Editorial

See corresponding article on page 64.

Fruit and vegetables: think variety, go ahead, eat![1,2]

Sebastian J Padayatty and Mark Levine

It is a fair generalization that fruit and vegetable consumption is associated with a reduction in heart and vascular diseases, such as stroke. Often, investigators have attributed benefits to specific nutrients measured in blood or urine, such as vitamin C, carotenoids, and flavonoids. Nutrients were selected for measurement because they were presumed to be the biologic modifiers on the basis of in vitro evidence. Given these assumptions, intervention trials were conducted to test proposed health benefits of selected nutrients. The results of such trials have often shown no effect or even an adverse outcome (1). Carotenoid research offers an example of this conundrum. Consumption of carotenoid-containing fruit and vegetables was shown to be associated with a lower cardiovascular disease risk, yet β-carotene supplementation either had no effect or increased mortality (2). Although there may be many explanations for such disappointments, we focus on flawed premise. A nutrient selected for study, because it is in certain foods, may be found in higher concentrations in people as their consumption of those foods increases and may correlate with the presence or absence of disease. However, the selected nutrient may not be the protective agent. Correlation is not causation, and the amounts of "protective nutrients" consumed or measured may simply be markers of some other causative or protective factors. And so we travel full circle to arrive at the beginning, as we think about fruit and vegetable consumption, disease outcome, and plasma vitamin C concentrations.

Several studies have shown that the higher the consumption of fruit and vegetables, the lower the incidence of cardiovascular disease (3–5), including strokes (6–11). These findings were attributed to many factors, including vitamin C. Others have shown that high plasma vitamin C concentrations are associated with a lower risk of stroke (12–14). In a study published in this Journal, Myint et al (15) confirms this in a revitalizing manner. As a prospective study of 20 649 people aged 40–79 y with an average follow-up of 9.5 y, it had the advantage of a large study population in whom many risk factors were measured. Plasma vitamin C was measured in all subjects. The study population had experienced 448 strokes, but those in the highest quartile of plasma vitamin C had 42% fewer strokes than did those in the lowest quartile. The authors concluded, correctly, that plasma vitamin C is a biomarker for the risk of stroke. The study is refreshing in that its findings are both clear and not overstated. On the basis of the evidence presented, the investigators did not advocate an increased intake of vitamin C to prevent stroke. Such strict interpretation of the data avoids a confusing correlation with causation and allows improved hypothesis generation, but is not sufficient grounds to advocate unfounded and possibly useless treatments.

The study by Myint et al was straightforward and transparent, but it had some imperfections. Only one nonfasting plasma vitamin C measurement was obtained, but plasma vitamin C concentrations probably fluctuated during the follow-up years, and non-fasting measurements may not represent steady-state values. The relation between stroke and vitamin C concentrations was independent of consumption of fruit and vegetables and supplements, although there were more supplement users in the highest quartile of plasma vitamin C concentrations. These results are perplexing because vitamin C had to come from somewhere. As the authors wrote, the results may reflect an inaccurate measurement of fruit and vegetable intake with food-frequency questionnaires. The authors estimated that the difference between the lowest and highest quartiles of vitamin C concentration was about one serving of a fruit or vegetable, perhaps an amount too small for the food-frequency questionnaires to detect. It is likely that there was less error in the supplement use data because of how these data were obtained.

Measurement of food intake, including fruit and vegetables, is a problem that bedevils most studies and requires improvement so that future endeavors are more informative. Without improvement, it will be difficult to move beyond describing simple relations between fruit and vegetable consumption and more easily measured endpoints such as stroke, myocardial infarction, or death. Despite limited accuracy, food recall surveys are widely used. Existing instruments do not discern more subtle effects of fruit and vegetables. Ideally, true food intake would be measured, but this is clearly impractical on a large scale or over long periods. More accurate methods of measurement of fruit and vegetable intake must be developed, and existing methods must be refined.

We need readily measurable and reliable biomarkers of fruit and vegetable intake. Candidate biomarkers should have a linear response to increasing fruit and vegetable intake, be stable and reproducibly quantified, and remain unaffected by commonly used supplements, drugs, or liver or renal impairment. The mark-

[1] From the Molecular and Clinical Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-1372.

[2] Address reprint requests to SJ Padayatty and correspondence to M Levine, Molecular and Clinical Nutrition Section, Building 10, Room 4D52-MSC 1372, National Institutes of Health, Bethesda, MD 20892-1372. E-mail: MarkL@intra.niddk.nih.gov.

ers should also reflect the variety of fruit and vegetable intake and, ideally, be able to discriminate different types of fruit and vegetables. Considering the chemical complexity of plant foods, it is likely that several substances in fruit and vegetables will fulfill one or more of these requirements. Current markers include vitamin C, carotenoids (9), and flavonoids (16). Similar to surveys, the validity of markers of fruit and vegetable intake should be established against known food consumption. One can foresee that well-validated quantitative surveys, panels of biomarkers, and new methods of measuring food consumption will give a much more accurate picture of fruit and vegetable consumption than currently possible, except in hospital settings.

Vitamin C is an attractive marker of fruit and vegetable intake because these foods are the primary sources of dietary vitamin C. However, use of vitamin C as an intake indicator has limitations. With ingestion of pure vitamin C, there is a steep sigmoidal dose-concentration relation in humans for doses between 30 and 100 mg. At 100 mg, fasting steady state plasma vitamin C concentrations are ≈60 μmol/L. At 200 mg, corresponding to an intake of ≈5 servings of fruit and vegetables, fasting steady state plasma concentrations are ≈70 μmol/L and do not increase much with higher doses (17). It is unknown whether the same dose-concentration relationships hold for vitamin C in foods. True bioavailability, as opposed to less exact relative bioavailability, has not been determined for vitamin C in food matrices. In vitro and animal data show that fruit and vegetable components, such as flavonoids, might impair vitamin C absorption (18). Relative bioavailability measurements, an imprecise indicator of bioavailability, generally show little difference in absorption between pure vitamin C and vitamin C in foods (19). If relative bioavailability and true bioavailability turn out to be similar, then vitamin C as a biomarker would not distinguish fruit and vegetable intakes of 5 servings daily from higher intakes. If true bioavailability of vitamin C is diminished by food components, then vitamin C would be a good candidate marker across a wider range of fruit and vegetable intake. Additional limitations of vitamin C as a marker are its instability without rigorous sample handling, its sensitivity to even minimal hemolysis (20), and its uncharacterized pharmacokinetic profiles in diabetes, kidney disease, pregnancy, and the elderly. Fasting samples are preferred, because plasma concentrations increase after meals, depending on the vitamin C content of foods consumed. The vitamin C content of fruit and vegetables varies and is affected by food processing, storage, and cooking. Because some foods and beverages are fortified with vitamin C, measurements may not reflect intake of fruit and vegetables alone.

How do fruit and vegetables work their magic? Here, answers are less satisfactory. Fruit and vegetables contain many vitamins, minerals, and phytochemicals, including those that have been widely studied, such as potassium, flavonoids, carotenoids, and vitamins C, and uncharacterized bioactive substances that could be beneficial, either alone or in combination. Fruit and vegetables serve as markers of a healthy lifestyle, education, or wealth, each of which is associated with beneficial effects on health. Fruit and vegetables may change gut flora and increase roughage and fiber (21, 22). They may slow carbohydrate absorption, attenuating rapid increases in blood glucose after meals—a risk factor in itself for cardiovascular disease (23). Finally, the observed beneficial association could be a negative one. That is, fruit and vegetables are generally low in calories and displace energy-dense foods. If you eat lots of carrots, you cannot eat so many sausages.

What should patients and the public be told? We should emphasize that fruit and vegetable intake is associated with many health benefits, including a reduction in stroke. Because we do not know why or how the benefit occurs or what fruit and vegetables are effective, it is prudent to consume a wide variety. The optimum intake for reduction of stroke and cardiovascular disease is unknown, but an intake of 5–9 servings daily is associated with benefit, and the public should aim toward the higher intakes. So, what to say about fruit and vegetables is clear: think variety, go ahead, eat!

The authors declared that they had no conflict of interest with regard to this manuscript.

REFERENCES

1. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007;297:842–57.
2. Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. Am J Clin Nutr 2006;83:1265–71.
3. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. Ann Intern Med 2001;134:1106–14.
4. Hu FB. Plant-based foods and prevention of cardiovascular disease: an overview. Am J Clin Nutr 2003;78(suppl):544S–51S.
5. Shimazu T, Kuriyama S, Hozawa A, et al. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int J Epidemiol 2007;36:600–9.
6. Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA 1999;282:1233–9.
7. Sauvaget C, Nagano J, Allen N, Kodama K. Vegetable and fruit intake and stroke mortality in the Hiroshima/Nagasaki Life Span Study. Stroke 2003;34:2355–60.
8. Johnsen SP. Intake of fruit and vegetables and risk of stroke: an overview. Curr Opin Clin Nutr Metab Care 2004;7:665–70.
9. Hak AE, Ma J, Powell CB, et al. Prospective study of plasma carotenoids and tocopherols in relation to risk of ischemic stroke. Stroke 2004;35:1584–8.
10. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. Neurology 2005;65:1193–7.
11. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. Lancet 2006;367:320–6.
12. Yokoyama T, Date C, Kokubo Y, Yoshiike N, Matsumura Y, Tanaka H. Serum vitamin C concentration was inversely associated with subsequent 20-year incidence of stroke in a Japanese rural community: the Shibata study. Stroke 2000;31:2287–94.
13. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. BMJ 1995;310:1563–6.
14. Eichholzer M, Stahelin HB, Gey KF. Inverse correlation between essential antioxidants in plasma and subsequent risk to develop cancer, ischemic heart disease and stroke respectively: 12-year follow-up of the Prospective Basel Study. EXS 1992;62:398–410.
15. Myint PK, Luben RN, Welch AA, Bingham SA, Wareham NJ, Khaw K-T. Plasma vitamin C concentrations predict risk of incident stroke over 10 y in 20 649 participants of the European Prospective Investigation into Cancer–Norfolk prospective population study. Am J Clin Nutr 2007;87:64–9.
16. Krogholm KS, Haraldsdottir J, Knuthsen P, Rasmussen SE. Urinary total flavonoid excretion but not 4-pyridoxic acid or potassium can be used as a biomarker for the intake of fruits and vegetables. J Nutr 2004;134:445–51.
17. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci U S A 2001;98:9842–6.

18. Song J, Kwon O, Chen S, et al. Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and Glucose. J Biol Chem 2002;277:15252–60.
19. Rumsey SC, Levine M. Absorption, transport, and disposition of ascorbic acid in humans. J Nutr Biochem 1998;9:116–30.
20. Levine M, Wang Y, Rumsey SC. Analysis of ascorbic acid and dehydroascorbic acid in biological samples. In: Packer L, ed. Methods of enzymology. Vol. 299. San Diego, CA: Academic Press, 1999:65–76.
21. Lairon D, Arnault N, Bertrais S, et al. Dietary fiber intake and risk factors for cardiovascular disease in French adults. Am J Clin Nutr 2005;82: 1185–94.
22. Pereira MA, O'Reilly E, Augustsson K, et al. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. Arch Intern Med 2004;164:370–6.
23. Oh K, Hu FB, Cho E, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol 2005;161:161–9.