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Differential risks of cancer types in people with Parkinson's disease: A national record-linkage study

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Abstract ***Background:*** There is evidence that people with Parkinson's disease (PD) have a decreased risk of developing cancer. PD has also variably been shown to be associated with an increased risk of cancers like melanoma and breast. We investigated this relationship in a very large cohort of PD patients.

Methods: We constructed two cohorts of people from an all-England record-linked hospital and mortality dataset spanning 1999–2011. One cohort comprised people with a record of PD; the other comprised people without a record of PD. We 'followed up' these two cohorts to determine observed and expected numbers of people with subsequent primary cancers in each, based on person-years at risk, and calculated standardised rate ratios (RRs).

Results: In 219,194 people with PD, the RR for all subsequent primary malignant cancers combined was 0.92 (95% confidence interval (CI) 0.91–0.93). Increased RRs ($p < 0.05$) were found for six out of the 31 cancer types investigated, including breast, melanoma, uterus, kidney, and neurological malignancies. Decreased RRs were found for 11 cancer sites, including lung and colon cancer.

Conclusions: We corroborate the findings of a reduced risk for the development of cancers in PD patients shown in smaller studies, including cancers associated and not known to be associated with smoking; and of an increased risk of melanoma and breast cancer. To the best of our knowledge, this is the first study to report an association between PD and elevated rates of uterine and renal cancer. Further work is warranted to understand the mechanisms behind these findings.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurological disorder caused by the degeneration and

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death of cells in the substantia nigra. There is increasing evidence from epidemiological studies showing that people with PD have a decreased risk of cancer compared with those without [1–3].

Many hypotheses exist for why those with PD are protected from a range of cancers. Smoking has been proposed as a major factor. There is strong evidence that smoking is protective for PD [4] and some evidence of decreased rates of smoking in those with PD [5]. Whilst reduced rates of smoking in those with PD might explain the decreased risks of developing smoking related cancers such as lung and bladder, it does not explain the decreased risks of malignancies not thought to be associated with smoking like prostate cancer [1,3].

The reduced cancer risk in PD patients might reflect an increased tendency for cells to undergo apoptosis. In support of this hypothesis, a number of genes involved in cell cycle regulation have been found to be abnormally expressed in PD and cancers [6,7].

Despite the overall decreased rates of cancer found in PD patients, PD has been variably found to be associated with high rates of certain cancers including malignant melanoma [1,3,8]. Shared biochemical pathways between PD and melanoma, and L-DOPA treatment have been suggested to underlie this association [9]. Some studies have also found PD patients to be at higher risk of developing NMSC, breast, and thyroid cancer, but the evidence for this is less consistent [2,3].

Our group has previously investigated these associations using local Oxford data, and showed an overall decreased risk of cancer after PD, but with no significant increased risks of any specific cancer [10]. Given the rarity of PD and individual cancers, the numbers in previous studies have been relatively small. We used a record-linked hospital and mortality dataset covering the whole of England during the period 1999–2011 to examine this relationship. To the best of our knowledge, this is the largest cohort of PD patients followed up for cancer, and it allowed us to stratify risks by cancer site and gender with greater statistical power.

2. Materials and methods

2.1. Population and data

The dataset comprised statistical information on all NHS hospital day cases and admissions, and on all deaths, in the whole of England from 1st January 1999 to 31st December 2011. The hospital data are from English national Hospital Episode Statistics (HES) supplied by the English national Health and Social Care Information Centre. The mortality data were derived from death certificates and were supplied by the Office for National Statistics. Both sets of data contain diagnosis codes using the International Classification of Diseases 10th Revision (ICD-10). For each individual, successive records were linked together based on encrypted values of each individual's unique NHS number, HES ID number, and encrypted postcodes and dates of birth. The record linkage was undertaken by the Oxford record linkage group. Use of the datasets was approved by the Central and South Bristol Research Ethics Committee (ref 04/Q2006/176).

2.2. Construction of the PD cohort and reference cohort

We constructed a cohort of people with a diagnosis of PD (the 'PD cohort') by identifying from the database the first episode of day case care, or admission, for PD during the study period. People were included in the PD cohort if they had a hospital record containing a diagnosis code within the range ICD-10 G20 specified anywhere on the record. For each person, the earliest known record containing the PD diagnosis was the record used in the analysis.

As in previous studies of disease associations by our group [11], a 'reference cohort' was also constructed for comparison. This cohort comprised individuals admitted to hospital with any one of a wide range of minor conditions listed in the footnotes to Table 2. For each person, the earliest known record of any one of these conditions was the record used in the analysis. Standard epidemiological practice was adopted in selecting a diverse range of conditions. None of the control conditions within the reference cohort, when studied separately, were associated with unusually high or low rates of cancer when compared with the other conditions in the reference cohort (data not shown). We considered that rates of people with subsequent cancer in the reference cohort would approximate those in the general population of England while allowing for migration in and out of it (data on migration of individuals were not available). Any person admitted initially to the reference cohort who later received a diagnosis of PD would contribute person-days to each cohort for their respective duration in each.

Any person who had a record of cancer dated earlier than, or at the same time as, the date of the PD record was ineligible for entry into the PD cohort, and we applied the equivalent rule to the reference cohort. The purpose of this was to identify, as best we could, the time sequence of cancer diagnosis after cohort entry and to minimise surveillance bias.

2.3. Cancer outcomes

The individuals in the PD cohort and reference cohort were then 'followed up' by searching the linked dataset for any subsequent care for, or death from, malignant cancer. We first searched for any malignant cancer within the range ICD-10 C00–C97, taking the first record of any cancer within that range as the out-

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