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Nicotine from edible *Solanaceae* and risk of Parkinson disease (ANA-12-1625)

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Abstract

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 ($p_{\text{trend}}=0.004$). An inverse association was also evident for peppers specifically ($p_{\text{trend}}=0.005$). 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 is needed to strengthen causal inferences that could suggest possible dietary or pharmaceutical interventions for PD prevention.

MeSH Key Words

Anatabine; bell pepper; Capsicum; diet; idiopathic Parkinson disease; potatoes; nicotine; *Solanaceae*; tomatoes; TRPV1 receptors

Introduction

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 $\alpha 4\beta 2$ 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 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.

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, a health maintenance organization in the Puget Sound region (GHC, 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 (GMF, WTL, PDS). 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 (e.g., 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 $\geq$ 24), 2) without PD, Alzheimer disease, multiple sclerosis or other neurodegenerative disorders, and 3) unrelated by blood or marriage to cases.

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 one of nine categories (almost never, 1–3 times/month, 1/week, 2–4/week, 5–6/week, 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 102.1 µg nicotine/kg). For tomatoes we only included measurements for fresh, ripe tomatoes (degree of ripening 7–12, median 43.8 µg nicotine/kg). For tomato juice (not included in the laboratory assessment), we used all measurements for processed tomato products (median 29.7 µg nicotine/kg). For potatoes we used measurements only for cooked potatoes (median 19.25 µg nicotine/kg). The median nicotine level for eggplant was below the limit of quantification.

Statistical analyses

We performed unconditional logistic regression analysis to calculate odds ratios and 95% confidence intervals (CIs) as an estimate of relative risk (RR) 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 (mg,¹⁹ continuous) because smoking and caffeine are associated with PD¹ 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 vs. rural residence, and family history of PD in the full dataset; and body mass index (at age 20 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 smoked >100 cigarettes or regularly used pipes, cigars or smokeless tobacco). 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).

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

Discussion

Epidemiologic studies have reported inverse associations of PD with consumption of tomatoes,²⁴ potatoes²⁵ 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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential Conflicts of Interest

All authors: grants/grants pending, NIH.

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Table 1Parkinson disease risk and edible *Solanaceae*^a and other vegetables, overall and by tobacco use^b

	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 <i>Solanaceae</i>^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 (102.1 µg/kg nicotine ^d)	0.43 (0.24–0.78)	0.66 (0.30–1.44)	0.24 (0.09–0.60)
Tomato (43.8 µg/kg nicotine ^d)	0.83 (0.56–1.24)	1.00 (0.61–1.66)	0.58 (0.30–1.14)
Tomato juice (29.7 µg/kg nicotine ^d)	0.77 (0.41–1.44)	0.54 (0.24–1.21)	2.16 (0.56–8.36)
Potato (19.25 µg/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 ^f	NA ^f	NA ^f
Other vegetables^g	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 Relative risk (odds ratio) and 95% confidence interval, 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 (mg, continuous); and adjustment for or stratification 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 (e.g. ripe tomatoes and cooked potatoes), derived from Siegmund et al. 1999^e Detected but below the limit of quantification^f Not assessed^g 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

Table 2Parkinson 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 n (%)	Controls N=636 n (%)	RR (95% CI) ^b	Cases N=245 n (%)	Controls N=397 n (%)	RR (95% CI) ^b	Cases N=241 n (%)	Controls N=239 n (%)	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/week	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/week	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/week	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

^aEver >100 cigarettes or regularly used cigars, pipes or smokeless tobacco^bRelative risk (odds ratio) and 95% confidence interval 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 (continuous), and adjustment for or stratification by tobacco use (ever vs. never >100 cigarettes or regularly used cigars, pipes or smokeless tobacco)