Cancer co-occurrence patterns in Parkinson's disease and multiple sclerosis – do they mirror immune system imbalances?

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Abstract

Background

To examine the site-specific cancer mortality among deaths registered with Parkinson's disease (PD) and multiple sclerosis (MS). We focused on the patterns related to the most frequent cancers.

Methods

We analyzed Swiss mortality data over a 39-year period (1969-2007), using a statistical approach applicable to unique daabases, i.e. when no linkage with morbidity databases or disease registries is possible. It was based on a case-control design with bootstrapping to derive standardized mortality ratios (SMR). The cases were defined by the cancer-PD or cancer-MS co-registrations, whereas the controls were drawn from the remaining records with cancer deaths (matching criteria: sex, age, language region of Switzerland, subperiods 1969-81, 1982-94, 1995-2007).

Results

For PD we found lower SMRs in lung and liver cancer and higher SMRs in melanoma / skin cancer, and in cancers of breast and prostate. As for MS, the SMR in lung cancer was lower than expected, whereas SMRs in colorectal, breast and bladder cancer were higher.

Conclusions

A common pattern of associations can be observed in PD and MS, with a lower risk of lung cancer and higher risk of breast cancer than expected. Thus, PD and MS resemble other

conditions with similar (schizophrenia) or reversed patterns (rheumatoid arthritis, immunosuppression after organ transplantation).

Keywords: cancer, multiple sclerosis, Parkinson's disease, comorbidity, epidemiology

1. Introduction

There are virtually no neurological or autoimmune diseases without a distinguishing cancer co-occurrence pattern. Therefore, cancer co-occurrence patterns provide promising clues not only to keep track of side and adverse effects of diseases and their therapies but also to achieve a better understanding of their etiopathogenesis. Research on cancer patterns in neurological diseases has revealed a mixture of both plausible and paradoxical findings. The most prominent finding is the association between brain tumors and epilepsy, as epileptic seizures are a common accompanying symptom of brain tumors [1]. A further well-known finding is the low rate of lung cancers in patients with PD [2], which parallels the paradoxically low rate of lung cancer in patients with schizophrenia [3, 4]. Further results have been replicated less consistently due to the impact of different data (incidence, prevalence, mortality) and methodology. Some authors questioned whether "a single definitive study" on cancer and cancer patterns in comorbid diseases would be feasible at all [4].

This study examined the mortality patterns of the most frequent cancers in Parkinson's disease (PD) and multiple sclerosis (MS) using data from the Swiss mortality statistics. Instead of addressing PD and MS in separate studies, a comparative approach promised to facilitate the interpretation of the findings. Furthermore, we extended this framework in the discussion by integrating findings related to cancer patterns in schizophrenia, rheumatoid arthritis and immunosuppression after organ transplantation.

2. Material and methods

2.1. Analysis design

This analysis assesses the co-occurrence of PD / MS and cancer solely on the basis of mortality statistics, i.e., when a linkage of mortality and morbidity data is not feasible [5]. Therefore, this approach pursues the exploitation of a mortality database via a case-control design with bootstrapping, i.e. repeatedly drawn random samples of matched controls, to derive standardized mortality ratios (SMRs). This approach is limited to specifying co-occurrence patterns: it reveals whether specific cancers in PD or MS occur more or less frequently than expected with regard to other cancers, i.e., to the baseline cancer pattern. The approach does not provide information whether the overall risk of cancer in association with PD or MS is increased or decreased.

2.2. Data

The analysis is based on individual records of Swiss mortality statistics over a 39-year period (1969-2007). Legally regulated, formalized death registration has existed in Switzerland since 1876, with deaths certified by a physician. Data from individual records is available in computerized form starting from 1969. Switzerland used the ICD-8 coding system until 1994 and then switched to ICD-10 in 1995. Furthermore, since 1995 the maximum number of registered causes of death has been increased from 3 to 4, thus changing the probabilities for the co-occurrence of diseases.

Before the switch to ICD-10, cancer – together with violent deaths and deaths due to infectious diseases – had priority in being registered as the underlying cause of death [6]. The current analyses were restricted to records with malignant neoplasms as the underlying cause

of death (ICD-8 140-209, ICD-10 C00-C97) with at least one additional or concomitant cause of death (labeled in the following as the "overall cancer sample"). If a neurological disease was listed in these records, it appeared automatically as one of the additional cause of death categories.

2.3. Methods: conceptual issues

In any study on co-occurrence patterns of diseases, adjustments for sex and age are required, and, in the mortality statistics, adjustments for biasing factors such as the regional registration and co-registration practices. Further factors that may interfere are:

- the registration priority of neurological or other chronic diseases;
- the probability of whether a chronic or a neurological disease is known to the physician filling in the death certificate;
- the co-registration practice in specific cancers or by specific subgroups of oncologists: for example, the probability of epilepsy being co-registered is greater in brain cancers than in intestinal cancers.

Moreover, studies which aim at deriving co-occurrence patterns of diseases from a single database need a different approach than studies which can rely on linkage of registries and population databases. For this purpose we developed novel analysis design and applied it first in the analysis of schizophrenia / psychotic disorders mortality [5]. The analysis design is based on a case-control approach and a bootstrapping procedure. To put it briefly: we compared the group of cases (e.g., deaths mutually registered with PD (or MS) and cancer) with a matched sample of controls (e.g., other deaths registered with cancer) randomly drawn from the mortality data base. Bootstrapping, i.e. repeating the matching and the analysis,

served to provide stable estimates. We applied 1000 repetitions. The final parameter of interest was the standardized mortality ratio (SMR) for each cancer in PD and MS, respectively.

2.4. Methods: details

In more detail, the analysis design entails three steps. In the first step we assessed preliminary co-registration patterns and adjusted them for the most obvious confounding factors. The cases are records with a specific neurological disease (MS and PD separately) registered as one of the additional causes of death and cancer registered as the main cause of death. We matched them 1:1 with randomly selected controls (deaths registered with cancer) from the rest of the database, using the following criteria:

- sex
- age (5-year age groups)
- language region (German part vs. French and Italian parts of Switzerland)
- time period (1969-81, 1982-94, 1995-2007)

Other variables such as marital status, religious affiliation or autopsy status were considered irrelevant within the given context and thus were not included in the matching criteria. In sum, the first step of the analysis provided preliminary frequencies and proportions of specific cancers from both the case and control subsets.

In the second step of the analysis, we weighted these frequencies in order to account for the co-registration practice in specific cancers. We suspected biasing effects that derive from inconsistent co-registering of brain diseases depending on oncological sub-speciality. Within this step, we derived weights by comparing the co-registration frequency of neurological and

psychiatric diseases (ICD-8 290-389, ICD-10 F00-G99) within a specific cancer as opposed to all cancers. The former delivered the cases and the latter the controls for this calculation. Both were randomly drawn from the specific cancer subset and the overall cancer subset, respectively, based on the cases profile adapted from the first step of the analysis and the very same matching criteria as described above. As mentioned above, the weights were used to correct the frequencies from the first step of analysis before entering them in the final analysis step.

In the final step, our main parameter of interest was the SMR. It was obtained by comparing the observed mortality with the expected mortality and is defined as a quotient: number of observed deaths / number of expected deaths. The second parameter of interest was the chi-square related to comparisons between sample and population frequencies. The mean and confidence intervals of the 1000 chi-squares after bootstrapping were assessed using univariate statistics. An SMR was considered to be relevant when:

- a) the confidence interval of the related chi-square remained above the chi-square value (1 d.f.) corresponding in PD to $p=.01$ (for trend level: $p=.05$) and in MS to $p=.05$ (for trend level: $p=.10$); the differing p-values were adapted to the different frequencies in PD and MS;
- b) condition a) was fulfilled both in the baseline calculation and after weighting.

In addition, we assumed consistent SMRs both in the baseline calculation and after weighting, i.e., both above or both below 1.

3. Results

Table 1 provides an overview of the frequencies of PD and MS cases and the proportions of cases either registered as main or additional cause of death in the Swiss mortality statistics. During the whole study period from 1969 to 2007, 608,865 cases with malignant neoplasms were registered in the database, with 580,570 (95.4%) cases reporting cancer as the underlying cause of death, and, of these, 398,246 cases (65.4%) reporting an additional cause of death. Switzerland had during this period an average population of 6.85 million inhabitants. Descriptive information about frequencies and mean age at death by cancer is displayed in Table 2. The comparison of age at death of cancers in PD, MS and in the population shows a range of up to 20 years between these three categories.

(Table 1)

(Table 2)

The SMR patterns of cancers in PD and MS are shown in Tables 3 and 4. In PD, the consistent findings relate to a decreased SMR in lung cancer (SMR = 0.52 in baseline calculation and 0.59 after weighting) and liver cancer (trend level, SMR = 0.45 in baseline calculation and 0.73 after weighting). Increased SMRs were found in melanoma / skin cancers (SMR = 2.10 in baseline calculation and 1.41 after weighting), breast cancer (SMR = 1.49 in baseline calculation and 1.32 after weighting) and prostate cancer (SMR = 1.41 in baseline calculation and 1.22 after weighting). In MS, decreased SMRs were found in lung cancer (trend level, SMR = 0.78 in baseline calculation and 0.86 after weighting), whereas three cancers had increased SMRs: intestines / colon (SMR = 1.76 in baseline calculation and

2.31 after weighting), breast (SMR = 1.59 in baseline calculation and 1.76 after weighting) and bladder (SMR = 2.19 in baseline calculation and 2.81 after weighting) cancer.

(Tables 3-4)

4. Discussion

This study examined the co-registration of different cancers in association with PD and MS in the Swiss mortality statistics. We used a recently developed methodological approach to handle this task within a single database [5]. Our results are comparable to findings from studies based on linkage of register data, i.e., incidence and prevalence data. Moreover, the comparative analysis evoked remarkable parallels between PD and MS: decreased SMRs in lung cancer and increased SMRs in breast cancer. These parallels are congruent with patterns found in schizophrenia [5], and they contrast patterns found in rheumatoid arthritis [7] and immunosuppression after organ transplantation [8, 9].

4.1. Specific findings

The most prominent cancer co-occurrence pattern in PD relates to the decreased risk of lung cancer. This has been observed since the 1950s [2], and has been thoroughly debated [10]. Nevertheless, the directional relation is still unclear: lung cancer is less frequent in PD patients, but PD is at the same time less frequent among smokers [10, 11]. With regard to the latter, a twin study examining the effect of pack-years in mono- and dizygotic twins demonstrated that smoking is a dose-dependent protective factor against the development of PD [12]. Additionally, previous studies have shown increased risk of breast cancer [11], melanoma and skin carcinoma in PD patients [11, 13, 14]. Again, contrasting underlying mechanisms have been discussed (i.e., genetics, drugs (levodopa use), other risk factors) [15-18]. Further cancers of interest have been colon cancer (increased risk) [19] and bladder cancer (decreased risk) [11]. In agreement with the PD literature, we found a decreased risk of lung cancer, and an increased risk of breast cancer, melanoma and skin carcinoma. An increased risk of cancer for intestines and colon was found at trend level. In contrast to

previous studies, prostate cancer seemed to be slightly increased and liver cancer decreased (trend level).

Divergences in rates or ratios of co-occurring cancers in MS patients have been reported in almost all relevant studies. An increased risk has been found not only for breast cancer [20-22], but also for cancers of the bladder / urinary organs [23, 24], small intestine cancer [24], and brain cancer [19]. Moreover, a decreased risk of colorectal cancer [25], various cancers of the digestive tract [26] and lung cancer [27] has been reported. Increased risk of nasopharyngeal cancers and Hodgkin lymphoma has also been proposed because of a probable link to Epstein Barr virus (EBV) infections that have been associated with MS [21, 23, 24]. Our study confirmed an increased risk of breast and bladder cancer related to MS. Moreover, a decreased risk of lung cancer also concurs with the literature. However, in contrast to the bulk of previous studies, we found an increased risk of cancers of the colon and intestines in association with MS.

4.2. Common findings: lung and breast cancer

The results from our study suggest a major parallel between PD and MS, namely a decreased risk of lung cancer, which contrasts with an increased risk of breast cancer. Strikingly, the same pattern has previously been shown in patients with schizophrenia [5].

The association with lung cancer is particularly intriguing. Smoking is not only a risk factor for lung and other types of cancer, but also for mental disorders [28] and neurological diseases, including MS [29] and amyotrophic lateral sclerosis [30]. Therefore, the decreased risk of lung cancer related to MS in our study seems counterintuitive. The decreased risk is particularly astonishing in schizophrenia [3, 4] where smoking is highly prevalent [31].

However, in PD the constellation is different. The prevalence of smoking is lower in PD patients than in the general population. Another explanation for the decreased risk of lung cancer in PD may be a protective effect from nicotine that enhances dopaminergic neurotransmission, thereby leading to less PD in smokers. Smoking is also protective for other autoimmune diseases, including ulcerative colitis, through an effect of nicotine activating a cholinergic anti-inflammatory pathway that requires the $\alpha 7$ nicotinic acetylcholine receptor (nAChR) on immune cells [32]. Through a downregulating effect on proinflammatory cytokine production, the $\alpha 7$ nAChR also mediates neuroprotection in PD [33], whereby in heavy smokers with prolonged exposure to nicotine, desensitization of the $\alpha 7$ nAChR could lead to squamous metaplasia, a predisposition for lung cancer [34].

There are no hypotheses available that directly link the association of lung and breast cancer with the two neurological diseases studied here. However, the relationship is intriguing and unlikely to occur by chance. It could suggest a mutual factor or mechanism protective against lung cancer but increasing the risk of breast cancer. We discuss in the following potential indications for such a mutual mechanism.

4.3. Common unifying hypotheses

The literature on risk factors of PD, MS and schizophrenia indicates that the most promising common framework might relate to infectious diseases and / or dysfunctional mechanisms of the immune system. The most prominent infectious disease candidates are EBV – due to its association with MS [35-37] – and *Helicobacter* species – because of their association with PD [38, 39]. However, no apparent role of EBV has been found in lung cancer [40]. The role of EBV in breast carcinoma is controversial [41-43]. The same is true for associations

between *H. pylori* and lung cancer [44-46], whereas, to our knowledge, no associations between *H. pylori* and breast cancer have been documented.

Therefore, attention switches to systemic immune mechanisms [47, 48]: do cancer co-occurrence patterns in PD and MS mirror immune system imbalances? A preliminary answer emerges from considering other neurological and autoimmune diseases with similar or reciprocal cancer patterns. The first candidates are rheumatoid arthritis (RA), which, contrary to PD, MS and schizophrenia, is associated with an increased risk of lung cancer and a decreased risk of breast cancer [7].

In congruence with this, RA and MS seem to be systematically opposed to each other. Comorbidity analyses of autoimmune diseases have indicated negative associations between MS and RA [49, 50], which, moreover, parallels the negative association between schizophrenia and RA [51]. Immunological interpretations have emphasized that the inflammatory disease processes in RA and MS are profoundly different. For instance, tumor necrosis factor (TNF)- α inhibitors are now a mainstay of anti-inflammatory therapy in RA, whereas TNF- α inhibitors are not advocated in MS because they induce relapses [52].

Another difference between RA and MS relates to the role of regulatory T cells (Treg). In fact, dysfunctional or deficient Treg activity has been shown both in RA [53] and in MS [54, 55], thus impairing the down-regulation of inflammatory immune processes. However, only RA studies have shown a collateral increase in Treg cell populations in subgroups of patients [53, 56]. Therefore, differences in underlying inflammatory mechanisms of autoimmune diseases might help to explain their rather specific coexistence with certain forms of cancer.

Comparing results related to lung and breast cancer may be the second step in discussing systemic mechanisms. Dysregulated inflammatory responses [57] or the immunological "tumor macroenvironment" [58] have been hypothesized to play a crucial role in lung cancer and in breast cancer, respectively. Notably, gastrointestinal infections [59, 60] and commensal gut bacteria [61, 62] were shown having reciprocal effects on breast cancer. T-cell subsets and enhanced secretion of cytokines supporting inflammatory or anti-inflammatory mechanisms seem to play a crucial role for such distal effects.

An additional revealing difference between lung and breast cancer comes from results related to immunosuppression after organ transplantation [8, 9]. Most cancers show increased frequencies after immunosuppression, including lung cancer, whereas decreased risk has been observed in breast and prostate cancers. This paradoxical finding parallels the cancer patterns in RA. The parallelism of cancer outcomes after immunosuppression and in diseases such as MS and RA provides a strong case for the diverging roles of immune system dysbalances in cancer risk.

4.4. Limitations

The main limitations of this study are related to registry data. The results can diverge depending on incidence, prevalence or, in this instance, mortality data. In particular, mortality data encompasses no information about health behaviors, disease course, medical and pharmacological treatments. Neither could we account for important behavioral factors such as smoking or sleep disruption, which regularly increase cancer risk [63].

The information on the main and additional causes of death relies on distinct registration priorities for the diseases of interest. While cancer is generally given high priority to be recorded as a main cause of death in mortality statistics, neurological diseases are typically

registered as additional causes and are thus underreported. In MS [64, 65], and PD [66] the registration level may be assumed to be quite high and to cover more than 60% of all patients.

Another limitation is the large study window encompassing a change in classification systems (ICD-8 to ICD-10), but also in diagnostic habits and registration practices for which matching designs can only partially account. Study findings might be biased towards more severe cases of PD and MS to the extent that these are preferably registered over milder cases.

4.5. Conclusions

We hypothesize that inflammatory immune system responses, that enhance the risk of MS, PD and schizophrenia, have, at the same time, a protective effect regarding lung cancer. The protective effect in lung cancer is contrasted by an increasing risk of breast cancer. This constellation is reversed in RA and in immunosuppression after organ transplantation. In this instance, the balance between pro-inflammatory and anti-inflammatory mechanisms appears to be skewed towards the latter.

Conflict of Interest

None.

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Note

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Table 1: ICD codes and frequencies in Parkinson's disease and multiple sclerosis

	Parkinson's disease	multiple sclerosis
all cases (N)	39066	5489
ICD-8 (1969-1994)	20272	3298
ICD-10 (1995-2007)	18794	2191
cases registered as main cause of death (N, %)	13676 35.0%	4225 77.0%
cases registered as additional cause of death (N, %)	25390 65.0%	1264 23.0%
cases registered as additional cause of death in cancers (N, %)	2481 6.4%	423 7.7%

Table 2: Frequencies and mean age at death of the most frequent cancers in Parkinson's disease, multiple sclerosis and in the population

malignant neoplasms	ICD-8	ICD-10	N			age at death: mean (SD)		
			PD	MS	overall mortality	PD	MS	population
stomach	151	C15	145	15	38,045	79.8 (7.4)	66.5 (16.5)	73.6 (11.9)
intestines, colon	152-3	C17-18	256	46	47,826	80.4 (7.4)	67.7 (9.4)	74.3 (11.7)
liver	155	C22	31	10	14,689	78.3 (7.8)	69.4 (8.4)	70.6 (11.8)
pancreas	157	C25	100	16	29,560	78.8 (7.5)	68.4 (12.5)	72.3 (11.4)
trachea, bronchus, lung	162	C33-4	203	57	98,655	77.3 (7.3)	62.1 (9.3)	68.4 (10.8)
melanoma, skin	172-3	C43-4	93	11	11,419	82.0 (8.3)	64.4 (14.0)	69.2 (16.7)
breast (women)	174	C50	234	85	54,429	80.7 (8.3)	62.3 (11.6)	69.0 (14.3)
cervix uteri, uterus	180-2	C53-5	64	20	16,405	82.7 (8.3)	63.6 (8.6)	70.0 (13.6)
ovaries	183	C56	44	24	16,661	78.3 (6.8)	59.0 (8.2)	69.1 (12.7)
prostate	185	C61	430	17	45,580	82.0 (6.0)	72.6 (9.2)	78.5 (8.5)
bladder	188	C67	92	18	17,312	81.7 (6.8)	62.3 (7.2)	75.3 (10.7)
brain	191	C71	27	9	12,601	76.1 (7.3)	56.2 (10.0)	58.8 (17.6)
lymphoma	200-2	C81-5	84	11	18,789	78.6 (6.6)	71.0 (8.4)	68.1 (16.8)
leukemia	204-9	C91-5	97	14	21,363	79.8 (8.49)	67.3 (10.8)	67.6 (20.1)

Table 3: Standardized mortality ratios (SMR) and chi²-bootstrapping results for the most frequent cancers in Parkinson's disease

	baseline			after weighting ¹		
	SMR	chi ² boot- strapped	chi ² ICI-uCI	SMR	chi ² boot- strapped	chi ² ICI-uCI ²
malignant neoplasms						
stomach	1.02	0.98	0.84-1.12	1.3	23.08	19.88-26.28
intestines, colon	1.17	6.45	5.91-6.99	1.28	28.55	24.52-32.58
liver	0.45	20.99	20.33-21.65	0.73	6.63	6.00-7.26
pancreas	0.81	4.93	4.55-5.31	1.22	14.58	12.34-16.82
trachea, bronchus, lung	0.52	82.75	81.19-84.30	0.59	61.45	57.83-65.07
melanoma, skin	2.10	52.28	49.94-54.62	1.41	9.24	8.11-10.37
breast	1.49	29.75	28.44-31.06	1.32	30.84	25.32-36.36
cervix uteri, uterus	1.17	2.67	2.29-3.04	1.10	5.94	4.65-7.22
ovaries	0.91	1.36	1.19-1.53	1.71	42.60	33.97-51.22
prostate	1.41	37.82	36.45-39.20	1.22	33.45	27.16-39.75
bladder	0.92	1.59	1.39-1.79	0.88	4.18	3.68-4.69
brain	1.05	1.03	0.87-1.2	0.22	16.57	16.04-17.09
lymphoma	1.01	0.99	0.84-1.13	1.10	4.28	3.58-4.99
leukemia	0.91	1.88	1.66-2.09	1.12	6.69	5.62-7.76

¹ Correction accounts for co-registration frequency of neurological and psychiatric diseases (ICD-8 290-389, ICD-10 F00-G99) within a specific cancer as opposed to the overall cancer sample.

² chi² at common p-values: 3.84 (p<.05), 6.63 (p<.01), 10.83 (p<.001)

Table 4: Standardized mortality ratios (SMR) and χ^2 -bootstrapping results for the most frequent cancers in multiple sclerosis

	baseline			after weighting ³		
	SMR	χ^2 boot- strapped	χ^2 ICI-uCI	SMR	χ^2 boot- strapped	χ^2 ICI-uCI ⁴
malignant neoplasms						
stomach	0.86	1.27	1.12-1.42	1.37	14.13	10.13-18.14
intestines, colon	1.76	14.50	13.39-15.61	2.31	68.28	56.95-79.61
liver	0.94	1.02	0.87-1.17	1.92	23.33	12.93-33.75
pancreas	0.78	2.14	1.91-2.37	1.63	30.62	12.51-48.72
trachea, bronchus, lung	0.78	4.08	3.73-4.44	0.86	14.76	11.71-17.81
melanoma, skin	1.88	5.66	4.55-6.78	1.17	2.19	1.69-2.69
breast	1.59	13.75	12.85-14.64	1.76	83.49	60.27-106.71
cervix uteri, uterus	1.11	1.24	1.03-1.46	1.99	59.97	33.96-85.97
ovaries	1.26	2.15	1.82-2.48	3.36	250.16	172.65-327.68
prostate	1.28	1.91	1.58-2.24	1.32	18.59	10.93-26.26
bladder	2.19	12.37	10.87-13.87	2.81	39.17	31.12-47.23
brain	0.85	1.29	1.12-1.46	0.18	8.33	7.98-8.69
lymphoma	0.73	2.17	1.94-2.4	0.70	3.65	3.18-4.16
leukemia	0.85	1.37	1.20-1.53	1.41	6.51	3.46-9.57

³ Correction accounts for co-registration frequency of neurological and psychiatric diseases (ICD-8 290-389, ICD-10 F00-G99) within a specific cancer as opposed to the overall cancer sample.

⁴ χ^2 at common p-values: 2.71 (p<.10), 3.84 (p<.05), 6.63 (p<.01)