Is the Risk of Motor Neuron Disease Increased or Decreased after Cancer? An Australian Case-Control Study

Alex Stoyanov, Roger Pamphlett*

The Stacey Motor Neuron Disease Laboratory, Department of Pathology, Sydney Medical School, The University of Sydney, Sydney, Australia

Abstract
Cancer appears to be inversely associated with both Alzheimer’s and Parkinson’s disease. The relationship between cancer and sporadic motor neuron disease (SMND), however, remains uncertain. Most previous cancer-SMND studies have been undertaken in northern hemisphere populations. We therefore undertook a case-control study to see if a link between cancer and SMND exists in an Australian population. A questionnaire was used to compare past cancer diagnoses in 739 SMND patients and 622 controls, recruited across Australia. Odds ratios with 95% confidence intervals were calculated to look for associations between cancer and SMND. A history of cancer was not associated either positively or negatively with a risk of subsequent SMND. This result remained when age, gender, smoking status, and the four SMND diagnostic subgroups were taken into account. No association was observed between SMND and specific tumours, including melanoma, a common malignancy in Australia. In conclusion, this Australian case-control study does not support an association between a past history of cancer and the development of SMND. This suggests that some pathogenetic mechanisms, such as apoptosis, are less relevant in SMND than in other neurodegenerative diseases where negative associations with cancer have been found.

Introduction
Uncontrolled cellular proliferation is responsible for cancer [1], in contrast to neurodegeneration, which appears to occur due to premature cell death [2]. The opposing mechanisms between these disease groups have led to the suggestion that an inverse association exists between them, with the occurrence of one conferring a decreased incidence of the other [3,4]. Several large epidemiological studies have demonstrated that both Alzheimer’s disease [5–8] and Parkinson’s disease [9–12] have negative associations with cancer. On the other hand, some individual tumours may confer an increased risk of Parkinson’s disease [13,14]. Mechanisms proposed to explain these findings include common pathways of cell cycle protein dysregulation [15,16], mitochondrial dysfunction [17], and aberrant oxygen sensing [18]. Further exploration of the relationship between neurodegenerative disease and cancer could provide information on their respective causes and assist in the development of new therapies.

Motor neuron disease (MND) is a neurodegenerative disorder that causes progressive muscle weakness, with an average survival of 3–5 years [19]. Early case studies reported a positive association between cancer and MND, in particular breast cancer, but these were based on small patient numbers [20–24]. More recently, five large epidemiological studies found no significant association between cancer and MND in northern hemisphere populations [25–29]. However, they did suggest the possibility of an association between two specific tumours and MND, i.e., an increased incidence of MND after melanoma [25,27] and a decreased incidence after prostate cancer [26,27]. Some limitations of these studies included the use of non-population controls [26] and the use of mortality rather than incidence data to diagnose MND [25,27]. Two studies used hospital and government registries to identify MND cases [28,29], and therefore could not include potentially confounding factors such as smoking.

The present study aimed to see if the associations between MND and cancer found in northern hemisphere countries could be replicated in a southern hemisphere population. This strategy has been used before in other epidemiological studies of MND, and have yielded different results to northern hemisphere studies, for example, in relation to smoking as a risk factor for MND [30]. Furthermore, Australia has the highest rate of melanoma in the world [31], and is well placed to determine whether the previous reports of an increased risk of MND after melanoma can be replicated. A questionnaire-based case-control study of previous cancer in an Australian MND population was therefore undertaken. The case-control design had the advantage of enabling potentially-confounding variables such as smoking to be taken into account.
Methods

Ethics statement
All participants gave written informed consent for the use of their clinical and environmental data. The collection of data was approved by the Human Research Ethics Committee of the Sydney South West Area Health Service.

Study participants
Participants were selected from eligible individuals who submitted self-completed questionnaires to the Australian Motor Neuron Disease DNA Bank, centred at the University of Sydney. The DNA Bank collected clinical, demographic and environmental data from patients with sporadic MND (SMND) and controls (individuals without SMND), recruited via MND Associations in each state of Australia. The duration of data collection was between 2000 and 2011. Inclusion criteria for this study included being a white Australian resident over the age of 26 years.

Cases were those individuals diagnosed with SMND for whom clinical notes and special investigations were available from treating neurologists. Patients with SMND were classified as having SALS if they fulfilled the probable or definite revised El Escorial criteria for ALS (with both upper and lower motor neuron signs) [32]. Patients with a progressive lower motor neuron disorder with no upper motor neuron signs were classified as having sporadic progressive muscular atrophy (SPMA); those with a progressive upper motor neuron disorder without lower motor neuron signs were classified as having sporadic primary lateral sclerosis (SPLS); and those who had a progressive upper and lower motor neuron disorder involving only the bulbar muscles were classified as having sporadic progressive bulbar palsy (SPBP). It was assumed a diagnosis of cancer was a significant health problem and therefore a diagnosis of cancer was based on individuals’ responses to the questions asking “List any significant past medical illness or health problems” and “List any previous injuries and/or surgeries”. It was assumed a diagnosis of cancer was a significant enough event to influence the likelihood of being included in the study of participants for almost full reporting. Keywords used to identify malignancies were “cancer”, “cancerous tumour”, “malignant tumour”, “malignancy” or specific individual malignancies such as “melanoma”. In addition, reporting a surgery or procedure that would be undertaken exclusively for a particular cancer was included as a cancer item (e.g., patients having undergone a radical prostatectomy were assumed to have had prostate cancer). No benign tumours were classified as cancers. For all cancers identified, the following details were noted: (1) year of diagnosis; (2) tumour type (e.g., carcinoma or sarcoma); and (3) the organ affected.

Identification of cancers
Identification of cancer was based on individuals’ responses to the questions asking “List any significant past medical illness or health problems” and “List any previous injuries and/or surgeries”. It was assumed a diagnosis of cancer was a significant enough event in the life of participants for almost full reporting. Keywords used to identify malignancies were “cancer”, “cancerous tumour”, “malignant tumour”, “malignancy” or specific individual malignancies such as “melanoma”. In addition, reporting a surgery or procedure that would be undertaken exclusively for a particular cancer was included as a cancer item (e.g., patients having undergone a radical prostatectomy were assumed to have had prostate cancer). No benign tumours were classified as cancers. For all cancers identified, the following details were noted: (1) year of diagnosis; (2) tumour type (e.g., carcinoma or sarcoma); and (3) the organ affected.

Diligence in answering the questionnaire
The presumably non-relevant questions “Have you ever had a pet?” and “If yes, list the types of pets you have had” were included to compare the diligence of the SMND and control groups in answering the questionnaire.

Statistical analysis
Data were analysed using SPSS v20. Chi-square and Fisher’s exact tests from contingency tables were used to determine odd ratios (ORs) with 95% confidence intervals (CIs) for developing SMND, in those with and without cancer. Unconditional logistic regression analyses were used to correct for confounding of covariates.

Unconditional logistic regression gives inaccurate estimates if a covariate has a strong association with both the dependent and independent variable [33]. Multiple regression analyses showed significant collinearity between age and both SMND and cancer incidence, so age was not corrected as a covariate in the analysis. Due to a statistically significant difference in average age between SMND and control females initially, a nested cohort was created in which female controls were randomly matched to a female SMND patient within a 5-year age range at a 1:1 ratio. This resulted in almost identical mean ages between the two cohorts for both males and females (Table 1), and allowed age to be excluded from the logistic regression analysis.

The potential covariates contributing to the risk of cancer were considered to be gender and smoking history. Subgroup analyses were undertaken in: (1) 10-year age groups from 41 to 90 years (this excluded 68 participants aged below 40 years and two aged over 90 years); (2) smokers and non-smokers; (3) different types of tumours; and (4) the four SMND clinical subgroups. Within the smoker and non-smoker subgroups, smoking-related cancers (of the oral cavity, throat, oesophagus, stomach, pancreas, lung, cervix, bladder, kidney and colon) and non-smoking-related cancers [34] were considered separately. Where numbers were insufficient for logistic regression (<5 individuals per cell), contingency tables were used to calculate ORs, 95% CIs and Fisher’s exact p-values [35].

Results

Cases and controls
739 (488 male, 251 female) patients made up the SMND group (Table 1). Of these, 78% had SALS, 14% had SPMA, 5% had SPLS and 3% had SPBP. 622 (371 male, 251 female) individuals comprised the control group, of these, 54% were partners of SMND patients, 28% were community volunteers, and 18% were friends of SMND patients.

The SMND group had a higher proportion of males (66%) compared to the controls (60%) but both had almost identical mean ages (Table 1). The proportion of SMND males and females who smoked, and the average pack years smoked, was similar to controls (Table 1).

Cancer risk in SMND patients and controls

Males and females combined. Sixty-four (8.7%) of the SMND patients had a history of cancer, compared to 59 (9.5%) of the controls. A history of cancer did not therefore significantly alter an individual’s risk of developing SMND (Table 2).

Males. 9.5% of SMND and 10.0% of control men had a history of cancer. The proportion of men with a previous cancer did not differ significantly between the groups (Table 2).

Females. 7.2% of SMND and 8.8% of control females had a history of cancer. The proportion of females with a history of cancer did not differ significantly between the groups (Table 2).

Cancer and SMND within age groups
No significant association was identified between a history of cancer and SMND in any 10-year age subgroups from 41–90 years (Table 3). The prevalence of both cancer and SMND increased with age ($\chi^2$ trend, $p = 0.037$). However, the prevalence of cancer between the two groups did not change with age ($\chi^2$ trend, $p = 0.19$).

Cancer and SMND in smokers
728 participants had a history of smoking, with an average of 11.7 pack years (SD 19.2 pack years) per participant, while the
remaining 633 had no history of smoking (Table 4). Of the smokers, 54% of the SMND patients smoked compared to 53% of controls. Unexpectedly, cancer prevalence was similar in smokers and non-smokers: 8.9% of smokers had a history of cancer compared to 9.2% of non-smokers. A history of cancer did not alter future SMND risk in either smokers or non-smokers (Table 4). When cancers were divided into smoking and non-smoking-related cancers, no association between SMND and either cancer group was found (Table 4).

SMND and tumour subgroups
The most common malignancies in the cohort were melanoma, prostate cancer, non-melanoma skin cancer, and colorectal cancer (Table 5). Several of the tumours (including lung, soft tissue, testicular and uterine tumours) had no cases in one of the groups, hence an odds ratio was unable to be calculated. Since this was a case-control study, cancers with low survival rates were almost non-existent so analysis of aggressive, short-survival tumours was not possible. Only one case of lung cancer was identified, while no brain, pancreatic or other high grade tumours were present.

Individuals with a history of cancer of unknown primary and males with prostate cancer tended to have a lower risk of SMND (Table 5), but these did not reach statistical significance. The rates of melanoma did not differ significantly between SMND and control groups (Table 5). No association between any other tumour subgroups and SMND was apparent.

Cancer in SMND clinical subgroups
8.8% of individuals within the SALS subgroup had a history of cancer compared to 7.8% in the SPMA, 21.0% in the SPBP, and 2.7% in the SPLS subgroups (Table 6). Despite the apparently increased history of cancer in the SPBP group, contingency table analysis showed no difference in cancer frequency between the four groups (p = 0.15). When individual SMND subgroups were compared to total numbers of controls, a history of cancer did not significantly alter SALS or SPMA risk (Table 6). Individuals with

Table 1. Gender, age and smoking status in SMND and control individuals.

|                        | SMND N (%) (SD) | Control N (%) (SD) |
|------------------------|-----------------|-------------------|
| **Males**              |                 |                   |
| Total                  | 488 (61)        | 371 (60)          |
| Age range (years)      | 30–90           | 27–94             |
| Mean age (years)       | 62.6 (11.2)     | 62.4 (12.6)       |
| Number of smokers      | 298 (61)        | 222 (60)          |
| Mean pack years smoked | 14.4 (20.9)     | 15.6 (22.6)       |
| **Females**            |                 |                   |
| Total                  | 251 (41)        | 251 (42)          |
| Age range (years)      | 27–82           | 35–86             |
| Mean age (years)       | 62.8 (9.8)      | 62.6 (9.9)        |
| Number of smokers      | 103 (41)        | 105 (42)          |
| Mean pack years smoked | 7.7 (14.9)      | 7.0 (14.2)        |

N: number, SD: standard deviation.

doi:10.1371/journal.pone.0103572.t001

Table 2. Comparison of cancer in SMND patients and controls.

|                        | SMND N (%) | Control N (%) | OR (95% CI) | p-value |
|------------------------|------------|---------------|-------------|---------|
| **Males and females**  |            |               |             |         |
| Total                  | 739        | 622           |             |         |
| Cancer                 | 64 (8.7)   | 59 (9.5)      | 0.90 (0.62–1.32) | 0.58 |
| Non-cancer             | 675        | 563           |             |         |
| **Males**              |            |               |             |         |
| Total                  | 488        | 371           |             |         |
| Cancer                 | 46 (9.5)   | 37 (10.0)     | 0.96 (0.61–1.52) | 0.86 |
| Non-cancer             | 442        | 334           |             |         |
| **Females**            |            |               |             |         |
| Total                  | 251        | 251           |             |         |
| Cancer                 | 18 (7.2)   | 22 (8.8)      | 0.79 (0.42–1.53) | 0.49 |
| Non-cancer             | 233        | 229           |             |         |

Odds ratios (ORs) adjusted for gender and smoking.
CI: confidence interval, N: number.

doi:10.1371/journal.pone.0103572.t002
cancer tended to be at increased risk of SPBP and decreased risk of SPLS, but these results did not reach statistical significance (Table 6).

Diligence in answering the questionnaire

Of the controls, 99.7% answered the question on having pets, and 83% listed the pets they had. In comparison, 99.6% of SMND patients answered the question on having pets, and 82% listed the types they had (both insignificant differences).

Discussion

This Australian case-control study found no association between a history of cancer and the later onset of SMND. A history of cancer did not increase or decrease the incidence of any SMND subgroups, including the most common subgroup, SALS. No cancer-SMND associations were present when age groups, gender, and smoker status were taken into account. In addition, no association with SMND was noted for either smoking or non-smoking related cancers. No individual tumours, including melanoma and prostate cancer, altered the risk of SMND.

The present study has several advantages over many of the previous studies of cancer and MND. This is largest cancer-MND case-control study to date, and the use of a questionnaire allowed the collection of lifestyle data including smoking history. No reliance on registry or post mortem data for diagnosis was needed, since all SMND patients had the diagnosis made by a neurologist with supporting clinical notes and investigations. This ensured

| Table 3. Comparison of cancer in SMND patients and controls in 10-year age groups. |
|---|
| Age groups | SMND N (%) | Control N (%) | OR (95% CI) | p-value |
| 41–50 y | | | | |
| Total | 77 | 80 | | |
| Cancer | 4 (5.2) | 5 (6.3) | 0.80 (0.20–3.17) | 0.75 |
| 51–60 y | | | | |
| Total | 200 | 142 | | |
| Cancer | 7 (3.5) | 7 (4.9) | 0.63 (0.22–1.85) | 0.40 |
| 61–70 y | | | | |
| Total | 268 | 221 | | |
| Cancer | 26 (9.7) | 19 (8.6) | 1.11 (0.60–2.07) | 0.74 |
| 71–80 y | | | | |
| Total | 146 | 138 | | |
| Cancer | 20 (13.7) | 24 (17.4) | 0.79 (0.41–1.54) | 0.50 |
| 81–90 y | | | | |
| Total | 26 | 20 | | |
| Cancer | 7 (26.9) | 4 (20.0) | 1.45 (0.36–5.97) | 0.59 |

Odds ratios (ORs) adjusted for gender and smoking.

| Table 4. Comparison of smoking and non-smoking-related cancers in SMND patients and controls. |
|---|
| SMND N (%) | Control N (%) | OR (95% CI) | p-value |
| Smokers | | | | |
| Total | 401 | 327 | | |
| Any cancer | 33 (8.2) | 32 (9.8) | 0.85 (0.50–1.42) | 0.53 |
| Smoking-related cancer | 10 (2.5) | 8 (2.4) | 1.01 (0.39–2.61) | 0.99 |
| Non-smoking-related cancer | 23 (5.7) | 24 (7.3) | 0.80 (0.44–1.46) | 0.52 |
| No cancer | 368 | 295 | | |
| Non-smokers | | | | |
| Total | 338 | 295 | | |
| Any cancer | 31 (9.2) | 27 (9.2) | 0.98 (0.57–1.69) | 0.94 |
| Smoking-related cancer | 8 (2.4) | 7 (2.4) | 0.96 (0.35–2.71) | 0.95 |
| Non-smoking-related cancer | 23 (6.8) | 20 (6.8) | 0.99 (0.53–1.84) | 0.97 |
| No cancer | 307 | 268 | | |

Odds ratios (ORs) adjusted for gender and smoking.

doi:10.1371/journal.pone.0103572.t003
doi:10.1371/journal.pone.0103572.t004
SMND diagnosis was accurate and that clinical information was available to identify SMND subgroups. Finally, the use of partner and friend controls, with similar social and environmental lifestyles, reduced the chance of type I statistical errors [36]. This cancer-SMND study is the first to control for smoking status. Smoking is a well-established risk factor for a large number of cancers [34] and may also increase the risk of developing SALS [37,38], though not all studies have found this [30]. Hence, the relationship between cancer and SMND may have been confounded by smoking status in previous studies.

This is the only overall cancer-SMND study to be conducted in the southern hemisphere; one joint USA-Australian study has looked specifically at melanoma and MND [39]. The findings of our study are consistent with most previous epidemiological studies of cancer and SMND in northern hemisphere populations. Two studies based on the SEER program of the US National Cancer Institute and death certificates found no association between cancer incidence and SALS mortality [25,29]. Because of their use of mortality data, these studies were only able to identify SALS cases with 70–90% accuracy [40]. Other studies investigating SALS incidence based on registries rather than mortality have also shown no differences in the incidence of cancer between SALS patients and controls [26,28,29]. The null association across genders, age groups and between smoking and non-smoking-related cancers in a Swedish case-control study [28] is consistent with our findings.

Previous studies indicating lower cancer rates in Alzheimer’s and Parkinson’s diseases suggested that these neurodegenerative disorders are pro-apoptotic states, while cancer is anti-apoptotic in nature. The role of apoptosis in MND is unclear, however, and the rapid morphological changes of apoptosis make it difficult to detect in post mortem tissue of a disease that progresses over years [41]. Alterations in the expression of regulatory apoptotic molecules including Bax, Bak, capsases and p53 have been observed in MND animal models [42,43] and human CNS samples have suggested that apoptosis is involved in MND [44].

| Table 5. Comparison of cancer subgroups in SMND patients and controls. |
| SMND / Control | Cancer N (%) | OR (95% CI) | p-value |
|----------------|--------------|-------------|---------|
| Total          | 739          | 622         | 0.90 (0.62–1.32) | 0.58 |
| Cancer         | 64           | 59          | 0.90 (0.62–1.32) | 0.58 |

**Tumour subgroup**

| SMND / Control | Cancer N (%) | OR (95% CI) | p-value |
|----------------|--------------|-------------|---------|
| Bladder        | 2            | 2           | 0.84 (0.12–5.99) | 1.00 |
| Breast         | 7            | 5           | 1.40 (0.44–4.50) | 0.57 |
| Colorectal     | 9            | 7           | 1.05 (0.39–2.83) | 0.93 |
| GIT other      | 1            | 1           | 0.84 (0.06–13.48) | 1.00 |
| Head and neck  | 3            | 4           | 0.63 (0.14–2.83) | 0.71 |
| Haematopoietic | 4            | 2           | 1.69 (0.31–9.24) | 0.69 |
| Renal          | 3            | 2           | 1.26 (0.21–7.59) | 1.00 |
| Lung           | 1            | 0           | NA          | 1.00 |
| Prostate       | 8            | 13          | 0.47 (0.19–1.13) | 0.09 |
| Melanoma       | 12           | 10          | 0.97 (0.42–2.30) | 0.97 |
| N-M skin cancer| 11           | 6           | 1.53 (0.57–4.21) | 0.40 |
| Soft tissue    | 0            | 1           | NA          | 0.46 |
| Testes         | 2            | 0           | NA          | 0.51 |
| CUP            | 1            | 3           | 0.28 (0.03–2.70) | 0.34 |
| Uterine        | 0            | 3           | NA          | 0.25 |

Odds ratios (ORs) adjusted for age, gender and smoking with logistic regression where case numbers were ≥5, and with contingency tables when case numbers were < 5. Where one cell contained no values, no ORs were calculated but p-values were calculated with Fischer’s exact test.

| Table 6. Cancer in SMND clinical subgroups compared to controls. |
| SMND subgroup | Total N | Cancer N (%) | OR (95% CI) | p-value |
|---------------|---------|--------------|-------------|---------|
| ALS           | 580     | 51 (8.8)     | 0.91 (0.62–1.36) | 0.66 |
| PMA           | 103     | 8 (7.8)      | 0.78 (0.36–1.70) | 0.53 |
| PBP           | 19      | 4 (21.0)     | 2.55 (0.82–7.92) | 0.11 |
| PLS           | 37      | 1 (2.7)      | 0.27 (0.04–1.97) | 0.24 |

Odds ratios (ORs) adjusted for gender and smoking using logistic regression where case numbers were ≥5. Where cases were <5 in number, ORs were calculated using contingency tables.

PLOS ONE | www.plosone.org 5 July 2014 | Volume 9 | Issue 7 | e103572
However, the null relationship between cancer and MND presented here supports the opposing concept that apoptosis is not a major pathological mechanism of motor neuron degeneration in MND [43–47].

Of interest is the reported association between MND and specific tumours, particularly melanoma [29,39]. We found a history of melanoma was not associated with SMND in an Australian population. Our findings are consistent with register studies from Sweden [28] and the USA [29] that found no melanoma-SMND association. In contrast, a joint USA-Australian study of post-melanoma survival found increased mortality due to MND and Parkinson’s disease [39], and survivors of melanoma were also found to have an increased risk of MND in another USA population [27]. However, these two studies could not define the temporal relationship between MND and melanoma diagnosis. This raises the possibility that the positive associations may have been due to a short-term increase in medical surveillance immediately after melanoma diagnosis. While a detailed temporal analysis was not possible in our study, all but one of our SMND diagnoses were made greater than five years after melanoma diagnosis, so here any association would be long term. An association between neurodegenerative disorders and melanoma does, however, remain plausible. Rihuzole, a drug used in the treatment of ALS, has been proposed as an anti-melanoma agent [48], suggesting a biochemical link between the two diseases. An increased risk of Parkinson’s disease after melanoma diagnosis has been described [49,50] and is thought to occur due to increased alpha-synuclein expression in melanocytic lesions [51–53] that may interact with cell cycle regulators [54]. Alpha-synuclein has been detected in MND animal models [55] and human spinal cords [56], making a similar mechanism in SMND possible. The relationship between MND and melanoma therefore requires greater exploration, with larger population sizes and accurate analysis of temporal relationships.

Previous studies have reported a negative association between prostate cancer and MND [26,27], whereas our study found only a trend towards a negative association. Assessments of this particular association are difficult due to wide variations in methods of prostate cancer detection, the range of malignancy in prostate neoplasms, and the rising detection of indolent prostate cancers via prostate specific antigen measurement, which would create changing detection rates of prostate cancer over follow-up periods [57].

Limitations of the present study are: (1) The small numbers in some subgroups, particularly of individual tumours. (2) The risk of recall bias with any questionnaire-based approach, though both SMND and control individuals appeared to answer the questionnaire with similar diligence. (3) Some participants may not have considered certain malignancies (such as non-melanoma skin cancers, which are common in Australia) to be clinically significant enough to list in their past medical history. (4) A number of respondents did not enter the year their cancer was diagnosed, which made a temporal analysis between cancer diagnosis and MND unfeasible.

In conclusion, this case-control study has shown no significant association, either positive or negative, between a history of cancer and the occurrence of SMND in an Australian population. This finding remained when adjusted for age, gender and smoking status. In contrast to previous studies, no specific individual malignancies appeared to be associated with a diagnosis of SMND, including melanoma and prostate cancer. The present findings support increasing evidence that cancer is not inversely associated with SMND. This suggests that pathogenetic mechanisms that can be expected to protect against cancer, in particular apoptosis, may not be primary pathological mechanisms in SMND. Our findings also imply that the pathogenesis of cell damage in SMND is likely to be different from that of Alzheimer’s and Parkinson’s diseases, where an inverse relationship between cancer and disease onset appears to be likely.

Acknowledgments

We thank participants for donating questionnaire data, neurologists for providing clinical details on their patients, and Motor Neuron Disease Associations in each Australian state who have aided patient recruitment for this research.

Author Contributions

Conceived and designed the experiments: RP AS. Performed the experiments: AS RP. Analyzed the data: AS. Contributed reagents/materials/analysis tools: RP. Contributed to the writing of the manuscript: AS RP.

References

1. Bertram JS (2000) The molecular biology of cancer. Mol Aspects Med 21: 167–223.
2. Driver JA (2012) Understanding the link between cancer and neurodegeneration. J Geriatr Oncol 3: 56-67.
3. Plun-Faveau H, Lewis PA, Hardy J, Martins LM, Wood NW (2010) Cancer and neurodegeneration: between the devil and the deep blue sea. PLoS Genet 6: e1001257.
4. Tabares-Seisdedos R, Dumont N, Baudot A, Valderas JM, Climent J, et al. (2011) No paradoxes, no progress: inverse cancer comorbidity in people with other complex diseases. Lancet Oncol 12: 604–609.
5. Driver JA, Reiser A, Au R, Kreger BE, Splansky GL, et al. (2012) Inverse association between cancer and Alzheimer’s disease: results from the Framingham Heart Study. BMJ 344: e1442.
6. Gangali M (2012) A reduced risk of Alzheimer’s disease in those who survive cancer. BMJ 344: e1662.
7. Roe CM, Fitzpatrick AL, Xiang C, Sieh W, Kuller L, et al. (2010) Cancer linked to Alzheimer disease but not vascular dementia. Neurology 74: 106-112.
8. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, Valderas JM, Gomez-Beneyto M, et al. (2014) Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 577,013 participants of 50 observational studies. Psychother Psychosom 83: 89–105.
9. Bajaj A, Driver JA, Schemhammer ES (2010) Parkinson’s disease and cancer risk: a systematic review and meta-analysis. Cancer Causes Control 21: 697-707.
10. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G (2007) Prospective study of prostate cancer and MND [26,27], whereas our study found only a
22. Forsyth PA, Dalman J, Grau F, Cook V, Rosenblum MK, et al. (1997) Motor neuron syndromes in cancer patients. Ann Neurol 41: 722–730.
23. Barrow KD, Rodicik LD (1982) Cancer and disorders of motor neurons. Adv Neurol 36: 267–272.
24. Vernieri D, Ceccolo MA, Jr. (1976) Amyotrophic lateral sclerosis in cancer. J Miss State Med Assoc 19: 201–204.
25. Freedman DM, Travis LB, Gridley G, Kunel RW (2005) Amyotrophic lateral sclerosis mortality in 1.9 million US cancer survivors. Neuroepidemiology 25: 176–180.
26. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ (2010) Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson’s disease: record linkage studies. J Neurol Neurosurg Psychiatry 81: 215–221.
27. Freedman DM, Curtis RE, Daugherty SE, Goedert JJ, Kunel RW, et al. (2013) The association between cancer and amyotrophic lateral sclerosis. Cancer Causes Control 24: 53–60.
28. Fang F, Al-Chalabi A, Romsne LO, Turner MR, Wiedfeldt K, et al. (2013) Amyotrophic lateral sclerosis and cancer: a register-based study in Sweden. Amyotroph Lateral Scler Frontotemporal Degener 14: 362–368.
29. Freedman DM, Wuj J, Daugherty SE, Kunel RW, Enewold LR, et al. (2014) The risk of amyotrophic lateral sclerosis after cancer in U.S. elderly adults: A population-based prospective study. Int J Cancer Epub date 2014/02/20 DOI 10.1002/ijc.28795.
30. Pamphlett R, Cochran Ward E. (2012) Smoking is not a risk factor for sporadic amyotrophic lateral sclerosis in an Australian population. Neuroepidemiology 38: 106–111.
31. Little EG, Eide MJ (2012) Update on the current state of melanoma incidence. Dermatol Clin 30: 355–361.
32. Brooks BR, Miller RG, Swash M, Munat T. (2000) El Escorial revised: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disorders 1: 293–299.
33. Shen J, Gao S (2008) A solution to separation and multicollinearity in multiple logistic regression. J Data Sci 6: 515–531.
34. Hecht S (2006) Cigarette smoking: cancer risks, carcinogens, and mechanisms. Langenbecks Arch Surg 391: 603–613.
35. Ruxton G, Neuhausser M (2010) Good practice in testing for an association in contingency tables. Behav Ecol Sociobiol 64: 707–715.
36. Rodman KJ (2010) Curbing type I and type II errors. Eur J Epidemiol 25: 223–224.
37. Armon C (2009) Smoking may be considered an established risk factor for sporadic ALS. Neurology 73: 1693–1696.
38. Wang H, O’Reilly EJ, Weiskopf MG, Logroscino G, McCullough ML, et al. (2011) Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. Arch Neurol 68: 207–213.
39. Baade PD, Fritschi L, Freedman DM (2007) Mortality due to amyotrophic lateral sclerosis and Parkinson’s disease among melanoma patients. Neuroepidemiology 28: 16–20.
40. Marin B, Couratier P, Preux PM, Logroscino G (2011) Can mortality data be used to estimate amyotrophic lateral sclerosis incidence? Neuroepidemiology 36: 29–38.
41. Sathasivam S, Shaw PJ (2005) Apoptosis in amyotrophic lateral sclerosis—what is the evidence? Lancet Neurology 4: 500–509.
42. Reyes NA, Fisher JK, Austgen K, VandenBerg S, Huang EJ, et al. (2010) Blocking the mitochondrial apoptotic pathway preserves motor neuron viability and function in a mouse model of amyotrophic lateral sclerosis. J Clin Invest 120: 3673–3679.
43. Pasinelli P, Belford ME, Lemon N, Baskai JJ, Hyman BT, et al. (2004) Amyotrophic lateral sclerosis-associated SOD1 mutant proteins bind and aggregate with Bcl-2 in spinal cord motor neurons. Neuron 43: 19–30.
44. Martin LJ (2000) p53 is abnormally elevated and active in the CNS of patients with amyotrophic lateral sclerosis. Neurobiol Dis 7: 613–622.
45. He BP, Strong MJ (2000) Motor neuronal death in sporadic amyotrophic lateral sclerosis (ALS) is not apoptotic. A comparative study of ALS and chronic aluminum chloride neurotoxicity in New Zealand white rabbits. Neupathol Appl Neuropathol 26: 150–160.
46. Tomik B, Adamek D, Pierzchalski P, Banares S, Duda A, et al. (2005) Does apoptosis occur in amyotrophic lateral sclerosis? TUNEL experience from human amyotrophic lateral sclerosis (ALS) tissues. Folia Neuropathol 43: 75–80.
47. Gould IW, Buss RR, Vinaint S, Prevette D, Sun W, et al. (2006) Complete dissociation of motor neuron death from motor dysfunction by Bax depletion in a mouse model of ALS. J Neurosci 26: 8774–8786.
48. McDonnell ME, Vera MD, Blasi BE, Pelllier JC, King RC, et al. (2012) Riluzole prodrugs for melanoma and ALS: design, synthesis, and in vitro metabolic profiling. Bioorg Med Chem 20: 5642–5648.
49. Ferreira JJ, Neutel D, Mestre T, Corroel M, Rosa MM, et al. (2010) Skin cancer and Parkinson’s disease. Mov Disord 25: 139–148.
50. Liu R, Gao X, Lu Y, Chen H (2011) Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology 76: 2002–2009.
51. Matsuo Y, Kamitani T (2010) Parkinson’s disease-related protein, alpha-synuclein, in malignant melanoma. PLoS One 5: e10481.
52. Israeli E, Yakanin E, Zainov Y, Haasbroek-Solovich A, Kiss H, et al. (2011) alpha-Synuclein expression selectively affects tumorigenesis in mice modeling Parkinson’s disease. PLoS One 6: e19622.
53. Chorfa A, Betemps D, Morigat E, Lazizzera C, Hogevreken K, et al. (2013) Specific pesticide-dependent increases in alpha-synuclein levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines. Toxocology 133: 289–297.
54. Yacoubian TA, Slone SR, Harrington AJ, Hamamichi S, Schieltz JM, et al. (2013) alpha-Synuclein expression selectively affects tumorigenesis in mice modeling Parkinson’s disease. J Neurosci 33: 176–180.
55. Yang EJ, Choi SM (2013) alpha-Synuclein modification in an ALS animal model. Evid Based Complement Alternat Med 2013: 259381.
56. Pasinelli P, Belford ME, Lemon N, Baskai JJ, Hyman BT, et al. (2004) Amyotrophic lateral sclerosis-associated SOD1 mutant proteins bind and aggregate with Bcl-2 in spinal cord motor neurons. Neuron 43: 19–30.