An apple a day to prevent Parkinson disease

Reduction of risk by flavonoids

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The search for environmental risk factors for Parkinson disease (PD) has yielded few potentially causal associations.[1] The recognition of genetic factors in the etiology of PD,[2,3] in conjunction with PD pathology, has led to the suggestion that PD results from abnormal α-synuclein, its propagation, eventual deposition as Lewy bodies, and subsequent neurodegeneration.[4,5] The potential role of oxidative damage in this process, possibly through mitochondrial insult by environmental toxins,[6] has provided additional leads for the effects of environmental factors, notably pesticides.[7] The search for environmental factors is made more difficult as the pathology is likely to have begun many years prior to the diagnosis of PD.[1]

The rarity of PD,[8] about 100 per 100,000 in the oldest age groups, presents a challenge for epidemiologic study. A longitudinal cohort study, starting with unaffected persons, requires large numbers and long follow-up to accrue an adequate number of cases for analysis. Another key requirement is reliable and accurate measurement of the hypothesized exposures, at baseline and throughout the study. Further, because "clinical incidence" may occur many years after pathology begins, it is important to consider when the exposure must have happened in order to cause the disease. Unfortunately, we do not know what that critical exposure time window is, or how it may differ depending on the exposed agent. The causal effect of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)[9] is rapid as compared to the possible protective effect associated with cigarette smoking.[1] Whether long-term, low-level exposures would sum to exert a cumulative effect is uncertain; some exposures at low levels may simply be insufficient to promote the disease process.

In this issue of *Neurology*®, Gao et al.[10] analyzed data from 2 large cohort studies addressing whether dietary flavonoid intake might influence the onset of PD. The Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) used similar methods but were conducted separately. The NHS began in 1976, and with 121,700 female registered nurses, 80,366 beginning with a 1984 baseline visit were included in this analysis. The HPFS began in 1986 and enrolled 51,529 male health professionals; 49,281 with a baseline 1986 visit were included in the present analysis. From among these cohorts, 805 incident PD cases occurred during 20–22 years of follow-up (about 20.1 and 42.5 cases per 100,000 person-years, in the NHS and HPFS). Self-report questionnaires were completed to capture incident PD (verified by medical records) and food frequency questionnaires were completed at baseline and subsequently every 4 years to report average food intake (type and amount) during the previous year. Flavonoid content was inferred based on standard content analyses. Flavonoid-rich food (tea, apples, blueberries/strawberries, red wine, oranges/orange juice) were captured as servings per week and then categorized into 6 subclasses of flavonoids, then further divided into about 30 flavonoid compounds. Quintiles of consumption were tested for their association with risk of PD and for any dosage trends. To ensure that flavonoid values might reflect consumption before clinical onset of PD only average cumulative intake up to 4 years prior to clinical onset was used.

In the primary analysis, after multivariate adjustment, including age and smoking, there was a decreased risk of PD in men for the fourth and fifth quintiles of total flavonoid intake and a significant trend suggesting a dose-response effect, with the decreased risk only in the HPFS and not in the NHS. This heterogeneity would argue against "pooling" the 2 datasets for analysis. Because the NHS is comprised of only women and the HPFS is only men, perhaps the difference indicates effect modification by sex rather than an effect of study differences; we cannot be sure. Examining flavonoid subclasses, only flavonols, polymers, and possibly anthocyanins were associated with decreased risk in men. Men who ate 5 or more servings of apples per week had a decreased risk of PD compared to those who eat less than 1 apple per

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month, but the same is not true among women in the NHS. Aside from the trend tests most quintile hazard ratios 95% confidence intervals include the null, for all exposure measures in both men and women.

Could there be a sex-specific difference in the way that flavonoids might be metabolized or might act to influence PD pathology? The Cytochrome P-450 enzyme system is affected by aging and has sex-dependent metabolic differences.[11] Flavonoid compounds hesperetin and diosmetin at relatively high levels can inhibit drug metabolism (e.g., nonsteroidal anti-inflammatory drugs, warfarin, metronidazole, midazolam) by CYP2C9 and CYP3A4/5.[12] Could these biotransformation enzymes provide some clues as to the mechanisms of action leading to different effects in men and women? These are tantalizing biological avenues that require additional research.

Despite the care taken by researchers in studies such as these, primary exposures determined by self-report, even with well-validated questionnaires, may result in misclassification. Would the same food frequency questionnaire be filled out systematically differently by men and women? Would those who were prone to report higher flavonoid consumption also be those less likely, in the future, be diagnosed with PD? After adjustment for a variety of factors, it would seem unlikely that a differential misclassification caused a biased estimate of risk. Conversely, we may worry that the many subclasses and compounds tested based on the report of food frequency create a multiple testing issue. Uncontrolled confounding may also exist. We await additional research to address these issues; until then, an apple a day might be a good idea.

DISCLOSURE

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