The role of statins in primary and secondary prevention of cardiovascular disease (CVD) is well established. As the use of statins gains popularity and becomes more common in the general population, questions regarding the role of a healthy diet in the prevention of CVD have been raised. In a recent study, Ferenzi et al.¹ wrote that increased CVD risk factors associated with a typical fast food meal (ie, a 7-oz hamburger with cheese and a small milkshake) could be neutralized with a starting dose of statins. This conclusion prompted media headlines that proclaimed, “Forget healthy eating – order a double McStatin.” It was suggested that fast food restaurants, such as McDonald’s, could offer statins to go with their meals, alongside condiments like ketchup, mayonnaise, salt, and pepper. However, no single drug or combination of drugs can completely counteract the wide range of harmful effects caused by poor eating habits. An unhealthy diet not only raises total and LDL cholesterol (LDL-C), but also increases blood sugar and blood pressure and leads to obesity. These risk factors have long-term consequences on cardiovascular as well as cancer morbidity and mortality.

Prevaling dietary recommendations focus on reducing and eliminating unhealthy food components, such as saturated and trans fats, sodium, and added sugar. This is an important way to improve overall diet quality, but there is also increasing interest in finding potentially beneficial ingredients for disease prevention. In particular, emerging evidence indicates that certain foods or their components might mitigate disease risk and promote general health and well-being. Common ingredients that have been studied include soluble fiber (from oats and psyllium); long-chain omega-3 fatty acids; plant sterols or phytosterols; polyphenols (from dark chocolate, red wine, green tea, or extravirgin olive oil); isoflavones from soy; Chinese red-yeast rice; and probiotics from dairy products.² These dietary components improve one or more CVD risk factors, such as blood lipids, blood pressure, or blood glucose. Some of these components have been approved for certain health claims by the Food and Drug Administration, and are widely marketed by the food industry as functional foods.

Although foods and beverages with functional ingredients claim to reduce CVD risk, functional foods have no legal or universally accepted definition, and no regulatory or standard guidelines for use exist. The Institute of Medicine’s Food and Nutrition Board³ loosely defined a functional food as “any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains.” This definition is vague, and scientific evidence to support the health benefits of functional foods is often limited and inconsistent. Thus, there is a clear need for more rigorous investigation of the potential role of dietary components as primary or adjunctive means to prevent or treat CVD risk factors.

In the current issue of Circulation, 2 carefully conducted randomized, clinical trials investigate the effect of dietary interventions on blood lipids and blood pressure. The first report, by Lin et al.,⁴ is a triple crossover feeding study among 21 hypercholesterolemic subjects to examine the combined effects of ezetimibe and phytosterols on cholesterol metabolism. Each subject received a low phytosterol diet plus (1) ezetimibe placebo+phytosterol placebo, (2) 10 mg ezetimibe per day + phytosterol placebo, and (3) 10 mg ezetimibe per day + 2.5 g phytosterols per day, for 3 weeks each. The results showed that combining phytosterols with ezetimibe significantly decreased intestinal cholesterol absorption but increased fecal cholesterol excretion, and led to greater plasma LDL-C reduction than ezetimibe alone. Ezetimibe alone reduced plasma LDL-C by 16% in the study population. The combination of ezetimibe and phytosterols reduced LDL-C by an additional 7%.

In the second study, He et al.⁵ conducted a randomized, double-blind crossover trial with 3 intervention phases among 352 healthy adults to examine the effects of substituting soy or milk proteins for carbohydrates on blood pressure. Participants were assigned to take 40 g/d of soy protein, milk protein, or carbohydrate supplementation, each for 8 weeks in a random order. In comparison with the carbohydrate group, both soy and milk protein supplementation significantly reduced systolic blood pressure by about 2.2 mm Hg. No significant effect on diastolic blood pressure was observed for either soy or milk protein.

The results from these 2 studies support the idea that incorporating functional ingredients, such as phytosterols or soy protein, into the diet can lead to clinically significant improvements in CVD risk factors. A recent meta-analysis showed an average reduction in LDL-C of 8.8% with a mean dose of 2.15 g of phytosterols.⁶ Phytosterols and phytostanols (formed by a commercial process that saturates plant sterols) have similar hypocholesterolemic efficacy. In 2000, the Food and Drug Administration approved CVD heart health claims

**Do Functional Foods Have a Role in the Prevention of Cardiovascular Disease?**

Frank B. Hu, MD, PhD

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA.

Correspondence to Frank B. Hu, MD, PhD, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115. E-mail frank.hu@channing.harvard.edu

(Circulation. 2011;124:538-540.)

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.111.042721

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for plant sterols and stanols. Phytosterol-enriched foods, including spreads, yogurts, bars, and juices, are marketed as cholesterol-lowering products. The American Heart Association and the Adult Treatment Panel III of the National Cholesterol Education Program have recommended the use of phytosterols to lower LDL-C. The additive effects of ezetimibe and phytosterols observed by Lin et al suggest that dietary phytosterols can be used as adjunctive therapy for the treatment of hypercholesterolemia. Adding plant sterols or stanols to statin treatment can also lead to a further reduction of LDL-C among hypercholesterolemic patients.8

Soy protein also has cholesterol-lowering effects, albeit more modest than phytosterols. The Food and Drug Administration approved soy protein’s heart health claim based on this benefit. Whether isoflavones (estrogen-like compounds mainly found in soy products) contribute to the benefit is controversial; recent clinical trials report only marginal results from isoflavone supplementation. Previous clinical trials typically compared soy protein with animal proteins, such as casein or dairy protein, rather than carbohydrates. The cholesterol-lowering effects of soy are likely to be derived from both the intrinsic effects of soy protein on cholesterol synthesis and the displacement of saturated fats and cholesterol from animal products.9

The study by He et al provides new evidence on the blood pressure-lowering effects of soy and milk protein. These results are consistent with observational studies showing an inverse association between protein intake and the risk of hypertension. It is unclear, however, whether the benefit is due to the effects of protein or the reduction of refined carbohydrates. Replacement of refined carbohydrates with either monounsaturated fat or plant-based protein improves blood lipids and blood pressure.10 A 20-year follow-up in the Nurses’ Health Study found that low-carbohydrate diets rich in plant-based fat and protein were associated with a significantly lower risk of coronary heart disease.11 The benefits of the plant-based low-carbohydrate diet on coronary heart disease are likely to stem from increased vegetable fat and protein intakes, and on the reduced glycemic load in the dietary pattern, as well.

Can the observed reduction in CVD risk factors associated with phytosterols or soy protein be translated into decreases in CVD morbidity and mortality? Currently, the long-term effects of either ezetimibe or phytosterols on CVD outcomes have yet to be determined. One concern is that phytosterols modestly lower blood concentrations of carotenoids and some fat-soluble vitamins, and the long-term consequences of these effects remain unclear. Likewise, data on the long-term effects of soy protein are limited. High soy intake has been associated with a lower risk of coronary heart disease and breast cancer in Asian populations,12,13 but it is unclear whether these results can be generalized to Western populations, with their very low habitual intake of soy.

The rigorous clinical trials conducted by Lin et al and He et al add to the emerging evidence that specific components of plant-based foods have significant health benefits. These studies also offer greater mechanistic understanding of the role of dietary factors in modulating cardiovascular risk. With the obesity epidemic and rising healthcare costs showing no signs of abating, consumer and food industry interest in functional foods is sure to grow.14 Thus, sound scientific evidence is critical to substantiate and comprehend the putative health effects of individual foods and ingredients. Randomized, clinical trials aimed at studying the effect of foods or food components on hard CVD end points are often infeasible because of the prohibitive expenses and poor adherence. Therefore, large, prospective cohort studies with detailed and periodic dietary assessments are crucial to evaluate the long-term relationship between specific dietary factors and risk of chronic disease morbidity and mortality.

Despite growing evidence to support the efficacy of food ingredients in improving CVD risk factors, several issues indicate a need for more realistic expectations about the benefits of functional foods. First, the health effects of individual foods or ingredients are only modest. Typically, the amount of a functional ingredient included in a serving size is too small to produce appreciable health benefits. In contrast, changing overall dietary patterns by modifying multiple components of a diet has a much greater effect on CVD risk factors.15,16

Second, the food industry typically produces functional foods by incorporating a variety of functional elements—eg, vitamins, minerals, and phytochemicals—into processed foods or supplements. Because the benefits of cardioprotective foods are likely to be derived from whole foods rather than individual nutrients or compounds, this reductionist approach has not worked very well for the prevention of chronic disease. For instance, most vitamin supplementations have failed to improve CVD outcomes, suggesting that high-dose antioxidants from supplements may have different long-term effects than those derived from dietary sources, probably because of the complex interactions among food ingredients. For CVD prevention, current evidence suggests that foods and diets rich in antioxidants or phytochemicals rather than high-dose supplementation of individual compounds should be recommended.

Finally, sprinkling phytosterols or statins over a fast food meal (McSterol or McStatin) does not address the root causes of the CVD epidemic and is unlikely to offset the myriad deleterious effects of unhealthy dietary choices on chronic disease risk. Given our obesogenic environment—with its sedentary lifestyle and abundance of highly processed, convenient, and cheap foods, it is exceedingly unlikely that a magic bullet for CVD prevention will be found. Rather, we need to seek behavioral and policy-level strategies that improve overall diet and lifestyle choices. Even though functional foods or ingredients with proven benefits can be incorporated into a healthful eating pattern, such a diet is difficult to sustain without changes in the broader food environment.

Disclosures
None.

Sources of Funding
Dr Hu’s research is supported by National Institutes of Health grants HL60712 and DK58845.
References


Key Words: Editorials cardiovascular disease diet lipids nutrition prevention
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Frank B. Hu

_Circulation_. 2011;124:538-540; originally published online July 18, 2011;
doi: 10.1161/CIRCULATIONAHA.111.042721
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/124/5/538

Data Supplement (unedited) at:
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Correction

In the article by Hu, “Do Functional Foods Have a Role in the Prevention of Cardiovascular Disease?” which was published online ahead of print on July 18, 2011, the sentence in column 2 on page 538, lines 24-27, should read:

“The results showed that combining phytosterols with ezetimibe significantly decreased intestinal cholesterol absorption but increased fecal cholesterol excretion, and led to greater plasma LDL-C reduction than exetimibe alone.”

The authors regret the error.