

## ONLINE FIRST

## Shared Predispositions of Parkinsonism and Cancer

*A Population-Based Pedigree-Linked Study*

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**Objective:** To use a statewide population-based genealogic database to evaluate the relationship between Parkinson disease (PD) and cancer subtypes.

**Design:** Using a computerized genealogy for the Utah pioneers and their descendants linked to a statewide cancer registry and statewide death certificates, we estimated relative risks for cancer in individuals with PD listed on their death certificate, and in their first-degree, second-degree, and third-degree relatives.

**Setting:** Utah Cancer Registry.

**Participants:** Approximately 2.3 million individuals in the Utah genealogic resource, including death certificates of 2998 individuals with PD listed as a cause of death from 1904 to 2008 and information on 100 817 individuals with a cancer diagnosis in the Utah Cancer Registry.

**Results:** Melanoma and prostate cancer were the only cancers observed in significant excess among PD cases; colorectal, lung, pancreas, and stomach cancers were observed in deficit. A significantly increased risk for pros-

tate cancer was observed in the PD population as well as among their relatives. A reciprocal significantly increased risk for PD was also found in the 22 147 prostate cancer cases and their relatives. A significantly elevated risk for melanoma was found in the Utah PD population as well as in their relatives. A reciprocal significantly increased relative risk for PD was found in 7841 Utah melanoma cases and their relatives.

**Conclusions:** Our study identified a novel association between PD and prostate cancer, which extended to first-degree, second-degree, and third-degree relatives. We also confirmed the reported risk association for melanoma in patients with PD; we extended the finding to include a significantly increased risk in relatives. These results strongly support a genetic link. This conclusion is further strengthened by observation of the reciprocal relationship, an increased risk for PD in relatives of individuals with melanoma or prostate cancer.

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**N**EURODEGENERATIVE DISEASES, in particular Parkinson disease (PD), may share common pathogenic mechanisms with some cancers.<sup>1,2</sup> If this common pathogenic mechanism were genetic, then the risk for particular cancer types would be associated with an increased risk for PD not only in individuals but also their relatives. Most studies demonstrate an overall decreased cancer rate in the PD population.<sup>3</sup> One exception is melanoma; several studies in Europe and the United States have shown an elevated risk for malignant melanoma in patients with PD.<sup>4-8</sup> Owing to limitations of study design, past studies have not been able to address the underlying causes of these associations,

failing to distinguish between the effects of PD treatments, environmental factors, and genetic causes. Genetic studies have been limited to first-degree relatives or by sampling that was not population based.

### See related editorial

A link between melanoma and PD was first suggested in 1972, when a malignant melanoma developed in a patient being treated with levodopa for PD.<sup>9</sup> Since this publication, there have been more than 50 additional case reports of melanoma in patients being treated with levodopa.<sup>10,11</sup> However, further evaluations of large populations of patients with PD have concluded that the relationship between mela-

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**Table 1. ICD Revision and Codes Used to Identify PD as a Cause of Death and Number of PD Deaths Identified**

ICD Revision	Code	Death Certificates, No.	Death of Individuals, Year Range	Average Age at Death With PD, y
6	350	12	1957-1957	74.4
7	350	111	1958-1967	71.2
8	342	156	1968-1978	73.1
9	332	953	1979-1998	80.2
10	G20	1766	1906-1956, 1998-2008	80.3

Abbreviations: ICD, *International Classification of Diseases*; PD, Parkinson disease.

noma and PD is independent of levodopa.<sup>12,13</sup> A reciprocal increased risk for PD has been reported in patients with melanoma and their first-degree relatives.<sup>14,15</sup> Although this may suggest a genetic link, first-degree relatives often share a similar environment. Furthermore, the strength of this association has recently been called into question. A study using the Danish Cancer Registry, which examined patients diagnosed as having melanoma before 50 years of age, found no relationship between melanoma and PD in the first-degree relatives.<sup>16</sup>

Smoking-related cancers, such as lung/bronchus and prostate cancers, have been reported to occur less frequently than expected in the PD population.<sup>4,17</sup> However, an inverse association was recently suggested in the STRIDE-PD (Initiating Levodopa/Carbidopa Therapy With and Without Entacapone in Early Parkinson Disease) study. In this study, the group of patients with PD treated with entacapone, carbidopa, and levodopa had a higher incidence of prostate cancer than the placebo group, resulting in an alert by the US Food and Drug Administration.<sup>18</sup>

We used a population-based resource in Utah to explore the association of PD with distinct cancers by estimating relative risks (RRs) in close and distant relatives of probands with PD. Identifying a genetic relationship between PD and cancer is critical to understanding underlying pathophysiologic changes in both diseases. Understanding this relationship could allow clinicians to provide proper assessment of cancer risk in patients with PD and might also have implications for the counseling of relatives of patients.

## METHODS

The Utah Population Database (UPDB) includes birth, death, and family relationship data for more than 2 million individuals, with some records extending back more than 15 generations. This computerized genealogic resource is derived from multiple record-linked data sources. The resource includes genealogic data for the original Utah pioneers (members of the Church of Jesus Christ of Latter-day Saints, or Mormons) and their descendants.<sup>19</sup> The original genealogy data have been supplemented with Utah vital records such as birth certificates (using father, mother, and child triplets). The genealogic data have been record-linked to disease data for the state including Utah death certificates dating back to 1904 and the Utah Cancer Registry. The Utah Cancer Registry was established in 1966 and became part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program in 1973. All independent primary cancers occurring in the state are reported by law.<sup>20</sup> The Utah Cancer Registry includes data for primary site, histology, and age at diagnosis for each cancer.

We included more than 2.2 million individuals in the UPDB belonging to genealogies with at least 3 generations of genealogic data and connecting to the original Utah genealogy data. Within this population of individuals with genealogy data, there were 388 221 individuals with a Utah death certificate. The cause of death on Utah death certificates was coded using the *International Classification of Diseases* with the respective revisions (ie, 6-10, depending on the decade of death). For all deaths occurring prior to 1956, *International Statistical Classification of Diseases*, 10th Revision coding was assigned. **Table 1** shows the *International Classification of Diseases* codes used to record PD as a cause of death and the number of individuals with PD as a cause of death. This resulted in identification of 2998 individuals with PD as a primary or contributing cause of death.

The analytic methods used have been previously applied to the analysis of various diseases.<sup>21-23</sup> To estimate the RRs of cancer among the relatives of any group of individuals in the UPDB, the observed number of cancers in the relatives of the individuals was compared with the expected number of cancers in the relatives, calculated internally in the UPDB, as follows. All individuals in the UPDB who belonged to at least 3 generations of genealogy and connected to the original Utah genealogy were assigned membership in 1 of 132 birth-year (5-year), sex, and birthplace-specific (Utah or not) cohorts. We determined internal cohort-specific rates for a selected cancer by summing the number of cancer cases in a cohort and dividing that by the total number of UPDB individuals in the cohort. The expected number of relatives with cancer of a specific site was estimated by counting all relatives of the PD deaths (by cohort, with no duplication), then multiplying the number of relatives (per cohort) by the cohort-specific rate of the selected cancer, and then summing over all cohorts. The number of observed cancer cases among the relatives of PD cases was counted, without duplication. The ratio of the observed number of cancers to the expected number of cancers is an unbiased estimator of RR and can be calculated for multiple different relationships. Two-sided probabilities for the alternative hypothesis test of  $RR \neq 1.0$  were calculated under the null hypothesis  $RR = 1.0$ , with the assumption that the number of cancers follows a Poisson distribution with the mean equal to the expected number of cancers. Estimation of the reciprocal RR for PD among relatives of cancer cases used a similar approach; however, only individuals with a Utah death certificate were assigned to cohorts and used to estimate PD rates. In addition, only relatives with a death certificate were used to count observed numbers of PD deaths and estimate the number of expected PD deaths. For instance, under the assumption of a dominant mode of inheritance, we expected each more-distant degree of relationship to include fewer relatives who shared the hypothesized predisposition variant, thus we expected RR estimates to be smaller for more-distant relationships than for close relationships. The hypothesis tests performed identified statistically, rather than biologically, significant effects.

**Table 2. Estimated RRs for Melanoma and PD**

Relationship	Observed, No.	Expected, No.	RR (95% CI)
<b>Estimates of RR for Melanoma Among 2998 Individuals With PD Who Died (Self) and Their Relatives</b>			
Self	48	24.6	1.95 (1.44-2.59)
First-degree relative	217	176.8	1.23 (1.07-1.40)
Second-degree relative	429	383.1	1.12 (1.02-1.23)
Third-degree relative	1013	958.4	1.06 (0.99-1.12)
<b>Estimates of RR for PD Death Among 7841 Individuals With Melanoma (Self) and Their Relatives</b>			
Self	48	29.1	1.65 (1.22-2.19)
First-degree relative	203	157.9	1.29 (1.12-1.48)
Second-degree relative	391	331.4	1.18 (1.07-1.30)
Third-degree relative	856	765.6	1.12 (1.04-1.20)

Abbreviations: PD, Parkinson disease; RR, relative risk.

**Table 3. Estimated RRs for Prostate Cancer and PD**

Relationship	Observed, No.	Expected, No.	RR (95% CI)
<b>Estimates of RR for Prostate Cancer Among the 2998 Individuals With PD Who Died (Self) and Their Relatives</b>			
Self	212	124.1	1.71 (1.49-1.96)
First-degree relative	765	613.6	1.25 (1.16-1.34)
Second-degree relative	1194	1098.7	1.09 (1.03-1.15)
Third-degree relative	3504	3251.1	1.08 (1.04-1.11)
<b>Estimates of RR for Death With PD Among the 22 147 Individuals With Prostate Cancer (Self) and Their Relatives</b>			
Self	212	152.4	1.39 (1.21-1.59)
First-degree relative	656	531.8	1.23 (1.14-1.33)
Second-degree relative	845	781.6	1.08 (1.01-1.16)
Third-degree relative	1703	1550.5	1.10 (1.05-1.15)

Abbreviations: PD, Parkinson disease; RR, relative risk.

To test the more general hypothesis of the association of cancer of any type with PD death, we estimated RRs for 35 other cancer sites among the 2998 individuals with PD who died. To correctly account for multiple hypothesis testing, we used a threshold of  $P < .001$  (0.05/35) for significance of any specific cancer site.

This study was approved by the University of Utah institutional review board and the Resource for Genetic and Epidemiologic Research.

## RESULTS

We identified 2998 individuals with genealogy data whose death certificate listed PD as a cause of death. Among these individuals with PD who died, we observed 48 cases of melanoma, with 24.6 cases expected; the estimated RR for melanoma in individuals who died of PD was 1.95 (95% CI, 1.44-2.59). Relative risks were computed by comparison, with cohorts matched for sex, age, and birth place (see "Methods" for details). The estimated RRs for first-degree, second-degree, and third-degree relatives are shown in **Table 2**, which includes the number of melanoma cases observed, the number expected, the estimated RR, and the 2-tailed 95% confidence interval. An increased risk for melanoma was observed among relatives of all degrees of relationship of individuals with PD who died. This excess was statistically significant among the first-degree and second-degree relatives. To validate this observed association of PD death and melanoma, we also estimated the reciprocal RR for PD among individu-

als diagnosed as having melanoma and among their first-degree, second-degree, and third-degree relatives. We identified 7841 individuals with the diagnosis of melanoma who had at least 3 generations of genealogy. Relative risks estimates for PD death among individuals diagnosed as having melanoma and among their relatives are shown in Table 2. A significantly increased risk for death with PD was noted among the melanoma cases themselves (self), (RR, 1.65; 95% CI, 1.22-2.19). A significantly increased risk for death with PD was also observed among all relatives of individuals diagnosed as having melanoma.

We estimated RRs for 35 other cancer sites among the 2998 individuals with PD who died to test the more general hypothesis of the association of cancer of any type with PD death with a threshold of  $P < .001$  for significance of any specific cancer site. Prostate cancer was the only other cancer observed in excess ( $P < .01$ ). We observed prostate cancer in 212 individuals with PD who died, while it was expected in only 124.1 (RR, 1.71; 95% CI, 1.49-1.96). A significantly elevated risk for prostate cancer was also observed among the first-degree, second-degree, and third-degree relatives of individuals with PD who died, as shown in **Table 3**. To validate this observed association of PD death and prostate cancer, we also estimated the reciprocal RRs for death with PD among individuals diagnosed as having prostate cancer and among their first-degree, second-degree, and third-degree relatives. We identified 22 147 individuals with

**Table 4. Estimates of Decreased RR for Specific Cancers in 2998 PD Cases for Whom a Significant Deficit Was Found**

Cancer Type	Observed, No.	Expected, No.	RR (95% CI)
Colorectal	29	52.5	0.55 (0.37-0.79)
Lung/bronchus	8	36.6	0.22 (0.09-0.43)
Pancreas	3	11.5	0.26 (0.05-0.76)
Stomach	2	9.3	0.22 (0.03-0.78)

Abbreviations: PD, Parkinson disease; RR, relative risk.

the diagnosis of prostate cancer who had at least 3 generations of genealogy. Relative risk estimates for PD death among individuals diagnosed as having prostate cancer and among their relatives are shown in Table 3. A significantly increased risk for death with PD was noted among the prostate cancer cases (self; RR, 1.39; 95% CI, 1.21-1.59) as well as their first-degree, second-degree, and third-degree relatives.

Four cancer sites were observed at a significant deficit among the 2998 PD cases: colorectal, lung/bronchus, pancreas, and stomach. However, only lung/bronchus cancer met the multiple testing significance threshold ( $P < .001$ ). **Table 4** shows the observed and expected numbers, RR, and the 2-tailed 95% confidence interval for these 4 cancers in PD cases. As a recent meta-analysis of melanoma in PD indicated sex-specific effects,<sup>24</sup> we analyzed cancers separately for 1886 men and 1112 women who died of PD. Lung, pancreas, and stomach cancer deficits were significant in men. In women, only colorectal cancer showed a significant deficit.

We estimated the RR for lung cancer in the relatives of PD cases. First-degree relatives showed no decreased risk (RR, 1.04; 95% CI, 0.91-1.19), but a significantly decreased risk for lung cancer was observed among the second-degree and third-degree relatives of the PD cases (RR, 0.85; 95% CI, 0.75-0.95 and RR, 0.89; 95% CI, 0.84-0.95, respectively). We also observed a significant deficit reciprocal RR for PD in 7353 lung cancer cases (RR, 0.12; 95% CI, 0.05-0.24). Reciprocal RR estimates for PD death among the first-degree, second-degree, and third-degree relatives of lung cancer cases were not significantly different from 1.0 (data not shown). As we did not capture smoking history, our observations for lung cancer need to be interpreted with caution.

## COMMENT

Using a unique population-based database, we studied the association between PD and cancer risk. To our knowledge, this is the first attempt to estimate cancer rates in first-degree, second-degree, and third-degree relatives of patients with PD. Significantly increased cancer risk in PD cases was restricted to melanoma and prostate cancers. In contrast, risk for lung/bronchus cancer was significantly reduced in patients with PD.

Our population-based approach, using statewide registries of death and cancer, reduced the identification of spurious associations solely based on the co-occurrence of diseases in probands, which may be multifactorial and

subject to significant bias in ascertainment. Use of this population-based resource with uniform and consistent identification of cancer types and PD deaths in a US state reduced the typical ascertainment and recall biases in studies attempting to estimate risks among relatives. This study has allowed the identification of genetic influences (in the presence or absence of environmental influences) on phenotypes through examination of both close and distant relatives.

Study limitations included censoring owing to cancers and deaths occurring outside the Utah timeframes represented in the UPDB, as well as missing or incorrect genealogical data. We assumed any such censoring to be unbiased in nature. It is conceivable that patients who had been diagnosed as having PD underwent closer medical scrutiny for melanoma. It is unlikely that this bias, if present, would extend to first-degree relatives or more distantly related individuals. Our study is also limited by the fact that we could not address the chronology of PD and cancer.

The Utah Cancer Registry has virtually complete ascertainment of melanoma, lung/bronchus, and prostate cases that went to clinical diagnosis. On the other hand, the inclusion of PD as a cause of death on death certificates may not be complete and may have included PD-like diseases such as progressive supranuclear palsy, multiple system atrophy, and other forms of parkinsonism including drug-induced parkinsonism or dementia with Lewy bodies. Furthermore, in individuals with a diagnosis of PD, the diagnosis may have appeared on death certificates only 54.8% of the time.<sup>25</sup> We assumed that these misclassification errors affecting death certificates were unbiased and would be observed equally across the population. Unbiased under-reporting or over-reporting of PD on death certificates would only reduce power to identify a true effect. Overall, our data appeared to be representative of PD death rates in the United States. There were 1445 PD deaths in Utah from 2000-2009, thus there was an average of 144.5 PD deaths per year in a population of 2.3 million. This rate of 6.3% per 100 000 population is close to the rate of 6.7% reported by the Centers for Disease Control and Prevention in 2004.<sup>26</sup>

The Utah population has been shown to have low to normal inbreeding levels compared with the United States and to be similar in genetic makeup to the northern European populations from which the founders originated.<sup>27,28</sup> Consistent with northern European descent and the high number of sunny days, Utah is among the states with the highest rate of melanoma.<sup>29</sup> The data set did not include information on smoking, caffeine intake, or alcohol use. As overall consumption of these substances in Utah is low, our results may not necessarily be generalized to other populations with higher rates of use. The adult smoking rate in Utah at 9.1% is lower than in any other US state and much lower than the US average of 19.3%.<sup>30</sup>

We demonstrated a significantly increased risk for melanoma in the PD population, as other studies have reported. However, we were able to expand on this relationship, demonstrating significantly increased risks for relatives of those who died of PD. We also observed significantly elevated RRs for PD death among the patients with melanoma and their close and distant relatives. These data strongly support the hypothesis of a common genetic link between PD and melanoma.



Some PD-related genes have been implicated in PD-melanoma relationships including *PARK2* and *LRRK2*. The PD-related protein  $\alpha$ -synuclein may also play a role in melanoma.  $\alpha$ -Synuclein aggregates are found throughout the central and peripheral nervous system in individuals with PD.<sup>31,32</sup> In melanoma tissue,  $\alpha$ -synuclein is also expressed and has recently been used as a histologic biomarker for the diagnosis of metastatic melanoma.<sup>33</sup>

Mutations in *PARK2*, encoding *parkin*, are responsible for a young onset form of PD.<sup>34</sup> *PARK2* is also a candidate tumor suppressor gene,<sup>35</sup> and loss of heterozygosity for a chromosomal region including the *PARK2* gene has been described in melanoma.<sup>36</sup> *Park7* (*DJ-1*) was initially identified as an oncogene and modifies *PTEN* function.<sup>37</sup> Mutations in *LRRK2* are associated with autosomal dominantly inherited PD.<sup>38</sup> The kinase domain of *LRRK2* is a homologue to the *BRAF* kinase, which is activated in malignant melanoma.<sup>39</sup> Based on our studies, we predicted that other PD genes would be found to play a role in tumorigenesis.

A prior study examining probands with PD had suggested a possible increased risk for prostate cancer,<sup>40</sup> but it could not differentiate between medication effects or shared environmental and genetic factors. We demonstrated a statistically significant increase in prostate cancer in probands with PD as well as in first-degree, second-degree, and third-degree relatives of the PD population. A genetic contribution was further supported by the fact that PD risk was significantly elevated in close and distant relatives of individuals with prostate cancer.

Recently, a novel compound used for the treatment of PD was found to be associated with prostate cancer. An analysis of the STRIDE-PD study<sup>41</sup> demonstrated a possible link between prostate cancer and study subjects taking Stalevo (carbidopa/levodopa/entacapone) vs carbidopa/levodopa.<sup>18</sup> In the STRIDE-PD study, subjects were followed up for more than 4 years, with a mean duration of exposure of 2.7 years. Nine of 245 men in the Stalevo group developed prostate cancer compared with 2 of 222 in the carbidopa/levodopa group. Further investigation into this relationship is currently underway. We estimated the RR for prostate cancer among those PD deaths occurring before 2003, prior to the marketing of Stalevo in the United States ( $n = 1951$ , data not shown). Our results did not change and suggested that data analysis in the STRIDE-PD study should stratify for prostate cancer in relatives.

In summary, this study demonstrated the strength of a statewide database linking genealogic data with medical records for the detection of disease associations. This population-based approach using statewide registries of death and cancer reduced the identification of spurious associations solely based on the co-occurrence of diseases in probands. This approach has significantly increased power over examining associations in probands only because increased risk in third-degree relatives strongly supports genetic risk factors (in addition to environmental risk factors). Decreasing RRs with increasing genetic distance are strongly supportive of a genetic interpretation for increased cancer occurrence in relatives. Thus, these data argue strongly for a significant shared genetic risk for specific cancers on the one hand

and neurodegeneration on the other. This conclusion was further strengthened by the finding of an increased reciprocal risk (ie, significantly increased risk for PD in relatives of patients with prostate cancer or melanoma). These studies provide a framework for future definition of the precise nature of shared genetic variation leading to neurodegeneration in some individuals, but skin or prostate cancers in others, and they may influence strategies for skin and prostate cancer screening. Prior large-scale DNA banking of high-risk melanoma and prostate cancer families will enable us to identify those pedigrees at high risk for death with PD, allowing identification of shared genetic variation by whole exome or whole genome sequencing.

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