Customized Diets for Cancer Prevention According to Genetic Polymorphisms: Are We Ready Yet?

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Since the early 1990s, numerous studies have examined gene-gene and gene-environment interactions in relation to disease risk. Of particular interest are data on how nutrient intakes modify genetic susceptibility to diseases, which may provide scientific bases for formulating preventive strategies through dietary modification. The enthusiasm in this scientific pursuit has been put into action by entrepreneurs who sell dietary recommendations and/or dietary supplements claimed to be tailored to one's genetic susceptibility to disease. Catchy terms such as “nutrigenetic testing,” “personalized supplements,” “feed your genes right,” and “intelligent diet” have been created and used to attract customers.

In this issue of the Journal, Lewis et al. (1) report the findings from their systematic reviews and meta-analyses of observational studies of dietary folate intake or circulating folate levels and breast cancer and of the C677T polymorphism in the methylene-tetrahydrofolate reductase (MTHFR) gene, which encodes a key enzyme in folate metabolism, and breast cancer. Their meta-analysis of the data from 13 case-control studies of folate intake suggested that for every 100-μg increase in folate intake, women were 9% less likely to develop breast cancer. One important finding of this analysis was evidence of publication bias among the case-control studies, such that small studies showed a greater magnitude of association between folate intake and breast cancer risk. Overall, none of the nine cohort studies included in the meta-analysis showed a significant association between folate intake and breast cancer risk, and limited data suggest no association between folate supplementation and breast cancer. Lewis et al. (1) also found no statistically significant difference in breast cancer risk between women with the MTHFR C677T TT genotype and women with the MTHFR C677T CC genotype and no evidence of a statistical interaction between folate intake and MTHFR genotypes.

Should we then conclude that folate is not protective against the development of breast cancer? Other than the limitations inherent in the case-control study design and the subgroup analyses that were discussed by Lewis et al., several issues should be addressed. First, although Lewis et al. compared breast cancer patients with control subjects from the same country or geographic area, they did not examine the heterogeneity across studies with respect to lifestyle, genetic makeup, and instruments used for dietary assessment, all of which are important to consider before quantitatively synthesizing the data. For example, a food frequency questionnaire with 60 food items may generate a lower estimate of folate intake than a food frequency questionnaire with 120 food items. Hence, it may not be appropriate to compile the absolute values of intake across studies. Second, the evidence on folate possibly promoting tumorigenesis cited by Lewis et al. is from animal studies and, thus, circumstantial. We need longitudinal data from human studies to understand in what stage of breast cancer development folate may or may not play a role. Third,
because nutrient intake is frequently associated with other lifestyle factors, the variability in the extent of adjustment for lifestyle factors among the studies makes results from their meta-analyses difficult to interpret. It is desirable to see both unadjusted and adjusted summary estimates and to see how other nutrients such as methionine, betaine, choline, and B vitamins might have influenced the association between folate and breast cancer risk. Fourth, we have learned the hard lessons from studies of antioxidant vitamins that, in most cases, observational studies do not yield results that are similar to those from randomized controlled trials (2); this is also likely to be true for studies of other factors that are associated with lifestyle, such as consumption of fruits and vegetables or folate. Randomized controlled trials that examine the effects of folate on an array of biomarkers of carcinogenesis such as DNA methylation are needed to help to bridge the gaps between observational studies and randomized controlled trials with clinical endpoints. Finally, we would have a better understanding of the evidence if we knew the quality of each study. The strength of the evidence can be evaluated with respect to the quality, quantity, and consistency of the evidence (3). Judging from the study design (i.e., observational studies), inconsistent results from case–control and cohort studies, publication bias, and sparse data, the strength of evidence on the association between folate intake and breast cancer risk is very low, suggesting that any estimate of the strength of evidence can be evaluated with respect to the quality, quantity, and consistency of the evidence (3). Judging from the study design (i.e., observational studies), inconsistent results from case–control and cohort studies, publication bias, and sparse data, the strength of evidence on the association between folate intake and breast cancer risk is very low, suggesting that any estimate of the effect is very uncertain (3).

A great challenge in any dietary assessment is handling measurement errors. The qualitative and quantitative complexity of nutrients in food and food products and the difficulty in recalling dietary intake make likely systematic as well as random errors. Because direct observation of food intake is not feasible in studies with a large sample size, nutritional epidemiologists often use data from a single 24-hour dietary recall performed once during each of the four seasons as an alloyed gold standard for true intake. Such data are then correlated with data from food frequency questionnaires, and the correlation coefficient is considered to be the validity coefficient. There are, however, several pitfalls in this approach. The idea of using a single 24-hour dietary recall per season to represent dietary intake over the entire season may be overly simplistic, particularly for data collected in countries where a wide variety of food is available. Furthermore, few dietary assessment studies have had a validity coefficient greater than 0.7; if the validity coefficient was calculated as a Pearson correlation coefficient, a validity coefficient of 0.7 would mean that only 0.7^2 (i.e., 49%) of the variation in one measurement could be explained by the alloyed gold standard (4). Methods have been developed to correct for measurement errors (5). However, it has been shown that depending on the extent of the errors in the measure of interest and in the alloyed gold standard and the correlation between the two measures, an estimate of relative risk or odds ratio may be overcorrected if a correction for measurement errors was performed (6).

Most epidemiologists recognize the substantial measurement errors in dietary assessment and thus forgo analyzing raw data of nutrient intake by categorizing intakes according to quartiles or quintiles. The lack of reasonable accuracy in assessing dietary intake has prevented us from informing the public of the optimal amounts of intake for disease prevention purposes. Disseminating messages such as “persons in the highest quintile category had the lowest risk” could mislead the public into spending unnecessarily on high-dose nutritional supplements and subjecting themselves to potential adverse effects. In addition to reporting relative risks or odds ratios that imply risk prediction, researchers should, whenever possible, present estimates of the absolute risk attributable to an exposure variable of interest and the corresponding confidence interval of the estimate.

Recent testimony by the US Government Accountability Office before the US Senate Special Committee on Aging stated that the nutrigenetic tests purchased from four Web sites mislead consumers by providing dietary or lifestyle recommendation based on polymorphisms of some genes (7). We cannot optimize our diet according to genetic profiles to prevent cancer until we have strong scientific evidence on an interactive effect of genes and nutrients on cancer risk. Although in most cases we have limited statistical power to detect interactions and limited ability to model, in statistical terms, the complex dynamics among nutrients and genes, we will be in a better position to find stronger evidence by using rigorous study designs and/or credible approaches to analyzing diet. Longitudinal, multiple real-time collections of dietary diaries with a computerized instrument, rather than dietary recalls on one or few occasions, will reduce measurement errors and better capture changes in dietary habits, food supplies, and nutrient compositions in food. Such an approach would allow for a reduced sample size at a given level of statistical power but would require more efforts on data collection. Because of measurement errors in dietary assessment and the intertwined relationship among nutrients that may not be fully described by a linear combination of the nutrients, dietary data collected through questionnaires or diaries in observational studies are useful for exploring dietary patterns rather than quantifying the intake and the net effects of a specific nutrient or food item. On the other hand, randomized controlled trials are the choice of study design for determining the effects of a specific nutrient or food item.

**REFERENCES**


