

Fruits, Vegetables, and Cancer Prevention: Turmoil in the Produce Section

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During the 1990s, enthusiasm swelled for increasing consumption of fruits and vegetables with the expectation that this would substantially reduce the risk of many cancers (1). Potential reductions as large as 50% were suggested. The National Cancer Institute's 5-A-Day program was developed in 1991 (http://dccps.nci.nih.gov/5ad_3_origins.html) (2) to promote increasing the average consumption of fruits and vegetables to five or more servings per day, and a major line of investigation was launched to identify and isolate the phytochemicals responsible for the apparent benefits. However, the evidence for a large preventive effect of fruits and vegetables came primarily from case-control studies, which can be readily biased by differences in recall of past diet by patients with cancer and healthy control subjects. Even more problematic, participation rates in surveys have fallen sharply over the past 50 years so that those who agree to be interviewed as control subjects are likely to overrepresent health conscience persons who smoke less, exercise more, and eat more fruits and vegetables compared with those who do not participate. Because participation rates of patients with cancer, who are already in a medical system, remain high, the result is an exaggerated apparent benefit of fruits and vegetables, even if both groups report their past diets perfectly.

Prospective studies largely avoid bias because of recall and selective participation. In the late 1990s, the results of large prospective cohort studies of diet and cancer began to accrue, and these did not confirm the strong inverse associations found in most case-control studies. Furthermore, a series of analyses that pooled the data from prospective studies for specific cancer sites confirmed the weak and non-statistically significant associations (3,4). In a comprehensive 2007 review (5), these findings led to the reversal of conclusions for strong benefits of fruits and vegetables for many cancer sites that had been considered convincing or probable in a similar earlier review 10 years before.

In this issue of the Journal, Boffetta et al. (6) report findings from a European cohort of nearly 400 000 men and women who developed approximately 30 000 cancers at all sites combined over nearly 9 years of follow-up. After accounting for measurement error, a very weak but statistically significant inverse association was seen—a 4% lower incidence of all cancers combined for an increment of 200 g of total fruits and vegetables per day, which corresponds to about two extra servings per day. Without question, large studies that include many cancer cases are desirable, but when they result in weak but statistically significant findings, the interpretation can be challenging. Epidemiological studies, particularly when they involve imperfectly measured exposures that are associated with other behavioral variables, will have difficulty distinguishing between relative

risks of 0.96 and 1.00. Most fundamentally, this study strongly confirms the findings from other prospective studies that the results of case-control studies were overly optimistic and that any association of intake of fruits and vegetables with risk of cancer is weak at best. The authors of the present report are appropriately cautious in interpreting their findings because they note the difficulty in excluding the possibility that the observed weak associations are because of residual confounding. Their more detailed analyses suggesting a stronger benefit among heavier consumers of alcohol lend some weight to a causal interpretation because other studies (7,8) have suggested that folate, primarily from fruits and vegetables, may be more beneficial in the context of regular alcohol consumption. If we had clearer evidence of a benefit of fruits and vegetables for one or a few cancer sites, which was diluted by combining all cancers, we would be more confident that the weak overall association was causal. However, this is the case neither in this cohort nor in the overall literature. To date, the strongest evidence for a benefit for fruits and vegetables is for renal cell cancer because a statistically significant inverse association was seen in the pooled analyses of prospective studies, but the number of cancer cases was not large (9). In the 2007 review (5), upper aerodigestive cancers were classified as probably reduced by greater consumption of fruits and vegetables, but this was largely based on the findings of case-control studies. Given previous experience with other cancers, we should be cautious about these conclusions until we have more data from prospective studies.

A very weak or undetectable association between fruits and vegetables and risk of cancer does not exclude the possibility that one or a small group of fruits or vegetables, or a specific substance in some of these foods, has an important protective effect. For example, considerable evidence suggests that lycopene and tomato products reduce the risk of prostate cancer (5). Furthermore, multiple lines of evidence indicate that ionizing radiation and some other risk factors for cancer can operate primarily in childhood and early adult life; thus, antioxidants or other protective constituents of fruits and vegetables may need to be present at that time to be effective. Like the European Prospective Investigation into Cancer and Nutrition (EPIC), almost all studies of diet and cancer would have missed such effects because they started decades later in life.

Even if we assume that the weak association seen in the EPIC cohort represents a true protective effect of fruits and vegetables, the question would still remain whether an effect of this magnitude should lead to clinical interventions or public health actions. Conveniently, although the evidence for benefits of fruits and vegetables against cancer was waning, data supporting benefits for

cardiovascular disease were accumulating (10,11). For example, in the same population of men and women that showed no association between fruits and vegetables and total cancer, incidence of coronary heart disease or stroke was 30% lower for those consuming five or more servings per day compared with those eating less than 1.5 servings per day (12). Data from a large randomized trial showing that increasing intake of fruits and vegetables reduces blood pressure (13), a major determinant of cardiovascular disease, make the case for causality compelling, although benefits through additional pathways are also possible. Thus, recommendations and actions to increase intake of fruits and vegetables have a sound basis.

In summary, the findings from the EPIC cohort add further evidence that a broad effort to increase consumption of fruits and vegetables will not have a major effect on cancer incidence. Such efforts are still worthwhile because they will reduce risks of cardiovascular disease, and a small benefit for cancer remains possible. Research should focus more sharply on specific fruits and vegetables and their constituents and on earlier periods of life. For prevention of cancer, the primary focus at present should be heightened efforts to reduce smoking and obesity because obesity in the United States has become similar in magnitude to smoking as an avoidable cause.

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