EDITORIAL

The Future Burden of Parkinson's Disease

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Dorsey and colleagues estimated that the number of persons with Parkinson's disease (PD) in the United States was approximately 340,000 in 2005 and projected that number to reach approximately 610,000 in 2030 as a result of population aging.[1] These projections were made under the simple assumption that the age- and sex-specific prevalence would remain stable over 25 years. However, the burden of diseases may be modified over time by human practices, including public health interventions and medicine.[2] Rossi and colleagues have suggested that the successful implementation of smoking cessation interventions in the United States may lead to an increase in the projected number of persons who will suffer from PD by 2040.[3] Their revised projections were based on a projected 46.2% increase in the population $\geq$ 50 years old and a 59.8% reduction in the percentage of smokers $\geq$ 50 years old between 2000 and 2040. They also made the fundamental assumption that smoking has a preventive effect on PD. Based on their assumptions and on the relatively conservative prevalence estimates published by Dorsey et al for 2005,[1] they projected for 2040 a total of 700,000 patients with PD because of population aging and an additional 70,000 patients (10% increase) because of the reduced frequency of smoking (total of 770,000 patients). Overall, they projected a 56% increase in the number of patients between 2005 and 2040. Rossi and colleagues argued that these revised projections are important to adequately plan for future cost and care needs related to PD.[3]

Whether or not smoking has a preventive effect on the risk of PD, the number of patients with PD is likely to increase by 2040 above and beyond the simple effect of population aging. There are now 3 studies from 3 continents showing an increase in the risk of PD over time (from the United States, Finland, and Taiwan).[4-6] However, there are also 3 studies showing a possible decline in risk over time (from the United Kingdom, Taiwan, and the Netherlands).[7-9] Assuming that all 6 studies have adequate methods (no major biases) and comparable study design, these discrepant findings may suggest that the risk factors for PD vary across countries, by sex, and over time. Our study in Olmsted County, Minnesota, showed an approximately 50% increase in the incidence of PD in men and women combined over 30 years (1976-2005; relative risk increase). The increase was more sizable in men age $\geq$ 70 years (approximate relative risk increase of 100%), and there was a significantly higher risk for men born between 1915 and 1924 (birth cohort effect).[4] If the increasing trend in the risk of PD observed in our study is confirmed in other US populations, the impact on prevalence projections for 2040 may be greater than predicted by Rossi et al.[3]

As recognized by Rossi and colleagues, the association between smoking and reduced risk for PD may be to some degree noncausal.[3] Avoidance of smoking initiation early in life or ease of smoking cessation later in life may be markers of a preexisting predisposition to PD (cause-effect inversion).[10] This predisposition may have genetic causes (eg, inherited genetic variants or epigenetic modifications), intrauterine causes (eg, infectious, toxic, or dietary exposures), or early developmental causes (eg, early-life infectious, toxic, or dietary exposures). Therefore, other environmental risk factors (eg, pesticides, infectious agents, and air, water, or soil pollutants) or other behavioral risk factors (eg, alcohol, coffee, diet, exercise, or head trauma) may be more important.[11] Interestingly, most of these environmental or behavioral risk factors have a different frequency or a different effect in men and women.[12,13]

The birth cohort effect observed in the Olmsted County study may help in establishing the chronology of etiologic exposures. Men born in the decade from 1915 to 1924 experienced an increased risk for PD compared with men born in other birth decades, both before and after. A similar trend was also observed for women, but the analyses did not reach statistical

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significance.[4] This birth cohort effect suggests that exposures that took place during intrauterine life or in early childhood (eg, infectious, toxic, or dietary exposures) may be more important than cigarette smoking during adult life.[14]

A group of Finnish investigators tested a different etiologic hypothesis. Instead of focusing on the reduction in smoking over time, they correlated the risk of PD with trends in rural environmental factors, primarily the use of pesticides and the consumption of well water. Because there has been a trend of reduced use of pesticides in agriculture and increased access to clean water (ie, piped water with contamination control) in Finland, they expected to observe a decline in the incidence of PD and a narrowing of the rural-to-urban incidence rate ratio. By contrast, they found an increase in the risk of PD from 1997 to 2014 in both rural and urban regions and no reduction in the rural-to-urban incidence risk ratio.[6] They suggested that the effects of rural environmental factors may have a long latency, and many decades may be required before an environmental change will modify the risk of PD. The time frame may be particularly long if the most important environmental exposures take place during intrauterine life or in the first years of life.

In conclusion, I agree with Rossi and colleagues that the projections published by Dorsey and colleagues in 2007 should be revised. However, I think that the increase in the number of patients with PD projected for 2040 may not be simply due to a change in smoking patterns, but rather to a number of more complex environmental and behavioral changes. If the trends observed in Olmsted County for 1976 to 2005 continue after 2005 and are confirmed in other US populations, the projected number of persons affected by PD in the United States by 2040 may be much higher than predicted by Rossi et al.[3] The number of persons affected by PD in 2040 will depend on changes over time in the age- and sex-specific prevalence of PD (number of patients per 100 persons in the population) and on changes in the demographic structure of the population (population aging because of the increase in life expectancy). In turn, the changes in prevalence percentages will depend on changes in incidence rates or risk of PD and on the length of survival of patients after they develop PD. Any change in incidence rates and survival in PD patients or changes in the demographic structure of the population in the coming decades may modify the projections. There is an urgent need for additional studies of the risk and protective factors for PD that may prompt preventive interventions to reduce the future burden of PD. ■

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