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## Smokeless Tobacco Use and the Risk of Parkinson's Disease Mortality

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**Abstract:** We examined the association between smokeless tobacco use and Parkinson's disease (PD) mortality as assessed by death certificate in a prospective cohort of 95,981 never-smoking men. In this cohort, smokeless tobacco use is inversely associated with PD mortality, with an age-adjusted risk

of 0.22 (0.07–0.67) among current users compared to never users. © 2005 Movement Disorder Society

**Key words:** smokeless tobacco; Parkinson's disease; mortality

Cigarette smokers have a lower risk of Parkinson's disease (PD) than nonsmokers.<sup>1</sup> However, there are no prospective data on the relationship between PD and smokeless tobacco use. A reduced risk of PD among smokeless tobacco users would suggest that some constituent in tobacco itself rather than a by-product of combustion may confer a neuroprotective effect.

### Patients and Methods

We assessed prospectively the association between smokeless tobacco and PD mortality as assessed by death certificate among men in the Cancer Prevention Study II (CPS-II), a cohort composed of 508,334 men and 676,306 women 30 years of age or older who were recruited by the American Cancer Society in 1982.<sup>2,3</sup> Information on smokeless tobacco use was not collected for women who were participants in CPS-II. Because of the strong inverse relation between smoking and risk of PD, only never smokers ( $n = 127,068$ ) were considered in the analyses. Furthermore, we excluded 8,617 men who died before 1989 because death codes specific to PD were not used before 1989, 12,626 men who reported a history of "any other serious illness" or stroke at enrollment because they may have had PD, and 9,844 men for whom smokeless tobacco use could not be determined, leaving 95,981 men in the analyses.

Participants were considered smokeless tobacco users if they reported at enrollment either chewing tobacco or using snuff, or both, at least once a week for at least 1 year. Information on tobacco use was not updated during follow-up.

Participants contributed follow-up time from 1 January 1989, to the earliest of date of death or 31 December 1998. Causes of death were ascertained through linkage with the National Death Index from 1 January 1989, onward. Age-adjusted (5-year groups) relative risks (RR) were calculated by dividing the PD death rate among past and current users by the corresponding death rate among non-users, using Mantel-Haenszel weights.<sup>4</sup> Cox proportional hazards regression was used to estimate RR and 95% confidence intervals (CI) in the multivariate setting. SAS Version 8.2 was used for the analyses.

### Results

During the follow-up, 15,250 men died from any cause and 459 (3%) men had PD listed in their death certificates as an underlying or contributing cause of death. The mean age at death for men with PD was 80 years.

Men who reported using smokeless tobacco were less likely to have completed college than never users (age-adjusted proportions, 15% for current users and 22.7% for past users vs. 47% for never users) or to use multivitamins regularly (9.3% and 9.9% vs. 16.3%), but more likely to consume one or more cups of coffee daily (54.4% and 50.8% vs. 48.6%), use alcohol (12.6 g/day and 13.6 g/day vs. 10.3 g/day), or participate in heavy exercise at work or play (24.2% and 20.3% vs. 13.4%). Possible confounding by these variables was addressed in multivariate analyses.

Men who were current users of smokeless tobacco at enrollment had a significantly lower risk of PD mortality (age-

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**TABLE 1.** Smokeless tobacco use and Parkinson's disease mortality among never smoking men in the Cancer Prevention Study II 1989–1998

	Person years	PD deaths (n)	Age-adjusted RR (95% CI)*	Multivariate-adjusted RR (95% CI)**
Smokeless tobacco use				
Never	870,751	452	Reference	Reference
Past	5,734	4	0.81 (0.30, 2.17)	0.86 (0.32, 2.31)
Current	21,384	3	0.22 (0.07, 0.67)	0.24 (0.08, 0.75)
<i>P</i> -trend <sup>a</sup>			0.004	0.01

\*Adjusted for age in groups: <50, 50–<55, 55–<60, 60–<65, 65–<70, 70–<75, 75–<80, 80+.

\*\*Adjusted for age, coffee intake (3–6 cups/week, 1 cup/day, 2 cups/day, 3 cups/day, 4 or more cups per day), alcohol (0 g/day, <5 g/day, <15 g/day, <30 g/day, 30+ g/day), and education (some HS, HS graduate, vocational school, some college, college graduate, graduate school).

<sup>a</sup>In *P* for trend calculation, smokeless tobacco was coded as never = 0, past = 1 and current = 2.

PD, Parkinson's disease; RR, relative risk; CI, confidence interval; HS, high school.

adjusted RR = 0.22; 95% CI, 0.07 to 0.67) than never users. The reduction in risk did not materially change if men with stroke were included in the analysis. A modest, nonsignificant reduction in risk was observed among past users (RR = 0.81; 95% CI, 0.30 to 2.17). The overall *P* for trend was 0.004 (Table 1). Multivariate adjustment for coffee and alcohol consumption and education attenuated the results only slightly (Table 1). Additional adjustment for multivitamin use and exercise did not change the association further. Because of the small number of cases, we could not assess the separate effects of chewing tobacco or snuff use on the outcome (of the 3 exposed cases, 2 were users of chewing tobacco only and 1 was a user of both snuff and chewing tobacco).

### Discussion

In this large cohort of never-smoking men, we found that smokeless tobacco use was associated with reduced PD mortality. This association is stronger than that found for cigarette smoking among men in this study (past smokers vs. never smokers, 0.79 [95% CI, 0.67–0.93]; current smokers vs. never smokers, 0.69 [95% CI, 0.54–0.87]).<sup>3</sup> These results are consistent with the findings of Benedetti and colleagues who reported a stronger reduction in PD incidence among ever users of smokeless tobacco in a case-control study (OR = 0.18; 95% CI, 0.04 to 0.82) than among ever smokers (OR = 0.69; 95% CI, 0.45 to 1.08).<sup>5</sup>

A limitation of our study is that the reporting of PD in death certificates is known to be incomplete (70–75%).<sup>6</sup> The main result is based on three exposed cases and, therefore, may be sensitive to underreporting of PD on death certificates. Underreporting PD would bias the relative risks estimates only if the probability of PD diagnosis and report in death certificates was related to smokeless tobacco use. Strong bias from this source seems unlikely, because the factors associated with smokeless tobacco use in this study that would be expected to affect the accuracy of death certificates (age and education) were included in the regression models. Another limitation is that the information on tobacco use was not updated; therefore, we cannot exclude the possibility that some users of smokeless tobacco started smoking during the follow-up. However, most subjects in this study were middle-aged or older and would be unlikely to start smoking. Restricting the analysis to men 60 years of age or older at baseline did not change the results.

As previously discussed for cigarette smoking, an artifactual explanation for this finding is that unrecognized symptoms of PD might cause subjects to reduce or terminate use of smokeless tobacco.<sup>1</sup> Alternatively, some component of smokeless tobacco, such as nicotine, may protect against dopaminergic neuron damage and the development of PD. This mechanism is not well understood, although the hypothesis is supported by limited experimental evidence.<sup>7</sup> Our finding is mechanistically relevant, although the toxicity and carcinogenicity of smokeless tobacco and active smoking preclude their therapeutic use.

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