Survival Study of Parkinson Disease in Olmsted County, Minnesota

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Objective: To compare survival in incident cases of Parkinson disease (PD) with survival in subjects free of PD from the general population.

Methods: We used the medical records linkage system of the Rochester Epidemiology Project to identify incident cases of PD in Olmsted County, Minnesota, for the period 1976-1995. Cases were matched by age and sex to referent subjects from the same population. For 196 cases and 185 referent subjects, we studied survival between the date of diagnosis of PD (or index date) and death, loss to follow-up, or end of the study (May 1, 2000).

Results: The median length of follow-up was 7.2 years for cases and 8.0 years for referent subjects; 110 patients with PD and 79 referent subjects died during follow-up. The median survival was 10.3 years in cases and 13.4 years in referent subjects. The relative risk (RR) of death was 1.60 (95% confidence interval [CI], 1.20-2.14; P = .002) overall, 1.81 (95% CI, 1.15-2.84; P = .01) in women, and 1.49 (95% CI, 1.01-2.20; P = .04) in men. There was a decreasing trend in the RR of death according to age at onset of PD (in tertiles): younger than 67 years, RR, 2.04 (95% CI, 0.99-4.19; P = .05); 67 to 76 years, RR, 1.76 (95% CI, 1.08-2.86; P = .02); and older than 76 years, RR, 1.48 (95% CI, 0.95-2.29; P = .08). Patients with PD who had both rest tremor and pronounced asymmetry had a better prognosis than patients with neither clinical characteristic. Patients with PD who smoked survived better than expected.

Conclusions: Patients with PD face a higher risk of death compared with subjects free of PD from the general population. Certain clinical characteristics and smoking modify survival.

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INCE THE 1967 report by Hoehn and Yahr, several studies have examined survival in patients with parkinsonism or Parkinson disease (PD). Most of these studies reported an increased risk of death in patients with parkinsonism or PD. In addition, it has been suggested that some prognostic factors (eg, dementia, severity of extrapyramidal signs, or gait disturbance) may modify survival. Whether sex and age at onset of the disease are prognostic factors remains debated.

In this study, we compared the survival of incident patients with PD in Olmsted County, Minnesota, to the survival of referent subjects from the same population. Our study has a number of strengths compared with previous studies that were almost invariably hospital-based and recruited cases of PD with longer duration or atypical features. In addition, the extent of follow-up was longer in our study.

METHODS

CASES

We used the medical records linkage system of the Rochester Epidemiology Project to identify all subjects residing in Olmsted County, Minnesota, who developed PD in the period 1976-1995. Details about the study population and the identification of incident cases were reported elsewhere. Our diagnostic criteria included 2 steps: the definition of parkinsonism as a syndrome and the definition of PD within the syndrome. Parkinsonism was defined as the presence of at least 2 of the following 4 cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. Parkinson disease was defined as the presence of parkinsonism with all 3 of the following clinical features: (1) no secondary cause (eg, repeated stroke with stepwise progression, repeated head injury, history of encephalitis, neuroleptic treatment within 6 months before onset, hydrocephalus, or brain tumor); (2) no documentation of unresponsiveness to levodopa treatment at doses of at least 1 g/d in combination with car-
bidopa (applicable only to patients who were treated); (3) no prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (eg, dementia or dystonemia) not explained otherwise. Our clinical classification of patients with PD through medical records review was found to be valid compared with a direct examination by a movement disorders specialist (J.H.B., D.M.M., or J.E.A.), as reported elsewhere.9,10

Onset of PD was defined as the year in which 1 of the 4 cardinal signs of PD was first noted by the patient, by family members, or by a health care provider or allied health professional (as recorded in the medical record). In addition, we collected certain clinical characteristics that may influence prognosis. We classified patients by the presence of rest tremor at any time during the disease course and by the presence of pronounced asymmetry in the parkinsonian symptoms (ie, documentation of a strictly unilateral onset or of a pronounced asymmetry persistent throughout the disease course).

REFERENT SUBJECTS

Each case was individually matched by age (±1 year) and sex to a general population referent subject residing in Olmsted County, Minnesota, and free of PD, other parkinsonism, or tremor of any type in the year of onset of PD in the matched case. The list of all county residents from which potential referent subjects were drawn randomly was provided by the records linkage system. This list has been shown to be complete by comparison with a random-digit-dialing telephone sample and by comparison with the census.9,10 Therefore, our referent subjects were not selected through their diseases or health conditions, but rather through their residency status.

Records of potential referent subjects were reviewed by a neurologist (D.M.M.) to exclude the presence of PD, other type of parkinsonism, or tremor of any type before or during the year of onset of PD in the matched case. The presence of dementia or other neurologic diseases was not an exclusion criterion. Our exclusion of parkinsonism in referent subjects through medical records review was found to be valid compared with a direct examination by a movement disorders specialist (J.H.B., D.M.M., or J.E.A.), as reported elsewhere.9,10

FOLLOW-UP PROCEDURES

The complete medical dossiers of cases and referent subjects were reviewed to abstract information about cigarette smoking preceding the onset of PD (or the corresponding year for referent subjects) as detailed elsewhere.9 The passive follow-up of cases and referent subjects was obtained through an existing computerized database that provided the date of last contact with the records linkage system, as well as the status at last contact. To evaluate the quality of this computerized database, we carried out a reliability study based on the medical records of 30 randomly selected subjects. Their status and the date of last contact were obtained independently by manually abstracting the records and by using the follow-up database. The agreement between the 2 sources was complete for status at last contact and date of death; the agreement was within 1 year for date of last contact.

Whenever a person was deceased at the time of the study, we obtained the death certificate. All entries in the death certificates were coded according to the International Classification of Diseases, Adapted Code for Hospitals by one of the investigators (A.E.) who was kept unaware of the case or referent status.11 The underlying cause of death was determined using standard rules.2,12-14

DATA ANALYSIS

We found 202 patients with onset of PD from 1976 through 1995, and we matched them by age and sex to 202 referent subjects. However, 6 subjects (5 cases and 1 referent subject) did not authorize the use of their medical records for research and the corresponding pairs were excluded. In addition, 9 referent subjects died and 2 were lost to follow-up between the onset year and the diagnosis date. Therefore, our survival analyses were based on a total of 196 cases and 185 referent subjects.

Of the cases, 121 (62%) were men and 75 (38%) were women; the median age was 71 years (age range, 41-97 years) at onset of PD and 72 years (age range, 42-97 years) at diagnosis. The median lag-time between onset and diagnosis of PD in cases was 1.0 year (range, 0-9.7 years); it was similar in men (median, 1.0 year; range, 0-6.7 years) and women (median, 0.9 year; range, 0-9.7 years) (P = .20, rank sum test). Age at onset and age at diagnosis were highly correlated (Spearman correlation coefficient, 0.99, P < .001). Most cases (86%) had been treated with levodopa at some point during the course of their disease. Among referent subjects, 112 (61%) were men and 73 (39%) were women. Their median age at the index date was 72 years (age range, 42-97 years).

The median length of follow-up (time between diagnosis and death, loss to follow-up, or the end of study) was 7.2 years for cases and 8.0 years for controls. One hundred ten cases (56%) and 79 referent subjects...
(43%) died during follow-up. The corresponding median survivals and RRs of death are given in Table 1. Among cases, the percent surviving was 79% at 5 years, 53% at 10 years, and 28% at 15 years. Among the referent subjects, the percent surviving was 84% at 5 years, 65% at 10 years, and 44% at 15 years. Kaplan-Meier survival curves, overall and according to sex and age at onset, are shown in the Figure. The overall curves for cases and referent subjects started to diverge approximately 5 years after the diagnosis date, and the

### Table 1. Survival Analyses Comparing Patients With Parkinson Disease With Referent Subjects, Olmsted County, Minnesota, 1976-2000

<table>
<thead>
<tr>
<th>Sample or Stratum</th>
<th>Patients With Parkinson Disease (Cases)</th>
<th>Referent Subjects</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at Risk</td>
<td>No. of Deaths</td>
<td>Median Survival, y</td>
<td>No. at Risk</td>
</tr>
<tr>
<td>Total Sample</td>
<td>196</td>
<td>110</td>
<td>10.3</td>
<td>185</td>
</tr>
<tr>
<td>Strata by sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>121</td>
<td>61</td>
<td>10.1</td>
<td>112</td>
</tr>
<tr>
<td>Women</td>
<td>75</td>
<td>49</td>
<td>10.3</td>
<td>73</td>
</tr>
<tr>
<td>Strata by age at onset, y‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-66</td>
<td>66</td>
<td>25</td>
<td>17.2</td>
<td>64</td>
</tr>
<tr>
<td>67-76</td>
<td>71</td>
<td>40</td>
<td>10.1</td>
<td>68</td>
</tr>
<tr>
<td>77-97</td>
<td>59</td>
<td>45</td>
<td>5.9</td>
<td>53</td>
</tr>
<tr>
<td>Strata by lag-time from onset to diagnosis¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lag-time &lt;1 y</td>
<td>93</td>
<td>59</td>
<td>10.8</td>
<td>91</td>
</tr>
<tr>
<td>Lag-time ≥1 y</td>
<td>103</td>
<td>51</td>
<td>9.4</td>
<td>94</td>
</tr>
</tbody>
</table>

*Relative risk (RR) (95% confidence interval [CI]) of death calculated using Cox proportional hazards models with adjustment for age at diagnosis (first quartile of age, reference group; second quartile, RR, 2.81; 95% CI, 1.71-4.60; P <.001; third quartile, RR, 5.40; 95% CI, 3.26-8.97; P <.001; and fourth quartile, RR, 10.24; 95% CI, 6.22-16.84; P <.001) and sex (men, RR, 1.40; 95% CI, 1.04-1.90; P =.03).

†Relative risk (95% CI) of death calculated using Cox proportional hazards models with adjustment for age at diagnosis. The difference in RR between men and women was not statistically significant.

‡Tertiles of the distribution of age at onset.

§More than 50% of the referent subjects were alive at the end of the study.

¶Lag-time between the onset of Parkinson disease and diagnosis date in cases; the median of the distribution was used as cutoff (median, 1 year).

#Relative risk (95% CI) of death calculated using Cox proportional hazards models with adjustment for age at diagnosis and sex. The difference in RR across strata was not statistically significant.
difference was maximum after 20 or more years of follow-up. The age- and sex-adjusted RR of death in cases compared with referent subjects was 1.60 (95% CI, 1.20-2.14; *P* = .002).

Women with PD faced a slightly higher RR of death than men; however, the difference was not statistically significant (Figure and Table 1). We observed a trend of decreasing RR of death with increasing age at onset (Figure and Table 1). In addition, cases with a longer lag-time between onset and diagnosis of PD seemed to have a worse survival than cases with a shorter lag-time (Table 1). However, none of these differences was statistically significant.

Table 2 summarizes our case-referent and case-case comparisons according to the presence of rest tremor, pronounced asymmetry of symptoms or signs, or their combination. Patients with rest tremor had a better prognosis than patients without, and patients with pronounced asymmetry had a better prognosis than patients without; however, these differences were not statistically significant. When both clinical characteristics were combined, patients with neither rest tremor nor pronounced asymmetry had the worst prognosis, patients with both rest tremor and pronounced asymmetry had the best prognosis, while patients with either symptom alone had an intermediate prognosis. There was a statistically significant difference (*P* = .01) between patients with neither of these clinical features and patients with both of them (Table 2).

Table 3 summarizes the results of our analyses on the individual and joint effects of smoking and PD on survival. As expected, smoking was associated with a poorer survival among referent subjects. As already noted, PD was also associated with an increased risk of death, and its individual effect in persons who never smoked tobacco (hereafter called “never-smokers”) combined (RR, 1.60; Table 1). The joint effect of smoking and PD was significantly weaker than expected assuming a multiplicative model of interaction (*P* = .03). Patients with PD who smoked survived better than expected from the combined effect of smoking and PD alone.

Among the 110 cases and 79 referent subjects who died during follow-up, we obtained a death certificate for 106 cases (96%) and 78 referent subjects (99%). Pneumonia was a significantly more frequent cause of death in cases of PD than in referent subjects. No significant association between PD and any other specific cause of death was observed; however, the numbers involved were generally small in each category. Finally, PD was recorded anywhere on the death certificate in only 60 (57%) of the cases who died.

Our study is consistent with previous reports of an increased mortality in cases of PD. However, the effect of PD on mortality in our study (RR, 1.6; 95% CI, 1.2-2.1) was weaker than in previous population-based or register-based studies. Previously reported RRs of death were 2.4 (99% CI, 1.6-3.4), 2.5 (the 95% CI was not reported), 2.7 (95% CI, 1.7-4.4), and 2.3 (95% CI, 1.8-3.0). However, with the exception of one, all previous studies included prevalent cases, who are expected to have a worse survival than incident cases. Despite some degree of overlap with the CIs of previous studies, our findings suggest that an RR of 1.6 is a more representative estimate of the effect of PD on mortality in the general population.

Three survival studies of incident patients with parkinsonism or PD were conducted in the same Olmsted County, Minnesota, population. The first study covered the period 1933-1966 and included all cases of parkinsonism. The second study covered the period 1967-1979 and included all cases of parkinsonism. A third

### Table 2. Survival Analyses Stratified by Presence of Clinical Characteristics, Olmsted County, Minnesota, 1976-2000

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Patients With Parkinson Disease (Cases)</th>
<th>Referent Subjects</th>
<th>Cases vs Cases</th>
<th>Cases vs Referent Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at Risk</td>
<td>No. of Deaths</td>
<td>Median Survival, y</td>
<td>No. at Risk</td>
</tr>
<tr>
<td>With rest tremor‡</td>
<td>149</td>
<td>82</td>
<td>10.1</td>
<td>141</td>
</tr>
<tr>
<td>Without rest tremor</td>
<td>37</td>
<td>22</td>
<td>10.3</td>
<td>34</td>
</tr>
<tr>
<td>With pronounced asymmetry</td>
<td>119</td>
<td>56</td>
<td>11.3</td>
<td>114</td>
</tr>
<tr>
<td>Without pronounced asymmetry</td>
<td>77</td>
<td>54</td>
<td>6.6</td>
<td>71</td>
</tr>
<tr>
<td>With rest tremor and asymmetry§</td>
<td>101</td>
<td>46</td>
<td>12.5</td>
<td>96</td>
</tr>
<tr>
<td>With asymmetry but no rest tremor</td>
<td>12</td>
<td>7</td>
<td>10.6</td>
<td>12</td>
</tr>
<tr>
<td>Without pronounced asymmetry</td>
<td>48</td>
<td>36</td>
<td>6.9</td>
<td>45</td>
</tr>
<tr>
<td>Without rest tremor and asymmetry</td>
<td>25</td>
<td>15</td>
<td>6.2</td>
<td>22</td>
</tr>
</tbody>
</table>

Abbreviations: Ref group, reference group.

*Stratified analyses comparing cases with a given clinical characteristic to the referent subjects matched to them, and comparing cases with a given clinical characteristic to cases without the clinical characteristic. Ellipses indicate not applicable.

†Relative risk (95% confidence interval) of death calculated using the Cox proportional hazards models with adjustment for age at diagnosis (quartiles of distribution) and sex.

‡Information on rest tremor was missing in 10 cases.

§Among cases, rest tremor and pronounced asymmetry were significantly associated (χ² = 15.54, *P* < .001).
The risk of misclassification is common to any study of multiple system atrophy that have a worse prognosis than parkinsonism such as progressive supranuclear palsy or tics. Accuracy. It is possible that some of the patients with genuine prognostic factors or may simply reflect diagnostic error. Mild asymmetry could not be investigated following a defined clinical protocol or using a quantitative clinical scale, we were only able to consider pronounced asymmetry that received routine documentation in the record. Milder asymmetry could not be investigated. Rest tremor or pronounced asymmetry may be genuine prognostic factors or may simply reflect diagnostic accuracy. It is possible that some of the patients without rest tremor or pronounced asymmetry had other causes of parkinsonism such as progressive supranuclear palsy or multiple system atrophy that have a worse prognosis than PD. The risk of misclassification is common to any study of prognosis of PD. However, the problem was less severe in our study because patients initially diagnosed with PD were followed for a median of 7.2 years; therefore, the appearance of atypical features during follow-up was considered in the diagnostic classification.

Several case-control studies, but also some cohort studies, have reported an inverse association between smoking and PD. Some investigators have speculated that the inverse association reported in case-control studies based on prevalent cases may have resulted from a prevalence-incidence bias. Consistent with a previous study, our findings suggest that the inverse association between smoking and PD is not the consequence of a higher mortality in PD cases who smoke (or smoked). In fact, in our study, PD cases who smoked survived better than expected from the combined effect of smoking alone and PD alone.

Parkinson disease was recorded anywhere in the death certificate in only 57% of the patients. This finding is in agreement with other studies showing a sizable underreporting of PD in death certificates. Underreporting should be considered when interpreting findings of studies based on PD cases identified through death certificates.

Our study has a number of strengths compared with previous studies that were hospital-based and were, therefore, likely to recruit patients with more advanced stages of PD or with atypical features (eg, poor response to treatment or comorbidities). With the exception of one study that included incident cases identified in a cohort of men of Okinawan ancestry, all other studies included prevalent cases. We included all incident cases of PD from a defined population over a defined time window and referent subjects derived from the same population over the same time window. Referral bias is expected to be minimal in this context.

Most previous studies evaluated survival from the date of enrollment in the study rather than from diagnosis. This design may cause an overestimation of relative mortality because cases and referent subjects started to differ only after 4 or 5 years of follow-up (Figure). A longer delay between diagnosis and enrollment into the study may cause a higher estimate of the RR.

Our investigation can be considered a long-term study of prognosis in PD. We followed 56% of the cases and 43% of the referent subjects through death, and we obtained estimates of survival as far as 15 and 20 years from diagnosis. This length of follow-up needs to be considered when comparing our findings to those from other studies with shorter follow-up. We noted that PD cases covered the period 1964-1978 and focused on PD alone. Unfortunately, our findings are not easily compared with those from previous studies because of the inclusion of other types of parkinsonism in 2 of them, and because of the use of published life-table expectations instead of referent subjects in 2 of them. The present study provides definite methodologic improvements compared with the previous studies in the same community and reflects a more contemporary time window (follow-up through May 1, 2000).

It has been suggested that survival may be worse in women than in men with PD; however, this pattern has not been confirmed by others. Our findings suggest that women with PD have a worse relative survival than men with PD; however, the difference was small and not statistically significant. The effect of age at onset of PD on survival has received little attention. Our data suggest that patients with onset of PD at a younger age have a worse relative prognosis than those with later onset. However, the difference in RRs of death between younger and older subjects was small and not statistically significant. In our study, age at diagnosis and age at onset of PD were highly correlated.

We also found that patients with neither rest tremor nor pronounced asymmetry had a worse prognosis than patients with either rest tremor or pronounced asymmetry, or with both characteristics. However, the definition of asymmetry in this retrospective review of medical records had limitations. Because patients with PD were not examined following a defined clinical protocol or using a quantitative clinical scale, we were only able to consider pronounced asymmetry that received routine documentation in the record. Mild asymmetry could not be investigated. Rest tremor or pronounced asymmetry may be genuine prognostic factors or may simply reflect diagnostic accuracy. It is possible that some of the patients without rest tremor or pronounced asymmetry had other causes of parkinsonism such as progressive supranuclear palsy or multiple system atrophy that have a worse prognosis than PD.

<table>
<thead>
<tr>
<th>Sample or Stratum</th>
<th>No. at Risk</th>
<th>No. of Deaths</th>
<th>Median Survival, y</th>
<th>Relative Risk (95% Confidence Interval)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smoker referent subjects</td>
<td>82</td>
<td>34</td>
<td>13.7</td>
<td>1.00 (Ref group)</td>
<td>. .</td>
</tr>
<tr>
<td>Never-smoker PD cases</td>
<td>102</td>
<td>62</td>
<td>10.6</td>
<td>2.25 (1.47-3.45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ever-smoker referent subjects‡</td>
<td>101</td>
<td>45</td>
<td>10.9</td>
<td>1.73 (1.09-2.76)</td>
<td>.02</td>
</tr>
<tr>
<td>Ever-smoker PD cases‡</td>
<td>94</td>
<td>48</td>
<td>9.9</td>
<td>1.96 (1.25-3.10)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: Ever-smoker, individual who ever smoked tobacco; Never-smoker, individual who never smoked tobacco; Ref group, reference group. Data on smoking were missing for 2 persons. Ellipses indicate not applicable. Relative risk (RR) (95% confidence interval [CI]) of death calculated using the Cox proportional hazards models with adjustment for age at diagnosis (first quartile of age, reference group; second quartile, RR, 2.91; 95% CI, 1.77-4.78; P = .001; third quartile, RR, 5.30; 95% CI, 3.19-8.82; P < .001; and fourth quartile, RR, 11.38; 95% CI, 6.84-16.92; P = .001) and sex (men, RR, 1.42; 95% CI, 1.03-1.95; P = .03). The P value for the interaction between smoking and PD was .03 (model adjusted for age and sex). Ever smoking before the onset of PD (for cases) or the onset of PD in the matched case (for referent subjects).

Table 3. Survival Analyses to Investigate the Possible Interaction Between Parkinson Disease (PD) and Smoking, Olmsted County, Minnesota, 1976-2000*
and referent subjects experienced a similar survival early in the follow-up but the 2 survival curves diverged noticeably after a number of years.

The main limitation of our study is that information on severity of PD symptoms and on treatment could not be investigated in a standardized way. In addition, many of the clinical variables of interest are time-dependent characteristics (eg, appearance of dementia, gait disturbance, and falls), and this makes the assessment of their precise chronology difficult at retrospective review of medical records. Finally, because of the overall smaller effect of PD on survival found in this study, our sample size was insufficient to adequately test the effects of sex and age at onset in the corresponding subgroup analyses.

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Author contributions: Study concept and design (Drs Bower, Maraganore, Ahlskog, and Rocca); acquisition of data (Drs Elbaz, Bower, Maraganore, and Rocca and Mr Peterson); analysis and interpretation of data (Drs Elbaz, Schaid, and Rocca, Mr Peterson, and Ms McDonnell); drafting of the manuscript (Drs Elbaz and Bower); critical revision of the manuscript for important intellectual content (Drs Elbaz, Bower, Maraganore, Ahlskog, Schaid, and Rocca, Mr Peterson, and Ms McDonnell); statistical expertise (Drs Elbaz, Schaid, and Rocca and Ms McDonnell); obtained funding (Dr Rocca); administrative, technical, and material support (Mr Peterson and Dr Rocca); study supervision (Drs Elbaz, Bower, Maraganore, and Rocca).

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