

Biomarkers of Nutritional Exposure and Nutritional Status: An Overview^{1,2}

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A nutritional biomarker can be any biological specimen that is an indicator of nutritional status with respect to intake or metabolism of dietary constituents. It can be a biochemical, functional or clinical index of status of an essential nutrient or other dietary constituent. Nutritional biomarkers may be interpreted more broadly as a biologic consequence of dietary intake or dietary patterns such as the relation of dietary folate and serologic homocysteine.

This series of papers addresses the use of biomarkers of exposure in nutritional epidemiology. Our goal was to critically evaluate the state of the science of biomarkers of nutritional intake. The use of biomarkers to evaluate intake and nutritional status is a rapidly changing field. Our hope in assembling this series of papers is to assess the state of the field, identify important questions that have not been answered and perhaps catalyze new research.

Included in this series are a number of papers that address the state of knowledge regarding biomarkers of intake and status for food energy, fat, protein, minerals, vitamins and some other food components that are not classified as nutrients. Some food components are not included. The focus is on biomarkers that are considered to have current or emerging interest for chronic disease and methodologic research and for

which a substantial body of literature regarding their measurement in humans exists. Some of the nutritional components with potential biomarkers that are not reviewed include phytochemicals, such as plant sterols and stanols, indoles or phenolic substances from spices and herbs. Many flavonoid compounds are not covered, but information is provided for isoflavonoids and lignans. Our purpose is not to be inclusive, but rather to highlight some of the areas where there is developing information. In addition to the papers about specific food components, several papers address methodologic issues with regard to the use of biomarkers in nutrition research. These include papers on biologic issues (1), statistical issues (2) and issues related to the interface between laboratory and epidemiologic research (3). Clearly there is evidence that the use of biomarkers in epidemiologic research requires careful attention to all three of these areas if data are to be collected correctly and interpreted appropriately. There is much left to understand about the underlying mechanisms, statistical interrelations of different biomarkers and strengths and limitations of the measurements themselves that must be taken into account when these markers are used in either research or clinical settings.

Uses of biomarkers

The nutritional biomarkers being reviewed can be designated into one or more of three categories. Biomarkers can be used as 1) a means of validation of dietary instruments; 2) surrogate indicators of dietary intake; or 3) integrated measures of nutritional status for a nutrient. Many biomarkers can of course fall into more than one of these categories, and for some food components, the biomarkers are not adequate and dietary-intake methods may provide better information.

For a biomarker to be used for validation of a dietary instrument, it should have a strong direct relationship with dietary intakes and be an independent assessment of the dietary intake of the nutrient of interest. Two important examples of such a biomarker are the use of doubly labeled water as a marker of dietary energy that is reviewed here by Livingstone and Black (4) and the use of urinary nitrogen as a marker of dietary protein, which is reviewed by Bingham (5). As noted above, a second category of biomarker would be indicators of dietary intake for situations where the direct measurement of dietary intake using traditional methods is difficult or impossible.

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Nutrients and food components can vary considerably for the same food depending on where or how the food was grown or how it was processed. In these cases, a biomarker may be a better indicator of dietary intake. Examples of this type of biomarker would include selenium, reviewed here by Hambidge (6); vitamin E, reviewed by Mayne (7) and mutagenic compounds, reviewed by Goldman and Shields (8). Multiple serologic measures of some food constituents may represent dietary intake better than a single or, possibly, multiple dietary assessments. In some cases too, complementary use of a biomarker and dietary assessment provides a better or different estimate of the nutritional exposure. Serologic measures of some carotenoids fall into this category, as discussed by Potischman (1). The third category of biomarkers are those that are integrated measures of nutritional status for a nutrient, which reflect not only intake but also metabolism of the nutrient and possibly effects from disease processes. Serologic measures of some antioxidants including carotenoids (7) and estimates of most fatty acids in adipose tissue or red blood cells would fall into this category. Biomarkers of fatty acids are reviewed by Arab (9). Serologic or urinary measures of isoflavones and metabolites of lignins can be indicators of intake, but also are products of metabolic processes, as Lampe (10) discusses. Some of the biomarkers of one-carbon metabolism such as homocysteine reflect not only nutritional intake, but also metabolic processes, as reviewed by Mason (11). It is important to note that a single biomarker may not reflect the status of a single nutrient, but may be reflective of several nutrients, their interactions and metabolism. Homocysteine falls into this latter category.

Finding and defining the appropriate exposure of interest may not be straightforward. Although dietary databases exist or are being developed for the known food components that are of interest to health, it is unclear whether biomarkers or dietary estimates are more informative for some of these. In addition, it is often unclear what the important exposure from a food source is: either the parent compound, a metabolite or some unknown covarying constituent in the food source. Any factor that is under physiologic control at intakes beyond minimum requirements is in the third category. For example, although they are not covered in this review, serum calcium and vitamin A are under homeostatic control; therefore, for healthy individuals, they do not provide indications of dietary intake. In the situation where currently available biologic markers provide less information than estimates of dietary intake, the use of biomarkers may not be possible. Some phytoestrogens may fall into this category (10).

The discovery of new biomarkers of nutritional intake and status and the critical evaluation of them and the known biomarkers are essential to our continuing progress in nutritional epidemiology. There is currently a need for more biomarkers that are clearly related to intake, which would be useful for validation of dietary instrumentation and in mea-

surement-error research. If we are to gain a better understanding of the roles of food components and nutrients in chronic disease and health, we must establish better markers of intake. Improved understanding of bioavailability and the metabolism of nutrients is important for the interpretation of most biomarkers of intake. Biologic measures of the intake of food groups or combinations of biomarkers that describe food patterns would enhance many research efforts. Emerging research into nutritional biomarkers will enhance our understanding, and hopefully it will also increase our precision in assessing nutritional status for a variety of dietary constituents. Ultimately having good biomarkers of nutritional intake and status is of considerable importance for public health and clinical practice. At this point, most of what we know about biomarkers is limited to research applications. If we are to use them in clinical practice as surrogate measures of intake or as measures of nutritional status, we need to have a much clearer understanding of not only how biomarkers are related to intake, but also what else affects their levels (e.g., genetic factors, pharmaceutical effects, disease effects). Furthermore, valid laboratory procedures are required that allow for comparisons among laboratories. Without such comparability, it is not possible to make recommendations regarding appropriate levels. For example, the standards that were created for cholesterol measurement have allowed for public health recommendations. Clearly there is a need for good biomarkers for clinical assessment and public health practice as well as for research purposes. Development of such biomarkers is a potential outgrowth of current efforts that requires concerted attention.

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