Evidence Against the Operation of Selective Mortality in Explaining the Association between Cigarette Smoking and Reduced Occurrence of Idiopathic Parkinson Disease

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To investigate the association between idiopathic Parkinson disease (IPD) and reduced frequency of prior cigarette smoking, the authors compared the 29-year follow-up mortality rates and IPD incidence rates of men who were either cigarette smokers or nonsmokers at the time of enrollment in the Honolulu Heart Study (1965–1968). Based on IPD cases detected up to June 30, 1994, the age-adjusted incidence rate in smokers was less than half that in nonsmokers: 34.4 versus 94.2 cases per 100,000 person-years of pre-illness follow-up, respectively. When data were stratified by 5-year age group, lower IPD incidence in smokers was observed at all ages between 50 and 90 years. Age-specific mortality trends for smokers and nonsmokers with and without IPD suggested that increased mortality in IPD patients was mostly associated with IPD itself and not with smoking. The slight excess mortality in smokers without IPD, versus nonsmokers without IPD, appeared insufficient to account for the "missing" incident IPD cases in smokers. These IPD incidence and mortality data are not highly consistent with the "selective mortality" hypothesis, which attributes reduced prior smoking frequency, typically reported by persons with IPD, to accelerated mortality in undiagnosed IPD-affected persons who smoke. The "protective" association of cigarette smoking with IPD occurrence may thus be real, suggesting the need for further study of biologic mechanisms of protection. Am J Epidemiol 1996;144: 400–4.

Parkinson disease; smoking

The allegedly "protective" association between cigarette smoking and idiopathic Parkinson disease (IPD) has been supported by numerous cross-sectional studies, case-control studies, and prospective studies following smokers and nonsmokers either to death or to incident disease (1, 2). Although possible protective mechanisms like enzyme induction, enzyme inhibition, and receptor blockade have been discussed (2), many believe the protective association must result from study biases, including "diagnostic displacement," temporal reversal of the exposure-outcome sequence, symptom or sign suppression by cigarettes, confounding “personality” differences, and effects of unrecognized confounding variables (2).

Among the strongest arguments against a protective effect of smoking, the "selective mortality" hypothesis (3–6) has been inspired by criticism of case-control studies in which persons with IPD recalled prior smoking behaviors, and by concerns about outcome detection in these and other types of studies (e.g., problems in follow-up and diagnosis, as well as death certificate accuracy and completeness). A decreased frequency of prior smoking in IPD case-patients compared with control patients—in both the recent and the remote past—has been almost universally observed in these studies (2). Proponents of the "selective mortality" hypothesis argue that smoking plus IPD increases mortality risk; smoking case-patients thus "die off" at an accelerated rate—selectively and continually dropping out of the pool of prevalent cases—and case-control studies consequently find none but nonsmoking case-patients to enroll. This leads, it is said, to the association of IPD with nonsmoking, and to the erroneous conclusion that smoking protects against IPD (2). An advanced version of the "selective mortality" explanation posits its operation in a subset of geneti-
cally primed individuals who are independently at risk for both IPD and early smoking-associated death (e.g., in association with the apolipoprotein E e4 allele (2, 7)).

Circumstantial evidence against the "selective mortality" explanation is that "smoking protection" is observed in case-control studies that enroll incident cases, as opposed to prevalent cases, and in prospective follow-up studies, including a study reported by our group (1), in which subjects were classified by smoking status long before detected disease onset. To further investigate the possible occurrence and operation of selective mortality, we report here data on 29 years of prospective follow-up of smokers and nonsmokers in which age-specific IPD incidence rates and mortality rates were compared over a 40-year age range.

**MATERIALS AND METHODS**

More detailed information on cohort study methods has been provided previously (1, 8). Data were obtained from the Honolulu Heart Study, an ongoing prospective study of 8,006 men of Japanese and Okinawan ancestry born between 1900 and 1919 who resided on O'ahu, Hawai'i, in 1965. The cohort has been periodically rescreened since 1965, with the most recent screening being undertaken from 1991 to 1994. There has been continual surveillance of hospital records and death certificates to detect health outcomes. Mortality determination is considered to be complete through December 31, 1992, and is ongoing for the period January 1, 1993, through November 30, 1994. Only five of 8,006 men (0.06 percent) have been lost to follow-up.

Data collected at the 1965–1968 baseline examination were used to determine the smoking exposure status of cohort members. Subjects were categorized as nonsmokers if they had smoked fewer than 100 cigarettes in their lifetimes. Current smokers and ex-smokers were both considered together in this analysis, since their IPD risks were similar in a previous report that examined this cohort (1). Use of other tobacco products was not considered.

Incident IPD cases (those detected after the baseline examination but before November 30, 1994) were identified through four sources: 1) review of all O'ahu hospitalization records of cohort subjects for new and preexisting diagnoses of IPD, 2) ongoing review of all Hawai'i death certificates, 3) a review of medical records at the offices of eight of 10 O'ahu neurologists (two neurologists declined to participate), and 4) a complete rescreening of the cohort (1991–1994). Screening included nonmedical observational examination supplemented by standardized questions about parkinsonism diagnoses, signs and symptoms, and medication usage, followed if necessary by comprehensive neurologic examination. Cases in which a known cause of parkinsonism had been established (e.g., medication use, encephalitis, lacunar infarct, head trauma) were eliminated from analysis.

Cases detected before 1991 in patients who were not later evaluated by us were included if the diagnosis of IPD had been confirmed by a neurologist or neurosurgeon, usually including response to dopamine therapy, and if our evaluation of the patient's records revealed no other likely diagnosis. Almost all of the 34 newly detected cases (i.e., those cases detected since the publication of a 1994 article that examined cohort data through 1992 (1)) were identified through rescreening and examination of the entire cohort. Cases found in patients who were undergoing examination by the projects' neurologists were diagnosed according to published research criteria (9).

**RESULTS**

On the basis of 54,155.5 person-years of pre-illness (i.e., pre-IPD) observation in nonsmokers and 119,156.1 person-years of pre-illness observation in smokers, we detected 92 incident cases of IPD through November 30, 1994. The IPD incidence rate in nonsmokers was 94.2 cases per 100,000 person-years, and the rate in smokers was 34.4 per 100,000 person-years. The age-adjusted relative risk of IPD associated with cigarette smoking was 0.40 (95 percent confidence interval 0.26–0.61). The incidence of IPD in smokers was less than that in nonsmokers over each 5-year age interval from 50 to 90 years (figure 1). Although standard errors around the age-specific incidence rates tend to be wide, because of comparatively small numbers of cases in each 5-year age range, the overall incidence pattern is consistent in indicating decreased IPD occurrence associated with smoking over the entire age range, including younger men (figure 1). As was shown previously in published data from a subset of this cohort (1), adjustment for coffee drinking and alcohol consumption slightly increased the magnitude of the relative risk to 0.39 (data not shown).

The age-specific mortality rates of smokers and nonsmokers without IPD were similar before age 60; thereafter, mortality in smokers increased notably (figure 2, table 1). Mortality in both smokers and nonsmokers with IPD increased markedly above ages 60–65 years (figure 2, table 1). Comparing age-adjusted early mortality (before age 65) in all smokers versus all nonsmokers, there were 148.9 excess deaths in smokers, excluding one male smoker who had al-
ready acquired IPD (table 1). At extreme ages, the mortality rates in smokers with and without IPD were actually lower than those in nonsmokers (figure 2), though relatively few deaths were recorded in these categories (table 1).

**DISCUSSION**

The fact that a reduced incidence of IPD was observed in cigarette smokers at all ages across a 40-year age span, including early in follow-up and at young

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**TABLE 1.** Age-specific mortality rates for cigarette smokers and nonsmokers with and without idiopathic Parkinson disease (IPD), Honolulu Heart Study, O'ahu, Hawai'i, 1965–1992

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Subjects without PD</th>
<th></th>
<th>Subjects with PD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmokers without PD</td>
<td>Smokers without PD</td>
<td>Nonsmokers with PD</td>
<td>Smokers with PD</td>
</tr>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Deaths per 100,000 person-years</td>
<td>SE*</td>
<td>No. of deaths</td>
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<td>251.9</td>
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<td>3,923.5</td>
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</tr>
</tbody>
</table>

* SE, standard error.
Cigarette Smoking and Parkinson Disease

Parsons with IPO who smoked Parsons with IPD who did not smoke
Well persons who did not smoke
Well persons who smoked

FIGURE 2. Age-specific mortality rates per 100,000 person-years, by 5-year age interval, in men with and without idiopathic Parkinson disease (IPD) who were classified as either nonsmokers or current/ex-smokers at study enrollment, Honolulu Heart Study, O'ahu, Hawai'i, 1965-1994. (Because of few actual deaths in subjects with IPD, mortality rates in adjacent 5-year age groups for subjects over age 80 were averaged.) Key: —x—, persons with IPD who did not smoke; — - -H- -, persons with IPD who smoked; - - A - -, well persons who did not smoke; —•—, well persons who smoked.

ages when mortality from any cause is low, constitutes an argument against there being an influence of selective mortality on the association between smoking and IPD occurrence. Since our data evaluated living incident cases rather than deaths, it is difficult to imagine how selective mortality could explain these findings. Even under the most extreme assumption—that cigarette smoking selectively killed off large numbers of younger persons otherwise predestined to acquire IPD in their later years—the consistent incidence differences between smokers and nonsmokers (figure 1) cannot be easily explained. Smoking is associated with moderately increased mortality over a broad age range, but the magnitude of the mortality risk difference between smokers and nonsmokers (figure 1) is similar for the persons who do and do not go on to acquire IPD.

The differential mortality rates between smokers and nonsmokers at younger ages (e.g., <65 years; figure 2) do not easily account for so many "missing" expected cases of IPD in later years. Under an assumption of no IPD risk differences between smokers and nonsmokers, it is observed, when examining age-specific incidence rates (e.g., ≥65 years), that the 51 "missing" incident IPD cases in older smokers consist of a fairly large percentage (34 percent) of the 149 excess deaths occurring in smokers before age 65. We are aware of no biologically plausible explanation for such a profound hidden mortality factor operating over such a broad age spectrum.

If selective mortality fails to explain the allegedly "protective" association of cigarette smoking with IPD, there are few remaining possibilities to consider other than powerful study biases, including "diagnostic displacement," cause-and-effect bias, unappreciated confounding, "innate predisposition" leading simultaneously to IPD and to nonsmoking, or a biologic effect of some component of cigarette smoke. As discussed elsewhere, we believe that, collectively, our data and those of others do not provide much evidence for the types of study biases we have considered (2).

Since cigarette smoking is highly injurious to health, it should be avoided by everyone, including those rare individuals at risk for familial IPD. Nevertheless, the observation of an apparently "protective" effect of smoking on IPD occurrence is important in suggesting the existence of unappreciated factors in the pathogenesis of IPD.
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REFERENCES