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Parkinson's disease and colorectal cancer risk—A nested case control study

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ABSTRACT

Background: A pro-inflammatory gut microbiota was described in both Parkinson's disease and colorectal cancer (CRC) and recently α-synuclein was demonstrated in the enteric nervous system. We sought to evaluate the association between Parkinson's disease and CRC.
Methods: We conducted a nested case-control study using a large primary-care database. Cases were defined as all individuals with CRC. Up to 4 controls were matched with each case based on age, sex, practice-site and duration of follow-up. The primary exposure of interest was diagnosis of Parkinson's disease prior to CRC as well as disease duration, and Parkinson's specific therapies. The primary analysis was a conditional logistic-regression to estimate odds ratios (ORs) and 95% confidence interval (95%CI).
Results: The study included 22,093 CRC cases and 85,833 matched controls. Past medical history of Parkinson's disease >1 year before index-date was associated with lower CRC risk (OR 0.74, 95%CI 0.59–0.94). The inverse association was more prominent among females compared to males (0.64, 95%CI 0.42–0.96 and 0.8, 95%CI 0.60–1.07, respectively). While patients who received no therapy or therapy with dopamine agonists had a non-significant decrease in cancer risk, patients who were treated with dopamine had a non-significant elevated cancer risk.
Conclusion: Parkinson's disease is inversely associated with CRC risk.

1. Introduction

Parkinson's disease is the second most common neurodegenerative disorder with a prevalence of 0.3% in the entire population and 1% in individuals above the age of 60 [1]. The disease is slowly progressive with characteristic death of dopamine producing cells in the substantia nigra. Typical manifestations secondary to dopamine deficiency include both motor symptoms such as tremor, bradykinesia and muscle rigidity and neuropsychiatric symptoms such as depression and dementia [2]. Most cases are sporadic and to date the exact etiology behind the dopaminergic cells death is unknown.

Parkinson's disease and cancer share several common risk factors such as aging, DNA damage in response to oxidative stress, metabolic dysregulation, and environmental exposure to chemicals (i.e. pesticides) [3]. In addition, a positive association between Parkinson's disease and melanoma was described, possibly due to the role of L-Dopa in melanin synthesis [4]. However, similar to other neuropsychiatric disorders, such as Alzheimer's disease and schizophrenia, and some non-neurological diseases [5] epidemiological studies described an intriguing inverse comorbidity between Parkinson's disease and cancer, mainly colorectal, lung, prostate and bladder cancers [4,6–15] although some studies showed inconclusive results [16–18]. Potential mechanisms explaining this association include: common genetic predispositions that are activated in opposite directions in neuronal compared to proliferating tissue (such as PIN1 and LRRK2) [19,20]; aberrations in the ubiquitin-proteasome system [21,22]; low levels of melatonin that can improve Parkinson's symptoms and appears to increase cancer risk [23]; smoking status, a known cancer risk factor that was shown to reduce risk for Parkinson's disease [24,25]; diabetes [24] and high levels of cholesterol and fatty acids [26] that were described in association with lower risk for Parkinson's disease; cancer promoting effect of anti-Parkinsonian medications, such as dopamine agonists [27]; survival bias due to early mortality in patients with Parkinson's disease; and detection bias secondary to different cancer screening practices among patients with neurodegenerative disorders due to disease severity or socioeconomic status.

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Recently, several studies demonstrated α-synuclein accumulation, a known pathologic change in the Parkinsonian brain, in biopsies from the enteric nervous system of patients and suggested that the disease might actually result from a yet unknown pathogen or toxin that is able to penetrate the gastrointestinal mucosa and spread in a retrograde direction to the brain through the vagus nerve [28–33]. Another study demonstrated a pro-inflammatory gut microbiota in Parkinson's disease that might induce α-synuclein accumulation [34]. A single epidemiological study in a Danish cohort demonstrated lower hazard for Parkinson's disease in individuals after truncal vagotomy and more than 20 years of follow-up [35]. Other studies demonstrated the significance of gut pathogens and changes in the composition and diversity of gut microbiota in the pathogenesis of colorectal cancer (CRC) [36–38]. Thus, raising the possibility that gut microbiota might explain the reciprocal association between Parkinson's disease and cancer, mainly colorectal cancer.

To date, epidemiological studies focused mainly on the association of specific groups of cancers, such as smoking related and non-smoking related, with Parkinson's disease; evaluated patients with specific malignancies and relatively short surveillance time; lacked proper adjustment for specific cancer risk factors and previous cancer screening; and did not evaluate the effect of Parkinson's therapy on cancer outcome.

The aim of the current study, is to evaluate the complex associations between the two conditions in a large population based dataset. In depth understanding of the protective effects of Parkinson's disease on CRC in a well conducted epidemiological study might serve for future investigations of specific disease related pathways and possibly new therapies.

2. Methods

2.1. Study design

We conducted a nested case control study with incidence density sampling using The Health Improvement Network (THIN), a population representative primary-care database from the United Kingdom (UK). This design was described in previous publications by our group [39]. The study was approved by the Institutional Review Board at the University of Pennsylvania and by the Scientific Review Committee of THIN.

2.2. Data source

THIN contains data on approximately ten million patients treated by general practitioners (http://www.thin-uk.com/) including information on patient demographics, socioeconomic status, medical diagnoses, lab results, and drug prescriptions. Registration date is defined as the date when patients were first registered with a practice in THIN and Vision date is the date that a practice began using in-practice Vision software that collects information for the THIN database [40]. Data quality is monitored through routine analysis of the entered data [41,42]. THIN has been previously used for pharmaco-epidemiology studies, showing excellent quality of information [43].

2.3. Study cohort

All people receiving medical care from 1995 to 2013 from a THIN practitioner were eligible for inclusion. Exclusion criteria included: Patients without acceptable medical records (i.e., incomplete documentation or out of sequence date of birth, registration date, date of death, or date of exit from the database); subjects who were diagnosed with CRC before the age of 40, had inflammatory bowel disease or a family history of CRC (in order to focus on average risk population); Subjects who were diagnosed with CRC within the first 183 days after registration date in order to avoid prevalent cases [44].

Follow-up started at the later of either the Vision date or 183 days after the date on which the patient registered with the general practitioner [44], and ended on the earliest of cancer diagnosis date, date of death, transferring out of the database, or the end date of the database.

2.4. Case selection

Cases were defined as all individuals in the cohort with at least one medical Read code (the standard coding system used by general practices in the UK) for CRC during follow-up [45–47]. The date of cancer diagnosis was regarded as the index-date for each case.

2.5. Selection of controls

Controls were selected using incidence-density sampling [48]. The eligible control pool consisted of all individuals who remained at risk for CRC at the time when the case was diagnosed. Up to 4 controls were matched with each case based on age, sex, practice site and both duration and calendar period of follow-up. Controls were assigned the same index-date as their matched cases.

2.6. Exposures and covariates

The primary exposure of interest was Parkinson's disease defined as any medical codes for the disease before cancer diagnosis. We also used two additional definitions: incident Parkinson's cases defined as patients that were diagnosed more than 183 days after registration with a THIN practitioner; and cases that were diagnosed more than 1 year before index date, in order to avoid possible detection bias. As a secondary exposure we evaluated duration of Parkinson's disease (calculated as the difference between CRC index date and Parkinson's diagnosis date and grouped as 0–1, >1–5, >5 years); age at Parkinson's disease diagnosis (categorized as 40–49, 50–75 and >75 years old); and Parkinson's specific therapies (grouped as no treatment, dopamine, dopamine agonists and combined therapy including MAO-B, COMT and cholinesterase inhibitors). Individuals without Parkinson's disease served as the reference group for all the above variables. As potential confounders, we evaluated obesity (BMI >30), smoking history (ever/never), and alcohol consumption (non-users, any use and alcoholism/alcohol dependence); medical co-morbidities including diabetes mellitus; medications that may influence cancer risk such as chronic aspirin/NSAIDs use (more than 1 year in duration and last prescription within 6 months prior to cancer diagnosis) and hormone replacement therapy; and previous screening colonoscopy. All covariates were measured prior to index-date.

2.7. Statistical analysis

Conditional logistic regression was used to estimate OR and 95% confidence intervals (CIs) for the association between Parkinson's disease, as well as disease duration, therapy and age at disease onset and CRC risk. In a secondary analysis we performed stratification according to sex due to previous reports showing lower cumulative incidence of parkinson's disease among females [49]. Analyses were adjusted for all measured CRC risk factors. Finally, we assessed for interactions between variables (i.e. older patients might be more likely to have longer disease duration and to receive treatment with dopamine) All analyses were performed using STATA 13 (Stata Corp., College Station, TX, USA).