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REVIEW ARTICLE

Cancer risk in Parkinson disease: An updated systematic review and meta-analysis

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Abstract

Background and purpose: Increasing evidence suggests significant associations between Parkinson disease (PD) and cancer risks. We conducted an updated review of studies that examined the risks of various cancer among PD patients and how this differed when cancer preceded PD diagnosis or PD diagnosis preceded cancer.

Methods: Four databases were searched for studies that examined the association between PD and incidence of cancer from database inception to 4 June 2021. Three independent reviewers screened the articles for eligibility and extracted study data. Pooled relative risk with 95% confidence intervals were calculated using a random effects model.

Results: Forty studies involving 11 case–control studies, two nested case–control studies, 22 cohort studies, and five cross-sectional studies were included. Compared to controls, PD patients had lower risks of lung, genitourinary, gastrointestinal, and haematological cancers. Conversely, higher risks of melanoma and brain cancer were noted among PD patients. No association was found between PD and risk of female cancers. Subgroup analysis found negative associations between PD patients and risks of colon cancer, rectal cancer, and non-Hodgkin lymphoma.

Conclusions: Findings from our meta-analysis suggest PD patients had lower risks of lung, genitourinary, gastrointestinal, and haematological cancers and increased risks of melanoma and brain cancer. Future research to investigate the underlying mechanisms between PD and cancers is warranted.

KEYWORDS
cancer risks, meta-analysis, Parkinson disease, relative risk

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder that is known to cause progressive impairment of voluntary motor control [1]. The prevalence of PD has doubled over the past 3 decades, with an estimated 6.1 million individuals living with PD in 2016 [2]. The risk of developing PD increases with age, from 1% of the population older than 60 years to 5% of the population older than 85 years [3,4]. In PD patients, there is loss of dopaminergic neurons in substantia nigra pars compacta, which is crucial for normal movement coordination [5]. As such, PD patients suffer from motor symptoms including resting tremor, bradykinesia, postural instability, and rigidity. Additionally, non-motor symptoms such as neurobehavioral complications, autonomic dysfunction, and sensory problems are commonly reported among PD patients [1]. Various cellular mechanisms including mitochondrial dysfunction, excitotoxicity, impaired autophagy, oxidative stress, accumulation of misfolded protein, and genetic mutations have been suggested to contribute to the neurodegeneration in PD [6,7].

Cancer is a complex disease that is characterized by infinite cell proliferation and metastasis [8]. Cancer and PD can be considered as opposite conditions, as the former is a result of uncontrolled cell division, whereas the latter results from cell death. As such, several epidemiological studies have attempted to examine the cancer risk among PD patients. A recent Korean nationwide case–control study including 52,009 PD patients and 260,045 control subjects was conducted, with a follow-up duration of 6 years [9]. This study reported a lower overall cancer risk in PD patients. Similarly, another cohort study published in 2010 that involved 2993 PD patients also indicated lower overall cancer risk, with the exception of melanoma [10]. On the other hand, a cohort study by Ryu et al. [11] suggested increased risk of skin cancer among Korean PD individuals.

Data from systemic reviews have been similarly inconclusive. The 2010 study by Bajaj et al. included 107,598 PD patients and reported that PD reduced the risk of all cancers by 27%. However, they found that the risk of melanoma and other skin tumours was actually higher in PD patients compared with individuals without PD [12]. Another study by Catala-Lopez et al. [13] in 2014 reported a similar finding, with reduced risks of prostate cancer, lung cancer, bladder cancer, stomach cancer, colorectal cancer, blood cancer, and uterine cancer in PD patients. Given the contradictory evidence and recent addition of new epidemiological studies, we conducted an updated study with meta-analysis to review and re-evaluate the association between cancers and PD.

METHODS

This review was conducted in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [14]. The study was registered with PROSPERO (CRD4202017619).

Literature search strategy

A comprehensive search was performed on the Ovid MEDLINE, Embase, PsychINFO, and Cochrane Central databases for studies conducted in humans from database inception to 4 June 2021. A combination of keywords and medical subject heading terms includes Parkinson disease, Parkinsons disease, Parkinson's disease, carcinoma, neoplasm*, and cancer. The full search can be found in Method 1 in Appendix S1. Reference lists of included articles and those listed in published reviews were also reviewed to identify additional articles. No language restriction was applied.

Study selection

To be included, studies had to investigate the association between PD and incidence of any cancer in human populations. These studies could be of any design, including case–control, cohort, or cross-sectional surveys. Abstracts, editorials, and unpublished reports were excluded. The studies were independently screened and selected based upon the criteria above by the three investigators (Y.Q.L., S.W.H.L., or K.Y.N.), and any disagreements were resolved by discussion.

Data extraction and study quality assessment

For each study, we extracted the information on study demographics (study author's name, year of publication, country performed, number of participants, follow-up period, sample size, sex, age, ethnicity), type of cancer exposure, relative risks, hazard ratios and 95% confidence intervals (CIs), and any variables adjusted in the analysis. These studies were then categorized based on their cancer location, which include female cancers (breast, ovarian), gastrointestinal cancer (colorectal, liver, stomach, oesophageal, pancreas), genitourinary cancers (bladder, kidney, uterine, prostate), haematological cancer (leukaemia, lymphoma), lung cancer, melanoma, and brain cancer. Studies were also classified into their predefined categories according to whether cancer occurred before PD diagnosis, after PD diagnosis, or at the same time (cross-sectional studies). Data were independently extracted by the three authors and verified independently by one of the authors (Y.Q.L., S.W.H.L., or K.Y.N.) for accuracy. We also assessed the risk of bias using the Cochrane Collaboration Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [15]. Any disagreement was resolved through adjudication and discussion with one of the senior authors (S.W.H.L. or K.Y.N.).

Data analyses

We assumed that the person-time of the unexposed group is vastly longer than that of the exposed group. As such, we made no distinction between standardized incidence ratios/standardized mortality ratios, incidence odds ratios (ORs), and relative risks (RRs), and combined them in our analyses, since ORs should approximate the RRs or hazard ratios. Hence, we reported all results as RRs. Study heterogeneity was assessed with Cochran *Q*-test and I^2 statistics with *p*-value for *Q*-test of ≤0.05 considered to reflect statistically significant heterogeneity [16,17]. Due to the heterogeneity of the data, we used a random effects model to calculate RRs with their corresponding 95% CIs for the cancer risks among PD patients. Otherwise, we conducted a fixed effects model pooling methods when the *p*-value for *Q*-test was >0.05. Publication bias was assessed using Egger test and Begg test if there were 10 or more studies, with $p < 0.05$ indicating publication bias. In addition, we also visually assessed for funnel plot asymmetry. In our subgroup analyses, we stratified studies by gender and when cancer was diagnosed (cancer preceding PD diagnosis, PD diagnosis preceding cancer, or cross-sectional studies, which do not assume causality). All analyses were performed in Stata 16.0.

RESULTS

Literacy search and study characteristics

The initial search identified 9147 articles, and 8125 were screened for initial eligibility after removal of duplicates (Figure 1). After a full-text screening, 56 articles were excluded. Therefore, a total of 40 studies, including 11 case–control studies, two nested case–control studies, 22 cohort studies, and five cross-sectional studies, were included in this study. These studies were conducted in the United States (10 studies), the United Kingdom (six studies), Denmark (six studies), Taiwan (five studies), Israel (three studies), Korea (two studies), and Canada (two studies), and one study each in France, Japan, and Sweden. Three studies were conducted in several regions. The studies had included 2,317,408 cases and 12,113,484 control subjects, and were published between 1995 and 2020. A summary of the baseline characteristics of the included studies is presented in Table 1.

Study quality

The risk of bias assessments using the ROBINS-I tool are summarized in Table S1. In general, most studies included in the current review had a low risk of bias. Eight studies were deemed to have a moderate risk of bias. This was primarily due to missing information about postoperative status of patients.

Overall cancer risk in PD patients

The relative risks of 16 types of cancer among PD patients are listed in Table 2 (see Figures S1–S11 for further details). PD patients were reported to have a lower risk of the following cancers: lung cancer (RR = 0.56, 95% CI = 0.48–0.66, I^2 = 91.3%, $p < 0.001$; Figure 2), genitourinary cancers (RR = 0.86, 95% CI = 0.81–0.91, I^2 = 75.1%, $p = 0.007$; Figure 3), gastrointestinal cancers (RR = 0.85, 95% CI = 0.80–0.91, I^2 = 0%, $p = 0.657$; Figure 3), and haematological cancers (RR = 0.81, 95% CI = 0.69–0.92, I^2 = 0%, $p = 0.795$; Figure 3). Conversely, PD patients had a significantly increased risk of melanoma (RR = 1.62, 95% CI = 1.36–1.94, I^2 = 81.90%, $p < 0.001$; Figure 4a) and brain cancer (RR = 1.38, 95% CI = 1.12–1.69, I^2 = 48.7%, $p = 0.025$; Figure 4b) compared to people without PD. No significant association was determined between PD and risk of any female cancers, gastrointestinal cancers, or haematological cancers.

When the data were further stratified into each individual cancer, PD patients were found to have a lower risk of bladder cancer (RR = 0.73, 95% CI = 0.64–0.83; Figure S1b), prostate

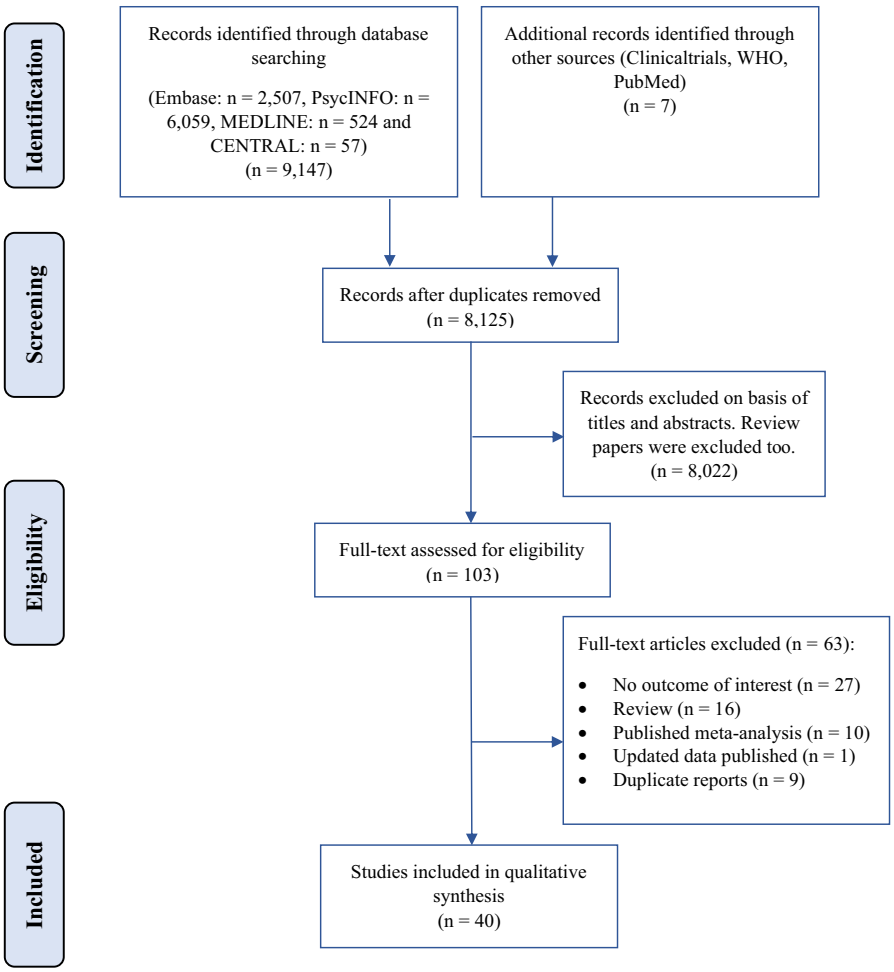

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram showing the selection of articles for the review. WHO, World Health Organization

TABLE 1 Baseline characteristics of included studies in the current review

First author	Year of publication	Country	Study design	Mean age, years		Total population	Sample size
				Cases	Control		
Cancer preceding PD diagnosis							
Elbaz [50]	2002	France	Case–control	71 (range = 41–97)	NR	380	196 cases; 185 controls
Olsen [51]	2006	Denmark	Case–control	73 (men: 72.6 women: 73.5)	NR	40,410	8090 cases; 32,320 controls
Powers [52]	2006	USA	Case–control	69 (range = 35–88)	71 (range = 38–85)	836	352 cases; 484 controls
Becker [10]	2010	UK	Nested case–control	40–59:57; 60–79: 178; ≥80: 231	40–59: 233; 60–79: 749; ≥80: 882	5996	466 cases; 1864 controls
Fois [53]	2009	UK	Cohort	<50: 76; 50–59: 187; 60–69: 613; 70–79: 1834; ≥80: 1645	N/A	26,064	26,064 cases
Lo [54]	2010	USA	Case–control	66	65.8	1453	692 cases; 761 controls
Lai [55]	2013	Denmark	Case–control	68.3	67.8	14,110	2822 cases; 11,288 controls
Jespersen [56]	2016	UK	Case–control	72 (range = 30–101)	NR	272,574	45,429 cases; 227,145 controls
Boursi [57]	2016	UK	Nested case–control	72.3 (range = 63.8–79.6)	71.9 (range = 63.3–79.3)	107,926	22,093 cases; 85,833 controls

Male sex, %	Duration of study, years	PD cases definition	Cancer types	Adjustment	Outcome of interest
21.5 cases; 23.1 controls	20	Medical records	Nonmelanoma skin cancer, lung, bladder, colorectal, skin cancer (nonmelanoma, melanoma), breast, prostate	Age, sex	OR
52.7	12	ICD-8 code 342 and ICD-10 code G20	Lung, larynx, urinary bladder, kidney, buccal cavity and pharynx, oesophagus, liver, cervix uteri, stomach, pancreas, breast, melanoma, colon, rectum, endometrium testis prostate, brain, leukaemia	Sex, year of birth	OR
61.6	14	97% of patients were diagnosed by a neurologist; the remaining were reviewed by three neurologists among authors	Breast, uterine, melanoma, ovarian, prostate, skin, bladder, colon and rectal	Age, sex, ethnicity, years of education, pack-years of smoking	OR
65.5	NR	Medical records	Lung, urinary tract, breast cancer, colorectal cancer, melanoma, lymphoma/leukaemia, prostate	Adjusted for age, sex, calendar time, BMI, smoking status	OR
49.37	3.2	ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, ICD-10 code G20	Larynx, oesophagus, stomach, colon, rectum, pancreas, lung, breast, cervix, ovary, uterus, prostate, kidney, bladder, malignant melanoma, other skin cancer, malignant & benign brain, bone, lymphoma, non-Hodgkin lymphoma, multiple myeloma, leukaemia, lymphoid leukaemia, myeloid leukaemia	Age, sex, time period in single calendar years, district of residence	RR
62.6 cases; 62.5 controls	4.3 (IQR = 1.9–8.1)	Medical records reviewed by movement disorders specialist	Melanoma, lung, bladder, breast, prostate, colorectal cancer	Age, sex, cigarette smoking (pack-years), alcohol consumption, body mass index, eye colour	OR
32.3	10	NR	Lung	Age, sex	OR
100	14	Danish version ICD-8 and ICD-10	Prostate	Duration of PD, stage of prostate cancer (localized and advanced), age, CCI scores, education level	OR
55.1	6 (3–9)	Diagnosed by the Health Improvement Network practitioner with at least one Read code	Colorectal	Age, sex, duration of PD, Parkinson-specific therapies, obesity (BMI > 30), smoking (ever), alcohol consumption, diabetes mellitus, chronic aspirin/NSAID use, hormone replacement therapy, previous screening colonoscopy	OR

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Study design	Mean age, years		Total population	Sample size
				Cases	Control		
Freedman [58]	2016	USA	Cohort	74	67	1,163,211	743,779 cases; 419,432 controls
Liao [59]	2017	Taiwan	Case–control	20.84		129,238	64,619 cases; 64,619 controls
Dalvin [60]	2017	Denmark	Case–control	75 ± 10		3896	974 cases; 2922 controls
PD diagnosis preceding cancer							
Moller [61]	1995	Denmark	Cohort	NR		7046	7046 cases
Minami [62]	2000	Japan	Cohort	66.2 ± 10.1	N/A	246	246 cases
Guttman [63]	2003	Canada	Cohort	>65	NR	45,912	15,304 cases; 30,608 controls
Olsen [64]	2004	Denmark	Cohort	72.8	N/A	14,088	14,088 cases
Constantinescu [65]	2007	USA, Canada	Cohort	61.1 ± 9.5	N/A	800	800 cases
Driver [25]	2007	USA	Cohort	59.7	59.8	1050	572 cases; 478 controls
Fois [53]	2009	UK	Cohort	<50: 76; 50–59: 187; 60–69: 613; 70–79: 1834; ≥80: 1645	N/A	26,064	26,064 cases

Male sex, %	Duration of study, years	PD cases definition	Cancer types	Adjustment	Outcome of interest
55.1 cases; 41.5 controls	10	ICD-9-CM code 332	Oesophageal, stomach, colon, rectum, pancreas, larynx, lung and bronchus, melanoma, breast, cervix, uterus, ovary, prostate, urinary bladder, kidney, thyroid, leukaemia	Race, sex and number of doctors' visits, stratified on birth year and cancer registry area, except that sex was not adjusted for in the subpopulation based on sex, nor race in the subpopulation defined by race	HR
57.3 cases; 56.1 controls	7	ICD-9 code 332.0	Colorectal	Sex, age, alcohol-related disease, chronic obstructive pulmonary disease, colorectal adenoma, diabetes mellitus, inflammatory bowel disease	OR
58% for PD cases	5 ± 5 for PD cases; 12 ± 8 for controls	33 H-ICDA codes and three ICD-9 codes	Melanoma	Age, sex	OR
49.25	4.6	NR	Mouth, oesophagus, stomach, colon, rectum, liver, gall bladder, pancreas, lung, breast, cervix, corpus uteri, prostate, ovary, kidney, urinary bladder, skin melanoma, brain, multiple myeloma, leukaemia	Age, calendar period	RR
42.28	8	Epidemiology survey	Stomach, lung, breast	Age, sex	SIR
NR	6	ICD-9-CM code 332	Prostate, bladder, colon, trachea, bronchus, lungs	N/A	SRR
51.03	Mean, 5; range, up to 23	ICD-8 code 342 and ICD-10 code G20	Lung, larynx, urinary bladder, kidney, buccal cavity and pharynx, oesophagus, liver, cervix uteri, stomach, pancreas, breast, melanoma, colon, rectum, endometrium, testis, prostate, brain, leukaemia, gall bladder, ovary	Age, calendar period of observation	SIR
66	4.6 (3691 person-years)	Examined by clinical investigators	Melanoma, basal cell carcinomas, unspecified skin malignancies	Age	SER
NR	5.2 (cases); 5.9 (controls)	Self-report PD diagnosis	Lung, colorectal, bladder, prostate, melanoma	Smoking history, alcohol use, physical activity, BMI	SRR
49.37	3.2	ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, ICD-10 code G20	Larynx, oesophagus, stomach, colon, rectum, pancreas, lung, breast, cervix, ovary, uterus, prostate, kidney, bladder, malignant melanoma, other skin cancer, malignant & benign brain, bone, lymphoma, non-Hodgkin lymphoma, multiple myeloma, leukaemia, lymphoid leukaemia, myeloid leukaemia	Age, sex, time period in single calendar years, district of residence	RR

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Study design	Mean age, years		Total population	Sample size
				Cases	Control		
Becker [10]	2010	UK	Cohort	40–59: 57; 60–79: 178; ≥80: 231	40–59: 233; 60–79: 749; ≥80: 882	5996	2993 cases; 3003 controls
Schwid [66]	2010	Canada	Cohort	60.15	N/A	806	806 cases
Lo [54]	2010	USA	Case–control	66	65.8	1453	692 cases; 761 controls
Sun [67]	2011	Taiwan	Cohort	63.5	63.1	24,785	4957 cases; 19,828 controls
Wirdefeldt [68]	2013	Sweden	Cohort	Male: 62.5	NR	70,716	11,786 cases; 58,930 controls
Ong [69]	2014	UK	Cohort	<50: 2292; 50–59: 6508; 60–69: 26,945; 70–79: 81 958; ≥80: 101,491	NR	9,234,808	219,194 cases; 9,015,614 controls
Tang [70]	2015	Taiwan	Cohort	68	67.4	14,990	2998 cases; 11,992 controls
Lin [71]	2015	Taiwan	Cohort	<50: 10,361; 50–59: 6794; 60–69: 12,394; ≥70: 32 474	<50: 20,722; 50–59: 13,588; 60–69: 24,788; ≥70: 64,948	186,069	62,023 cases; 124,046 controls
Peretz [72]	2016	Israel	Cohort	Males: 71.1 ± 10.6; females: 71.5 ± 10.7	NR	7125	7125 cases: 3838 males and 3297 females

Male sex, %	Duration of study, years	PD cases definition	Cancer types	Adjustment	Outcome of interest
65.5	NR	Medical records	Lung, larynx, pharynx, buccal cavity, oesophagus, stomach, urinary tract and pancreas, breast, colorectal, prostate, melanoma, lymphoma, leukaemia, female reproductive organs, CNS, liver, gallbladder, thyroid gland	Adjusted for age, sex, calendar time, BMI, smoking status	IRR
64	1.8	Examined by PRECEPT investigators	Melanoma, lung, colon, leukaemia, prostate, breast, brain, basal cell, squamous cell	N/A	RR
62.6 cases; 62.5 controls	4.3 (IQR = 1.9–8.1)	Medical records reviewed by movement disorders specialist	Melanoma, lung, bladder, breast, prostate, colorectal cancer	Age, sex, cigarette smoking (pack-years), alcohol consumption, BMI, eye colour	OR
51.7	5	ICD-9-CM code 332	Colorectal, melanoma, skin cancers, oropharynx, hypopharynx, oesophagus, stomach, pancreas, lung, cervical, kidney, bladder, liver, breast, prostate	Age, sex, urbanization	HR
60.5	NR	ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, ICD-10 code G20	Oesophagus, stomach, liver, pancreas, nose and nasal sinuses, larynx, trachea, bronchus, lung, pleura, cervix uteri, kidney, small intestine, peritoneum, mediastinum, breast, prostate, testis, bone, connective tissue, muscle, endocrine cancers, malignant melanoma of the skin, nervous system, colon, rectum, anus, corpus uteri, ovary, and the thyroid gland, lymphoma, multiple myeloma, lymphatic leukaemia	Age, sex, educational level	HR
62.8	12	ICD-10 code G20	Breast, melanoma, uterus, kidney, stomach, neurological malignancies, lung, colon, rectum, bladder, bone, brain, cervix, larynx, leukaemia, liver, ovary, prostate, pancreas, testis, thyroid, uterus, multiple myeloma, melanoma	Age, sex, calendar year of first recorded admission, region of residence, quintile of patients' Index of Deprivation score (a standard English measure of socioeconomic status)	SRR
52.4	NR	ICD-9-CM code 332	Brain cancer	Age, sex	HR
49.2	7	ICD-9-CM code 332	Malignant brain tumours, oesophageal, stomach, liver, gall bladder, colorectal, pancreas, lung, uterine, cervical, prostate, kidney, bladder, leukaemia/ lymphoma, melanoma, skin cancer	Age, sex	HR
53.7	10	Purchasing profile of APD	Lung, colon (lower), breast, CNS, kidney, leukaemia, lymphoma, melanoma, ovarian, pancreatic, prostatic, rectal, thyroid	Age	SIR

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Study design	Mean age, years		Total population	Sample size
				Cases	Control		
Freedman [58]	2016	USA	Case–control	74	74	979,816	836,947 cases; 142,869 controls
Tacik [73]	2016	USA	Cohort	73	69	1449	971 cases; 478 controls
Lerman [74]	2018	Israel	Cohort	Overall mean, 42.6; PD cases, 69.9		1,251,695	7727 cases; 1,243,968 controls
Agalliu [75]	2019	Europe, Israel, USA	Case–control	67.8	64	1187	969 cases; 218 controls
Ording [76]	2019	Denmark	Cohort	75	N/A	28,835	28,835 cases
Park [9]	2019	Korea	Cohort	71 ± 10		312,054	52,009 cases; 260,045 controls
Ryu [11]	2020	Korea	Cohort	71.58 ± 9.62	71.58 ± 9.62	424,399	70,730 cases; 353,669 controls
Cross-sectional study							
Bertoni [77]	2010	USA, Canada		68.6	N/A	2106	2106 cases
Inzelberg [78]	2011	Israel		69.5 ± 10.6	N/A	1375	1395 cases
Kareus [79]	2012	USA		NR	N/A	2998	2998 cases
Rugbjerg [24]	2012	Denmark		72.7	NR	20,343	20,343 cases

Male sex, %	Duration of study, years	PD cases definition	Cancer types	Adjustment	Outcome of interest
Cases: 54.5; controls: 54.8	10	ICD-9-CM code 332	Oesophageal, stomach, colon, rectum, pancreas, larynx, lung and bronchus, melanoma, breast, cervix, uterus, ovary, prostate, urinary bladder, kidney, thyroid, leukaemia	Race, sex, and number of doctors' visits, stratified on birth year and cancer registry area, except that sex was not adjusted for in the subpopulation based on sex, nor race in the subpopulation defined by race	OR
NR	10	Diagnosed by Mayo Clinic movement disorder specialists using UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria	Breast, colon, prostate, bladder, pancreas, ovaries, lungs, bile duct, uterus, oesophagus, thyroid, kidney, testicles, leukaemia, lymphoma, nonmelanoma skin cancer	Age and sex, with the exception of sex-specific cancers (breast, prostate, ovarian, uterine, testicular), which were not adjusted for sex; for types of cancer that occurred in <10 individuals, no model adjustment was made	OR, SRR
51.95	>15	ICD-9	Melanoma and keratinocyte carcinoma: squamous cell carcinoma and basal cell carcinoma	Age at index date, sex, residence area, birth area, smoking history	HR
53.41	NR	Medical charts	Skin cancer, melanoma, nonskin cancer, smoking-related cancers, colon cancer, kidney cancer, leukaemia, lymphoma, hormonal cancer (women and men), breast, prostate	Age, sex, Ashkenazi Jewish ethnicity, study centre, smoking status, body mass index, drinking habits	OR
54	10	ICD-8 and ICD-10	Colon, pancreas, lung, breast, prostate, liver, melanoma, kidney, bladder	Age, sex, calendar period of PD diagnosis, CCI score, CCI diseases	SIR
41	6	ICD-10 code G20 and code V124	Oral cavity, pharyngeal, laryngeal, oesophageal, stomach, colorectal, liver, pancreas, biliary, lung, kidney, bladder, thyroid, leukaemia, lymphoma, multiple myeloma, skin melanoma, cervix uteri, corpus uteri, ovary, testis, prostate	Age, sex, hypertension, diabetes mellitus, hyperlipidaemia, income	HR
41.74	8	ICD-10 G20 and PD registration code (V124)	Skin cancer, melanoma, nonmelanoma skin cancer	Age, sex, comorbidities (diabetes mellitus, hypertension, dyslipidaemia, income status)	HR
68.2	2	Examined by movement disorder neurologists	Melanoma	Age, sex	RR
63	7.3 ± 6	Diagnosed by a movement disorder specialist at each centre	Melanoma	Gender, age, race	OR
NR	NR	ICD-6 code 350, ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, ICD-10 code G20	Colorectal, lung, prostate, melanoma	Sex, age, birth place	RR
52.7	Mean, 5.7; range = 0–32	ICD-8 code 342 and ICD-10 code G20	Malignant melanoma, nonmelanoma skin cancer, brain, breast, bladder, liver, lung, larynx, stomach, ovary, colorectal, prostate, multiple myeloma, lymphatic leukaemia, non-Hodgkin lymphoma, uterine, ovarian, prostate	N/A	SIR

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Study design	Mean age, years		Total population	Sample size
				Cases	Control		
Shalaby [80]	2016	USA		71	72	425	108 cases; 124 controls

Abbreviations: APD, antiparkinsonian drugs; BMI, body mass index; CCI, Charlson Comorbidity Index; CM, Clinical Modification; CNS, central nervous system; H-ICDA, Hospital-International Classification of Diseases Adopted; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; IRR, incidence rate ratio; N/A, not applicable; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PD, Parkinson disease; PRECEPT, Parkinson Research Examination of CEP–1347 Trial; RR, relative risk; SER, standardized event ratio; SIR, standardized incidence ratio; SRR, standardized relative risk.

cancer (RR = 0.89, 95% CI = 0.82–0.98; Figure S1c), colorectal cancer (RR = 0.82, 95% CI = 0.75–0.89; Figure S2b), pancreatic cancer (RR = 0.85, 95% CI = 0.76–0.95; Figure S2d), lymphoma (RR = 0.79, 95% CI = 0.64–0.97; Figure S3a), leukaemia (RR = 0.82, 95% CI = 0.68–0.99; Figure S3b), and ovarian cancer (RR = 0.77, 95% CI = 0.64–0.92; Figure S4b) compared to people without PD.

In the studies that had reported cancer risk of colon and rectal cancer separately, negative associations between PD patients and the risks of colon cancer (RR = 0.87, 95% CI = 0.78–0.96; Figure 5) and rectal cancer (RR = 0.85, 95% CI = 0.76–0.94; Figure 5) were reported. Moreover, our study also revealed a negative association between PD patients and non-Hodgkin lymphoma (RR = 0.80, 95% CI = 0.74–0.87; Figure 6). No associations were found with the subtypes of leukaemia (Figure S5).

Subgroup analyses

Cancer preceding PD diagnosis

Compared to people without PD, we found that there were inverse associations between PD patients and the risks of lung cancer (RR = 0.63, 95% CI = 0.48–0.83), bladder cancer (RR = 0.75, 95% CI = 0.59–0.94), prostate cancer (RR = 0.87, 95% CI = 0.78–0.97), colorectal cancer (RR = 0.82, 95% CI = 0.67–0.99), and ovarian cancer (RR = 0.71, 95% CI = 0.53–0.96) when cancer preceded PD diagnosis. No other associations were found with the other cancers (see Table 2, Figures 2, S1b,c, S2b, and S4b).

PD diagnosis preceding cancer

Positive associations were reported between PD patients and the risks of melanoma (RR = 1.54, 95% CI = 1.22–1.95) and brain cancer (RR = 1.60, 95% CI = 1.23–2.07) when PD diagnosis preceded cancer. Conversely, lower risks of lung cancer (RR = 0.58, 95% CI = 0.48–0.71), bladder cancer (RR = 0.76; 95% CI = 0.65–0.89), prostate cancer (RR = 0.88, 95% CI = 0.78–0.99), colorectal cancer (RR = 0.83, 95% CI = 0.73–0.94), and ovarian cancer (RR = 0.79, 95% CI = 0.63–0.99) were observed. No other significant associations were observed with other cancers (Table 2, Figures 2, 4, S1b,c, S2b, and S4b).

Cross-sectional study

We found that PD patients had lower risks of lung cancer (RR = 0.63, 95% CI = 0.48–0.83) and ovarian cancer (RR = 0.63, 95% CI = 0.41–0.97). Conversely, PD patients had higher risks of melanoma (RR = 2.35, 95% CI = 1.52–3.64) and breast cancer (RR = 1.17, 95% CI = 1.02–1.34; Table 2, Figures 2, 4a, and S4b).

Cancer risk stratified by gender

We subsequently examined whether participants' gender would have any influence on risk of cancer. Of the 40 included studies, only six studies investigated cancer risks stratified by gender. The results showed no difference in the risk of cancer for all analyses between different genders (Figure S6).

Publication bias

No significant publication bias was detected for all cancer risks except melanoma (Egger test: $p = 0.031$; Table S2) and ovarian cancer (Egger test: $p = 0.017$; Table S2; see Figures S7–S11 for further details).

DISCUSSION

In this review of 40 studies including 14,430,892 individuals, pooled results indicated that PD patients had lower risks of lung cancer, genitourinary cancers, gastrointestinal cancers, and haematological cancers compared to people without PD. Conversely, PD patients had increased risks of melanoma and brain cancer. No association was reported between PD patients and female cancers. These results corroborate with the previous meta-analyses,

Male sex, %	Duration of study, years	PD cases definition	Cancer types	Adjustment	Outcome of interest
44.4	NR	Medical records diagnosed by neurologists and reviewed by one of the authors	Melanoma	Age, gender, race, education	OR

TABLE 2 Association between PD and risks of cancers

Cancer type	Studies included, *n*	RR (95% CI)				
		Cancer diagnosis after PD	Cancer diagnosis before PD	Cross-sectional	Overall	
Lung cancer	28	0.58 (0.48–0.71)[a]	0.63 (0.48–0.83)[a]	0.34 (0.20–0.57)[a]	0.56 (0.48–0.66)[a]	
Melanoma	32	1.54 (1.22–1.95)[b]	1.43 (0.95–2.15)	2.35 (1.52–3.64)[b]	1.62 (1.36–1.94)[b]	
Brain cancer	13	1.60 (1.23–2.07)[b]	1.07 (0.75–1.52)	0.99 (0.68–1.43)	1.38 (1.12–1.69)[b]	
Genitourinary cancers						
Kidney cancer	16	1.03 (0.86–1.24)	0.92 (0.72–1.16)	–	1.00 (0.86–1.16)	0.86 (0.81–0.91)[a]
Bladder cancer	23	0.76 (0.65–0.89)[a]	0.75 (0.59–0.94)[a]	0.48 (0.38–0.60)	0.73 (0.64–0.83)[a]	
Prostate cancer	28	0.88 (0.78–0.99)[a]	0.87 (0.78–0.97)[a]	1.01 (0.55–1.88)	0.89 (0.82–0.98)[a]	
Uterine cancer	13	0.91 (0.71–1.17)	1.00 (0.86–1.16)	0.82 (0.59–1.14)	0.93 (0.80–1.08)	
Female cancers						
Breast cancer	25	1.06 (0.96–1.17)	0.99 (0.92–1.08)	1.17 (1.02–1.34)[b]	1.05 (0.97–1.13)	0.98 (0.91–1.05)
Ovarian cancer	12	0.79 (0.63–0.99)[a]	0.71 (0.53–0.96)[a]	0.63 (0.41–0.97)[a]	0.77 (0.64–0.92)[a]	
Gastrointestinal cancers						
Liver cancer	11	1.10 (0.80–1.50)	0.68 (0.58–0.80)	0.92 (0.63–1.34)	1.01 (0.76–1.32)	0.85 (0.80–0.91)[a]
Colorectal cancer	26	0.83 (0.73–0.94)[a]	0.82 (0.67–0.99)[a]	0.70 (0.48–1.03)	0.82 (0.75–0.89)[a]	
Stomach cancer	14	0.94 (0.77–1.14)	0.90 (0.73–1.11)	0.54 (0.18–1.63)	0.90 (0.77–1.05)	
Pancreatic cancer	14	0.90 (0.80–1.00)	0.68 (0.59–0.79)	–	0.85 (0.76–0.95)[a]	
Oesophageal cancer	13	0.88 (0.71–1.09)	0.77 (0.52–1.14)	–	0.85 (0.72–1.00)	
Haematological cancers						
Lymphoma	15	0.80 (0.62–1.05)	0.69 (0.41–1.18)	0.73 (0.53–1.01)	0.79 (0.64–0.97)[a]	0.81 (0.69–0.92)[a]
Leukaemia	17	0.90 (0.71–1.14)	0.65 (0.42–1.00)	0.66 (0.43–1.01)	0.82 (0.68–0.99)[a]	

Abbreviations: CI, confidence interval; PD, Parkinson disease; RR, relative risk.

[a]Significant reduced risk.

[b]Significant increased risk.

which found that PD patients had significantly decreased risks of lung, digestive, and urinary cancers and significantly increased risk of melanoma and brain cancer [12,18].

We offer several explanations for these findings. First, the hypothetical causal link between PD and increased cancer risks could be affected by the medication. Several studies have suggested that

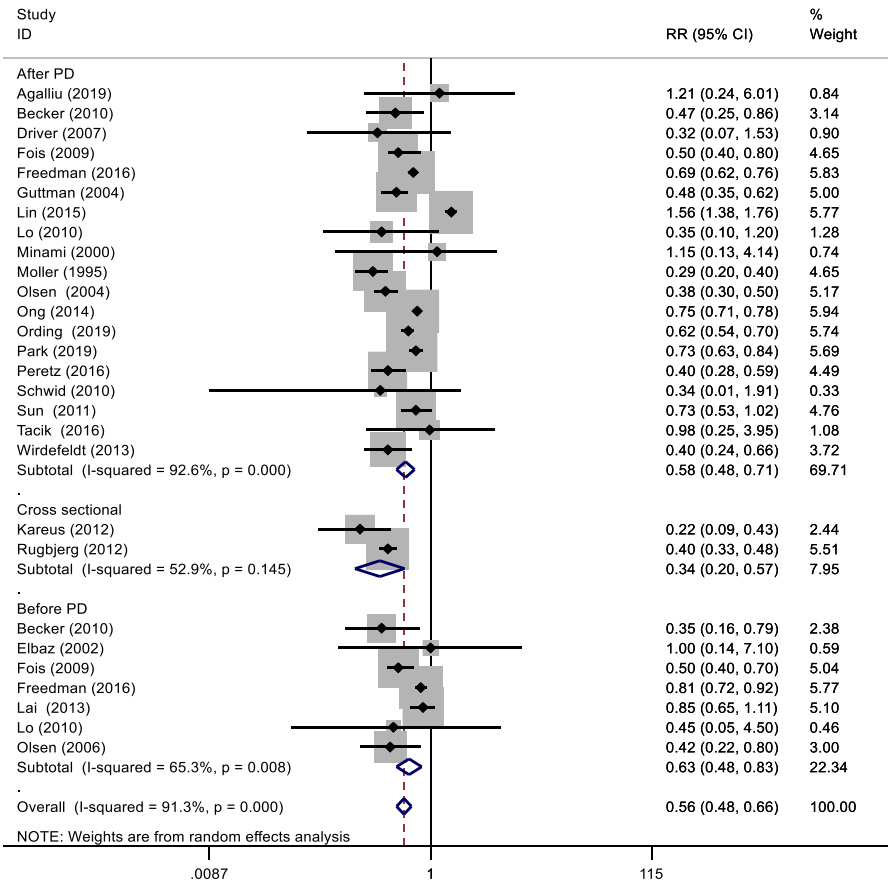

FIGURE 2 Forest plots of the negative association between Parkinson disease (PD) and risk of lung cancer in all populations. CI, confidence interval; RR, relative risk

levodopa might increase the risk of melanoma and brain cancer. Although the iatrogenic relationship between melanoma and brain cancer and levodopa remains speculative [19,20] levodopa is thought to affect tumour generation by inducing cellular oxidative stress [21-23]. An alternative explanation for such close associations between PD and cancer risks might be confounded by environmental factors such as lifestyle (cigarette smoking, coffee and alcohol consumption). For example, several studies in this review attempted to examine whether cigarette smoking could significantly modify the association between cancer and PD [10,24,25]. These include lung cancer, stomach cancer, oesophageal cancer, pancreatic cancer, bladder cancer, and kidney cancer, which were found to be lower among those who were smoking. Several studies also showed a weak inverse association between coffee and alcohol consumption and PD risk, where these factors were found to contribute to cancer risks too [26-28]. Nevertheless, given that these studies were not powered to study these relationships, further studies examining individuals' lifestyles and cancer risks are warranted in future investigations.

Another possible reason is the common genetic features identified in both PD and cancers. For instance, some genes found in PD including alpha synuclein (*SNCA*), parkinsonism-associated deglycase (*PARK7/DJ-1*), PTEN-induced kinase 1 (*PINK1*), and *PARK2* have been linked to various cancers [29-31]. *SNCA* is the main component of Lewy bodies, which are the inclusion bodies found in the midbrain of PD patients [32]. The expression of SNCA is not restricted to brain region, as studies have reported its presence in the peripheral tissues and body fluids [33,34]. Several studies have indicated that *SNCA* dysregulation was detected in various cancers including lung cancer [35] colorectal cancer [36] ovarian cancer [37] breast cancer [37]and non-Hodgkin lymphoma [38]. For instance, a recent study showed that downregulation of *SNCA* contributes to the development of lung adenocarcinoma via bioinformatics analyses, indicating that *SNCA* probably functions as a tumour suppressor gene in lung cancer [35]. Another study by Li et al. revealed that *SNCA* overexpression potentially inhibits tumour invasion by inducing apoptosis in medulloblastoma cell lines [39]. In contrast, two studies showed that *SNCA* overexpression promotes tumourigenesis by regulating cell proliferation and cell cycle [40,41]. *PARK2*, the E3 ubiquitin ligase, is identified as a potential tumour suppressor gene in glioblastoma, and colorectal and lung cancer [42]. Although the role of *PARK2* in tumour growth remains elusive, *PARK2* was reported to inhibit tumour growth by regulating cell cycle and apoptosis [43,44]. On the other hand, *DJ-1* was discovered as an oncogene that participates in cell proliferation, metastasis, and apoptosis cancer by modulating p53 or PI3K-AKT-mTOR pathway in breast cancer, lung cancer, gynaecologic cancer, bladder cancer, and pancreatic cancer [45-47]. A study by Ibáñez et al. [48] revealed the inverse comorbidities (asthma, human immunodeficiency virus, malaria, sarcoidosis, and dystrophy) between central nervous system disorders (including PD) and cancer. This study suggested that certain differentially expressed genes might decrease the risk of PD while increasing the risk of cancer [48]. For example, *ATP13A2* (also known as *PARK9*)

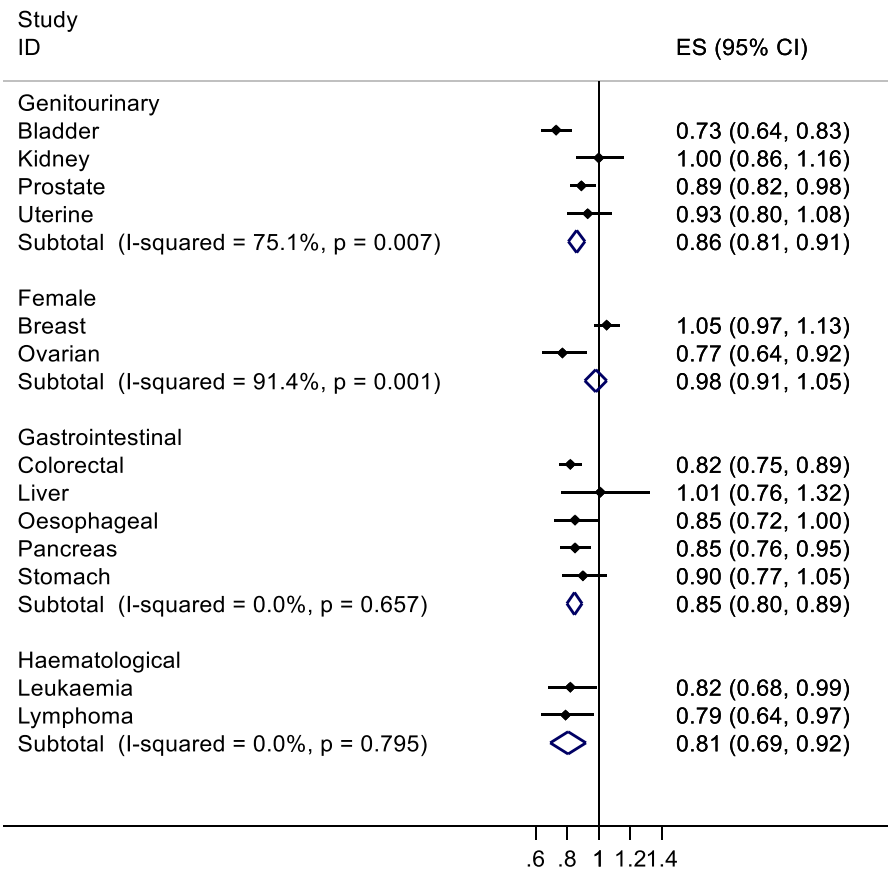

FIGURE 3 Forests plots of the associations between Parkinson disease and risks of female cancers, gastrointestinal cancers, genitourinary cancers, and haematological cancers. CI, confidence interval; ES, effect size

is a gene involved in intracellular cation homeostasis. Its autosomal recessive mutations result in loss of function of the gene and are associated with early onset PD [47]. It was described that this gene is downregulated in PD patients without cancer but upregulated in patients with lung cancer, colorectal cancer, and prostate cancer [48]. Another study has revealed that knockdown of *ATP13A2* would decrease tumourigenesis via inhibition of autophagy [49]. Nevertheless, it is unknown whether these dual effects are interrelated or causative to each other. In short, not only does involvement of these PD-associated genes in cancers make them potential treatment targets for cancer therapy, but they might also be ideal biomarkers for cancers. On the other hand, the molecular mechanisms of these PD-associated genes in cancers remain elusive, and this leaves important research gaps to be addressed in the future.

We also stratified our results by examining whether these cancers preceded PD diagnosis or vice versa. Results did not indicate any difference in the risk of any cancers between PD patients and people without PD. We hypothesized that the study might contain noise attributed to some individuals who are either at the asymptomatic phase (preclinical PD) or at the stage at which the presence of subtle motor and nonmotor symptoms have yet to meet the diagnostic criteria of PD (prodromal PD) being mistakenly included as people without PD in the analysis, but being found to have cancer [20,21]. Nevertheless, most of the studies found in the current review are underpowered to detect such association, and thus this remains speculative at the moment. Hence, this stresses the need of PD patients to undergo extensive examinations for better cancer detection. Also, given the close relationship found in our study, additional screening for either condition (cancer preceding PD diagnosis or PD diagnosis preceding cancer) could be useful for detecting early stages of both diseases.

Strengths and limitations

This study offers several strengths. We conducted a comprehensive review and found 18 additional studies compared to the latest published review [18]. Whenever possible, we assessed the associations by gender, cancer sites, and cancer subtypes. Nevertheless, our study has some potential limitations. First, although we have conducted a comprehensive search on four databases, it is possible that some studies might still be missed. Nevertheless, our analyses for publication bias suggest no such association in most cases. Second, results from the meta-analyses were highly heterogenous. This could be due to the differences in the demographics of the study population, such as ethnicities as well as differences in lifestyle, including smoking status. Unfortunately, due to the lack of details, we could not perform any additional subgroup analyses to examine these associations. Finally, this study could not conclude whether the oncogenic mechanisms arise before or after PD diagnosis. Studies that have examined these associations have not been able to provide consistent findings. As such, future studies are required to understand these associations with the complex temporal relationship in mind.

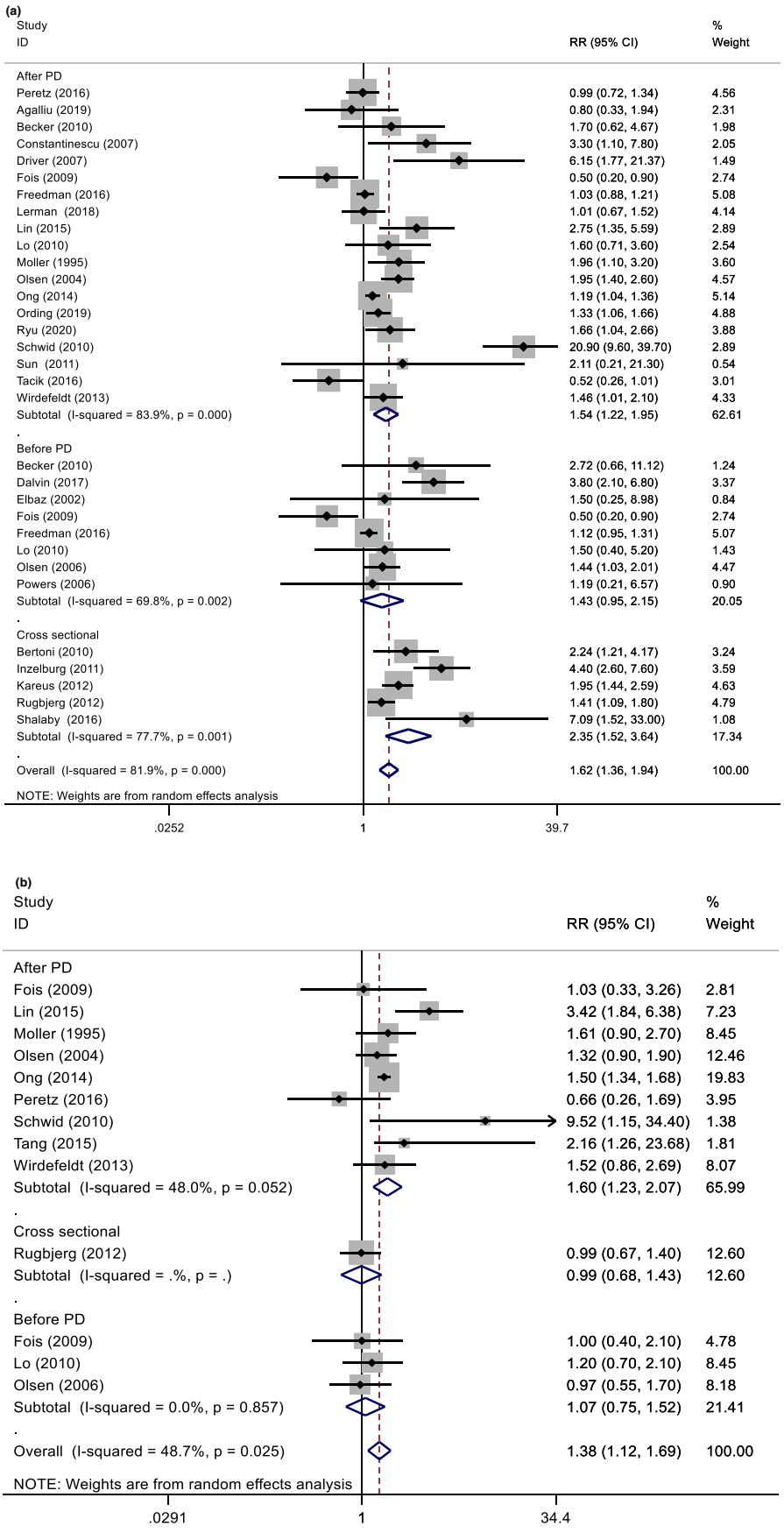

FIGURE 4 Forest plots of the positive associations between Parkinson disease (PD) and risk of (a) melanoma and (b) brain cancer in all populations. CI, confidence interval; RR, relative risk

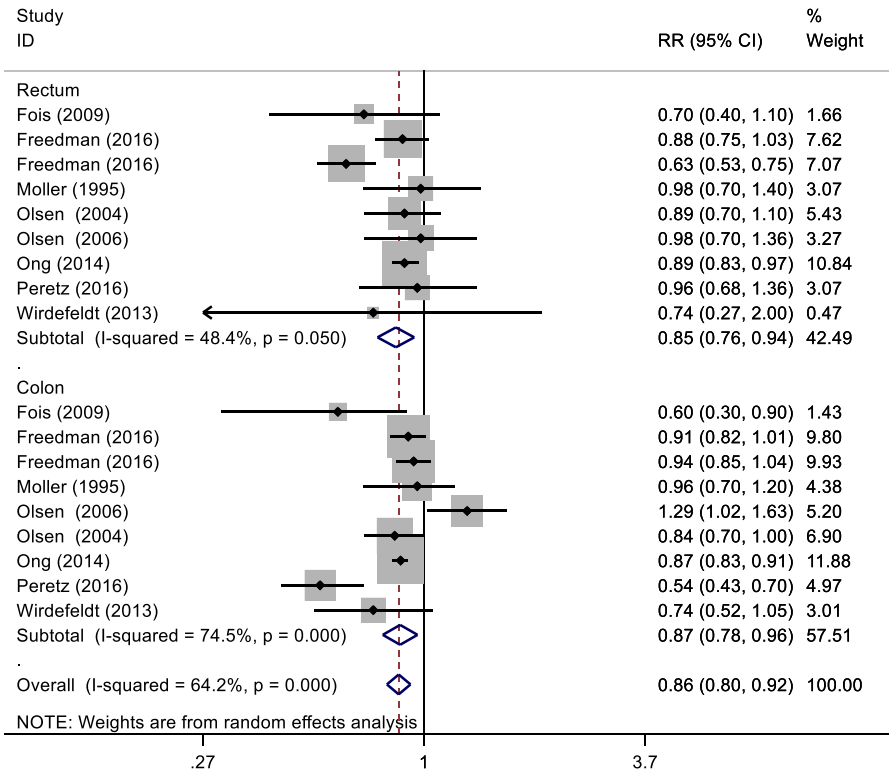

FIGURE 5 Forest plots of the associations between Parkinson disease and risk of colon and rectal cancer. CI, confidence interval; RR, relative risk

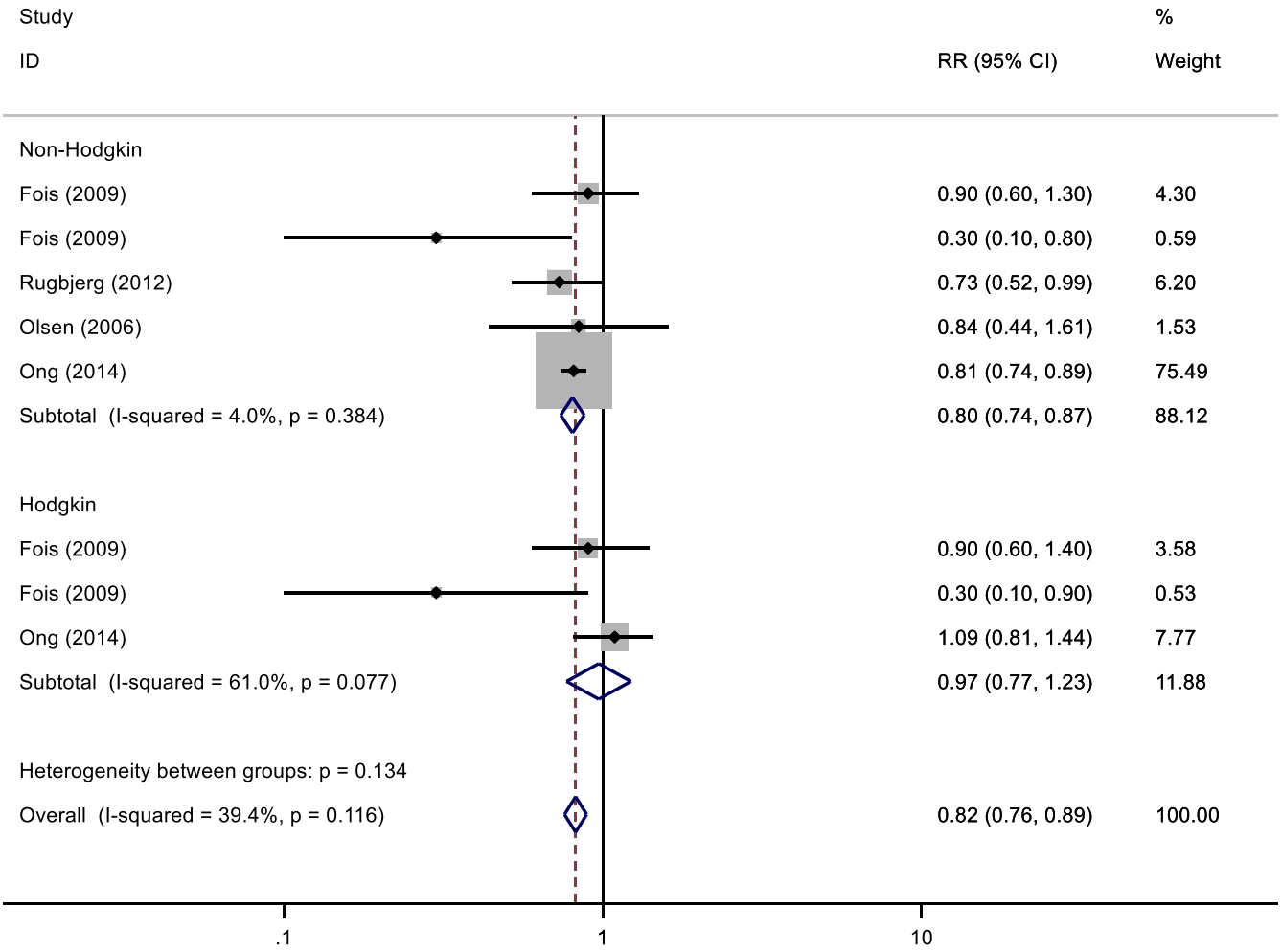

FIGURE 6 Forest plots of the associations between Parkinson disease and risks of non-Hodgkin lymphoma and Hodgkin lymphoma. CI, confidence interval; RR, relative risk

CONCLUSIONS

In summary, our meta-analysis indicated that patients with PD were significantly associated with a reduced risk of lung cancer, genitourinary cancers, gastrointestinal cancers, and haematological cancers and higher occurrence of melanoma and brain cancer. The identified associations between PD and cancer risks suggest that screening for either condition could be useful for early diagnosis, as these two distinct diseases might share some underlying biological pathways that lead to comorbidity. Nevertheless, future prospective studies should attempt to establish a more detailed relationship between cancers and PD patients' demographic characteristics, such as risk factors, ethnics, stage of disease, and medical treatment. This will help us to elucidate the interrelationship between cancers and PD.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Yong Qi Leong: Data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), software (equal), visualization (lead), writing–original draft (lead). **Shaun Wen Huey Lee:** Conceptualization (supporting), data curation (equal), formal analysis (lead), funding acquisition (supporting), investigation (equal), methodology (equal), software (lead), supervision (equal), validation (equal), writing–review & editing (equal). **Khuen Yen Ng:** Conceptualization (lead), data curation (equal), formal analysis (equal), funding acquisition (lead), investigation (equal), methodology (equal), project administration (equal), resources (lead), software (supporting), supervision (equal), validation (equal), visualization (supporting), writing–original draft (supporting), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary Appendix S1 of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Appendix S1

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