ONLINE FIRST

# Families With Parkinson Disease and Cancer

We are reaching the convergence of 2 important lines of research on the etiology of Parkinson disease (PD). The first line involves the accumulation of evidence on the familial aggregation of multiple neurodegenerative diseases, including PD. The second line involves the accumulation of evidence on the association of PD with a decreased risk of some types of cancer and an increased risk of some other types of cancer, primarily melanoma.

Along the first line of research, first-degree relatives of patients with younger-onset PD were found to have an increased risk not only of PD or parkinsonism but also of essential tremor, cognitive impairment or dementia, anxiety disorders, and depressive disorders, compared with relatives of controls.[1-3] A reciprocal familial aggregation of other neurodegenerative disorders, including PD, was also found among relatives of patients with amyotrophic lateral sclerosis or with dementia.[4,5] These studies suggest that some genetic or environmental factors may cluster in some families and may cause several distinct neurologic or psychiatric diseases.

## *See related article*

Along the second line of research, several studies have shown an association of PD with a decreased risk of some types of cancers and an increased risk of some other types of cancers. Although the literature concerning PD and most cancers remains controversial,[6,7] a consistent association between PD and increased risk of melanoma has been reported. In a recent review of the literature,[6] the association was found to be significant when a diagnosis of PD preceded a diagnosis of melanoma but not when a diagnosis of melanoma preceded a diagnosis of PD, and the association was stronger for men than for women. Another study[8] showed that a positive family history of melanoma among first-degree relatives was a risk factor for PD after adjustment for known environmental risk factors. However, that study[8] did not find a significant association of family history of other types of cancers (such as colorectal, lung, prostate, or breast cancer) with the risk of PD.

In this issue of *Archives of Neurology*, Kareus and colleagues[9] report new findings from the Utah statewide linkage database suggesting that PD is associated with melanoma at the individual level and also across first-, second-, and third-degree relatives. Thus, relatives of patients with PD had an increased risk of melanoma. In separate analyses, relatives of patients with melanoma also had an increased risk of PD, suggesting common underlying causes of both diseases. The study[9] also showed an association between PD and risk of prostate cancer, both at the individual level and across relatives. In separate analyses, relatives of patients with prostate cancer also had an increased risk of PD, again suggesting common underlying causes of both diseases. Because the strength of these associations declined with a more distant genetic relationship but remained statistically significant (the risk was higher for first-degree relatives than for second-degree relatives, and for second-degree relatives than for third-degree relatives), the associations are more likely mediated by shared genetic factors than by shared environmental exposures. Shared environmental exposures are expected to affect only first-degree relatives because they generally live in the same house for part of their life and thus share air, water, food, and other environmental factors.

Environmental factors such as smoking or diet may be involved in explaining the associations at the individual level. However, a simple theory does not fit the data completely. For example, smoking is associated with a reduced risk of PD and with an increased risk of some cancers (defined as smoking-related).[7] Thus, one would expect a reduced risk of cancer in patients with PD. A reduced risk of cancer was observed in the Utah study[9] for patients with PD, but the reduced risk was restricted to colorectal, lung and bronchus, pancreas, and stomach cancers. By contrast, PD was associated with an increased risk of melanoma and prostate cancer. Prostate cancer is considered a smoking-related cancer.[9] This apparent paradox may result from a more complex interplay between genetic predisposition and environmental factors. A further complexity revealed by the Utah study[9] and by other studies[6] is the different pattern of associations between certain types of cancer and PD for men and women. This dimorphic pattern may relate to genetic, hormonal, or social and cultural factors.[10]

The study by Kareus et al[9] has some unique strengths and also some limitations. A major strength of their study[9] is the size of the statewide linkage system and of the multigeneration genealogy database, which allows for the study of second- and third-degree relatives. The limitations of their study[9] include the diagnostic uncertainty of causes of death reported in death certificates and the lack of information about the age at onset of PD, about the time sequence of the association at the indi-

vidual level (diagnosis of cancer preceding or following the onset of PD), and about smoking or other environmental factors. Some behavioral factors (such as the use of alcohol, tobacco, and coffee) were particularly uncommon in this population because of religious and cultural traditions.[9]

The findings from Kareus et al,[9] combined with previous findings in the literature, suggest that some families have a genetic predisposition that can manifest as PD, as other types of parkinsonism, as essential tremor, as cognitive impairment or dementia, as amyotrophic lateral sclerosis, as anxiety disorders, as depressive disorders, or as nonneurological conditions such as melanoma and prostate cancer. This theory has both clinical and research implications. Clinically, it is important to explain to patients with PD and their family members that the genetic predisposition to PD is restricted to patients with younger onset of symptoms.[1-3] In addition, within the few families with a genetic predisposition to PD, family members may experience a wide range of clinical manifestations, not simply PD. Knowledge of this clustering of disease within families may also guide preventive interventions (such as particular screening tests) for family members of patients with PD who may be at particularly high risk.

From a research prospective, it is important to understand the mechanisms that cause this clustering of conditions. If the mechanisms are primarily genetic, as suggested by Kareus and colleagues,[9] then it may be possible to identify genetic variants that predispose to accelerated neurodegeneration and to increased oncogenesis in the same individual or among members of some particular families. On the other hand, if PD is multifactorial at the individual level, dimorphic in men and women, and heterogeneous at the population level, the search for one or several genetic variants may not be productive.[10]

The findings from the Utah statewide linkage study[9] led us to a higher vista point. We have made one more step toward weaving several apparently conflicting observations from different lines of research into a coherent theory. Unfortunately, as is often the case in science, from this new higher vista point, we also see a broader horizon rich with new complexities and new challenges.

*Walter A. Rocca, MD, MPH*

**Published Online:** September 3, 2012. doi:10.1001/archneurol.2012.2664
**Author Affiliations:** Division of Epidemiology, Department of Health Sciences Research, and Department of Neurology, College of Medicine, Mayo Clinic, Rochester, Minnesota.
**Correspondence:** Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (rocca@mayo.edu).
**Financial Disclosure:** None reported.

## REFERENCES

1. Rocca WA, Bower JH, Ahlskog JE, et al. Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. *Arch Neurol*. 2007;64(10):1458-1464.
2. Rocca WA, Bower JH, Ahlskog JE, et al. Increased risk of essential tremor in first-degree relatives of patients with Parkinson's disease. *Mov Disord*. 2007;22(11):1607-1614.
3. Arabia G, Grossardt BR, Geda YE, et al. Increased risk of depressive and anxiety disorders in relatives of patients with Parkinson disease. *Arch Gen Psychiatry*. 2007;64(12):1385-1392.
4. Fallis BA, Hardiman O. Aggregation of neurodegenerative disease in ALS kindreds. *Amyotroph Lateral Scler*. 2009;10(2):95-98.
5. van Duijn CM, Clayton D, Chandra V, et al; EURODEM Risk Factors Research Group. Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies. *Int J Epidemiol*. 1991;20(suppl 2):S13-S20.
6. Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology*. 2011;76(23):2002-2009.
7. Elbaz A, Peterson BJ, Yang P, et al. Nonfatal cancer preceding Parkinson's disease: a case-control study. *Epidemiology*. 2002;13(2):157-164.
8. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. *Neurology*. 2009;73(16):1286-1291.
9. Kareus SA, Figueroa KP, Cannon-Albright LA, Pulst SM. Shared predispositions for parkinsonism and cancer: a population-based pedigree-linked study [published online September 3, 2012]. *Arch Neurol*. doi:10.1001/archneurol.2012.2261.
10. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Risk factors for Parkinson's disease may differ in men and women: an exploratory study [published online June 8, 2012]. *Horm Behav*. doi:10.1016/j.yhbeh.2012.05.013.