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LETTERS TO THE EDITOR

RE: "DIETARY FLAVONOID INTAKE AND RISK OF CARDIOVASCULAR DISEASE IN POSTMENOPAUSAL WOMEN"

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The prospective study by Yochum et al. (1) reveals a protective association between intake of flavonoids and risk of death from coronary heart disease (CHD) in postmenopausal women. However, the evidence that flavonoids themselves are protective against CHD has several weaknesses that require further investigation.

The protective association between flavonoids and fatal CHD in the above study was largely due to certain fruits and vegetables, especially broccoli. However, in the multivariate analysis no correction was made for possible confounding by fruit and vegetables. Could it be that flavonoids were merely a surrogate measure of these foods?

A major source of flavonoids is tea. In prospective studies the relative risk (RR) of death from CHD when comparing the highest and lowest consumers of tea has been reported as 0.89 (1), 0.45 (2), 1.6 (3), and 2.3 (4). Such large discrepancies clearly make it impossible to draw any conclusions.

In only one study does the evidence clearly indicate that total intake of flavonoids protects against CHD. Knekt et al. (5), in Finland, reported a relative risk of approximately 0.69; the sample size was large (470 cases of fatal CHD) and the data were adjusted for vitamin C and beta-carotene (which corrects to a large extent for confounding by fruits and vegetables). The study by Rimm et al. (3) in the United States reported a protective association for fatal CHD (RR = 0.77, not significant; adjusted for carotene but not vitamin C) but saw no such association with nonfatal myocardial infarction. The study by Hertog et al. (4) in Wales observed that flavonoids, which were derived mainly from tea, were positively associated with fatal CHD (RR = 1.6). Hertog et al. (2, 6), in the Netherlands, detected a protective relation; however, in their earlier study, this is based on small numbers (43 cases of fatal CHD) (2), while in their follow-up study, although the number of cases had increased to 90, no correction was made for factors associated with fruits and vegetables (6).

Until a clearer and more consistent picture emerges, it would be premature to make any inferences as to the relation between intake of flavonoids and risk of CHD.

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THREE OF THE AUTHORS REPLY

We thank Dr. Temple for his observations (1) about our recently published article on dietary flavonoids (2). He is concerned that the inverse association of flavonoids with coronary heart disease (CHD) death was only due to certain fruits and vegetables and that we did not correct for possible confounding by total fruits and vegetables. In addition, he suggests our conclusion that flavonoids may be inversely associated with CHD death is premature in light of the inconsistencies in the literature.

While it is true that the inverse association between flavonoids and CHD death was largely due to certain fruits and vegetables, we originally included dietary fiber, whole grains, and vitamin E in the model to adjust for possible confounding by dietary components. Other fruit and vegetable components previously found to have a protective effect on CHD (mainly carotenoids and vitamin C) were not associated with a lower rate of CHD death in this cohort (3).

However, adjusting our analyses for total fruit and vegetable intake strengthened the flavonoid association with CHD death. When our results were adjusted for fruit and vegetable intake, we observed a 40 percent reduced risk of CHD death, compared with a 32 percent reduced risk prior to this adjustment. Relative risks for total flavonoid intake and CHD death from lowest to highest intake categories were: 0.64 (95 percent confidence interval: 0.47, 0.86), 0.59 (95 percent confidence interval: 0.43, 0.83), 0.55 (95 percent confidence interval: 0.61, 1.16), and 0.60 (95 percent confidence interval: 0.43, 0.86), p for trend = 0.09, after additional adjustment for these foods. Thus, it appears that the inverse association we observed was not due to confounding by fruits and vegetables.

Temple also states that it is impossible to draw any conclusions about tea, a source of flavonoids. The evidence for a protective effect of tea is inconclusive (2, 4–6), but there may be issues about the availability of flavonoids from this source (6, 7). We do not draw any specific conclusions about the effect of flavonoids from tea in our article. Tea is only one of many sources of flavonoids.

When examining the totality of evidence about the flavonoid and CHD association, it is not premature to make some inferences. There is a clear biologic mechanism by which flavonoids may decrease risk of CHD. Flavonoids are known to be free-radical scavengers (8–10). They have been shown to prevent cytotoxicity of low density lipoproteins (11) and low density lipoprotein oxidation in vitro (12). In addition, flavonoids may be more potent antioxidants than is vitamin E (13), which has been inversely associated with death from CHD in several epidemiologic investigations (3, 14, 15).