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Cancer in patients with motor neuron disease, multiple sclerosis, and Parkinson's disease: record-linkage studies.

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ABSTRACT

Objective: To determine the risk of cancer before and after the diagnosis of motor neuron disease (MND), multiple sclerosis (MS), and Parkinson's disease (PD).

Methods: Analysis of statistical database of linked statistical abstracts of hospital and mortality data in an area in southern England.

Results: Only people with PD showed a significant difference in the overall incidence of cancer compared to controls (rate ratio (RR) 0.76, 95 % confidence intervals 0.70-0.82 before PD; RR 0.61, 0.53-0.70, after PD). Rate ratios were close to one for cancer in patients after MND (0.98, 0.75-1.26) and after MS (0.96, 0.83-1.09). There were high rate ratios for malignant brain cancer (RR 7.4, 2.4-17.5) and Hodgkin's lymphoma (5.3, 1.1-15.6) in patients diagnosed with MND after cancer. In people with MS, malignant brain cancer also showed an increased rate ratio both before hospital admission with a diagnosis of MS (RR 3.2, 1.1-7.6) and after (RR 2.4, 1.2-4.5). In people with PD, several specific cancers showed significantly and substantially reduced rate ratios for cancer, notably smoking-related cancers including lung cancer (RR 0.5, 0.4-0.7, before PD; 0.5, 0.4-0.8, after PD) but also cancers that are not strongly smoking-related including colon cancer (RR 0.7, 0.6-0.9, before PD; 0.5, 0.4-0.8, after PD).

Conclusions: People with MND, or MS, do not have an altered risk of cancer overall. There may sometimes be misdiagnosis between MND or MS and brain tumours. PD

carries a reduced risk of cancer overall, of some smoking-related cancers, and of some cancers that are not smoking-related.

INTRODUCTION

Disease association studies, to investigate whether diseases co-exist in individuals more or less commonly than expected by chance, can help gain insights into diseases of obscure aetiology. There is a rich case-report literature on cancer, as a marker for a number of different pathological processes, in people with motor neuron disease (MND), multiple sclerosis (MS), and Parkinson's disease (PD). The epidemiological literature is more sparse.

The aetiology of MND, and amyotrophic lateral sclerosis (ALS) in its commonest form, is poorly understood. A minority of cases are associated with single gene mutations, and although there may be several inherited susceptibility genes, the disease is best considered as a sporadic disorder.[1] An association between MND and cancer has been postulated in the literature, largely based on case reports with relatively small numbers of cases.[2, 3] Some studies have reported remission of an apparently paraneoplastic form of MND upon treatment of the underlying tumour;[4, 5] and associated anti-neuronal antibodies (especially anti-Hu and anti-Yo antibodies) have been sought and found by some authors[6, 7] but not found by others.[8]

The aetiology of MS, an inflammatory, demyelinating disease of the central nervous system, is similarly thought to involve a "complex genetic-risk profile" but in typically younger people than MND and with clearer evidence about the role of environmental influences.[9] The literature about MS and cancer has mainly focused on Hodgkin's lymphoma and the evidence that Epstein-Barr virus (EBV) infection may be implicated in

the aetiology both of it and of MS;[10-12] and on breast cancer[13] and brain tumours.[14] Elevated cancer rates have also been suspected to result from immunosuppressive pharmacological therapy for MS.[15]

PD, in contrast, has been reported to be associated with significantly low rates of some cancers, but also with significantly high rates of breast cancer and melanoma.[16] Some of these associations have generated, or been taken to support, various hypotheses, including the possible neuro-protective effects of smoking (lower rates of smoking-related cancers in PD), L-dopa treatment as a cause of malignant melanoma, and genetic mutations as a common aetiological factor in both PD and cancer.[16, 17]

Diseases can co-exist in an individual by chance. We have used a large epidemiological database to study cancer in people with MND, MS or PD, with the aim of distinguishing between chance and true associations.

MATERIALS AND METHODS (SEE APPENDIX FOR FURTHER DETAILS)

Population and data

The Oxford record linkage study (ORLS) includes brief statistical abstracts of records of all hospital admissions, including day-cases, in UK National Health Service (NHS) hospitals, and all deaths in a defined population in southern England from 1963-1999.[18] The hospital data were collected routinely in the NHS as the (former) Oxford Regional Health Authority's hospital discharge statistics. The death data derive from death certificates. The current programme of analysis of the data has been approved by

the English NHS Central Office for Research Ethics Committees (reference number 04/Q2006/176). With changes to NHS information systems, data in the ORLS cannot be linked between the pre-1999 era and the present system of data collection.

Construction of cohorts

The methods used to study people with each neurological condition were the same and will be described for MND. For people with MND, their first admission to hospital or day-case care during the study period was identified. A control cohort was constructed by identifying the first admission of individual patients in the ORLS for a range of common orthopaedic, dental, ENT and other relatively minor disorders (details in table footnotes). This is based on a ‘reference’ group of conditions that has been used in a series of other studies of cancer in people with other non-malignant disease.[19-21] We searched the dataset for any subsequent hospital admission or day-case care for, or death from, each cancer in these cohorts. We used the reference cohort from within the ORLS dataset, rather than external population-based rates, to calculate expected numbers of people with each cancer in the MND cohort. We did so because there is migration into and out of the Oxford region, without the ability to follow the medical records of those who move. This means that whilst absolute rates of cancer occurrence after MND cannot be calculated, relative rates, comparing the MND and reference cohort, can (see below).

Statistical methods

We calculated rates of each cancer based on person-years at risk. We took “date of entry” into each cohort as the date of first admission for the exposure condition, or the

reference condition, and we took “date of exit” for each individual disease as the date of subsequent admission for cancer (if any occurred), death, or 31 March, 1999, whichever was the earliest.

In comparing the MND and reference cohorts, we first calculated rates of each subsequent cancer, standardised by age at entry (in five-year age groups), sex, calendar year of first recorded admission, interval from study entry and district of residence, using the indirect method of standardisation and taking the combined MND and reference cohorts as the standard population. We applied the stratum-specific rates from the standard population to the MND cohort and to the reference cohort, in order to obtain standardised rates for each cohort. We then calculated the ratio of the standardised rate of each cancer in the MND cohort relative to the rate of the same cancer in the reference cohort, with the 95% confidence interval for the rate ratio, using the methods of Breslow and Day.[22] In the reference cohort, we included all the people in the dataset with the comparison conditions in each age group. We did this to maximize the numbers in each stratum in the reference cohort and thereby to maximize the statistical power of the study. Our purpose in standardizing for age, year of admission and district of residence was to ensure that the exposure cohorts and the reference cohort were equivalent in these respects. We give figures for rate ratios and their 95% confidence intervals at one decimal place except that, in analyses with all cancers combined, we show two decimal places. We then used the same procedures, but in reverse, to calculate rate ratios for MND (and MS and PD) after each cancer (see Appendix). Because we make multiple comparisons, we have given exact p values so that the reader may assess the level of

significance of each comparison. In comparisons with an 'expected' value of five or less, we have quoted the exact test based on the binomial distribution.[22]

RESULTS

The age and sex distributions of the patients are shown in Table 1. The mean period of follow up from neurological disease to first occurrence of cancer was 3.1 years for MND, 6.9 for MS and 3.2 for PD; and that from cancer to neurological disease was 3.4 years.

Table 1. Number (and percentage) of people admitted to hospital with motor neuron disease, multiple sclerosis or Parkinson's disease in each age-group stratum, with the matching ratio of numbers of cases in the reference cohort per case in each age stratum with each neurological disease

| Age group (yrs) | Motor neuron disease ¹ | | | Multiple sclerosis ² | | | Parkinson's disease ³ | | |
|-----------------|-----------------------------------|-----------------|----------------|---------------------------------|-----------------|----------------|----------------------------------|-----------------|----------------|
| | Males No. (%) | Females No. (%) | Matching ratio | Males No. (%) | Females No. (%) | Matching ratio | Males No. (%) | Females No. (%) | Matching ratio |
| <25 | 28 (3.3) | 20 (3.4) | 4362 | 86 (5.9) | 191 (6.8) | 972 | 6 (0.3) | 5 (0.2) | 24482 |
| 25-29 | 16 (1.9) | 6 (1.0) | 1840 | 103 (7.2) | 286 (10.2) | 104 | 1 (0.1) | 2 (0.1) | 13491 |
| 30-34 | 11 (1.3) | 8 (1.4) | 1807 | 152 (10.6) | 310 (11.0) | 74 | 4 (0.2) | 3 (0.1) | 4904 |
| 35-39 | 22 (2.6) | 10 (1.7) | 941 | 183 (12.7) | 323 (11.5) | 60 | 4 (0.2) | 8 (0.4) | 2509 |
| 40-44 | 26 (3.1) | 12 (2.0) | 731 | 139 (9.7) | 341 (12.1) | 58 | 11 (0.5) | 4 (0.2) | 1853 |
| 45-49 | 33 (4.0) | 15 (2.5) | 564 | 179 (12.4) | 338 (12.0) | 52 | 17 (0.8) | 11 (0.5) | 967 |
| 50-54 | 75 (8.9) | 40 (6.8) | 230 | 183 (12.7) | 286 (10.2) | 56 | 30 (1.4) | 29 (1.3) | 449 |
| 55-59 | 75 (8.9) | 57 (9.6) | 192 | 137 (9.5) | 218 (7.8) | 71 | 70 (3.3) | 58 (2.6) | 198 |
| 60-64 | 142 (17.0) | 74 (12.5) | 111 | 116 (8.1) | 185 (6.5) | 79 | 106 (4.9) | 98 (4.4) | 117 |
| 65-69 | 125 (14.9) | 82 (13.9) | 103 | 73 (5.1) | 138 (4.9) | 101 | 223 (10.4) | 186 (8.4) | 52 |
| 70-74 | 128 (15.3) | 109 (18.4) | 79 | 54 (3.8) | 90 (3.2) | 76 | 407 (18.8) | 354 (16.1) | 25 |
| 75-79 | 92 (11.0) | 83 (14.0) | 84 | 18 (1.3) | 61 (2.2) | 186 | 549 (25.5) | 524 (23.8) | 14 |
| 80-84 | 45 (5.4) | 45 (7.6) | 102 | 12 (0.8) | 33 (1.2) | 205 | 418 (19.4) | 507 (23.0) | 10 |
| 85+ | 20 (2.4) | 30 (5.2) | 134 | 3 (0.2) | 12 (0.4) | 447 | 304 (14.1) | 416 (18.9) | 9 |

| | | | | | | | | | |
|-------|---------|---------|-----|---------|---------|-----|---------|---------|-----|
| Total | 838 | 591 | 403 | 1438 | 2812 | 135 | 2150 | 2205 | 132 |
| | (100.0) | (100.0) | | (100.0) | (100.0) | | (100.0) | (100.0) | |

¹ ICD codes used for motor neuron disease, and the precise nomenclature in the coding manual, were: ICD7 356 used from 1963-7 (motor neurone disease and muscular atrophy – the code 356.2 was ‘spinal type of muscular atrophy’ and we excluded it); ICD8 348 used from 1968-78 (motor neurone disease); ICD9 335.2 used from 1979-1994 (motor neurone disease); ICD10 G12.2 used from 1995 (motor neuron disease).

² ICD codes used for multiple sclerosis were: ICD7 345; ICD8 340; ICD9 340; ICD10 G35 (all four edition codes specified ‘multiple sclerosis’)

³ ICD codes used for Parkinson’s disease were: ICD7 350 (paralysis agitans, with subheadings (but not separately identifiable codes) for Parkinson’s syndrome, Parkinsonian epilepsy, Parkinsonism); ICD8 342 (nomenclature as for ICD7); ICD9 332 (Parkinson’s disease); ICD10 G20 (Parkinson’s disease).

Motor neuron disease (Table 2)

The ORLS data (Table 2) showed no significant overall association between cancer and MND. The rate ratio (RR) for cancer diagnosed after MND, relative to cancer in the control cohort, was 0.98 (95 % confidence interval (CI) 0.75-1.26). The rate ratio for MND after cancer was 0.84 (95 % CI 0.66-1.07). Within this group the rate ratios were significantly high for malignant brain tumours (RR 7.4, 95 % CI 2.4-17.5) and Hodgkin's lymphoma (5.3, 1.1-15.6) prior to MND diagnosis, but these associations disappeared if patients who were diagnosed with these conditions within a year of each other were excluded (footnote table 2 for rate ratios). Rate ratios were high, in patients diagnosed with MND first, for cancer of the salivary gland (2 observed cases, 0.2 expected; RR 9.5, 1.1-35.0); and low for prostate cancer (no observed cases, 6.1 expected, $p=0.007$, Table 2).

Table 2. Occurrence of cancer¹ in people admitted with motor neuron disease before or after an admission for cancer: number of people in the reference cohort² with each cancer, observed and expected number of cases in the motor neuron disease or cancer cohorts, ratio of rate in the motor neuron disease or cancer cohort to that in the reference cohort, and 95% confidence intervals for the rate ratio.

| Cancer (ICD code) ³ and number of cases in reference cohort (n) | Cancer after motor neuron disease | | | | Cancer before motor neuron disease | | | |
|--|-----------------------------------|-----------------|---|---------|------------------------------------|-----------------|---|---------|
| | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value |
| All cancers (140-208), n=29196 | 62 | 63 | 0.98 (0.75-1.26) | 0.95 | 96 | 108.5 | 0.84 (0.66-1.07) | 0.15 |
| Larynx (161), n=281 | 3 | 0.9 | 3.5 (0.7-10.2) | 0.09 | 2 | 1.9 | 1.0 (0.1-3.8) | 0.77 |
| Salivary gland (142), n=105 | 2 | 0.2 | 9.5 (1.1-35.0) | <0.004 | 2 | 0.7 | 3.0 (0.4-10.8) | 0.11 |
| Stomach (151), n=1410 | 7 | 3.7 | 1.9 (0.8-3.9) | 0.15 | 2 | 3.3 | 0.6 (0.1-2.2) | 0.66 |
| Colon (153), n=2680 | 4 | 7.5 | 0.5 (0.2-1.4) | 0.28 | 10 | 10.8 | 0.9 (0.4-1.7) | 0.80 |
| Rectum (154), n=1570 | 4 | 4.5 | 0.9 (0.2-2.3) | 1.00 | 11 | 8.6 | 1.3 (0.6-2.4) | 0.40 |
| Lung (162), n=4587 | 15 | 11.4 | 1.3 (0.7-2.2) | 0.28 | 10 | 10.2 | 1.0 (0.5-1.8) | 0.94 |
| Breast (174, 175), n=2717 | 6 | 4.6 | 1.3 (0.5-2.9) | 0.67 | 13 | 16.1 | 0.8 (0.4-1.4) | 0.43 |
| Prostate (185), n=2448 | 0 | 6.1 | 0 (0-0.5) | 0.007 | 13 | 10.8 | 1.2 (0.6-2.2) | 0.48 |
| Bladder (188), n=1766 | 6 | 4.7 | 1.3 (0.5-2.8) | 0.71 | 6 | 11.9 | 0.5 (0.2-1.1) | 0.08 |
| Non-melanoma skin cancer (173), n=1957 | 4 | 4.9 | 0.8 (0.2-2.1) | 0.86 | 13 | 14.1 | 0.9 (0.5-1.6) | 0.77 |
| Malignant brain (191), n=543 | 2 | 1.1 | 1.9 (0.2-6.8) | 0.70 | 5 | 0.7 | 7.4 (2.4-17.5) ⁵ | <0.001 |
| Lymphoma (200,202), n=925 | 6 | 2.3 | 2.6 (0.9-5.6) | 0.06 | 2 | 3.3 | 1.3 (0.4-3.1) | 0.48 |
| Hodgkin's disease (201), n=204 | 1 | 0.3 | 3.3 (0.9) | 0.72 | 3 | 0.6 | 5.3 (1.1-15.6) ⁶ | 0.014 |

¹Data not shown for 16 cancers studied, with non-significant results and fewer than five observed cases in people with motor neuron disease (combining cancers before and after MND). The cancers that were studied in addition to those shown in the tables were (with number of cases before and after MND): oral cavity and pharynx (3),

nasopharynx (0), oesophagus (4), liver (0), pancreas (0), cervix (4), ovary (0), uterus (2), testis (0), kidney (2), malignant melanoma (1), other nervous system (1), thyroid (1), bone (2), leukaemia (4), benign brain (3). Full results available on request from the authors.

²Conditions used in reference cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 3 for operations and ICD9 code for diagnosis (with equivalent codes used for other coding editions): appendicectomy (441-444), hip arthroplasty (810, 811), knee arthroplasty (812), tonsillectomy (230-236), squint (378), otitis externa, otitis media (380-382), varicose veins (454), haemorrhoids (455), upper respiratory tract infections (460-466), deflected septum, nasal polyp (470-471), impacted tooth and other disorders of teeth (520-521), inguinal hernia (550), ingrowing toenail and other diseases of nail (703), sebaceous cyst (706.2), internal derangement of knee (717), bunion (727.1), selected fractures (810-816, 823-826), dislocations, sprains and strains (830-839, 840-848), superficial injury and contusion (910-919, 920-924).

³ ICD 9 codes for each cancer (equivalent codes were used for cases coded in ICD Revisions 7, 8 and 10.)

⁴ Adjusted for sex, age in 5-year bands, time-period in single calendar years and district of residence.

⁵ Exclusion of cases of MND that occurred within a year of malignant brain tumours left no observed cases and therefore a rate ratio of 0.

⁶ When excluding cases that occurred within a year, the rate ratio for MND in people with Hodgkin's lymphoma was 4.1, 0.5-15.0, based on 2 observed cases and 0.5 expected.

Multiple sclerosis (Table 3)

There was no significant association between MS and cancer overall, irrespective of whether MS was diagnosed before cancer (RR 0.96, 95 % CI 0.83-1.09) or after cancer (0.88, 0.70-1.09). Malignant brain cancer showed an increased rate ratio both after an admission for MS (2.4, 1.2-4.5) and before it (3.2, 1.1-7.6). The rate ratios for kidney cancer (2.1, 1.0-4.0) and bone cancer (4.0, 1.5-8.9) after MS were significantly elevated; and that for non-melanoma skin cancer after MS was reduced (0.4, 0.2-0.9).

Table 3. Occurrence of cancer¹ in people admitted with multiple sclerosis before or after an admission for cancer: number of people in the reference cohort² with each cancer, observed and expected number of cases in the multiple sclerosis or cancer cohorts, ratio of rate in the multiple sclerosis or cancer cohort to that in the reference cohort, and 95% confidence intervals for the rate ratio.

| Cancer (ICD code) ³ and number of cases in reference cohort (n) | Cancer after multiple sclerosis | | | | Cancer before multiple sclerosis | | | |
|--|---------------------------------|-----------------|---|---------|----------------------------------|-----------------|---|---------|
| | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value |
| All cancers (140-208), n=25690 | 222 | 230.5 | 0.96 (0.83-1.09) | 0.20 | 99 | 110.4 | 0.88 (0.70-1.09) | 0.23 |
| Oesophagus (150), n=882 | 8 | 6.4 | 1.2 (0.5-2.5) | 0.54 | 0 | 1.2 | 0 (0-3.1) | 0.52 |
| Stomach (151), n=1342 | 14 | 8.5 | 1.7 (0.9-2.8) | 0.06 | 3 | 2.3 | 1.3 (0.3-3.8) | 0.89 |
| Colon (153), n=2604 | 13 | 20.8 | 0.6 (0.3-1.1) | 0.09 | 7 | 7.8 | 0.9 (0.4-1.9) | 0.77 |
| Rectum (154), n=1540 | 11 | 13.2 | 0.8 (0.4-1.5) | 0.55 | 7 | 5.2 | 1.4 (0.5-2.8) | 0.43 |
| Liver (155), n=335 | 6 | 2.8 | 2.2 (0.8-4.8) | 0.11 | 0 | 0.7 | 0 (0-5.3) | 0.81 |
| Pancreas (157), n=924 | 5 | 8.4 | 0.6 (0.2-1.4) | 0.24 | 2 | 1.2 | 1.7 (0.2-6.0) | 0.78 |
| Lung (162), n=4586 | 25 | 34.7 | 0.7 (0.5-1.1) | 0.10 | 8 | 6.9 | 1.2 (0.5-2.3) | 0.67 |
| Breast (174, 175), n=2714 | 59 | 48.2 | 1.2 (0.9-1.6) | 0.12 | 24 | 29.6 | 0.8 (0.5-1.2) | 0.29 |
| Cervix (180), n=257 | 6 | 4.8 | 1.3 (0.5-2.8) | 0.75 | 6 | 7.7 | 0.8 (0.3-1.7) | 0.53 |
| Ovary (183.0), n=521 | 9 | 8.5 | 1.1 (0.5-2.0) | 0.87 | 4 | 4.3 | 0.9 (0.3-2.4) | 0.92 |
| Uterus (182), n=385 | 11 | 6.2 | 1.8 (0.98-3.2) | 0.06 | 4 | 5.5 | 0.7 (0.2-1.9) | 0.51 |
| Prostate (185), n=2458 | 4 | 9.9 | 0.4 (0.1-1.03) | 0.06 | 4 | 2.2 | 1.8 (0.5-4.7) | 0.38 |

| | | | | | | | | |
|---|----|------|----------------|-------|---|-----|----------------|------|
| Kidney (189.0,189.1), n=533 | 10 | 4.7 | 2.1 (1.02-4.0) | 0.03 | 1 | 1.5 | 0.7 (0-3.7) | 0.41 |
| Bladder (188), n=1755 | 16 | 12 | 1.3 (0.8-2.2) | 0.25 | 4 | 6.8 | 0.6 (0.2-1.5) | 0.28 |
| Malignant melanoma (172), n=430 | 4 | 4.7 | 0.9 (0.2-2.2) | 0.98 | 1 | 4 | 0.3 (0-1.4) | 0.13 |
| Non-melanoma skin cancer (173), n=1710 | 6 | 13.9 | 0.4 (0.2-0.9) | 0.03 | 9 | 7.1 | 1.3 (0.6-2.4) | 0.47 |
| Malignant brain (191), n=519 | 10 | 4.2 | 2.4 (1.2-4.5) | 0.01 | 5 | 1.6 | 3.2 (1.05-7.6) | 0.02 |
| Bone (170), n=185 | 6 | 1.5 | 4.0 (1.5-8.9) | 0.001 | 0 | 0.9 | 0 (0-4.3) | 0.14 |
| Lymphoma (200-202), n=1062 | 9 | 9.9 | 0.9 (0.4-1.7) | 0.78 | 1 | 4.6 | 0.2 (0-1.2) | 0.15 |
| Non-Hodgkin's lymphoma (200,202), n=926 | 8 | 8.9 | 0.9 (0.4-1.8) | 0.77 | 0 | 3 | 0 (0-1.2) | 0.15 |
| Benign brain (225), n=306 | 7 | 3.7 | 1.9 (0.8-4.0) | 0.15 | 4 | 3.4 | 1.2 (0.3-3.0) | 0.96 |

¹ Data not shown for 9 cancers studied, with non-significant results and fewer than five observed cases in people with multiple sclerosis (combining cancers before and after MS). The cancers that were studied in addition to those shown in the tables were (with number of cases before and after MS): oral cavity and pharynx (1), larynx (1), salivary gland (4), nasopharynx (0), testis (2), 'other nervous system' (3), thyroid (3), Hodgkin's disease (2), leukaemia (4). Results available on request from the authors.

²⁻⁴ See footnotes to Table 2.

Parkinson's disease (Table 4)

There was a highly significant reduction ($p < 0.001$) in the risk of cancer in patients with PD, both after the first recorded admission with PD (RR 0.61, 95 % CI 0.53-0.70) and before it (0.76, 0.70-0.82). Several specific cancers showed markedly low rate ratios, most strikingly lung cancer (0.5, 0.4-0.8, after PD; 0.5, 0.4-0.7, before PD), bladder cancer (0.5, 0.3-0.9, after PD; 0.7, 0.6-0.9, after PD) and colon cancer (0.5, 0.4-0.8, after PD; 0.7, 0.6-0.9, before PD). Cancers of the oropharynx, stomach and prostate, non-melanoma skin cancer and non-Hodgkin's lymphoma were significantly low after PD; cancers of the oesophagus, rectum, pancreas and cervix, and malignant melanoma were significantly low before PD; and breast cancer was borderline significantly low both before and after admission for PD (all shown in Table 4).

Table 4. Occurrence of cancer¹ in people admitted with Parkinson's disease before or after an admission for cancer: number of people in the reference cohort² with each cancer, observed and expected number of cases in the Parkinson's disease or cancer cohorts, ratio of rate in the Parkinson's disease or cancer cohort to that in the reference cohort, and 95% confidence intervals for the rate ratio.

| Cancer (ICD code) ³ and number of cases in reference cohort (n) | Cancer after Parkinson's disease | | | | Cancer before Parkinson's disease | | | |
|--|----------------------------------|-----------------|---|---------|-----------------------------------|-----------------|---|---------|
| | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value | Observed number | Expected number | Adjusted rate ratio (95% confidence intervals) ⁴ | p value |
| All cancers (140-208), n=26064 | 219 | 357.3 | 0.61(0.53-0.70) ⁵ | <0.001 | 926 | 1106.2 | 0.76 (0.70-0.82) | <0.001 |
| Oral cavity, pharynx, lip (140-141,143-146,148-149), n=414 | 1 | 5.6 | 0.2 (0-0.99) | 0.05 | 18 | 23.8 | 0.8 (0.5-1.2) | 0.23 |
| Larynx (161), n=282 | 1 | 4 | 0.3 (0-1.4) | 0.08 | 14 | 18.4 | 0.8 (0.4-1.3) | 0.30 |
| Oesophagus (150), n=887 | 12 | 12.8 | 0.9 (0.5-1.6) | 0.82 | 8 | 17.7 | 0.5 (0.2-0.9) | 0.02 |
| Stomach (151), n=1403 | 14 | 25.4 | 0.6 (0.3-0.9) | 0.02 | 36 | 46 | 0.8 (0.5-1.1) | 0.14 |
| Colon (153), n=2668 | 24 | 44.1 | 0.5 (0.4-0.8) ⁶ | 0.002 | 97 | 130.5 | 0.7 (0.6-0.9) | 0.002 |
| Rectum (154), n=1561 | 18 | 25.1 | 0.7 (0.4-1.1) ⁷ | 0.15 | 61 | 96.3 | 0.6 (0.5-0.8) | <0.001 |
| Pancreas (157), n=932 | 11 | 14.2 | 0.8 (0.4-1.4) | 0.39 | 7 | 15.4 | 0.5 (0.2-0.9) | 0.03 |
| Lung (162), n=4573 | 30 | 56.4 | 0.5 (0.4-0.8) ⁸ | <0.001 | 47 | 90.9 | 0.5 (0.4-0.7) | <0.001 |
| Breast (174, 175), n=2697 | 21 | 31.6 | 0.7 (0.4-1.0) | 0.10 | 133 | 154.3 | 0.9 (0.7-1.0) | 0.08 |
| Cervix (180), n=262 | 1 | 1.8 | 0.5 (0-3.0) | 0.33 | 10 | 19.3 | 0.5 (0.3-1.0) | 0.03 |
| Ovary (183.0), n=525 | 3 | 5.6 | 0.5 (0.1-1.6) | 0.28 | 14 | 16 | 0.9 (0.5-1.5) | 0.61 |
| Uterus (182), n=391 | 4 | 5.1 | 0.8 (0.2-2.0) | 0.61 | 31 | 33.6 | 0.9 (0.6-1.3) | 0.64 |
| Prostate (185), n=2425 | 29 | 42 | 0.7 (0.5-1.0) | 0.04 | 118 | 130.1 | 0.9 (0.7-1.1) | 0.27 |
| Kidney (189.0,189.1), n=557 | 3 | 6.1 | 0.5 (0.1-1.4) | 0.20 | 10 | 15.8 | 0.6 (0.3-1.2) | 0.14 |

| | | | | | | | | |
|---|----|------|----------------------------|------|-----|-------|---------------|-------|
| Bladder (188), n=1755 | 12 | 23 | 0.5 (0.3-0.9) ⁹ | 0.02 | 106 | 140.3 | 0.7 (0.6-0.9) | 0.003 |
| Malignant melanoma (172), n=431 | 0 | 3.7 | 0 (0-1.01) | 0.10 | 9 | 18.3 | 0.5 (0.2-0.9) | 0.03 |
| Other skin cancer (173), n=1943 | 17 | 29.4 | 0.6 (0.3-0.9) | 0.02 | 168 | 175 | 1.0 (0.8-1.1) | 0.58 |
| Malignant brain (191), n=540 | 2 | 2.6 | 0.8 (0.1-2.8) | 0.95 | 6 | 6.1 | 1.0 (0.4-2.1) | 0.96 |
| Bone (170), n=187 | 2 | 1.8 | 1.1 (0.1-4.0) | 0.89 | 3 | 4.9 | 0.6 (0.1-1.8) | 0.53 |
| Lymphoma (200-202), n=1057 | 3 | 11.1 | 0.3 (0.1-0.8) | 0.02 | 24 | 27.1 | 0.9 (0.6-1.3) | 0.55 |
| Non-Hodgkin's lymphoma (200,202), n=922 | 3 | 10.2 | 0.3 (0.1-0.9) | 0.02 | 21 | 23.7 | 0.9 (0.6-1.4) | 0.58 |
| Multiple myeloma (203), n=502 | 5 | 8.6 | 0.6 (0.2-1.4) | 0.22 | 11 | 13.7 | 0.8 (0.4-1.4) | 0.47 |
| Leukaemia (204-208), n=875 | 10 | 11.6 | 0.9 (0.4-1.6) | 0.64 | 14 | 19.1 | 0.7 (0.4-1.2) | 0.24 |
| Lymphoid leukaemia (204), n=426 | 5 | 5.7 | 0.9 (0.3-2.1) | 0.76 | 8 | 10.5 | 0.8 (0.3-1.5) | 0.43 |
| Myeloid leukaemia (205), n=438 | 5 | 5.2 | 1.0 (0.3-2.3) | 0.92 | 5 | 7.5 | 0.7 (0.2-1.6) | 0.36 |
| Benign brain (225), n=306 | 2 | 1.5 | 1.3 (0.2-4.8) | 1.00 | 14 | 11.4 | 1.2 (0.7-2.1) | 0.45 |

¹ Data not shown for 7 cancers studied, with non-significant results and fewer than five observed cases in people with Parkinson's disease (combining cancers before and after PD). The cancers that were studied in addition to those shown in the tables were (with number of cases before and after PD):¹ Cancers with fewer than five observed cases in people with Parkinson's disease are not shown. Cancers that were studied in addition to those shown in the tables were (with total number of cases): salivary gland (4), nasopharynx (0), liver (4), testis (3), other nervous system (2), thyroid (1), Hodgkin's disease (3). Results available on request from the authors.

²⁻⁴ See footnotes to Table 2.

⁵ All cancer after PD: RR in males was 0.60 (0.49-0.72); RR in females was 0.59 (0.47-0.73).

⁶ Colon cancer after PD: RR in males was 0.78 (0.42-1.31); RR in females was 0.32 (0.13-0.66)

⁷ Rectal cancer after PD: RR in males was 0.41 (0.13-0.97); RR in females was 0.94 (0.45-1.74)

⁸ Lung cancer after PD: RR in males was 0.61 (0.38-0.93); RR in females was 0.59 (0.25-1.16)

⁹ Bladder cancer after PD: RR in males was 0.56 (0.25-1.06); RR in females was 0.21 (0.01-1.18)

DISCUSSION

Strengths and weaknesses of the study

The strengths of using the ORLS dataset are that it is large in scale and it covers many years of ‘follow up’ after a first diagnosis with the neurological diseases studied. The data were used to calculate ‘expected’ numbers of cases of diseases that occurred in combination, and therefore to assess the statistical significance of disease combinations. The use of a single population dataset to study the cancer profiles of different neurological diseases allows comparisons to be made between them: for example, the cancer profile of PD was very different from that of MND or MS. Moreover, measuring separately the numbers of cancer cases occurring before MND/MS/PD and the numbers occurring after MND/MS/PD provides some information about the temporal (and hence potentially the causal) nature of any associations found. For example, if a drug used to treat MS were thought to cause a particular cancer type, one might expect to see an excess of cases of this cancer being diagnosed after MS, but not before it. This is a particular strength of our methodology compared to past epidemiological studies, which generally investigate only one temporal direction of association or else do not distinguish between the two in data collection.[10, 15]

The data also have some limitations. Data collection was limited to those in receipt of hospital care, though we think that the majority of people with MND, MS, and most

cancers, and quite a high percentage of people with PD, will have been admitted to hospital or seen as a day case at least once. Our data identified the first recorded hospital episode of neurological disease before cancer (and vice versa), but we cannot know whether the neurological diagnosis was invariably made before the diagnosis of cancer. There is, no doubt, some misclassification of some patients in the study, in the temporal sequence of disease occurrence. Accordingly, we have greater confidence in findings on disease associations that are similar regardless of which disease is recorded as having been hospitalised first. The data are confined to patients who remain within the area, and who are admitted to the hospitals, covered by ORLS data collection. These factors are part of our reasoning for including a comparison cohort from the same dataset and for tight ‘matching’, through stratified analysis, for district of treatment and for year of first recorded diagnosis as well as for age and sex. There are no data on lifestyle factors, notably none on smoking, which makes it impossible to explore some of the proposed mechanisms for cancer associations. Current privacy regulations preclude accessing original clinical records and checking on whether (for example) diagnoses of cancer were histologically confirmed. We have had to accept the coded diagnoses on the statistical summary record.

In studying a large number of associations between diseases one must consider the effect of making multiple comparisons. For instance, with a level of significance of $p < 0.05$, one expects one ‘significant’ result at this level for every 20 comparisons made by the play of chance alone. For this reason we have given exact p values so that the reader may assess the level of significance of each comparison. Unexpected significant associations,

especially with low numbers of observed cases, such as that between MND and cancer of the salivary gland (two observed cases), may be explained by chance. However, even with the number of comparisons made, associations where $p < 0.001$ (e.g. the low levels of cancer in people with PD) are very unlikely to be the result of chance alone.

Motor neuron disease

No significant association was found between MND and cancer overall. Despite the case reports implicating various cancers in MND, the overall lack of association between MND and cancer in our study, whether cancer was recorded before or after MND, accords with the limited epidemiological evidence to date.[23, 24] In the largest study thus far, Freedman *et al.* used data from US cancer registries along with death certificates to ascertain cases of MND and showed no increase in MND occurrence in 1.9 million US cancer survivors (their standardised mortality ratio was 1.0 (95 % CI 0.9-1.1)).[24] They also reported no excess or deficit of any specific cancers apart from an excess of melanoma, for which chance (due to multiple comparisons) or ascertainment bias were cited as potential explanations.

An association between breast cancer and MND in female patients has been noted in several case series,[2, 3, 25] but, as breast cancer is common, any association must be shown to be more than coincidence. Sadot *et al.* reported 7 female patients from their MND clinic with breast cancer, and concluded that there was an over-representation (23 % compared to the normal female population 12 % cumulative lifetime incidence). [3] As in previous studies,[25] an upper motor neuron-predominant form of ALS was

noted in the patients. The lack of any association in our data is in accordance with another large epidemiological study.[24] However, despite the overall size of our study, it is nonetheless small and lacking in power in respect of individual site-specific cancers. A paraneoplastic ‘MND-like disorder’ is likely to be a very rare and distinct entity from the sporadic disorder of MND, supported by the absence of both distinguishing clinical features in MND patients with cancer[26] and common paraneoplastic antibodies in MND patient sera.[8] However, the majority of neurological paraneoplastic disorders do precede the detection of the underlying tumour,[27] which may be undetectable at subsequent autopsy if the patient succumbs rapidly. Whilst this phenomenon is unlikely to confound results in relatively slowly progressive disorders like MS and PD, the typically rapid progression of MND (2-4 years median survival from symptom onset) raises the potential for some under-ascertainment of underlying malignancies in this disorder.

Some apparent MND-cancer associations were demonstrated by the ORLS data. Most striking was that between malignant brain cancer and the subsequent development of MND. One plausible explanation might be the initial misdiagnosis of brain cancer in patients presenting with an apparent bulbar palsy. Diagnostic confusion between MND and other CNS cancers has been reported,[28] with even ‘distant’ brain cancers occasionally known to yield bulbar palsies,[29] but usually in the reverse situation i.e. MND misdiagnosed initially. The association between MND and a subsequent diagnosis of Hodgkin’s lymphoma may also be attributable to misdiagnosis, or chance (only 3 cases observed, 0.6 expected), although a known mimic of lower motor neuron-predominant

MND (namely autoimmune multifocal motor neuropathy) has been reported in a case of B-cell lymphoma.[30] There appears to be a highly significant reduction in the incidence of prostate cancer in patients diagnosed with MND (RR 0; 95 % CI 0-0.45, p 0.007) in our data, which is not reported in the literature. This may simply reflect the rapidity with which MND progresses preventing the symptomatic manifestations of this common though often indolent cancer.

Multiple Sclerosis

The absence of a significant association between MS and cancer, overall, accords with the epidemiological literature. A record linkage study, combining data from the Danish MS and cancer registers, found a non-significant decrease in cancer in patients with MS compared with the general population, with a standardised incidence ratio of 0.94 (95 % CI 0.89-1.00).[10] Our rate ratio – a comparable measure – was 0.96 (0.83-1.09).

The apparently increased incidence in our data of kidney and bone cancer after MS, and malignant brain cancer before and after MS, has not been reported in other epidemiological studies. However, case reports of MS and subsequent brain cancer have been published,[14, 31] with the suggestion of gliomatous transformation of demyelinating lesions. Reports of MS mimicking brain tumours clinically and radiologically could potentially explain the reverse association of brain cancer before MS,[32, 33] as could a brain tumour associated with T2 hyperintensity on MRI mimicking MS. The observed reduction in non-melanoma skin cancers in patients diagnosed with MS may be a reflection of the well-established increased incidence of MS

at higher latitudes where exposure to sunlight is diminished, and is a finding that has been reported from the ORLS previously.[34]

The relationship between MS and Hodgkin's lymphoma has been studied closely since EBV, a closely associated agent in Hodgkin's (and Burkitt's) lymphoma, has been hypothesized as a risk factor for MS.[35] The possibility of an association between MS and Hodgkin's lymphoma has received some support from case reports,[35] a small Italian case-control study,[12] and a study showing familial clustering.[11] However, an association between MS and Hodgkin's lymphoma was not found in the large Danish record linkage study[10] and, albeit that our numbers were small, there was no hint of an association in our study.

It has been suggested that an association between MS and subsequent breast cancer, found in some small case series, may result from immunosuppressive treatment for MS.[13, 15] Using data from European MS and cancer registries, Lebrun *et al.* examined the cancer and pharmacological therapy profiles in 7418 MS patients and found a significant elevation in cancer risk (particularly for breast cancer) in patients taking immunosuppressive drugs to treat their MS.[15] The authors commented on the carcinogenic potential of azathioprine and cyclophosphamide in MS and also suggested that the use of NSAIDs in some patients may also have an effect on the cancer profiles by lowering the risk of many cancers, including breast cancer. Our data showed no significant increase in the incidence of breast cancer either after MS or before it. However, the risk ratio for breast cancer after MS (1.20, 95 % CI 0.9-1.6, p=0.12), while

non-significant, nevertheless agrees closely with the value provided by the Danish record linkage study (standardized incidence ratio 1.21, 95 % CI 1.05-1.39).[10] Moreover, the risk ratio for breast cancer before MS does not show this upward trend (RR 0.8, 95 % CI 0.5-1.2), also in accordance with a mechanism involving drugs for MS increasing the rates of breast cancer. No data were collected in our study regarding the use of immunomodulatory or immunosuppressive drugs, and many of them were used only in a limited capacity in the timescale of our study, so we are unable to comment further on the potential role of these drugs in this context.,Nevertheless, vigilance must be maintained, not least with the more widespread use of monoclonal antibody therapies, one of which (natalizumab) has been the subject of anecdotal reports of association with melanoma.[36] Associations between two diseases, where one is a consequence of therapy for the other, will only be found in populations and at times where and when the therapy is used, and therefore ongoing study of these associations and the roles of new disease-modifying therapies is required.

Parkinson's Disease

Our data showed a low incidence of cancer in PD. Rate ratios were low for several smoking-related cancers such as lung, bladder and oesophageal cancer, and also for some cancers that are not strongly smoking-related, such as those of the colon and rectum.

There is good evidence that colorectal cancer is associated with diet - for example, it is elevated in association with high protein and low fibre diet - and it is possible that people with PD tend to have had a 'healthy lifestyle' in respect not only of smoking but also other factors. A large Danish record-linkage cohort study[37] reported a borderline low

standardised incidence ratio for colon cancer (RR 0.84; 95% CI 0.7-1.0) and showed low cancer risks at a number of cancer sites that are not smoking-related.

Our results for smoking-related cancers accord with a large Danish record-linkage study and an American cohort study.[37, 38] It is conceivable that there is a higher-than-average level of smoking by people in our reference cohort (as stated above, we do not have smoking histories to judge); and, in theory, this could account for low levels of cancer in our neurological cohorts. This seems an unlikely explanation for the low levels of cancer in PD, because the finding is specific for PD and not found in the MND or MS cohorts. A prevailing theory is that tobacco smoke, though it promotes some cancers, may also possess components that diminish the neurotoxicity involved in triggering PD.[37] Prospective studies have demonstrated a significantly reduced incidence of PD among current and past smokers compared to those who have never smoked, and a dose-response relationship between PD incidence and time since quitting smoking.[39] Twin studies have also shown that the risk of PD in both monozygotic and dizygotic twins is inversely associated in a dose-dependent fashion with smoking.[40] Nicotine seems the likely candidate to be neuroprotectant, since it stimulates dopaminergic release, and also protects against neuronal insults in experimental models.[41] Genetic factors have also been hypothesized to play a role in the reduction in cancer incidence in PD patients, with mutations in *parkin* and other genes implicated in the tumourigenesis of several cancers.[16]

Previously reported evidence for an increased incidence of breast cancer and strong evidence for an increased incidence of malignant melanoma in PD were not reproduced in this study, though the small number of expected cases of melanoma herein prevents strong conclusions.[16, 37, 38] The increased incidence of breast cancer has been variously attributed to detection bias (though this would not explain reduced levels of most other cancers), elevated nocturnal prolactin in PD patients, and increased oestrogen levels.[16] The use of L-dopa to treat PD has been implicated as the agent linking PD with malignant melanoma since it is a substrate for the enzyme tyrosine hydroxylase which ultimately converts it to melanin and is overexpressed in melanoma tumour cells.[16] Epidemiological evidence for this mechanism is lacking however.[42]

Conclusions

Record-linkage datasets, based on routinely collected administrative data, provide useful tools for scanning for disease associations. Their findings should generally be regarded as suggestive rather than definitive. Unlike case-control and cohort studies based on personal interviews with individual patients, routine data lack scope for identifying information about lifestyle, treatment, and other potential causes and confounders. However, studies based on personal interviews, to ascertain the co-occurrence of two diseases both of which are uncommon, may be prohibitively expensive.

By contrast with most case series, population-based record-linkage datasets can be used to identify 'expected' values for the co-occurrence of any two diseases. Our data showed no significant overall association between MND and cancer, or between MS and cancer.

The apparent association of malignant brain cancers with both MND and MS is likely to be explained by misdiagnosis in the early stages of illness. Our data add further weight to the evidence that, in PD patients, there is a significantly low risk of cancers including some cancers that are unrelated to smoking as well as those that are smoking-related.

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Appendix: Further Methods

Data collection covered part of one health district from 1963 (population 350 000), two districts from 1966 (population 850 000), six districts from 1975 (population 1.9 million) and all eight districts of the region from 1987 to March 31 1999 (population 2.5 million). With the agreement of the Region's Data Protection Steering Group, the data for each individual were linked together routinely, as records accrued, as part of the region's health information system. The data are now anonymised and archived.

In analyses where we studied MND or the other neurological conditions first (the 'exposure cohort') and then each cancer (the 'outcome'), we excluded individuals for whom the cancer was recorded before, or at the first admission for, MND or reference condition. Exclusion of 'simultaneous' cases avoided the potential bias of identifying people for the MND cohort (or reference cohort) simply because they had an admission for cancer. We then repeated the analysis for the next cancer, until we had analysed the data for every cancer in turn. We then analysed each cancer in turn after MS; and then each in turn after PD.

When we studied MND after cancer, we reversed the method as follows. Each individual 'exposure' cohort was now a cohort of people with each individual cancer; and we 'followed up' the individuals in each individual cancer cohort, and in the corresponding reference cohort, for the subsequent occurrence of MND. Follow-up was censored, on the same principles as previously described (see Method), by the date of subsequent occurrence of MND (if it occurred), death or the end of the study period. In studying MND after cancer, we excluded individuals for whom MND was recorded in the same admission as, or in an admission before, the cancer. We then repeated the

analysis for each successive cancer in turn; and repeated the analysis for each successive cancer followed by MS and then for each successive cancer followed by PD. The diagnoses of MND, the reference conditions, and each cancer were accepted as those coded on the hospital record abstract. Privacy regulations preclude access to the full records to study the criteria on which the diagnoses were based.

The flow chart and equations used for calculating the rate ratios and statistical inferences based on Breslow and Day²² are as follows:

- (1) calculate the rate ratio using equation 3.8
- (2) calculate the binomial parameters π_L and π_U using equation 3.9
- (3) substitute π_L and π_U into equation 3.6 to calculate the CI's for the rate ratio from (1)
- (4) use equation 3.7 to calculate chi-squared statistic and the appropriate SAS function (probchi(...)) to calculate the p-value.

We grouped the conditions in the reference cohorts into four main groups. We show the numbers of cases in each group:

Gastro-inguinal hernia group (n=186 879): inguinal hernia (n=79 339),
haemorrhoids (n=29 899), appendicectomy (n=77 641)

Lumps & bumps group (n=52 451): bunions (n=4617), sebaceous cyst (n=20 283),
nasal polyp (n=27 551)

Trauma & orthopaedic group (n=213 316): knee internal-derangement (n=26 394), dislocations, sprains & strains (n=23 066), superficial injury & contusion (n=29 965), fractures (n=98 046), hip replacement (n=26 495), knee replacement (n=9 350)

'Other' group (n=298 854): upper respiratory tract infections (n=79 641), , otitis media (n=68 573), diseases of nails (n=14 241), disorders of teeth (n=74 968), squint (n=18 040), varicose veins (n=43 391).