Nicotine from Edible *Solanaceae* and Risk of Parkinson Disease

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Objective: To test whether risk of Parkinson disease (PD) is associated with consumption of nicotine-containing edibles from the same botanical family as tobacco, *Solanaceae*, including peppers, tomatoes, and potatoes.
Methods: In a population-based study with 490 newly diagnosed idiopathic PD cases diagnosed during 1992–2008 at the University of Washington Neurology Clinic or Group Health Cooperative in western Washington State and 644 unrelated, neurologically normal controls, we examined whether PD was associated with self-reported typical frequency of consumption of peppers, tomatoes, tomato juice, and potatoes during adulthood, while adjusting for consumption of other vegetables, age, sex, race/ethnicity, tobacco use, and caffeine.
Results: PD was inversely associated with consumption of all edible *Solanaceae* combined (relative risk [RR] = 0.81, 95% confidence interval [CI] = 0.65–1.01 per time per day), but not consumption of all other vegetables combined (RR = 1.00, 95% CI = 0.92–1.10). The trend strengthened when we weighted edible *Solanaceae* by nicotine concentration ($p_{trend} = 0.004$). An inverse association was also evident for peppers specifically ($p_{trend} = 0.005$). The potentially protective effect of edible *Solanaceae* largely occurred in men and women who had never used tobacco or who had smoked cigarettes <10 years.
Interpretation: Dietary nicotine or other constituents of tobacco and peppers may reduce PD risk. However, confirmation and extension of these findings are needed to strengthen causal inferences that could suggest possible dietary or pharmaceutical interventions for PD prevention.

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The most consistent findings from epidemiologic research on environmental factors and Parkinson disease (PD) have been reduced risks related to cigarette smoking and use of other forms of tobacco.[1] Exposure to environmental tobacco smoke may possibly confer protection as well.[2–4] Nonetheless, it remains unresolved whether nicotine or other constituents of tobacco smoke are truly protective, or rather, that failure to smoke indicates preclinical behavioral differences in persons predisposed to develop PD.

Several mechanisms by which tobacco smoking might reduce PD risk have been hypothesized. Tobacco smoke contains thousands of chemicals, but notably, experimental studies indicate that nicotine is neuroprotective.[5] Nicotine is the addictive phytochemical in tobacco, which is derived from plants in the *Nicotiana* species of the *Solanaceae* family. Other species in this family include *Capsicum* and *Solanum*, whose edible fruits and tubers include peppers, tomatoes, potatoes, and eggplants. All contain nicotine.[6–10] The amount of nicotine absorbed from these foods is negligible relative to the amount obtained from active smoking, and probably lower than that from environmental tobacco smoke.[11] However, even nicotine blood levels reached from environmental tobacco smoke exposure, much lower than that from active smoking, are sufficient to saturate a substantial portion of $\alpha4\beta2$ nicotine receptors in the human brain.[12] Stimulation of nicotine receptors protects dopaminergic neurons in animal models of PD using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[13] or rotenone.[14]

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Therefore, given the strength of the association we recently observed between PD and environmental tobacco smoke, which was similar to that for active smoking,[2] we investigated whether nicotine from dietary sources might also demonstrate an inverse association with PD in the same case–control study population.

Subjects and Methods

Study Population

We conducted a population-based case–control study in western Washington State.[15,16] Briefly, cases (n = 490) were newly diagnosed with idiopathic PD at Group Health Cooperative (GHC), a health maintenance organization in the Puget Sound region (n = 387), or the University of Washington Neurology Clinic (n = 103) in Seattle in 1992–2008. Diagnoses were made by movement disorder specialists or were verified by consensus chart reviews performed by a team of neurologists (G.M.F., W.T.L., P.D.S.). All cases had ≥2 of 4 cardinal signs of PD (bradykinesia, resting tremor, cogwheel rigidity, postural reflex impairment). Exclusion criteria were (1) an established cause of secondary parkinsonism (eg, stroke, brain tumor, selected medications), (2) enrollment >4 years after diagnosis, or (3) abnormal (<24) Mini-Mental State Examination (MMSE) score. We identified controls (n = 644) from among GHC enrollees who were frequency matched to cases on sex, age (within 10 years), race/ethnicity, clinic, and year of GHC enrollment. Controls were (1) cognitively normal (MMSE ≥ 24); (2) without PD, Alzheimer disease, multiple sclerosis, or other neurodegenerative disorders; and (3) unrelated by blood or marriage to cases. We obtained Human Subjects approval and written informed consent prior to study conduct.

Assessment of Solanaceae Exposure

We administered a standardized in-person questionnaire to assess dietary and tobacco use histories. We defined tobacco use as ever smoking >100 cigarettes, or ever regularly using cigars, pipes, or smokeless tobacco. The questionnaire, a modified version of the Willet food frequency questionnaire as of 1991, elicited information on typical frequency of consumption during adulthood of 71 foods and beverages covering all major food groups and sources of caffeine.[17,18] Complete tobacco and diet histories were obtained for 486 (99%) of cases and 636 (99%) of controls.

The *Solanaceae* family edibles we assessed were peppers, tomatoes, tomato juice, and potatoes (baked or mashed). We also assessed consumption of other vegetables: broccoli, cauliflower, cabbage, Brussels sprouts, radishes, lettuce, spinach/other greens, carrots, peas/lima beans, corn, sweet potatoes/yams, cucumbers, zucchini, yellow/winter squash, and onions/scallions. Participants reported frequency of consumption of each in 1 of 9 categories (almost never, 1–3×/mo, 1×/wk, 2–4×/wk, 5–6×/wk, daily, 2–3×/day, 4–6×/day, >6×/day). We weighted these responses according to the relative frequency per day, and then summed them to obtain combined measures of frequency of consumption of: (1) all edible *Solanaceae* and (2) all other vegetables. In addition, we created a variable for the former in which we also weighted by nicotine concentration of the individual *Solanaceae* foods. We used results from the most sensitive comprehensive laboratory analysis of nicotine in edible *Solanaceae* published to date.[6] Specifically, we used the median dry-weight nicotine concentration for all measurements of foods as they would be consumed, because water content and ripening, and possibly peeling and cooking, affect nicotine content. We included all measurements for peppers (median 102.1μg nicotine/kg). For tomatoes, we only included measurements for fresh, ripe tomatoes (degree of ripening = 7–12, median = 43.8μg nicotine/kg). For tomato juice (not included in the laboratory assessment), we used all measurements for processed tomato products (median = 29.7μg nicotine/kg). For potatoes, we used measurements only for cooked potatoes (median = 19.25μg nicotine/kg). The median nicotine level for eggplant was below the limit of quantitation.

Statistical Analyses

We performed unconditional logistic regression analysis to calculate odds ratios and 95% confidence intervals as an estimate of relative risk of PD in relation to edible *Solanaceae*. We adjusted for frequency matching variables age, sex, and race/ethnicity, as well as for frequency of consumption of all non-*Solanaceae* vegetables combined, tobacco products (ever vs never regular use), and caffeine (milligrams,[19] continuous), because smoking and caffeine are associated with PD[1] and dietary patterns.[20–22] We also verified the absence of confounding (<10% change in relative risk estimates) by extent of cigarette smoking (years, packs per day, pack-years, recentness), consumption of alcohol (drinks per day), other individual foods and food groups, estimated alternate Mediterranean Diet Score,[23] education, birth year, urban versus rural residence, and family history of PD in the full data set; and body mass index (at age 20 years and at interview) and environmental tobacco smoke exposure at home and work in 154 cases and 173 controls for whom those data were available.[2]

Because the amount of nicotine from active tobacco use would likely eclipse that from dietary sources, we repeated all analyses stratified by tobacco use (ever vs never regular use). We formally tested any potential interactions between PD, edible *Solanaceae*, and tobacco use in logistic regression on a multiplicative scale with main effects terms in the model.

Results

Participant characteristics have been described previously.[16] Briefly, most cases and controls were non-Hispanic Caucasians (93% and 92%, respectively) and were men (63% and 64%, respectively). Cases' mean age was 65.6 years at diagnosis, and controls' was 68.0 years at reference. Relatively few cases (11%) and controls (5%) had a first-degree relative with PD. Half of cases and 62% of controls had ever smoked tobacco products, and among ever cigarette smokers, controls smoked more than cases by several measures, including mean duration of years smoked (22.5 for cases, 26.8 for controls).

TABLE 1. Parkinson Disease Risk and Edible *Solanaceae*[a] and Other Vegetables, Overall and by Tobacco Use[b]

Vegetable	All Participants, 486 Cases/636 Controls, RR (95% CI)[c]	Ever Used Tobacco,[b] 245 Cases/397 Controls, RR (95% CI)[c]	Never Used Tobacco, 241 Cases/239 Controls, RR (95% CI)[c]
Edible *Solanaceae*[a]	0.81 (0.65–1.01)	0.89 (0.68–1.17)	0.69 (0.47–1.00)
p_{trend}	0.07	0.42	0.05
Nicotine[d]-weighted p_{trend}	0.004	0.23	0.002
Pepper, 102.1μg/kg nicotine[d]	0.43 (0.24–0.78)	0.66 (0.30–1.44)	0.24 (0.09–0.60)
Tomato, 43.8μg/kg nicotine[d]	0.83 (0.56–1.24)	1.00 (0.61–1.66)	0.58 (0.30–1.14)
Tomato juice, 29.7μg/kg nicotine[d]	0.77 (0.41–1.44)	0.54 (0.24–1.21)	2.16 (0.56–8.36)
Potato, 19.25μg/kg nicotine[d]	1.12 (0.73–1.70)	1.25 (0.72–2.18)	0.91 (0.47–1.76)
Eggplant, μg/kg nicotine < LOQ[d,e]	NA	NA	NA
Other vegetables[f]	1.00 (0.92–1.10)	0.99 (0.88–1.11)	1.03 (0.90–1.18)
p_{trend}	0.95	0.84	0.63

[a]All assessed edible *Solanaceae*: green, yellow, or red peppers; tomatoes; tomato juice; and baked or mashed potatoes.
[b]Ever smoked >100 cigarettes or regularly used cigars, pipes, or smokeless tobacco.
[c]RR (odds ratio) and 95% CI, per once daily increase in typical adult life frequency of consumption, adjusted for age (continuous), sex, race/ethnicity, consumption of other vegetables (continuous), and caffeine (milligrams, continuous), and adjusted for or stratified by tobacco use (ever vs never >100 cigarettes or regularly used cigars, pipes, or smokeless tobacco).
[d]Median dry-weight nicotine concentration in each *Solanaceae* as typically consumed (eg, ripe tomatoes and cooked potatoes), calculated from data published in Siegmund et al.[6]
[e]Detected but below the LOQ.
[f]All assessed non-*Solanaceae* vegetables combined: broccoli, cauliflower, cabbage, Brussels sprouts, radishes, lettuce, spinach/other greens, carrots, peas/lima beans, corn, sweet potatoes/yams, cucumbers, zucchini, yellow/winter squash, and onions/scallions.
CI = confidence interval; LOQ = limit of quantitation; NA = not assessed; RR = relative risk.

Frequency of consumption of edible *Solanaceae* (peppers, tomatoes, tomato juice, and potatoes combined) was inversely related to PD risk ($p_{trend} = 0.07$, Table 1). In contrast, we observed no association with the frequency of consumption of all other vegetables combined ($p_{trend} = 0.95$). The inverse PD–*Solanaceae* association strengthened when we weighted by nicotine concentration ($p_{trend} = 0.004$). There was only a suggestion of an inverse trend for tomatoes and tomato juice, and no inverse association for potatoes, but there was a strong inverse association for peppers ($p_{trend} = 0.005$). We confirmed a dose–response association in an unconstrained model; eating peppers 2 to 4× or more per week was consistently associated with a ≥30% reduction in risk of developing PD (Table 2). The potentially protective effects of edible *Solanaceae* in general, or peppers specifically, were very similar in men and women (Supplementary Table 1), but were mainly evident in men and women who had never used tobacco regularly or who had smoked cigarettes <10 years (see Tables 1 and 2; Supplementary Table 2). However, interactions between PD, edible *Solanaceae*/peppers, and tobacco use were not statistically significant (all $p_{interaction} \geq 0.15$).

Discussion

Epidemiologic studies have reported inverse associations of PD with consumption of tomatoes,[24] potatoes,[25] and a "Mediterranean" diet high in vegetables including tomatoes and peppers.[23,26] However, to our knowledge, this is the first study of PD focused on dietary nicotine or consumption of *Solanaceae* other than tobacco. Similar to the well-established inverse association between PD and tobacco use, we observed an inverse association between PD and edible *Solanaceae*, especially peppers. We observed no inverse association between PD and combined frequency of consumption of non-*Solanaceae* vegetables, indicating some specificity of the association. Furthermore, the PD–*Solanaceae* association was largely confined to men and women who never used tobacco or only did so for a relatively short period.

Some caution in interpreting these results is required. Relative to active tobacco use, diet is a modest contributor to daily nicotine dose, and biological effects on the human brain from dietary nicotine from edible *Solanaceae* are not established. It is known, however, that a substantial number of $\alpha4\beta2$ nicotine receptors become occupied at nicotine blood levels achieved without active

TABLE 2. Parkinson Disease Risk and Peppers, Overall and by Tobacco Use[a]

Consumption of Peppers	All Participants			Ever Used Tobacco[a]			Never Used Tobacco		
	Cases, n = 486, No. (%)	Controls, n = 636, No. (%)	RR [95% CI][b]	Cases, n = 245, No. (%)	Controls, n = 397, No. (%)	RR [95% CI][b]	Cases, n = 241, No. (%)	Controls, n = 239, No. (%)	RR [95% CI][b]
<Weekly	283 (58)	333 (52)	1.0 [reference]	146 (60)	219 (55)	1.0 [reference]	137 (57)	114 (48)	1.0 [reference]
1 × /wk	103 (21)	120 (19)	0.95 [0.69–1.31]	47 (19)	70 (18)	1.02 [0.65–1.58]	56 (23)	50 (21)	0.92 [0.57–1.47]
2–4 × /wk	78 (16)	130 (20)	0.70 [0.50–1.00]	39 (16)	80 (20)	0.77 [0.48–1.23]	39 (16)	50 (21)	0.59 [0.35–0.99]
5–6 × /wk	12 (2)	29 (5)	0.48 [0.23–0.99]	5 (2)	13 (3)	0.70 [0.23–2.09]	7 (3)	16 (7)	0.37 [0.14–1.00]
Daily	10 (2)	24 (4)	0.50 [0.22–1.15]	8 (3)	15 (4)	0.88 [0.34–2.31]	2 (1)	9 (4)	0.13 [0.02–0.73]
p_{trend}			0.005			0.30			0.003

[a]Ever >100 cigarettes or regularly used cigars, pipes, or smokeless tobacco.
[b]RR (odds ratio) and 95% CI for typical adult life frequency of consumption of green, yellow, or red peppers, adjusted for age (continuous), sex, race/ethnicity, consumption of tomatoes, tomato juice, potatoes, other vegetables, and caffeine (milligrams, continuous), and adjusted for or stratified by tobacco use (ever vs never >100 cigarettes or regularly used cigars, pipes, or smokeless tobacco).
CI = confidence interval; RR = relative risk.

smoking; and that 1/3 of the receptors are occupied for >3 hours by a single cigarette puff, whereas complete saturation is only achieved after multiple cigarettes.[12] This biological effect of a relatively small amount of nicotine may offer some supporting evidence for a neuroprotective effect of nicotine from diet.

We also note that tomatoes and potatoes are probably more important than peppers with regard to the absolute amount of nicotine ingested,[11] yet the PD–*Solanaceae* association we observed was largely due to peppers. An absence of data on foods such as tomato-based sauces and salsas, and boiled and fried potatoes including chips and French fries, may have muted associations for tomatoes and potatoes. In addition, because of first-pass metabolism of nicotine in the liver, perhaps ingested nicotine is required to be obtained from a concentrated source to reach the brain. The dry-weight concentration of nicotine may be substantially greater in peppers than in tomatoes and potatoes.[6,7]

Finally, constituents of peppers other than nicotine may be neuroprotective. Given the possible interaction between PD, peppers, and tobacco use, shared phytochemicals are of particular interest. Another alkyloid, anatabine, is an intriguing possibility, because it has anti-inflammatory properties[27–29] and might be more feasibly employed as a neuroprotective chemical than nicotine due to its longer half-life and perhaps lower toxicity and addictive potential. Alternatively, capsinoids in peppers and capsaicinoids in spicy peppers activate transient receptor potential cation channel subfamily vanilloid member 1 (TRPV1) receptors.[30] These receptors are in the substantia nigra, and they and capsaicin may affect survival of midbrain dopaminergic neurons.[31,32] Given the relatively weak results for tomatoes, it is unlikely that lycopene or vitamins A and C account for our findings.

The strength of our study comes from the use of newly diagnosed cases and a highly comparable control group unrelated to cases by blood or marriage. The main limitation is that we obtained diet data retrospectively by self-report, and we did not assess diet for different periods of life. Although we inquired about typical consumption in adulthood, PD or its medical correlates may affect diet[33] and therefore may have influenced our results somewhat. For the possible inverse associations we report here, heartburn is of greatest concern. Constipation and dysphagia are unlikely to underlie the associations. More detailed assessment of diet for different periods of life also would have improved our ability to focus on the effect of dietary nicotine in the years without active tobacco use. An additional limitation is the lack of environmental tobacco smoke exposure data for most participants.

Epidemiological studies designed to address these limitations, while retaining the considerable strengths of the present work, may shed further light on our somewhat novel hypothesis and findings. Although they are consistent with the well-established inverse association between PD and tobacco use, it remains unknown whether nicotine reduces PD risk and whether TRPV1 agonists, including those in peppers, are neuroprotective or neurotoxic.[31,32] Replication of our findings will be needed to strengthen causal inferences that might eventually lead to dietary or pharmaceutical interventions designed to help prevent PD.

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Authorship

H.C. obtained funding. H.C., G.M.F., W.T.L., and P.D.S. obtained data and made critical revisions to the text. S.S.N. had full access to the data, conducted statistical analysis, wrote the manuscript, and takes full responsibility for the article.

Potential Conflicts of Interest

S.S.N., G.M.F., W.T.L., P.D.S., H.C.: grants/grants pending, NIH.

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