpretation of “risk” of vitamin C deficiency.

Regarding the validity and reliability of dietary intake, errors could be both random and systematic. In addition, use of the Recommended Dietary Allowance (RDA) may not be appropriate because the RDA was not established for a population half of which is East Asian. RDA-equivalent values in Asian countries are different: for example, 70 mg/d in South East Asia and 100 mg/d in Japan (4, 5). Furthermore, it is known that racial-ethnic differences can influence FFQ validity according to differences in food selection and serving sizes (6). Finally, the differences may cause differential errors across genotypes due to population admixture, which poses confounding by genes. Therefore, more careful arguments need to be provided for FFQ validity in estimates of dietary intakes in absolute and relative scales and for racial-ethnic differences in FFQ validity and the effect on potential differential misclassification. In addition, results based on analyses that use ranking within each racial-ethnic stratum may be more helpful than results based on a dichotomy given the fixed cutoff.

Finally, I would like to note that the study may offer an innovative opportunity. In the field of nutritional epidemiology, blood vitamin C is considered an objective marker of vitamin C exposure and used to validate dietary assessment of vitamin C intake (7). Cahill et al (1) provided evidence that the common use of blood vitamin C for FFQ validation is not optimal because blood vitamin C depends on genotypes and the validity of vitamin C intake from FFQ may be underestimated in general. Gene-diet interaction for validation of dietary assessment in this context was recently recognized (8). For vitamin C, sodium-dependent vitamin C transporter protein (SVCT1) was taken as an example, because SVCT1 is known to influence serum vitamin C concentrations (8). To my knowledge, gene-nutrient interaction or confounding for validation of dietary assessments has not yet been confirmed using actual data. Thus, I would like the authors to investigate and present the multivariate-adjusted measures of validity of vitamin C intake estimate not only in their overall cohort but also in each stratum of GST genotype. The results will be the first to show that incorporation of genetic information in validation analyses will improve validation of dietary questionnaires.

The author did not have any conflicts of interest.

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Dear Sir:

We thank Imamura for his interest in our work on vitamin C deficiency and the common GST polymorphisms. Imamura expresses concern that we do not provide measures of validity or reliability in our assessment of serum ascorbic acid and in our estimate of dietary vitamin C. We indicated that serum ascorbic acid concentrations were measured by using HPLC together with certified controls from the National Institute of Standards and Technology, which is considered the gold-standard approach for determining serum ascorbic acid concentrations (1). Dietary vitamin C was measured by using a food-frequency questionnaire (FFQ), which has been shown to provide comparable estimates to other methods of dietary assessment and is considered suitable for the purpose of assessing dietary intake in population-based studies of gene-diet interactions (2).

Imamura suggests that our odds ratio results may have been biased toward statistical significance. A significant odds ratio for serum ascorbic acid deficiency should not be unexpected for the lower dietary vitamin C group compared with the higher dietary vitamin C group because dietary vitamin C is the only source of circulating vitamin C in humans. The potential bias toward deficiency that Imamura describes in his letter would exist in both genotypes, yet the GSTT1 null genotype. As such, this potential bias would not explain the effects we observed.

Imamura questions our use of the Recommended Dietary Allowance (RDA) to stratify subjects into high and low dietary vitamin C categories. We used the RDA as a cutoff because it is the recommended intake in Canada and the United States. We recognize that potential misclassification could occur, regardless of the cutoff used. We ran the analysis used for Table 2 and Figure 1 in our article (3) using the median vitamin C intake value to stratify subjects into dietary vitamin C categories, and the results were similar to those when we used the RDA as the cutoff. For example, the GSTT1 null genotype had lower serum ascorbic acid concentrations than the functional genotype only among those in the lower dietary intake group. Imamura suggests that the RDA values may not be appropriate for Canadians of Asian ancestry because daily dietary vitamin C recommendations are either 70 or 100 mg/d in some Asian countries as compared with the RDA of 75 mg/d (women) and 90 mg/d (men) for North America. We do not believe that these marginally different cutoffs would materially alter the findings we report. Nevertheless, we repeated our analysis among subjects of East Asian ancestry using these different dietary cutoffs suggested by Imamura and found similar results.

We agree with Imamura that racial-ethnic differences can influence FFQ validity and lead to population admixture. However, we explained in our article that the diet-gene interactions “remained when the subjects were grouped into the 2 main ethnocultural groups (GSTM1: P = 0.008 for whites, P = 0.01 for East Asians; GSTT1: P = 0.001 for whites, P = 0.02 for East Asians; data not shown), indicating that the interaction effect was not due to population admixture” (p 1414) (3).

We agree with Imamura that the incorporation of genetic information in validation analyses could potentially improve the validation of dietary questionnaires. Indeed, we have previously reported that sodium-dependent vitamin C transporter (SVCT) 1 and 2 genotypes modify the vitamin C diet-serum correlations (4). Imamura asks us to present the correlation in our overall cohort, which we have published previously (5). In response to his request for the correlations by GST genotype, the multivariate-adjusted diet-serum Spearman correlation was 0.14 (P = 0.004) for the GSTM1 functional and 0.18 (P = 0.0001) for the nonfunctional genotype. The correlation was 0.13 (P = 0.002) for the GSTT1 functional and 0.26 (P = 0.0001) for the nonfunctional genotype. Individuals with both nonfunctional GSTM1 and GSTT1 genotypes had a diet-serum correlation of 0.26 (P < 0.0001), whereas those with both functional genotypes had an r of 0.09 (P = 0.14). These correlations suggest that individuals with the nonfunctional genotypes may be more responsive to changes in vitamin C intake, which is consistent with the conclusions we made in our article based on the data we presented using the RDA value as a cutoff.

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