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Risk of Parkinson's disease-related death in cancer survivors: A population-based study in Japan

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A B S T R A C T

Background: The risk of Parkinson's disease (PD)-related death in patients with cancer largely unexplored.
Methods: We analyzed data from the Neoplasms ANd other causes of DEath (NANDE) study, which investigates the causes of death in patients with cancer in Japan. Standardized mortality ratios (SMRs) were calculated to compare the risk of PD-related deaths in patients with cancer to that of the general population. Poisson regression models were employed to estimate the relative risk of PD-related death in the subgroups.
Results: The cohort included 548,485 patients with cancer, yielding 2,047,398 person-years at risk from 1995 to 2013. During the study period, 242,250 patients died and 145 deaths were attributable to PD. The SMR for PD-related death was 2.34 (95% confidence interval [CI]: 1.99–2.75). Patients who were diagnosed with cancer before 70 years of age had a high SMR (>5) for PD-related deaths. The SMR of patients with mouth-to-stomach cancers (lip, oral cavity, pharynx, esophagus, and stomach cancers) was 3.72 (95% CI: 2.84–4.86), while that of those with other cancers was 1.93 (95% CI: 1.57–2.37). The multivariate Poisson regression model revealed that patients with mouth-to-stomach cancers were more likely to die of PD than those without (relative risk 2.07, 95 % CI; 1.46–2.93).
Conclusions: Patients with cancer are at a high risk of PD-related death; particularly, mouth-to-stomach cancers and potentially obstructing medication for PD are attributable to a high mortality risk. Careful management, including adequate PD treatment, would benefit cancer survivors with PD and reduce the risk of PD-related death.

1. Introduction

Cancer is a significant public health concern, with approximately 10 million cancer-related deaths reported worldwide in 2020 [1,2]. Since cancer is the leading cause of death in Japan, which is one of the most aged countries [3], the importance of cancer in public health would further increase with the aging population. Moreover, since advances in cancer therapy have improved the prognosis of patients with cancer, the number of cancer patients with comorbidities has also increased [4]. Thus, the management of comorbidities is becoming increasingly important for better quality of life (QOL) and prognosis of cancer survivors.

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), which are other major concerns in the elderly population, are associated with their QOL and mortality [5,6]. Among neurodegenerative disorders, PD is the most common movement disorder affecting the patients' daily life owing to motor symptoms and multiple non-motor symptoms [7]. Patients with PD are commonly treated with oral pharmacotherapy, mainly levodopa replacement therapy, which has markedly improved their QOL and prognosis [8]. As indicated in previous studies, appropriate management of PD-related symptoms is essential for better QOL and survival outcomes [9–11].

An aging population increases the number of patients with cancer and PD [12,13]. In general, cancer and PD are classified into unrelated disease categories. However, PD and cancer have some common genetic and molecular properties. Some PD-related genes are oncogenes, and genetic background that is protective against cancer could be a risk factor for PD, and vice versa [14,15]. Actually, cancer is based on uncontrolled cell proliferation with suppressed immune defense against tumor cells, whereas the pathological feature of PD includes neuronal cell death with abberant neuroinflammation. Numerous epidemiological studies also reported the inverse relationship between development of PD and cancer, although a certain type of cancer, such as melanoma and brest cancer, may be related to an increased risk of PD [16–20]. On

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the other hand, little is known about the impact of having both cancer and PD on patients' clinical course and prognosis. The patients' physical, mental, and cognitive conditions attributed to diseases, as well as treatment of cancer and PD, could influence each other, potentially complicating care. Both cancer and PD impair the performance status [7,21], potentially affecting clinical decisions, such as the choice of treatment, thereby increasing the mortality risk. Certain patients may experience difficulty in eating and ensuring compliance with oral medications owing to the cancer itself and/or the adverse effects of cancer treatment [22]. This results in poor control of PD symptoms, which is associated with an increased risk of PD-related death. It is hypothesized that cancer patients with PD possess an increased risk of death from PD-related symptoms compared to that of the general population. However, no reports have investigated the risk of PD-related death in patients with cancer.

In this study, we analyzed the risk of PD-related death in patients with cancer compared to that of the general population. Our findings would be helpful to clinicians in formulating treatment guidelines for these patients in clinical practice.

2. Methods

2.1. Ethics approval and consent to participate

The requirement for informed consent was waived owing to the retrospective nature of the study. The Institutional Review Board of Osaka University, Suita, Japan approved the study protocol (approval number:17315-3).

2.2. Data sources and processing

We used data from the Neoplasms ANd other causes of DEath (NANDE) study, which investigated the causes of death in patients with cancer in Japan. The NANDE database was created by linking the Osaka Cancer Registry (OCR) with vital statistics in Japan [23]. The OCR has been operating since 1962 and covers approximately eight million residents in the Osaka Prefecture, Japan. The OCR includes cancer-related information, such as sex, age at diagnosis, year of diagnosis, cancer type, stage at diagnosis, follow-up period, and death. The OCR follows enrolled patients for up to 10 years and investigates deaths; however, it does not contain detailed causes of death. Therefore, we used vital statistics in Japan, which included the individual causes of death based on the death certificate completed by a doctor. We merged the OCR and vital statistics using sex, date of birth, date of death, and municipality of residence data. Based on this combination, data concerning 96.6 % of patients with cancer were collated. We deleted personal information after matching to create the database. Thus, the NANDE database contains cancer-related patient information, including sex, age at diagnosis, year of diagnosis, cancer type, stage at diagnosis, survival time, and cause of death.

In Japan, the International Classification of Diseases (ICD)-10 has been in operation since 1995, and PD has been available as a cause of death information. The NANDE database contains data on patients with cancer diagnosed between 1985 and 2013. Therefore, we used data from patients diagnosed with cancer between 1995 and 2013. A total of 778,816 patients with cancer were identified during the study period. Of which, we excluded cases with the following uncertain information: (1) date of death; (2) final date of survival confirmation; (3) date of first cancer diagnosis; (4) date of second cancer diagnosis; and (5) age at first cancer diagnosis. We also excluded cases with death certificate notification or death certification only and patients with simultaneous or synchronous cancer. Simultaneous cancer refers to multiple tumors identified at the time of diagnosis. Synchronous tumors were defined as those diagnosed within two months of each other, while the definition of synchronous tumors varies among studies, ranging from two to six months between the diagnoses [24,25]. A total of 548,485 patients were included in the final analysis. The details are shown in Supplementary Fig. S1.

Age at diagnosis was grouped into four categories: $\leq$59, 60–69, 70–79, and $\geq$80 years. We also divided the year of diagnosis into two periods:1995–2004 and 2005–2013. The stage at diagnosis was classified into seven groups: (i) intraepithelial (abnormal cells are present but have not spread to nearby tissues); (ii) localized (cancer is limited to the organ where it originated, with no sign of spread); (iii) lymph node metastasis (cancer has spread to regional lymph nodes); (iv) infiltration to adjacent organs (cancer has spread to nearby tissues or organs); (v) distant metastasis (cancer has metastasized to distant parts of the body); (vi) unknown (insufficient information to determine the stage); and (vii) N/A (not applicable). Since nearly all the anti-PD drugs available in Japan during the study period were oral formulations, we hypothesized that cancers at the route of oral administration have a negative influence on the management of PD symptoms, resulting in an increased risk of PD-related death. To examine the relationship between PD-related death and cancer types from this viewpoint, we further categorized the cancers into two groups: mouth-to-stomach cancers (lip, oral cavity, pharynx, esophagus, and stomach cancers) and others. Cancers in the duodenum and intestine are rare and were categorized as other malignant neoplasms in this database (Supplementary Table S1).

PD was identified using ICD–10 code G-20. Cancers were coded according to the International Classification of Diseases, Oncology, and Oncology Third Edition. Details of the assignment of codes are provided in Supplementary Table S1. Details concerning the assignment of codes and number of patients (those included, excluded, and lost to follow-up) are shown in Supplementary Table S2.

2.3. Statistical analysis

We analyzed the risk of PD-related deaths after cancer diagnosis. PD-related death was defined as the cause of death on the death certificate as PD. The observation period was January 1995 to December 2013. Patients diagnosed with a second cancer during the observation period were censored at the time of diagnosis of the second cancer. The survival time was measured in days, with a minimum and maximum of 1 and 3652 days, respectively.

To compare the risk of PD-related death in patients with cancer with that in the general population, we calculated standardized mortality ratios (SMRs) and their 95 % confidence intervals (CIs) as the ratio of the observed to the expected number of deaths. The control group consisted of individuals from the general Japanese population, irrespective of their cancer status. The expected number of deaths was computed using annual Japanese sex- and age-specific death rates. These death rates were calculated by dividing the number of deaths by the national population within each 5-year age group and sex category for a calendar year. Both the national population and number of deaths, including patients with or without cancer, are available from the Portal Site of Official Statistics of Japan, also known as the Japanese government statistics portal site (https://www.e-stat.go.jp). The SMRs were calculated for PD-related deaths.

To compare the risk of PD-related death among patients in various cancer subgroups, we used Poisson regression models to estimate the relative risk (RR) and 95 % CI. The RRs were adjusted for sex, age at diagnosis, period of diagnosis, stage at diagnosis, and cancer type.

Statistical analyses were performed using Stata 17/MP (StataCorp, College Station, TX, USA) and R (https://cran.r-project.org/). The level of significance was set at $P < 0.05$. All the tests were two tailed.

2.4. Data and materials availability statement

Data are available on reasonable request to the corresponding author.

3. Results

The cohort included 2,047,398 person-years at risk, with a median follow-up period of 4.25 years after cancer diagnosis. By the end of December 2013, 242,250 patients had died. Of these, 145 were attributed to PD-related deaths.

The baseline characteristics of the study population are summarized in Table 1. Among the 548,485 patients with cancer, 243,272 (44.4 %) were female. More than 60 % of the patients were diagnosed with cancer between 2005 and 2013. The most common stage at presentation was localized cancer (41.0 %), followed by distant metastasis (16.7 %), infiltration to adjacent organs (13.3 %), lymph node metastasis (11.7 %), intraepithelial (6.2 %), and unknown (8.9 %). Considering the cancer type, 20.9 % of the patients had mouth-to-stomach cancers.

As shown in Table 1, the age at diagnosis of cancer differed between men and women. Of the female patients, 36.4 % were diagnosed with cancer at ≤ 59 years of age, followed by 25.0 %, 24.3 %, and 14.3 % in 60–69, 70–79, and ≥80 years of age, respectively. Of the male patients, 33.5 % and 33.0 % were diagnosed with cancer at 60–69 and 70–79 years of age, respectively, followed by 21.6 % and 11.9 % in those aged ≤59 and ≥80 years, respectively. Additionally, the cancer type differed by sex (Supplementary Table S3). Breast cancer was the most common type of cancer in female patients (22.5 %). In contrast, stomach cancer was most common in male patients (19.4 %). Owing to these differences, we analyzed the risk of PD-related death by sex.

3.1. Increased risk of death attributed to PD-related symptoms in patients with cancer

The results of the SMRs for PD-related death in the patients with cancer compared with the general population are summarized in Table 2. The rate of PD-related death was 7.08 per 100,000 person-years. The SMR for PD-related death was 2.34 (95% CI: 1.99–2.75). Females had a higher SMR for PD-related death than males: the SMR of females was 2.71 (95% CI: 2.09–3.51) and that of males was 2.15 (95% CI: 1.75–2.65). Patients who were diagnosed with cancer before 70 years of age had a high SMR for PD-related deaths (SMR >5). In contrast, no significant increase in the SMR for PD-related death was observed in populations who were diagnosed with cancer at ≥ 80 years of age. Patients diagnosed with cancer between 2005 and 2013 had a higher SMR for PD-related deaths than those diagnosed between 1995 and 2004. From the viewpoint of cancer stage at diagnosis, patients with intraepithelial cancer had the highest SMR of 2.89. Considering the primary lesion of cancers, patients with mouth-to-stomach cancers had an SMR of 3.72 (95 % CI: 2.84–4.86), and those with other cancers had an SMR of 1.93 (95 % CI: 1.57–2.37). This tendency was observed when analyzed by sex (Supplementary Table S4). The SMR for PD-related death in female patients with mouth-to-stomach cancers was 4.81 (95 % CI: 3.07–7.55), while that for other cancers was 2.22 (95 % CI: 1.62–3.05). In male patients, those with mouth-to-stomach cancers had an SMR of 3.30 (95 % CI: 2.35–4.61), and those with other cancers had an SMR of 1.77 (95 % CI: 1.35–2.31).

Fig. 1 illustrates the trends in the SMR for PD-related deaths based on age at cancer diagnosis and the timing of cancer diagnosis. As indicated in Table 2, the SMR for PD-related deaths was highest in the 60–64 age group and gradually decreased with increasing age (Fig. 1A). Furthermore, we observed an increasing trend in the SMR for PD-related deaths as the timing of cancer diagnosis became more recent (Fig. 1B).

3.2. RR of PD-related death increased by aging and mouth-to-stomach cancers

The RR of PD-related deaths among patients with cancer are shown in Table 3. The RR of PD-related death was higher in patients diagnosed at ≥ 60 years of age compared to those diagnosed at < 60 years. Patients with an unknown stage of cancer had a higher risk of PD-related death than those with intraepithelial disease; however, no significant difference was observed. Notably, patients with mouth-to-stomach cancers had a higher risk of death from PD than those with other types of cancers (RR [95 % CI], 2.07 [1.46–2.93]). There was no difference in the risk of PD-related death between the sexes and years of diagnosis. When analyzed by sex (Supplementary Table S5), the RR of PD-related death was significantly higher in patients with mouth-to-stomach cancers in both men and women (RR [95 % CI], 2.31 [1.32–4.06] for females and 1.91 [1.23–2.96] for males).

4. Discussion

In this study, we used 2,047,398 person-years of data across 19 years in Japan and found that patients with cancer have a significantly higher

Table 1
Baseline characteristics.

	All		Female		Male	
	N	%	*N*	%	*N*	%
Patients	548,485	100.0 %	243,272	100.0 %	305,213	100.0 %
Age at diagnosis						
≤59	154,240	28.1 %	88,454	36.4 %	65,786	21.6 %
60–69	163,291	29.8 %	60,929	25.0 %	102,362	33.5 %
70–79	159,833	29.1 %	59,138	24.3 %	100,695	33.0 %
≥80	71,121	13.0 %	34,751	14.3 %	36,370	11.9 %
Period of diagnosis						
1995–2004	199,373	36.4 %	87,898	36.1 %	111,475	36.5 %
2005–2013	349,112	63.7 %	155,374	63.9 %	193,738	63.5 %
Stage at diagnosis						
Intraepithelial	33,755	6.2 %	19,572	8.0 %	14,183	4.6 %
Localized	224,920	41.0 %	100,333	41.2 %	124,587	40.8 %
Lymph node metastasis	63,969	11.7 %	32,761	13.5 %	31,208	10.2 %
Infiltration to adjacent organs	72,885	13.3 %	29,906	12.3 %	42,979	14.1 %
Distant metastasis	91,569	16.7 %	34,128	14.0 %	57,441	18.8 %
Unknown	48,895	8.9 %	21,226	8.7 %	27,669	9.1 %
N/A	12,492	2.3 %	5346	2.2 %	7146	2.3 %
Cancer type						
Mouth-to-stomach	114,665	20.9 %	34,324	14.1 %	80,341	26.3 %
Others	445,838	81.3 %	213,714	87.8 %	232,124	76.1 %

N/A, not applicable.

Table 2
Standardized mortality ratios for Parkinson's disease-related death in patients with cancer compared to the general population.

	Person-years	PD-related death		PD-related death rate[a]	SMR (95 % CI)[b]
		Observed	Expected		
All patients	2,047,398	145	61.95	7.08	2.34 (1.99–2.75)
Sex					
Female	1,009,092	57	21.05	5.65	2.71 (2.09–3.51)
Male	1,038,305	88	40.90	8.48	2.15 (1.75–2.65)
Age at diagnosis					
≤59	751,417	1	0.18	0.13	5.47 (0.77–38.86)
60–69	629,817	24	4.64	3.81	5.18 (3.47–7.72)
70–79	511,729	85	27.15	16.61	3.13 (2.53–3.87)
≥80	154,434	35	29.98	22.66	1.17 (0.84–1.63)
Period of diagnosis					
1995–2004	1,026,769	70	36.96	6.82	1.89 (1.50–2.39)
2005–2013	1,020,628	75	24.98	7.35	3.00 (2.39–3.76)
Stage at diagnosis					
Intraepithelial	154,132	6	2.08	3.89	2.89 (1.30–6.43)
Localized	1,095,193	85	31.35	776	2.71 (2.19–3.35)
Lymph node metastasis	274,372	12	7.22	4.37	1.66 (0.94–2.93)
Infiltration to adjacent organs	192,559	12	7.12	6.23	1.69 (0.96–2.97)
Distant metastasis	126,292	5	6.20	3.96	0.81 (0.34–1.94)
Unknown	168,947	23	6.88	13.61	3.34 (2.22–5.03)
N/A	35,903	2	1.10	5.57	1.82 (0.46–7.29)
Cancer type					
Mouth-to-stomach	413,158	53	14.27	12.82	3.72 (2.84–4.86)
Others	1,634,239	92	47.68	5.63	1.93 (1.57–2.37)

CI, confidence interval; N/A, not applicable; SMR, standardized mortality ratio.
[a] Per 100,000 person-years.
[b] SMRs may not equal the number of observed deaths divided by expected deaths because expected deaths are only listed to two decimal places.

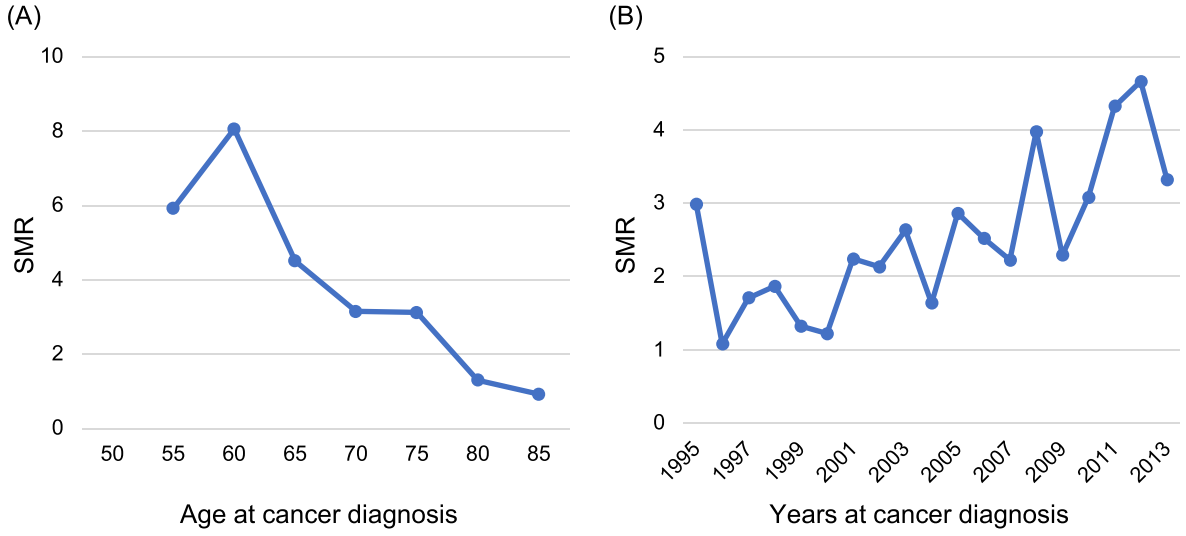

Fig. 1. The trend of the standardized mortality ratio for Parkinson's disease-related deaths based on age/years at cancer diagnosis.
(A) The standardized mortality ratio (SMR) for Parkinson's-related deaths was highest among patients diagnosed with cancer between 60 and 64 years and then gradually declined. (B) SMRs for Parkinson's disease-related deaths tended to increase with more recent cancer diagnosis. SMR = standardized mortality ratio.

risk of PD-related death than the general population. Notably, patients with mouth-to-stomach cancers, including lip, oral cavity, pharynx, esophagus, and stomach cancers, have a higher risk of PD-related death than those with other types of cancers. To the best of our knowledge, this is the first large-scale study to demonstrate the risk of PD-related death in patients with cancer.

Advances in cancer therapy have improved the prognosis of cancers, and with an aging society, an increasing number of cancer survivors suffer from multiple comorbidities, such as aging-related neurodegenerative disorders and cardio- and cerebrovascular diseases. In this setting, medical management becomes complicated, and the clinical course of comorbidities may change, potentially resulting in a high risk of comorbidity-related death. A previous study analyzing the causes of death in patients with cancer indicated that cardiovascular disease was the most common cause of death in patients with cancer [26]. We previously reported that the risk of death owing to cardiovascular disease increases in patients with cancer [23,27]. Among neurodegenerative diseases, the risk of death attributed to AD increases in elderly patients with cancer [26]; however, the risk of PD-related death in patients with cancer remains elusive. Upon analyzing the data from one of the largest population-based cancer registries in Japan, we found that patients with cancer had a 2.3-fold increased risk of PD-related death compared to the general population. It is noteworthy that patients with cancer, except for a certain type of cancer such as melanoma, have a reduced risk of

Table 3
Relative risk of Parkinson's disease-related death in patients with cancer.

	RR	95 % CI	*P*-value
Sex			
Female	1.00	–	
Male	1.11	0.80–1.56	0.53
Age at diagnosis			
≤59	0.04	0.01–0.27	0.001
60–69	1.00	–	
70–79	4.44	2.82–6.99	<0.001
≥80	6.08	3.60–10.27	<0.001
Period of diagnosis			
		1.00	–
2005–2013	0.84	0.60–1.17	0.29
Stage at diagnosis			
Intraepithelial	1.00	–	
Localized	1.23	0.53–2.85	0.63
Lymph node metastasis	0.82	0.30–2.21	0.69
Infiltration to adjacent organs	1.01	0.38–2.70	0.99
Distant metastasis	0.66	0.20–2.16	0.49
Unknown	2.38	0.96–5.87	0.06
N/A	1.58	0.32–7.81	0.58
Cancer type			
Others	1.00	–	
Mouth-to-stomach	2.07	1.47–2.93	<0.001

CI, confidence interval; N/A, not applicable; RR, relative risk.

developing PD; however, the association between cancer and PD remains controversial [16–21,28]. Additionally, smoking, which is a significant risk factor for cancer [29], is negatively correlated with the development of PD [7]. Of note, mouth-to-stomach (lip, oral cavity, pharynx, esophagus, and stomach) cancers are positively associated with smoking [30,31]. These reports suggest that cancer is negatively correlated with PD development, and that patients with cancer have a decreased probability of developing PD as a comorbidity. Our data demonstrated that once patients with cancer are obfuscated with PD, they face an increased risk of PD-related death. The reason why cancers, especially mouth-to-stomach cancers, being linked to smoking are associated with increased PD-related deaths, when PD actually rather relates to no-smoking, may be attributed to increased frailty in smokers once they develop PD after having suffered cancer. However the mechanistic connection between smoking, cancer and PD-related death, still remains largely unknown.

In this study, the cause of death was collected from the death certificate and the direct (primary) cause of death for each patient was not available. A number of reports investigating the primary cause of death in patients with PD exist [32–35]. Pneumonia is often identified as the most common cause of death, and aspiration, suffocation, senile deterioration, and cardiac-related deaths are repeatedly listed as the causes of death in patients with PD. Falls (trauma) and sudden death are also considered to be related to PD. A previous study using ICD-10 data demonstrated that the causes of death in 143 patients with idiopathic PD (iPD) in the United Kingdom were iPD (29 %), malignancy (12 %), ischemic heart disease (12 %), pneumonia (11 %), and cerebrovascular disease (9 %) [33]. Since 45 % patients with iPD developed pneumonia as a terminal event in the same study, the cause of death of a substantial proportion of patients with PD who had pneumonia and died was PD. In Japan, Doi et al. randomly selected 477 death certificates from 4589 certified deaths attributed to PD (ICD-10 code: G20) in 2008 and found that the immediate causes of death were aspiration or suffocation (22.2 %), followed by pneumonia (14.7 %), respiratory failure (12.8 %), senile deterioration (10.9 %), and heart disease (6.3 %) [34]. Based on these reports, the PD-related deaths in our study consisted mainly of decedents who died of respiratory-related complications.

There are several possible explanations for the higher risk of PD-related death in cancer patients than in the general population. First, some cancer survivors have a poor performance status compared to that of the general population, leading to an increased risk of developing pneumonia, falls, and senile deterioration, which could account for PD-related death. Second, impairment of immune function owing to malignancy itself or chemotherapy increases vulnerability to pneumonia and other infectious diseases [35]. Patients with PD and cancer have a high risk of developing pneumonia with increased vulnerability, leading to an increased risk of death, which is judged to be PD-related. Third, surgical treatment of cancer, especially lung and stomach cancer, increases the risk of postoperative pneumonia [36]; nevertheless, death could be judged as cancer-related in most cases. Fourth, patients with cancer often experience adverse effects of cancer treatment (such as nausea and damping syndrome) and sequelae of the cancer itself. Such patients could experience unstable and/or limited medication dosing, disrupting fine control of PD. It is well known that the mainstay of PD treatment is oral pharmacotherapy. The available anti-parkinsonian treatments except for oral medications during the study period (1995–2013) in Japan were as follows: levodopa infusion without a decarboxylase inhibitor (available in the 1970s), ultra-short-acting apomorphine injection (available in 2012), rotigotine patch (available in 2013), and neurosurgery/deep brain stimulation (available in 2000). Therefore, when oral medication becomes insufficient and/or unstable, especially owing to mouth-to-stomach cancer, alternative treatments are very limited, resulting in poor control of PD symptoms. Additionally, malabsorption may occur owing to resection or reconstruction of the duodenum or proximal small intestine in stomach cancer surgery, which is the site of levodopa absorption [37]. Management of PD is important for good QOL and prognosis [8,9], and poor symptom control increases the risk of aspiration, suffocation, pneumonia, and falls, all of which account for PD-related death. In our analysis, mouth-to-stomach cancers significantly increased the risk of PD-related death in both male and female patients (Tables 2 and 3 and Supplementary Tables 4 and 5). Fifth, anti-cancer treatment can cause gastric and intestinal mucosal injury, which potentially decreases levodopa absorption and affects symptom control in PD [38]. Both PD and cancer can lead to reduced food intake and weight loss. Both PD and cancer cause gastrointestinal tract-related symptoms, such as constipation and delayed gastric emptying, leading to decreased food intake and increased risk of gastroesophageal reflux [39]. These conditions can be associated with an increased risk of PD-related death in patients with cancer. Considering the potential mechanisms underlying the increased risk of PD-related death in patients with cancer and PD, clinical management, including the following, may be important in such patients: (1) paying attention to the increased risk of pneumonia and PD-related critical events, (2) sufficient treatment for PD for controlling symptoms, (3) medication based on the comorbidity, physical condition, and drug interaction, (4) rehabilitation and social activities to maintain good performance status and swallowing function, and (5) oral care to reduce the risk of aspiration pneumonia. Recent advances in PD therapies, including drugs with non-oral formulation and device-assisted treatment, would benefit patients with cancer and PD.

In this study, we analyzed the association of age or stage of cancer with the SMRs of PD-related deaths. The group diagnosed with cancer at an older age had lower SMRs for PD-related deaths than the younger group; however, the RRs for PD-related deaths increased with age. This is could be attributed to the increase in PD-related deaths at older age in the general population. Additionally, younger patients are usually unlikely to die from conditions associated with PD. The tendency for SMRs to be higher in patients with intraepithelial and localized cancer than in those with lymph node and distant metastases could be since the former group is composed of a larger proportion of younger patients. Patients with advanced-stage cancer are more likely to die from the cancer itself, resulting in a relative decrease in PD-related deaths.

Another intriguing finding of this study is the observed increase in the SMR for PD-related deaths as the timing of cancer diagnosis becomes more recent. Advances in cancer treatment have led to improved survival rates among cancer patients [4]. Consequently, there has been an

increase in the proportion of non-cancer-related deaths among cancer survivors [26]. The results of our study are expected to serve as valuable information for clinicians managing PD in cancer patients.

This study had several limitations. First, this study was based on death certificates, and we were unable to analyze the direct cause of death in the cohort, as mentioned above. Second, if patients with PD die from conditions such as pulmonary embolism, urinary sepsis, or aspiration pneumonia, the lack of mention of PD on the death certificate may result in an underestimation of PD-related deaths. Third, information regarding cancer treatment for each patient was unavailable. Finally, the study population consisted of only Japanese participants. Thus, further studies are warranted to clarify whether our findings can be applied to other populations with different genetic, environmental, and clinical backgrounds.

In conclusion, patients with cancer are at high risk of PD-related deaths. In particular, mouth-to-stomach cancers have a higher risk of mortality than other types of cancer. Careful clinical management, including adequate PD treatment in patients with cancer and PD, would benefit cancer survivors in reducing the risk of PD-related death.

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CRediT authorship contribution statement

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Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105966.

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Update

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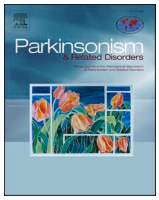

Corrigendum

Corrigendum to "Risk of Parkinson's disease-related death in cancer survivors: A population-based study in Japan" [Park. Relat. Disord. 119 (2024) 105966]

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The authors regret that there is an error in Table 3. The correct Table 3 is as follows.

The authors would like to apologise for any inconvenience caused.

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Table 3
Relative risk of Parkinson's disease-related death in patients with cancer.

	RR	95 % CI	*P*-value
Sex			
Female	1.00	–	
Male	1.11	0.80–1.56	0.53
Age at diagnosis			
≤59	0.04	0.01–0.27	0.001
60–69	1.00	–	
70–79	4.44	2.82–6.99	<0.001
≥80	6.08	3.60–10.27	<0.001
Period of diagnosis			
1995–2004	1.00	–	
2005–2013	0.84	0.60–1.17	0.29
Stage at diagnosis			
Intraepithelial	1.00	–	
Localized	1.23	0.53–2.85	0.63
Lymph node metastasis	0.82	0.30–2.21	0.69
Infiltration to adjacent organs	1.01	0.38–2.70	0.99
Distant metastasis	0.66	0.20–2.16	0.49
Unknown	2.38	0.96–5.87	0.06
N/A	1.58	0.32–7.81	0.58
Cancer type			
Others	1.00	–	
Mouth-to-stomach	2.07	1.47–2.93	<0.001

CI, confidence interval; N/A, not applicable; RR, relative risk.