Functional foods: the US perspective¹⁻³

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ABSTRACT Widespread interest in the possibility that selected foods might promote health has resulted in the coining of the term functional food, although agreement about what is and what is not a functional food is lacking. Public interest in functional foods is increasing because of higher health care costs; the passage of federal legislation affecting many food categories, including the expanded category of dietary supplements; and recent scientific discoveries linking dietary habits with the development of many diseases, including coronary heart disease and some cancers. A variety of foods have been proposed as providing health benefits by altering one or more physiologic processes. Biomarkers are needed to assess the ability of functional foods or their bioactive components to modify disease and to evaluate the ability of these foods to promote health, growth, and well-being. Evidence suggests that several biomarkers may be useful for distinguishing between diseased and nondiseased states and even for predicting future susceptibility to disease. A variety of biomarkers will probably be needed to develop a profile for an individual that reflects the impact of diet on performance and health. Another area of interest is the interaction of nutrients and their association with genetics. These interactions may account for the inconsistent interrelations observed between specific dietary constituents and the incidence of disease. Greater understanding of how diet influences a person’s genetic potential, overall performance, and susceptibility to disease can have enormous implications for society. As new discoveries are made in this area, consumers will need access to this information so that they can make informed decisions. Am J Clin Nutr 2000;71(suppl):1654S–9S.

KEY WORDS Functional food, biomarkers

INTRODUCTION Cultural beliefs in the mystical powers of foods have been handed down for generations (1). The ability of specific foods to prevent or reduce the severity of symptoms arising from what are now frequently recognized as nutritional inadequacies has been recorded in a variety of historical documents. Interestingly, as scientists unravel the mysteries about specific nutritional needs, it becomes apparent that some dietary components that may not be required for human existence may indeed markedly influence quality of life by modifying one or more physiologic processes. The ability of such foods to influence these processes is likely dependent on several factors, including interactions with other constituents in the overall diet and the consumer’s physiologic state, behavior pattern, and genetic background. People throughout the world are becoming increasingly convinced that the foods they consume can not only modulate performance but also influence their risk of acquiring a variety of diseases (2). It is logical to assume that consumer demand for these health-promoting foods and the physiologically active compounds they contain will continue to grow in the foreseeable future, as will the availability of novel foods.

Consumers must be provided with the information necessary to make informed decisions as to whether they should adjust their intake of specific foods and their associated components. Several fundamental issues that need addressing become immediately apparent, however, when attempting to provide information about potential benefits and risks accompanying increased consumption of any food or component. Unlike the case with drugs, it is generally assumed that increased consumption of foods and food constituents is safe and that any response will be associated with a reduction in risk rather than with a cure or treatment. Even these general beliefs are questionable, however, because toxicity is a function of the quantity consumed. Hence, it is inappropriate to consider use of functional foods and their bioactive components as being without some degree of risk. A more fundamental issue is the relative benefit or risk that might accrue from the increased ingestion of such foods. To assess the relative merits and concerns about this issue, some scientific agreement is needed, even though such agreement is also somewhat relative because some persons may value particular information more than others when establishing beliefs and opinions.

Experience has taught us that scientific opinion can be in error, such as when disagreements surfaced about the cause of gastric ulcers. Nevertheless, even though scientific agreement may not totally eliminate the possibility of error, it certainly reduces its probability. The alternative of an ill-informed society based on minority agreement or, perhaps even worse, agreement based on an inadequate science base, would unquestionably raise the chance for error and probably result in deleterious effects to society. History has revealed that although knowledge

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is important, wisdom about how and when to use this information is critical. Unfortunately, consequences other than those intended have been documented when intake of foods or their components is excessive (3, 4).

FUNCTIONAL FOOD

Widespread interest in the possibility that selected foods might promote health has resulted in the coining of the generic term functional food. The Food and Nutrition Board (FNB) of the National Academy of Sciences defines a functional food as one that encompasses potentially healthful products, including “any modified food or food ingredient that may provide a health benefit beyond that of the traditional nutrients it contains” (5). Although the term functional food is increasingly recognized as a household word, it has not been embraced totally by the health and scientific communities. Controversies about what is and what is not a functional food remain at the forefront of discussions (6–8). Many believe that the promotion of food as “good” or “bad” is inappropriate and scientifically indefensible. Furthermore, many nutritionists are adamant that only diets can be classified as good or bad, not foods per se (9). It is unlikely that a nonfunctional food exists. Thus, in the broadest context, all foods must be considered “functional.” Nevertheless, some foods may be particularly beneficial in selectively altering specific physiologic processes that improve the quality of life or reduce the risk of acquiring a disease. The wholesomeness of any diet depends on the supply of individual food components, interactions among components, and meeting needs dictated by an individual’s genetic background and physiologic state.

The suggestion that certain foods or their components might offer some unique health benefit has blurred the distinction between foods and drugs. Classically, a drug is any article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Modification of the FNB definition to reflect “functional” rather than “health” might help to resolve some of these drugs-versus-nutrients concerns. In addition, the promotion of increased consumption of functional foods and their associated bioactive components should be viewed as an approach to optimized nutrition rather than as an endorsement of enhanced consumption of good foods or as a simple marketing strategy. Whether or not functional foods persist as a term, it is imperative that consumer confidence in the food supply not be jeopardized. Promotion of good and bad foods must be avoided.

REASONS FOR PUBLIC INTEREST

Increased interest in functional foods is likely occurring for 3 reasons: increased health care costs, recent legislation, and scientific discoveries. Expenditures associated with health services, as a percentage of national wealth (the gross national product, or GNP), continue to rise worldwide (10). Health care in the United States accounts for ~60% of the gross national product (11), with use influenced by several factors, including age, sex, and previous medical condition.

Coronary heart disease is the most common cause of death today. It accounts for ~44% of the mortality and much of the morbidity in the United States (12). It accounts for two-thirds of deaths from heart disease and accounts for ~70% of all deaths among persons older than 75 y. As the world’s population increases in age, concerns will certainly intensify about how best to reduce the risk of death and disability from this disease. A recent estimate put the economic cost of atherosclerotic cardiovascular disease at $259 billion. The role of diet in this disease has yet to be clarified, but if this estimate of cost is accurate, a small percentage of responders to dietary change could have a substantial impact on health cost. Tucker and Miguel (13) estimated that improving the nutritional status of some persons can be expected to reduce hospital costs. Although the benefits of reducing hospital costs should not be understated, it is likewise important to recognize that preventive nutrition strategies will likely have an even greater impact on health care costs.

Correlations have been reported between dietary habits and ~60% of cancers in women and >40% of cancers in men (14). It is likely that several essential and nonessential dietary components influence the risk of developing cancer. Because ~25% of Americans will ultimately deal with the complications of cancer, anything that reduces its risk can substantially reduce health care costs. However, increased supplement usage among cancer patients raises questions not only about effective dosages of dietary constituents and their cost but also about their safety (14, 15).

An estimated 6% of the national health expenditure is associated with treatment of obesity (16). Several dietary components may influence energy intake and metabolism (17, 18). Recent evidence that conjugated linoleic acid, a functional food component found primarily in animal tissues and fluids, can alter lipid homeostasis provides evidence that the potential health benefits of foods are not limited solely to plant sources (19).

Three US legislative acts of the 1990s have likely had a significant effect on the promotion of the concept of functional foods. The first, the Nutrition Labeling and Education Act, passed in 1990 (20), mandated that the Food and Drug Administration (FDA) establish regulations requiring most foods to have a uniform nutrition label and also established circumstances under which claims about content and disease prevention could be made about nutrients in foods. The second piece of legislation, the Dietary Supplement Health and Education Act of 1994 (21), defined dietary supplements as any product that contains one or more dietary ingredients, such as vitamins, minerals, herbs or other botanicals, amino acids, or other ingredients used to supplement the diet. Additionally, it created a mechanism for dealing with safety issues, regulation of health claims, and labeling of dietary supplements; provided for good manufacturing practices; established new government entities to review regulations; and encouraged research on dietary supplements. Finally, the FDA Modernization Act of 1997 (22) amended the Federal Food, Drug, and Cosmetic Act by allowing health claims that are not preauthorized by FDA if the claims are based on “authoritative statements” of government agencies such as the National Academy of Sciences or the National Institutes of Health.
Partial list of functional foods and their physiologic effects

<table>
<thead>
<tr>
<th>Food</th>
<th>Physiologic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple, barley, blackberry, blueberry, carrot, eggplant, oats, garlic, ginger, ginseng, mushroom, onion, soybean, tea</td>
<td>Lipid lowering</td>
</tr>
<tr>
<td>Lemon, apple, cranberry, garlic, beet, cucumber, squash, soybean, cabbage, Brussels sprouts, cauliflower, kale, broccoli, spinach</td>
<td>Enhanced drug detoxification</td>
</tr>
<tr>
<td>Ginseng, licorice, oats, parsley</td>
<td>Antinflammatory</td>
</tr>
<tr>
<td>Cranberry, garlic, onion, green tea</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Anise, fennel, soybean, cabbage</td>
<td>Antiestrogenic</td>
</tr>
<tr>
<td>Orange, green tea, garlic</td>
<td>Antiproliferative</td>
</tr>
</tbody>
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Epidemiologic and laboratory findings are continuing to provide convincing evidence that increased consumption of fruit and vegetables can significantly modify disease risk. Interestingly, a rather large number of chemical compounds found in fruit and vegetables appear to offer protection (25, 26). Evidence exists that these essential and nonessential nutrients modify several cellular processes. Unquestionably, dietary habits are not the sole determinant of disease states, but adjusting the diet likely represents a significant way of reducing risk.

CHARACTERIZATION OF FOODS

A partial list of foods that have been proposed to provide benefits by altering one or more physiologic processes is presented in Table 1. Nuts, whole grains, fruit, and vegetables contain a variety of compounds associated with reduced risk of heart disease, cancer, diabetes, hypertension, and a variety of other medical conditions. Although substantial evidence exists that foods such as grains, garlic, and soybeans can decrease the risk of both heart disease and cancer, evidence for other foods is equivocal (25–27). Widely diverse components in whole grains that may provide protection by influencing the environment of the gastrointestinal tract include dietary fiber and other indigestible components; several types of antioxidants, such as trace minerals and phenolic compounds; and several phytoestrogens that may alter hormonal homeostasis (28, 29).

Cabbage, onions, garlic, celery, cucumber, endive, parsley, radish, and legumes are among the nongrains that have been reported to have some health benefits (25, 29). The benefits of functional foods are not limited to natural foods, however, because they can result from the generation of novel foods as well. For example, low-fat foods may provide some benefits in reducing the risk of heart disease. Gould (30) suggested that vigorous lowering of cholesterol by using low-fat foods and lipid-active drugs, controlling hypertension, and abstaining from smoking stabilizes plaque and markedly reduces coronary events and angina pectoris, with greater improvement in survival than reported for elective, invasive revascularization procedures.

Many types of compounds found in foods may be responsible for the health benefits attributed to functional foods. Alkyl compounds, such as those found in garlic and related foods, have been used in various parts of the world not only for aroma and flavor but also as antimicrobials, insect repellants, and modifiers of the risks of cancer and heart disease (27). Other compounds that may contribute to observed protection include carotenoids, which are found in vegetables and fruit; flavonoids, found in fruit, vegetables, nuts, and grains; and indoles and isothiocyanates, both found in cruciferous vegetables.

An enormous number of carotenoids are found throughout the plant kingdom. These compounds, many of which do not possess vitamin A activity, can influence numerous biological functions by serving as antioxidants, modulators of cell growth regulation, regulators of gene expression, and immunoregulators (31, 32). Indole-3-carbinol is one of several carotenoids found in cabbage, broccoli, Brussels sprouts, and other Brassica vegetables reported to exhibit anticarcinogenic properties in experimental animals. In addition, recent studies suggest indole-3-carbinol may be a safe, well-tolerated, and efficacious treatment for recurrent respiratory papillomatosis (33).

More than 100 sulfur-containing glycosides known collectively as glucosinolates occur naturally in cruciferous vegetables. On hydrolysis, they yield thiocyanate, nitrate, and isothiocyanates. Isothiocyanates influence a variety of biological reactions (17, 25, 29).

More than 4000 flavonoids, which are polyphenolic compounds found ubiquitously in foods of plant origin, have been described and categorized into flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids. Flavonoids potentially have a variety of biological effects, including serving as antioxidants, influencing drug detoxification mechanisms, and altering cell proliferation (34).

BIOMARKERS

Almost any measurement that reflects a change in a biochemical process, structure, or function that results from an interaction between a biological system and an environmental agent, including a dietary component, can serve as a biomarker. Biomarkers are needed not only to assess the value of functional foods and their biological components as modifiers of disease, but also to evaluate their ability to promote health, growth, and well-being. Evidence is emerging that several biomarkers may be used successfully to distinguish between disease and nondisease states and, in some instances, to predict future susceptibility to disease (35). Use of such biomarkers as indicators of biological responses to selected foods and food components is critical because long-term dietary interventions are virtually impossible to conduct for numerous reasons, including cost.

Several sensitive, reliable biomarkers are likely needed to adequately assess the benefits and risks associated with increased consumption of specific foods and their bioactive components, but without question these biomarkers must not be extremely expensive. Intake, biological effect, and susceptibility biomarkers will probably be needed to evaluate adequately the effectiveness of functional foods and their bioactive components (Figure 1).

Intake biomarkers are useful for reflecting the amount of food or metabolite present in cells, tissues, or body fluids. With these biomarkers, differences between absorption and accumulation must be considered. Assessment of intake indicators is relatively straightforward analytically, but their use is complicated by the need to know the best time for their measurement after consumption and by variability in rates of metabolism and accumulation across tissues and biological fluids (36).

The usefulness of biological effect biomarkers can also be influenced by several methodologic issues. Among the most germane of these issues are the association of these biomarker-
ers with causal pathways and their probability of detecting effects coinciding with either the maintenance of health or progression to a disease state. Effect biomarkers are particularly useful if they can predict a potentially detrimental response long before it occurs. Unfortunately, at present, few biomarkers are universally accepted as being this reliable. The range of effect biomarkers required is immense because they are needed to detect a variety of metabolic events that alter cognitive and physical performance or change the risk of disease. Associating genetic polymorphisms with carcinogen-DNA adduct measurements to assess cancer risk is beginning to show promise (37). Other creative approaches will likely be needed to develop a battery of biomarkers that can be used to evaluate the effectiveness of the food supply in influencing the overall quality of life.

Many biomarkers are beginning to emerge that might be used effectively to monitor the impact of dietary habits on growth and development, including platelet-derived growth factor, transforming growth factor, basic fibroblast growth factor, epidermal growth factor, insulin-like growth factor, and hepatocyte growth factor (38). New approaches will be required to unravel the effects of dietary habits on these and other effect biomarkers.

Susceptibility biomarkers are also critical for evaluating the merits of changing one’s dietary habits. These biomarkers allow the measurement of individual differences associated with genetic background, or variation associated with many environmental factors (35, 39). The ability of genetic differences to activate or detoxify genotoxic agents is becoming increasingly recognized as an appropriate susceptibility biomarker. Many genes, associated products, or receptors are now under investigation as markers of susceptibility, including those associated with OB, UCP, erbB-2, ras, myc, p53, BCL-2, Ki-67, and HNF-1-α (39–41). Although several single-gene mutations have been shown to cause problems in experimental animal models, such as those that occur in some causes of obesity, the situation in humans is likely to be considerably more complex. Interactions among several genes, environmental factors, and behavior make the search for appropriate gene markers especially challenging. Nevertheless, new markers are being developed that should offer exciting opportunities for clarification of the effect of genes and the environment.

Overall, a variety of biomarkers will probably be needed to develop a profile for an individual that reflects the effect of diet on performance and health. To assess the benefits of foods or their components, additional attention must be paid to examining the variability in response among populations and individuals, the strengths of any association or correlation, the specificity of the relation, the reversibility of the response, and the biological basis for any proposed benefits.

The development and application of biomarkers have enormous importance not only in improving health but also in demonstrating the importance of dietary habits. Without question, any information related to a biomarker must be consistent with scientific standards for statistical significance. Before a claim is made about the benefits of a particular functional food or bioactive component, the following types of information must be evaluated: epidemiologic evidence (25%), intervention studies (35%), animal models (25%), and mechanism of action (15%). These estimates (percentages in parentheses) of the weighting that might appropriately be given to each type of evidence in evaluating the totality of information are presented to initiate debate rather than to establish a meaningful basis for evaluation. This is in no way a novel approach; it was used in preparing 6 consensus statements about chronic disease (42). The opinion reflected here represents the thoughts of one individual (with no statistical freedom) and, therefore, is not an expression of an official position. The
following questions must be asked: What is the minimal acceptable score for a claim? Would this minimum value differ if a functional or a health claim was being proposed?

**INTERACTIONS AMONG NUTRIENTS**

Elucidation of the specific roles and interactions of nutrients and their associations with genetics will assist in the identification of critical times for intervention and lead to sound and accurate dietary guidance that can be tailored to reduce disease risk of individuals. Interactions among dietary constituents may contribute to the inconsistent relations observed between specific dietary constituents and the incidence of disease.

Although interactions among nutrients have been inadequately examined, a few examples of negative and positive interactions exist. Vitamin C has been reported to reduce selenium’s effectiveness against chemically induced colon cancer (43). The significance of such interactions may be even more pronounced because selenium has been shown to enhance the ability of garlic to inhibit chemically induced mammary cancer in experimental animals (44). Nonessential and essential nutrients cannot be considered to operate in isolation; rather, they work in a dynamic, constantly changing milieu. Greater attention to all components of the diet and elaboration of their interactions should make possible specific and appropriate recommendations for the general population and allow for recommendations tailored to specific subgroups or individuals.

**EFFECT OF PROCESSING**

The processing of foods can influence the availability of nutrients either positively or negatively. Stahl and Sies (45) found that lycopene bioavailability was improved by heating tomato preparations either positively or negatively. Stahl and Sies (45) found that boiling garlic for 15 min markedly reduced its ability to inhibit chemically induced mammary cancer in experimental animals (44). Nonessential and essential nutrients cannot be considered to operate in isolation; rather, they work in a dynamic, constantly changing milieu. Greater attention to all components of the diet and elaboration of their interactions should make possible specific and appropriate recommendations for the general population and allow for recommendations tailored to specific subgroups or individuals.

**CONCLUSION**

Development of the scientific underpinning of functional foods and their bioactive components as health promoters is emerging as a new frontier for nutritionists and other health professionals. Greater understanding of how diet influences an individual’s genetic potential, overall performance, and susceptibility to disease can have enormous implications for society. As new discoveries are made in this area, the new information will be needed by consumers so that they can make informed decisions.

**REFERENCES**