BMC Neurology

SYSTEMATIC REVIEW Open Access

Risk of colorectal cancer in Parkinson's disease: a systematic review and meta-analysis of 11 million participants

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Abstract

Background In the last twenty years, epidemiological research has suggested a potential decreased susceptibility to cancer among individuals diagnosed with Parkinson's disease (PD), although conflicting findings exist regarding the connection between PD and Colorectal cancer (CRC). This systematic review and meta-analysis were conducted to investigate the contemporary epidemiological data on the risk of CRC in PD.

Methods A comprehensive search of the literature was conducted utilizing three databases: PubMed, Scopus, and Web of Science. We included observational studies (cross-sectional, case-control, and cohort) that examined the relationship between PD and CRC. We also analyzed data obtained from the Parkinson's Progression Markers Initiative (PPMI) to evaluate the frequency of CRC among individuals diagnosed with PD, control participants, and PD patients carrying the LRRK2 genetic variant.

Results We included 22 studies with a total of 1,3137,089 PD cases were included in our study. Our analysis demonstrated a significant relationship between PD and a reduced incidence of CRC (pooled RR = 0.80, 95% CI = 0.69–0.91). Subgroup analysis based on study design revealed a significant association in the cohort (pooled RR = 0.80, 95% CI = 0.66–0.93) and case-control studies (pooled RR = 0.77, 95% CI = 0.66–0.89). Also, sub-group analysis based on the study continent showed no significant association in North America (pooled RR = 0.83, 95% CI = 0.51–1.18, and Asia (pooled RR = 0.85, 95% CI = 0.55–1.15). However, analysis based on continents indicated significant results solely in Europe (pooled RR = 0.79, 95% CI = 0.71–0.86). PPMI analysis revealed distinct differences in CRC frequencies across the three groups ($p < 0.001$) with PD patients with LRRK2 genetic variant exhibited the highest frequency of colorectal cancer, followed closely by healthy subjects.

Conclusion In conclusion, our study demonstrates a decreased risk of CRC in individuals with PD, suggesting an inverse association between the two diseases. Further research is warranted to elucidate the underlying mechanisms

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driving this correlation, paving the way for the development of targeted strategies for the prevention and management of both PD and CRC.

Keywords Parkinson's disease, Colorectal cancer, Cancer, Treatment

Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative condition characterized by a range of motor impairments [1], alongside non-motor symptoms like constipation and depression [2, 3]. The precise origins of PD remain ambiguous, with a combination of genetic and environmental factors thought to play a role [4]. It is believed that degeneration of dopaminergic neurons in the substantia nigra leading to the motor symptoms in PD [5], while the understanding of non-motor symptoms remains incomplete. The theory of the "gut-brain axis" suggests that the enteric microbiota may impact cognitive brain function [6], and the presence of α-synuclein protein aggregates in the enteric system has been associated with PD [7, 8].

Colorectal cancer (CRC) stands as the third most prevalent cancer type and the second most significant contributor to cancer-related deaths on a global scale, with an estimated 1.8 million new cases and approximately 881,000 fatalities reported worldwide in 2018 [9, 10]. The epidemiology of CRC demonstrates significant diversity across different geographical regions, age groups, genders, and racial backgrounds. This observed diversity may be attributed to various factors such as exposure to risk factors, demographic variations, genetic predisposition, and mutations, all of which influence prognosis and response to treatment [10, 11].

Evidence derived from research on PD and CRC indicates a potential interplay between the underlying mechanisms affecting the brain and the gut. Previous epidemiological investigations conducted in China have produced conflicting outcomes, underscoring the necessity for further exploration. Recent epidemiological studies spanning the last two decades have suggested a potential decreased risk of cancer in PD patients [12–14], although discordant evidence exists regarding the correlation between PD and CRC [14]. Various publications have presented divergent results concerning the relationship between PD and CRC. While some studies have indicated a reduced risk of CRC in individuals with PD [15, 16], others have not identified a significant inverse association between the two conditions [17]. Moreover, certain studies have proposed an elevated risk of CRC among PD patients [14]. Noteworthy is a study by Bajaj et al., which investigated the link between PD and all cancer types, revealing a notable connection between PD and the risk of CRC [18]. Given that both PD and CRC are common, age-related diseases, understanding their connection could lead to improved clinical practices for managing the health of aging populations. However, due to the limited sample size and included studies, the conclusions of this study were considered inconclusive. A comprehensive large-scale pooled study is warranted to address the ongoing debate and there is a clear need for a robust and comprehensive review that synthesizes the available data, helping to reconcile the conflicting findings and clarify the potential biological and epidemiological connections between these two diseases. Therefore, this systematic review and meta-analysis aim to examine the current epidemiological evidence concerning CRC in the context of PD. For further evaluate the relationship between CRC and PD we aimed to use the PPMI data.

Methods

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Search procedure and selection criteria

We systematically searched databases including Medline, Scopus, Embase, and Web of Science up to October 2023 to identify pertinent research studies. The primary search terms utilized were: ("Parkinson's disease" OR "Parkinsonism") AND ("cancer" OR "tumor" OR "neoplasm" OR "carcinoma"). Furthermore, the reference lists of relevant reviews and selected articles were manually scrutinized. Two independent reviewers (A & B) screened the identified studies for relevance, with any discrepancies resolved through consensus with a third reviewer (C). The selected studies needed to include cohort and case-control designs providing risk ratios (RR) or odds ratios (OR) with their corresponding 95% confidence intervals (CI) relating to PD and the associated risks of colorectal cancer. Additionally, studies were considered suitable for inclusion if the odds ratios (RR) and 95% CI could be calculated based on the data presented in the studies.

Data extraction and quality assessment

Two investigators, authors A & B, autonomously assessed the selected studies. Data extracted from each study encompassed details such as the primary author, publication year, study methodology, characteristics of case and control groups (including sample size, origin, demographics), primary outcomes, and follow-up duration. The Newcastle-Ottawa Quality Assessment Scale (NOS) was utilized to evaluate the quality of the included studies. Studies achieving NOS scores of 6 or higher were categorized as high-quality investigations.

PPMI data

Participants were recruited through the Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org/), initially enrolling individuals diagnosed with early-stage, untreated de novo PD, healthy controls HC matched for age and sex, from June 7, 2010, to May 27, 2013. In 2014, PPMI expanded its enrollment criteria to incorporate genetic cohorts, including PD patients and asymptomatic individuals carrying mutations in SNCA, LRRK2, or GBA genes. Our analysis included 367 participants with de novo PD and 176 HCs. Following a review of genetic profiles, we excluded 36 PD subjects with identified GBA gene variants. Ultimately, our study cohort comprised 228 idiopathic PD (iPD) patients and 103 PD patients harboring LRRK2 mutations (LRRK2-PD). Ethical approval was granted by the institutional review boards at all sites involved in the study, and all participants provided written informed consent prior to their inclusion. The study adhered rigorously to the relevant ethical guidelines and regulatory requirements. PD diagnosis adhered to Movement Disorder Society (MDS) diagnostic criteria, and disease severity was assessed using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Additionally, dopamine transporter deficits were evaluated through DAT imaging. Individuals diagnosed with neurological or psychiatric disorders other than PD were excluded. Only drug-naïve PD patients categorized as Hoehn and Yahr (H&Y) stages I or II were included. Participants underwent comprehensive motor and non-motor evaluations at baseline. Motor assessments consisted of H&Y staging and the MDS-UPDRS. Genetic testing was performed centrally by the genetic testing core of PPMI, specifically assessing LRRK2 gene mutations (G2019S, R1441G/C, and N1437H).

Statistical analysis

All statistical analyses were performed using R 4.2.2. Pooled estimates along with their corresponding 95% CI were calculated utilizing the generic inverse variance method. The analysis was carried out employing the Random-effects model with the DerSimonian and Laird approach. Due to the relatively low prevalence of colorectal cancer and Parkinson's disease, the OR was utilized as an approximation of RR. The RR was employed as a proxy for OR to combine data with OR in this investigation. Furthermore, We used Cochran's Q test and I2 statistics to evaluated heterogeneity. Publication bias was assessed through a funnel plot. A significance level of $P < 0.05$ was considered statistically significant in all analyses.

Results

Literature search

The primary database search yielded 744 outcomes as illustrated in Fig. 1. Subsequently, two additional studies were included manually. Following the elimination of duplicates, 632 studies underwent screening. Out of these, 469 studies were excluded during the initial screening phase, and the full texts of 163 studies were evaluated for eligibility. Ultimately, 22 studies were selected for both qualitative and statistical analysis [14, 15, 17, 19–37].

Study characteristics

We included 22 studies published between 2003 and 2023 (Table 1). The included research encompassed 17 cohort studies and five case-control studies carried out in diverse geographical locations. The combined total of participants across all studies amounted to 1,3137,089 individuals. The average quality score determined using the NOS was calculated to be 7.04.

Risk of CRC in PD

Twenty two studies reported RRs demonstrated a significant relationship between PD and a reduced incidence of CRC (pooled RR = 0.80, 95% CI = 0.69–0.91, with high heterogeneity I2 = 90%, Q = 158, $p < 0.001$) (Fig. 2). Subgroup analysis based on study design revealed a significant correlation in cohort (pooled RR = 0.80, 95% CI = 0.66–0.93, with high heterogeneity I2 = 93%, Q = 155, $p < 0.001$) and case control studies (pooled RR = 0.77, 95% CI = 0.66–0.89, with low heterogeneity (I2 = 0%, Q = 3, $p = 0.55$). Also, sub-group analysis based on study continent showed no significant association in North America (pooled RR = 0.83, 95% CI = 0.51–1.18, with high heterogeneity I2 = 82%, Q = 19, $p < 0.001$) and Asia (pooled RR = 0.85, 95% CI = 0.55–1.15, with high heterogeneity I2 = 96%, Q = 100, $p < 0.001$) (Fig. 3). However, analysis based on continents indicated significant results solely in Europe (pooled RR = 0.79, 95% CI = 0.71–0.86, with high heterogeneity I2 = 56%, Q = 19, $p = 0.02$).

The visualization of the funnel plot suggested a minimal presence of publication bias across the studies (Figs. 4). We performed Beggs ($p = 0.0342$) and Egger test ($p = 0.0724$) in order to represents meta bias across studies.

In our analysis, most studies demonstrated a reduced risk of CRC in individuals with PD (RR < 1). However, a few studies reported an RR > 1, indicating a potential increased risk of CRC among PD patients. The number of studies with RR > 1 was relatively small compared to those reporting RR < 1. It is important to note that studies with RR > 1 exhibited a range of quality in terms of design and sample size. Several factors could explain the findings of increased risk. Some of these studies had smaller

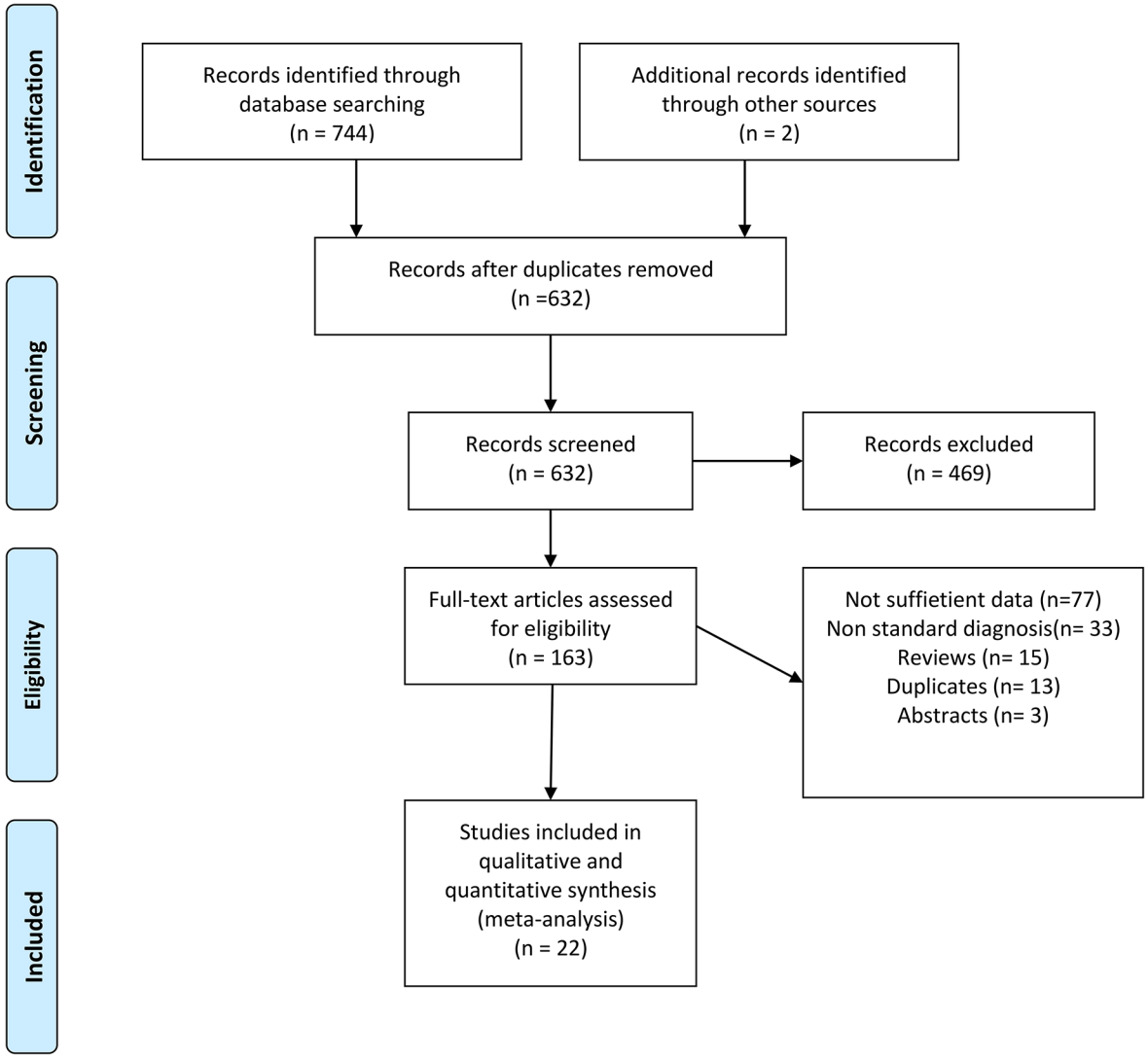

Fig. 1 PRISMA diagram of the selection process. PRISMA = preferred reported items for systematic reviews and meta-analyses

sample sizes, which may lead to greater variability and potential overestimation of risk. Additionally, the methodological quality varied, with some studies being prone to biases such as selection bias or confounding factors that were inadequately adjusted for.

PPMI findings

In this study, we analyzed data obtained from the PPMI to evaluate the frequency of CRC among individuals diagnosed with PD, control participants, and PD patients carrying the LRRK2 genetic variant. Demographical and clinical charcateristics of subjects represented in Table 2.

Our analysis revealed distinct differences in CRC frequencies across the three groups ($p < 0.001$) (Fig. 5). Notably, PD patients with LRRK2 genetic variant exhibited the highest frequency of colorectal cancer, followed closely by healthy subjects. In contrast, patients with PD without the LRRK2 mutation demonstrated a significantly lower frequency of CRC. Specifically, the percentage of CRC occurrences in the control group and the LRRK2-positive Parkinson's group was higher compared to the PD group without the LRRK2 mutation. This trend suggests a possible protective association between Parkinson's disease without LRRK2 mutations and the incidence of colorectal cancer, though further investigation is warranted.

Discussion

Increasing evidence indicates that individuals diagnosed with PD may present a notably reduced occurrence of cancer, yet the relationship with CRC risk remains less clear. Prior to our study, only one meta-analysis had investigated the connection between PD and CRC. Our study showed that there is signficant association between PD and lower rate of CRC. In the sub-group analysis, this result was only replicated in studies conduted on European population.

Table 1 Baseline characteristic of included studies

Author	Year	Region	Study design	Number of patients with PD	Number of controls	adjusted	NOS
Agalliu	2019	Germany, Spain	Cohort	969	218	age, sex	7
Becker	2010	UK	Cohort	2993	3003	age, sex, smoking, body mass index,	8
Boursi	2016	UK	Case-control	22,093	85,833	Obesity, diabetes, alcohol consumption, NSAIDs use, hormone replacement therapy	7
Cui	2019	Denmark	Case-control	1813	1887	age, aex	8
Driver	2007	USA	Cohort	487	487	age	8
Elbaz	2012	USA	Cohort	195	186	age, sex	8
Fois	2009	UK	Cohort	4355	574,860	age, sex, year of first hospital admission, region	6
Freedman (1)	2016	USA	Case-control	836,947	142,869	age, sex, selection year	6
Freedman (2)	2016	Asia	Case-control	20,267	5558	age, sex, selection year	8
Guttman	2003	Canada	Cohort	15,304	30,608	age, sex	7
Kim	2023	Korea	Cohort	8381	33,524	age, sex, income, region	7
Lin	2015	Taiwan	Cohort	62,023	124,046	age, sex	8
Lo	2010	USA	Cohort	692	761	age, sex, ethnicity, education (years), annual income, smoking, alcohol consumption, body mass index	7
Olsen	2005	Denmark	Cohort	14,088	NM	age, sex	8
Ong	2014	UK	Cohort	219,194	9,015,614	age, sex, calendar year, region of residence, quintile of patients	6
Ording	2019	Denmark	Cohort	28,838	NR	age, sex, calendar year	7
Park	2019	Korea	Cohort	52,009	260,045	age, sex, hypertension, hyperlipidemia	5
Peretz	2016	Israel	Cohort	7125	NM	age, sex, chronological year	7
Powers	2005	USA	Case-control	352	484	age, education, smoking	7
Rugbjerg	2012	Denmark	Cohort	20,343	32,360	age, sex, calendar year	7
Sun	2011	Taiwan	Cohort	4957	19,828	age, sex	6
Wirdefeldt	2014	Sweden	Cohort	11,786	58,930	sex, age	7

NM Not Mentioned, NOS Newcastle-Ottawa Scale

Multiple potential reasons underlie the inverse relationship between PD and CRC risk. Firstly, the distinctive nature of these two conditions and their differential impacts on cellular proliferation likely play a role. PD, characterized by the degeneration of dopaminergic neurons in the substantia nigra, contrasts with CRC, a disorder characterized by uncontrolled cell growth and decreased apoptosis. It is posited that cells in PD patients may have an increased propensity for apoptosis as a defense mechanism against cancer progression [38]. Additionally, observations of cell apoptosis and neurodegeneration beyond the substantia nigra, such as in the olfactory nucleus, basal forebrain, and the enteric nervous system among PD patients, lend support to this hypothesis [39]. Secondly, heightened levels of melatonin circulating in PD patients may also contribute to a diminished CRC risk [40]. Thirdly, PD treatment could offer an additional rationale, with studies suggesting that dopamine, an anti-Parkinsonian medication, acts as a suppressor of tumor angiogenesis and vascular endothelial growth factor, potentially lowering the likelihood of CRC [41]. Fourthly, research indicates that smoking and diabetes exert differing effects on PD and CRC risk, partially elucidating the inverse correlation between PD and CRC risk [36, 42]. Conversely, alterations in gut microbiota have been implicated in the development of both PD and CRC [43, 44]. Changes in microbiota composition in fecal matter and colonic mucosa in PD patients may lead to dysbiosis and gastrointestinal symptoms [45], potentially benefiting from preventive measures like colonoscopies and ongoing monitoring by gastroenterologists, thereby reducing CRC risk [46]. Nonetheless, conflicting findings exist regarding the impact of microbiota alterations in PD patients on CRC risk, necessitating further research to resolve this discrepancy [47].

One of the most compelling explanations for the observed positive or negative relationships between PD and specific cancer types lies in the presence of shared mutations in both disorders. Molecular studies have revealed that the proteins encoded by genes associated with PD play a role in mitochondrial functions, and modifications in these proteins impact both neuronal degeneration and tumor formation. Notably, proteins like α-synuclein, PARKIN, PINK1, and DJ-1, which are linked to PD, collectively contribute to various cellular processes, influencing antioxidative responses and the structure and function of mitochondria, particularly in tissues sensitive to hypoxia [48]. These findings collectively

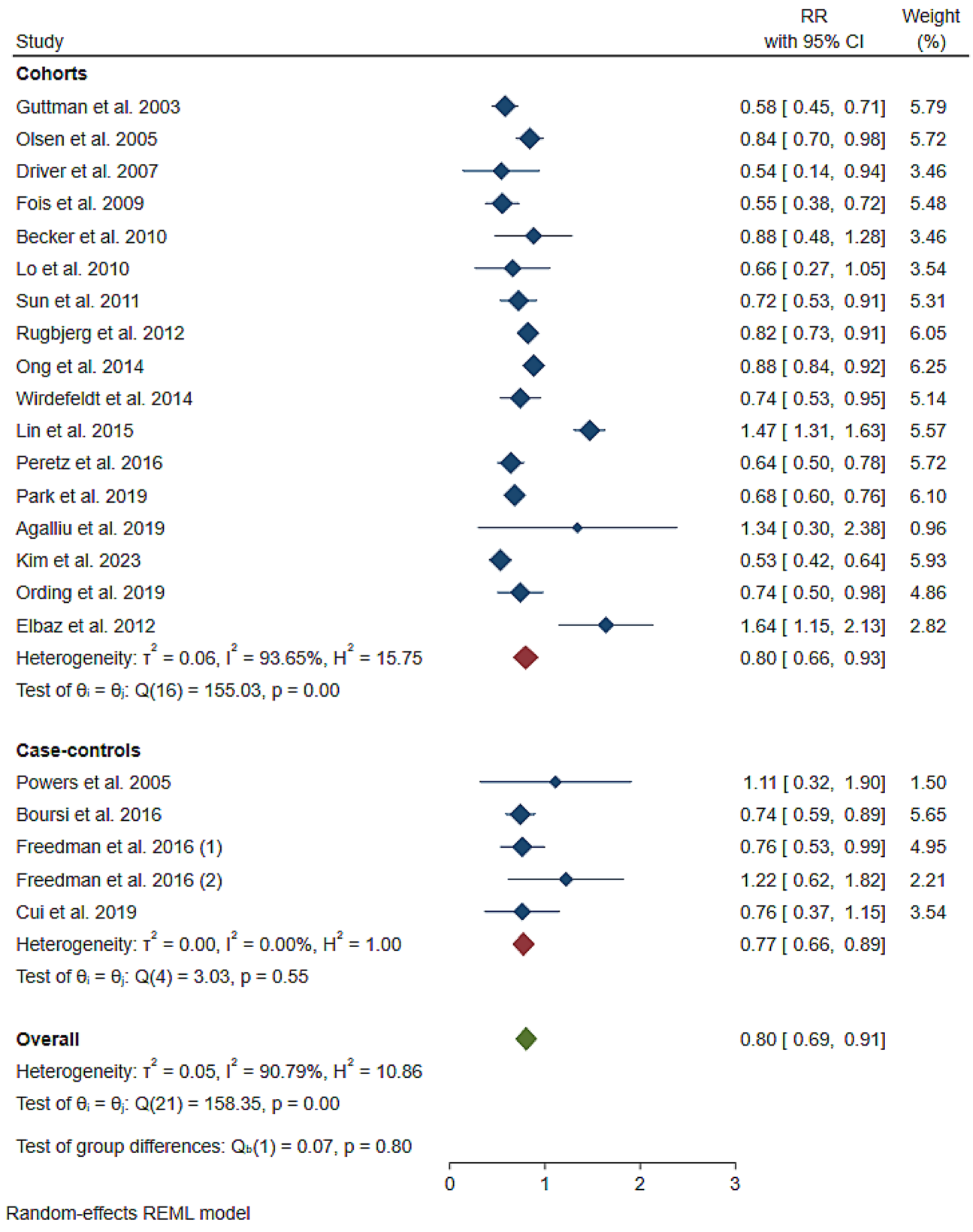

Fig. 2 Forest plot of RR of CRC in patients with PD based on study design

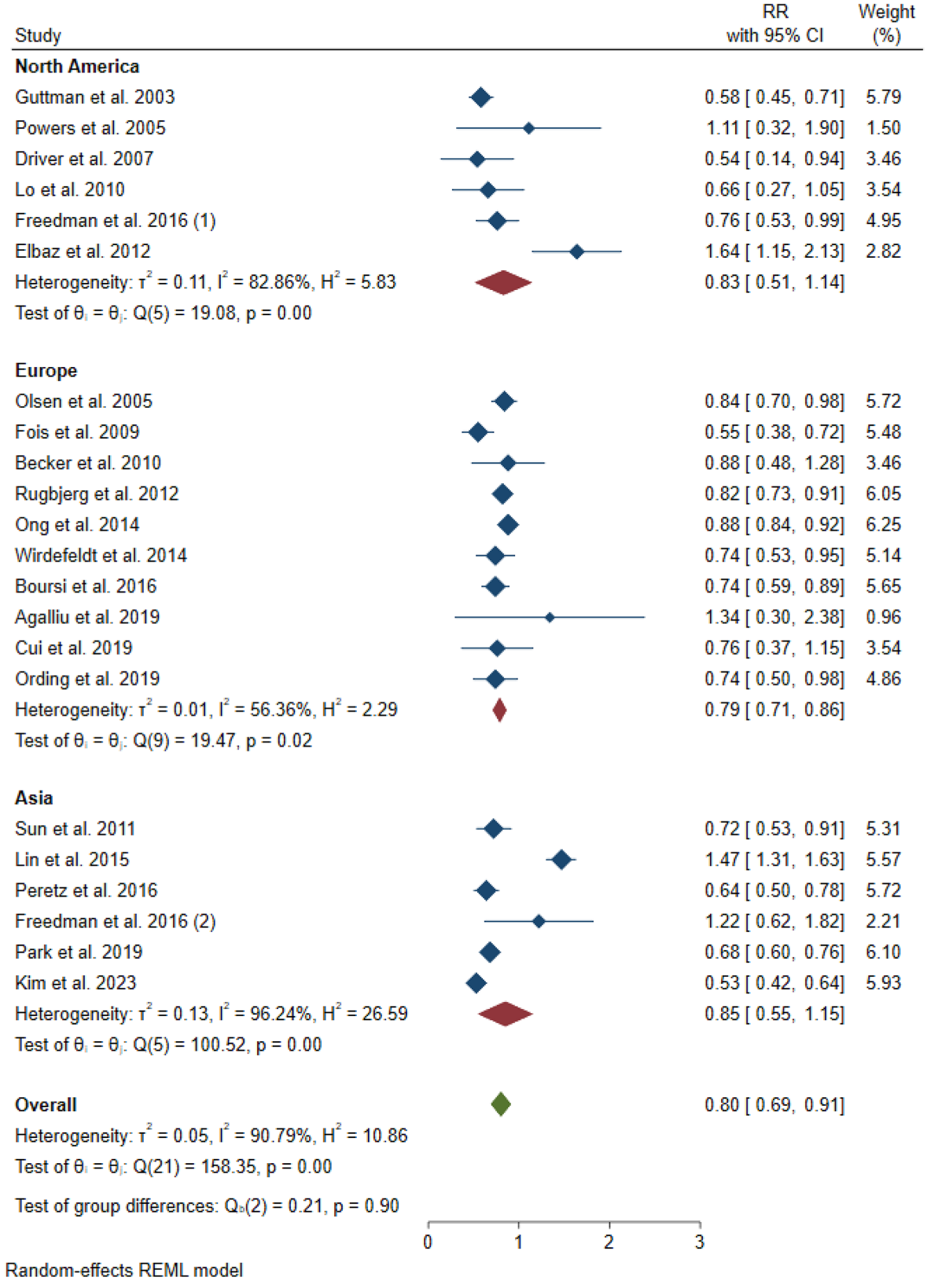

Fig. 3 Forest plot of RR of CRC in patients with PD based on continent

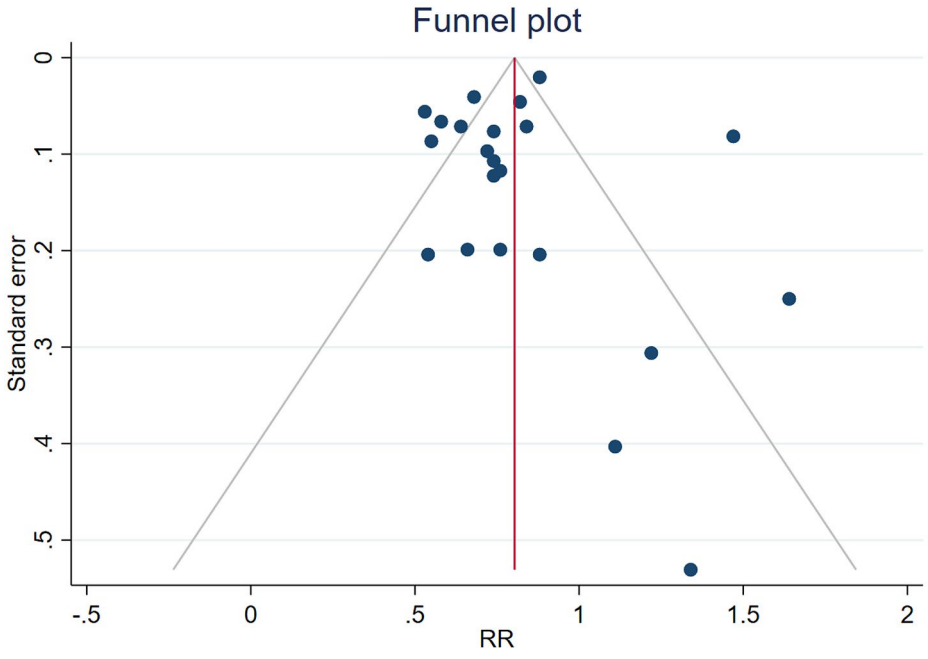

Fig. 4 Funnel plot of RR of CRC in patients with PD

Table 2 Demographical characteristics of HCs and patients with PD

Variable	HCs (*n* = 176)	iPD (*n* = 228)	LRRK2-PD (*n* = 103)	*P*-value
Age, mean (SD), years	61.5 (10.9)	63.1 (9.2)	61.5 (10.1)	0.213
Female/Male, No	58/118	75/153	36/67	0.634
Left-handed/Right-handed, No	26/150	19/209	10/93	0.042
Colorectal Cancer, No	16	11	12	**< 0.001**
Education, mean (SD), years	16.0 (2.8)	15.3 (3.0)	15.8 (2.9)	0.031
Disease duration, mean (SD), months		10.6 (6.5)	9.4 (4.6)	
MDS-UPDRS part I score, mean (SD)	0.5 (1.1)	1.1 (1.4)	1.1 (1.2)	**< 0.001**
MDS-UPDRS part II score, mean (SD)	0.4 (1.0)	6.0 (4.2)	5.8 (4.0)	**< 0.001**
MDS-UPDRS part III score, mean (SD)	1.2 (2.2)	20.7 (9.0)	20.4 (7.7)	**< 0.001**

HCs, healthy controls; iPD, idiopathic Parkinson's disease; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessments; ESS, Epworth Sleepiness Scale; LNS, Letter Number Sequencing

Significant results are bolded after correction

suggest that PARKIN acts as a tumor suppressor, and mutations in PARKIN may compromise its ability to inhibit carcinogenesis [49].

This meta-analysis has provided the most up-to-date synthesis of CRC risk in individuals with PD. Assessing the risk of PD in patients with CRC poses challenges, given the typically more aggressive disease trajectory observed in CRC patients compared to those with PD. Consequently, our study has robustly established a decreased CRC risk in the Western PD population, while uncertainties persist for the Asian population due to significant heterogeneity and limited available datasets. It is crucial to acknowledge the potential presence of publication bias and other biases, as well as the incomplete nature of a more detailed subgroup analysis due to insufficient data from primary sources. Unfortunately, the study did not clarify whether the findings reflected the impact of PD on cancer risk or vice versa. Additionally, combining results from cohort studies and case-control studies with differing designs is methodologically incorrect. Nonetheless, our study possesses numerous strengths, including an extensive literature search for the most recent data, a substantial number of cases, and a rigorous evaluation of evidence quality, collectively enhancing the reliability of the outcomes compared to previous research.

Our meta-analysis has presented the most current overview of the CRC risk among PD patients. Calculating the risk of PD in CRC patients is challenging, given the often more aggressive disease course observed in CRC patients compared to PD patients. Consequently, our study has confidently established an inverse CRC risk in the Western PD population, while the situation for the Asian population remains unclear due to substantial

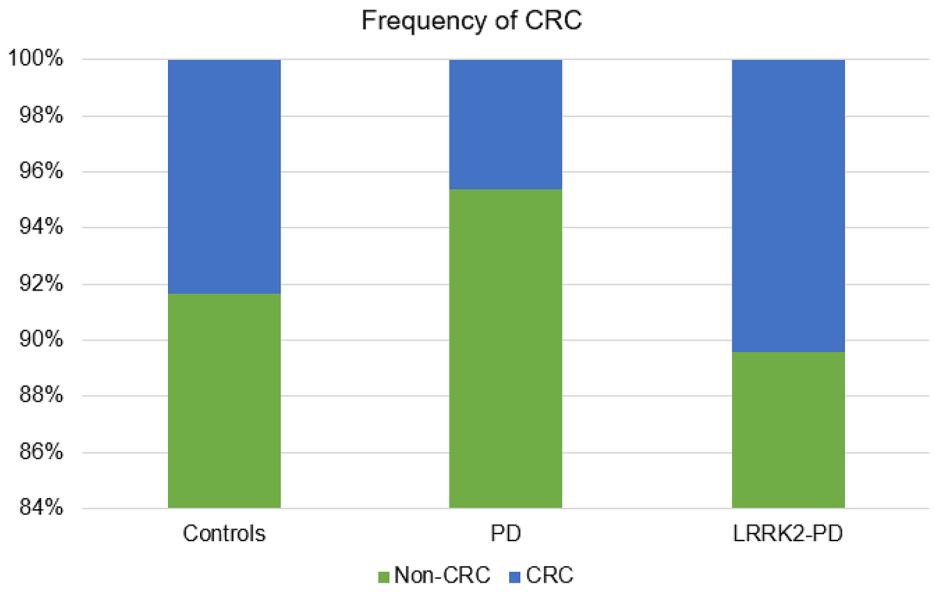

Fig. 5 Bar Plot of CRC in patients with PD, LRRK2-PD, and controls from PPMI

heterogeneity and limited available datasets. It is important to acknowledge the potential existence of publication bias and other forms of bias, and the incomplete nature of a more detailed subgroup analysis due to insufficient data from primary articles. Regrettably, it was unclear whether the results reflected the influence of PD on cancer risk or vice versa. Moreover, it is methodologically incorrect to amalgamate the results from cohort studies and case-control studies due to their differing designs. Nevertheless, our study boasts several strengths, including an extensive literature search for the latest data, a large number of cases, and a meticulous assessment of evidence quality, collectively enhancing the reliability of the results compared to earlier studies. We observed high heterogeneity. This elevated heterogeneity may stem from multiple factors, including differences in study designs (cohort vs. case-control), geographical variations (Asian vs. Western populations), varying definitions or diagnostic criteria for PD and colorectal cancer, and differences in the demographic characteristics or comorbidities of study participants. Additionally, variability in how covariates (e.g., smoking status, medication use, or genetic predispositions) were measured or adjusted for in the primary studies could have introduced further inconsistency across results.

In conclusion, our findings reveal an inverse association between PD and CRC that may be driven by shared mechanisms, such as enhanced pro-apoptotic signaling, the anti-angiogenic effects of dopaminergic therapy, and changes in the gut microbiota. These insights suggest that repurposing dopaminergic agents, modulating the gut microbiome, or targeting mitochondrial dysfunction could offer dual therapeutic benefits for both conditions. Future research should focus on these avenues to develop integrated treatment strategies.

Author contributions
M.S. and E.F. wrote the main manuscript text and M.S. prepared Figs. 1-4. All authors reviewed the manuscript. N.B., F.HS, and Z.F. obtained PPMI data and performed revision. S.A. visualized Fig. 5 and Table 2.

Funding
We do not have any financial support for this study.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 25 June 2024 / Accepted: 24 April 2025
Published online: 08 May 2025

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