Published in final edited form as:

Cancer Epidemiol. 2016 August ; 43: 9–14. doi:10.1016/j.canep.2016.05.007.

Parkinson's disease and colorectal cancer risk – a nested case control study

Ben Boursi, M.D.^{1,2,3}, Ronac Mamtani, M.D. M.S.C.E.^{1,2}, Kevin Haynes, PharmD, M.S.C.E.¹, and Yu-Xiao Yang, M.D., M.S.C.E.¹

¹Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

²Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

³Tel-Aviv University, Tel-Aviv, Israel

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.

Keywords

Parkinson's disease; colorectal cancer; dopamine; age; risk; microbiota

Please address correspondence to: Yu-Xiao Yang, M.D., M.S.C.E., F.A.C.P., Perelman School of Medicine, University of Pennsylvania, 733 Blockley Hall, 423 Guardian Drive, Philadelphia, Pennsylvania 19104-6021, Fax: (215)349-5915; Telephone: (215)573-5027, yangy@mail.med.upenn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: None of the authors has any relevant conflict of interest to declare.

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.

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.

Methods

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.

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).

Study cohort

All people receiving medical care from 1995–2013 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.

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.

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.

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.

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).

Results

The study population included 22,093 CRC cases and 85,833 matched controls with a median age of 72 (IQR 63–79) and a median duration of follow-up of 6 years (IQR 3–9).

Characteristics of cases and controls are presented in table 1. Obesity, ever smoking, alcohol consumption, comorbidity with diabetes and recurrent antibiotic exposure were associated with higher CRC risk while previous screening colonoscopy was associated with lower risk.

There were 117 patients with Parkinson's disease among CRC cases (0.5%) compared to 541 among controls (0.5%). Past medical history of Parkinson's disease was associated with lower CRC risk with a fully adjusted OR of 0.84 (95%CI 0.69–1.03) (Table 2). When only incident cases of Parkinson's disease were included the OR was 0.77 (0.62–0.95). When the definition of Parkinson's disease was limited to those who were diagnosed more than 1 year before index date, in order to avoid possible detection bias, the OR was 0.74 (95%CI 0.59–0.94) and after stratification according to gender the OR was 0.8 for males (95%CI 0.60–1.07) and 0.64 for females (95%CI 0.42–0.96). There was no change in CRC risk with Parkinson's disease duration of 1–5 years and more than 5 years.

The inverse association between Parkinson's disease and CRC was mainly seen in individuals at the main age group (50–75 years). Among the small group of individuals with a diagnosis of Parkinson's disease at the age of 40–49 years there was a non-significant increase in CRC risk (the risk reached significance among males). In individuals who were diagnosed above the age of 75 there was no change in CRC risk (Table 2).

There was no association between anti-parkinsonian drugs and CRC risk. However while patients who received no medical therapy or therapy with dopamine agonists had a non-significant decrease in cancer risk, patients who were treated with dopamine showed a non-significant increase in risk (Table 2). When medication effect was evaluated only among cases and controls with Parkinson's disease there was no change in results.

When the analyses for disease duration, age at onset and anti-Parkinsonian treatment was stratified according to sex there was no change in the above results (Table 3 and Table 4), however the inverse association between any medical code for Parkinson's disease and CRC was more prominent among females compared to males, although not statistically significant.

Of note, there were no interaction between age at diagnosis of Parkinson's disease, anti-parkinsonian medications used and duration of Parkinson's disease before CRC diagnosis.

Discussion

The current large population based study provide further support to the inverse association between Parkinson's disease and CRC (with an adjusted OR of 0.74 and 95%CI 0.59–0.94) and enhance our understanding of the possible biological mechanisms behind this association.

Our first goal was to exclude bias as a possible explanation to the inverse comorbidity. By using a nested case control study design with matching on duration of follow up we were able to prevent possible survival bias if patients with Parkinson's disease had worse survival, and as a result lower opportunity for CRC diagnosis. We were also able to adjust for previous screening colonoscopies in order to exclude different screening frequencies among

Parkinson's patients, either lower screening due to poor medical status or increased screening due to better medical surveillance, thus avoiding detection bias. Since patients who undergo medical evaluation are at higher risk for incidental comorbidities, excluding Parkinson's diagnosis in the year prior to cancer diagnosis prevented this additional type of detection bias in the secondary analysis.

We further evaluated possible biological explanations for the observed inverse comorbidity. While factors such as smoking, diabetes and obesity were previously described as having differential effect on Parkinson's disease and CRC risk (24–26) including these variables in the multivariate model did not change the association between the two diseases. The gut microbiota and bacterial dysbiosis might also serve as a common pathway in the pathogenesis of both Parkinson's disease and CRC, and recurrent antibiotic exposure was shown to increase CRC risk by 20% (39). However adjusting to recurrent antibiotic exposure that can change the composition of the microbiota, did not influence the inverse association.

The anti-Parkinsonian drug dopamine was recently reported to inhibit vascular endothelial growth factor A (VEGFA) and tumor angiogenesis (50), thus possibly lowering cancer risk. In the current study only a small number of patients were treated solely with dopamine, however patients that were treated with dopamine agonists or other medical combinations that contain dopamine did not have statistically significant lower CRC risk. These results are similar to data from one previous epidemiological study focusing on any cancer incidence following Parkinson's diagnosis (16). In addition, if the association between Parkinson's disease and CRC risk was secondary to drug effects we would expect to see a more prominent association with disease duration and duration of therapy, an effect that was not seen in the current study.

Furthermore, our analysis did not show a significant association between age at Parkinson's disease onset and CRC risk. The above results points toward a genetic explanation that is not affected by age, disease duration or therapy and remain stable during follow-up. Since CRC risk was lower among women (OR 0.64, 95%CI 0.42–0.96) compared to males (OR 0.8, 95%CI 0.60–1.07) for cases that were diagnosed more than 1 year before cancer diagnosis, it is possible that the association is related to estrogenic influence on dopaminergic pathways. It was previously shown that estrogen deprivation might lead to death of dopamine neurons (51).

The current study had several limitations. Sample size was small for some of the subgroup analyses, mainly for anti-parkinsonian medications and for subjects diagnosed before the age of 50, thus the study might be underpowered for these analyses. Since THIN database lacks information regarding cancer stage, location and histopathology we were not able to test possible association of Parkinson's disease with these variables. Future studies are needed in order to evaluate whether the protective effect differ in early compared to advanced disease and in proximal compared to distal lesions (that are known to differ in their genetic landscape). The database did not include information regarding symptoms of Parkinson's disease, mainly neurologic symptoms such as constipation or bacterial overgrowth that might be related to CRC risk. However those manifestations are associated with higher cancer risk and would not explain the inverse association. Additionally, although

Parkinson's disease is associated with several genetic mutations, mainly in familial cases (such as the SNCA, PARKIN, PIN and LRRK gene mutations), we did not have genetic information of the subjects and could not differentiate between familial and sporadic Parkinson's disease.

The use of a large primary care population representative database with detailed information regarding CRC risk factors, anti-parkinsonian medications and lifestyle habits allowed us to provide the most extensive analysis to date of the inverse comorbidity between CRC and Parkinson's disease. We were able to focus on average risk CRC patients without family history of cancer or personal history of inflammatory bowel disease. By using such an electronic medical database we were also able to focus on incident cancer cases. The THIN database was previously shown to be valid for CRC studies (45).

In summary, our current study demonstrated lower CRC risk among patients with a previous diagnosis of Parkinson's disease. The association was independent of age of Parkinson's diagnosis, disease duration or therapy used and did not change after adjustment to known CRC risk factors and recurrent antibiotic exposure. Of note, the observed effect was more prominent among females compared to males, although not statistically significant. Future studies should focus on the role of genetic pathways, such as those involved in apoptosis and cellular metabolism, that might explain cellular proliferation in CRC on the one hand and dopaminergic cell death in Parkinson's disease on the other hand.

Acknowledgments

Funding: This study was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR000003. Dr. Mamtani was supported by NIH K23 grant CA187185.

References

1. de Lau L, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006; 5(6):525–35. [PubMed: 16713924]
2. Rodriguez-Oroz MC, Jahanshahi M, Krack P, et al. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *Lancet Neurol*. 2009; 8(12):1128–1139. [PubMed: 19909911]
3. Ganguli M. Cancer and dementia, it's complicated. *Alzheimer Dis Assoc Disord*. 2015; 29(2):177–182. [PubMed: 25710132]
4. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T. A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(6):1260–1265. [PubMed: 17548694]
5. Benito-Leon J, Aleja JG, Martinez-Salio A, Louis ED, Lichtman JH, Bermejo-Pareja F. Symptomatic Atherosclerotic Disease and Decreased Risk of Cancer-Specific Mortality: A Prospective, Population-Based Study (NEDICES). *Medicine*. 2015; 94(32):e1287. [PubMed: 26266364]
6. Tabares-seisdedos R, Dumont N, Baudot A, et al. No paradox, no progress: inverse cancer comorbidity in people with other complex diseases. *Lancet Oncol*. 2011; 12:604–608. [PubMed: 21498115]
7. Rujbjerg K, Friis S, Lassen CF, Ritz B, Olsen JH. Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. *Int J Cancer*. 2012; 131(8):1904–1911. [PubMed: 22278152]

8. Kareus SA, Figueroa KP, Cannon-Albright LA, Pulst SM. Shared predispositions of parkinsonism and cancer: a population-based pedigree-linked study. *Arch Neurol*. 2012; 69(12):1572–1577. [PubMed: 22945795]
9. Doshay LJ. Problem situations in the treatment of paralysis agitans. *J Am Med Assoc*. 1954; 156(7): 680–684. [PubMed: 13201370]
10. Elbaz A, Peterson BJ, Yang P, et al. Nonfatal cancer preceding Parkinson's disease: a case-control study. *Epidemiology*. 2002; 13(2):157–164. [PubMed: 11880756]
11. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellekjaer L, Møller H. Atypical cancer pattern in patients with Parkinson's disease. *Br J Cancer*. 2005; 92(1):201–205. [PubMed: 15583688]
12. Vanacore N, Spila-Alegiani S, Raschetti R, Meco G. Mortality cancer risk in parkinsonian patients: a population-based study. *Neurology*. 1999; 52(2):395–398. [PubMed: 9932965]
13. Ong EL, Goldacre R, Goldacre M. Differential risks of cancer types in people with Parkinson's disease: a national record-linkage study. *Eur J Cancer*. 2014; 50(14):2456–2462. [PubMed: 25065294]
14. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Cancer risk in association with Parkinson disease: a population-based study. *Parkinsonism Relat Disord*. 2010; 16(3):186–90. [PubMed: 19945903]
15. Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes Control*. 2010; 21(5):697–707. [PubMed: 20054708]
16. Elbaz A, Peterson BJ, Bower JH, et al. Risk of cancer after the diagnosis of Parkinson's disease: a historical cohort study. *Mov Disord*. 2005; 20(6):719–725. [PubMed: 15704188]
17. Lin PY, Chang SN, Hsiao TH, Huang BT, Lin CH, Yang PC. Association between Parkinson disease and risk of cancer in Taiwan. *JAMA Oncol*. 2015; 1(5):633–640. [PubMed: 26181771]
18. Lo RY, Tanner CM, Van Den Eeden SK, Albers KB, Leimpeter AD, Nelson LM. Comorbid cancer in Parkinson's disease. *Mov Disord*. 2010; 25(12):1809–1817. [PubMed: 20669266]
19. Ibanez K, Boulosa C, Tabares-Seisdedos R, Baudot A, Valencia A. Molecular evidence for the inverse comorbidity between central nervous system disorders and cancers detected by transcriptomic meta-analyses. *PLoS Genet*. 2014; 10(2):e1004173. [PubMed: 24586201]
20. Agalliu I, San Luciano M, Mirelman A, et al. Higher frequency of certain cancers in LRRK2 G2019S mutation carriers with Parkinson disease: a pooled analysis. *JAMA Neurol*. 2015; 72(1): 58–65. [PubMed: 25401981]
21. Driver JA. Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. *Biogerontology*. 2014; 15(6):547–57. [PubMed: 25113739]
22. Sherman MY, Goldberg AL. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. *Neuron*. 2001; 29(1):15–32. [PubMed: 11182078]
23. Schernhammer E, Chen H, Ritz B. Circulating melatonin levels: possible link between Parkinson's disease and cancer risk? *Cancer Causes Control*. 2006; 17(4):577–82. [PubMed: 16596313]
24. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk. *Parkinsonism Relat Disord*. 2006; 12(3):185–9. [PubMed: 16364673]
25. Rostami-Hodjegan A, Lennard MS, Woods HF, Tucker GT. Meta-analysis of studies of the CYP2D6 polymorphism in relation to lung cancer and Parkinson's disease. *Pharmacogenetics*. 1998; 8(3):227–38. [PubMed: 9682268]
26. Tan LC, Methawasini K, Tan EK, et al. Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study. *J Neurol Neurosurg Psychiatry*. 2015; doi: 10.1136/jnnp-2014-310065
27. Wang V, Chao TH, Hsieh CC, Lin CC, Kao CH. Cancer risks among the users of ergot-derived dopamine agonists for Parkinson's disease, a nationwide population-based survey. *Parkinsonism Relat Disord*. 2015; 21(1):18–22. [PubMed: 25457814]
28. Fasano A, Visanji NP, Liu L, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol*. 2015; 14(6):625–639. [PubMed: 25987282]

29. Gold A, Turkalp ZT, Munoz DG. Enteric alpha-synuclein expression is increased in Parkinson's disease but not Alzheimer's disease. *Mov Disord.* 2013; 28(2):237–240. [PubMed: 23362176]
30. Bottner M, Zorenkov D, Hellwig I, et al. Expression pattern and localization of alpha-synuclein in the human enteric nervous system. *Neurobiol Dis.* 2012; 48(3):474–480. [PubMed: 22850485]
31. Braak H, Rub U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm.* 2003; 110(5):517–536. [PubMed: 12721813]
32. Wakabayashi K, Takahashi H, Takeda S, Ohama E, Ikuta F. Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses. *Acta Neuropathol.* 1988; 76(3):217–221. [PubMed: 2850698]
33. Lebouvier T, Neunlist M, Bruley des Varannes S, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms. *PLoS ONE.* 2010; 5(9):1–9 e12728.
34. Keshavarzian A, Green SJ, Engen PA, et al. Colonic bacterial composition in Parkinson's disease. *Mov Disord.* 2015; 30(10):1351–1360. [PubMed: 26179554]
35. Svensson E, Horvath-Puho E, Thomsen RW, et al. Vagotomy and Subsequent Risk of Parkinson's Disease. *Ann Neurol.* 2015; 78(4):522–529. [PubMed: 26031848]
36. Boursi B, Haynes K, Mamtani R, Yang YX. Impact of antibiotic exposure on the risk of colorectal cancer. *Pharmacoepidemiol Drug Saf.* 2015 May; 24(5):534–542. [PubMed: 25808540]
37. Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation - Another step in understanding the role of the human microbiota? *Eur J Cancer.* 2015; pii: S0959-8049(15)00805-9. doi: 10.1016/j.ejca.2015.08.015
38. Schulz MD, Atay C, Heringer J, et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature.* 2014; 514(7523):508–512. [PubMed: 25174708]
39. Boursi B, Haynes K, Mamtani R, Yang YX. Impact of antibiotic exposure on the risk of colorectal cancer. *Pharmacoepidemiol Drug Saf.* 2015; 24(5):534–542. [PubMed: 25808540]
40. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Safe.* 2009; 18:76–83.
41. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care.* 2004; 12:171–177. [PubMed: 15606990]
42. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Safe.* 2007; 16:393–401.
43. Hollowell J. The general practice research database: quality of morbidity data. *Popul Trends.* 1997; 87:36–40. [PubMed: 9134574]
44. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the general practice research database. *Pharmacoepidemiol Drug Saf.* 2005; 14:443–451. [PubMed: 15898131]
45. Haynes K, Forde KA, Schinnar R, et al. Cancer incidence in The Health Improvement Network. *Pharmacoepidemiol Drug Saf.* 2009; 18:730–6. [PubMed: 19479713]
46. Chisholm J. The Read clinical classification. *BMJ.* 1990; 300:1092. [PubMed: 2344534]
47. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. *Inform Prim Care.* 2011; 19:173–82. [PubMed: 22688227]
48. Lubin JH, Gail MH. Biased selection of controls for case-control analysis of cohort studies. *Biometrics.* 1984; 40:63–75. [PubMed: 6375751]
49. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic parkinson's disease by age, ethnic group, and sex in northern manhattan, 1988–1993. *Am J Epidemiol.* 1995; 142(8):820–827. [PubMed: 7572958]
50. Sarkar C, Chakroborty D, Dasgupta PS, Basu S. Dopamine is a safe antiangiogenic drug which can also prevent 5-fluorouracil induced neutropenia. *Int J Cancer.* 2015; 137(3):744–749. [PubMed: 25556636]

51. Leranth C, Roth RH, Elsworth JD, Naftolin F, Horvath TL, Redmond DE Jr. Estrogen is essential for maintaining nigrostriatal dopamine neurons in primates: implications for Parkinson's disease and memory. *J Neurosci*. 2000; 20(23):8604–8609. [PubMed: 11102464]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Characteristics of cases and controls

Parameter	Cases (n=22,093)	Controls (n=85,833)	P-value
Age at CRC diagnosis (median, IQR)	72.3 (63.8–79.6)	71.9 (63.3–79.3)	NA
Male sex (%)	12,142 (55.1%)	47,113 (55.1%)	NA
Duration of follow-up before CRC diagnosis (median IQR)	6 (3–9)	6 (3–9)	NA
Diabetes mellitus (%)	2,844 (12.9%)	8,551 (10.0%)	<0.0001
Obesity (BMI >30) (%)	4,580 (20.7%)	15,807 (18.4%)	<0.0001
Smoking (ever) (%)	10,338 (46.8%)	35,551 (41.4%)	<0.0001
Alcohol use (%)	11,319 (51.2%)	41,374 (48.2%)	<0.0001
Alcoholism (%)	161 (0.7%)	414 (0.5%)	<0.0001
Chronic Aspirin/NSAIDs use (%)	7,398 (33.5%)	28,350 (33.0%)	0.26
Hormone replacement therapy (%)	1,391 (6.3%)	5,759 6.7%)	0.04
Previous screening colonoscopy (%)	325 (1.5%)	1,430 (1.7%)	0.03
Number of penicillin course:			
No penicillin treatment	10,054 (45.5%)	41,739 (48.6%)	Ref.
1 course	9,052 (41.0%)	33,636 (39.2%)	<0.0001
2–5 courses	2,070 (9.4%)	7,372 (8.6%)	<0.0001
>5 courses	917 (4.2%)	3,086 (3.6%)	<0.0001

Table 2

Association between Parkinson's disease and CRC risk

Parameter	Cases N (%)	Controls N (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95% CI)
Parkinson's disease	117 (0.5%)	541 (0.6%)	0.81 (0.67–0.99)	0.85 (0.69–1.04)	0.84 (0.69–1.03)
Duration of Parkinson's disease before CRC diagnosis					
No disease	21,976 (99.5%)	85,292 (99.4%)	Ref.	Ref.	Ref.
0–1 years	32 (0.1%)	84 (0.1%)	1.39 (0.92–2.10)	1.36 (0.90–2.05)	1.37 (0.91–2.08)
>1–5 years	50 (0.2%)	277 (0.3%)	0.69 (0.51–0.93)	0.73 (0.54–0.99)	0.73 (0.54–0.98)
>5 years	35 (0.2%)	179 (0.2%)	0.73 (0.51–1.06)	0.77 (0.54–1.11)	0.77 (0.53–1.10)
Age at diagnosis of Parkinson's disease					
No disease	21,976 (99.5%)	85,292 (99.4%)	Ref.	Ref.	Ref.
40–49 years	3 (0.01%)	4 (<0.01%)	3.0 (0.67–13.40)	3.26 (0.73–14.60)	3.33 (0.74–14.95)
50–75 years	52 (0.2%)	287 (0.3%)	0.69 (0.52–0.93)	0.73 (0.54–0.98)	0.73 (0.54–0.98)
>75 years	62 (0.3%)	250 (0.3%)	0.92 (0.69–1.22)	0.94 (0.71–1.25)	0.94 (0.71–1.25)
Therapy for Parkinson's disease					
No disease	21,976 (99.5%)	85,292 (99.4%)	Ref.	Ref.	Ref.
No medical therapy	63 (0.3%)	299 (0.4%)	0.81 (0.62–1.06)	0.82 (0.62–1.08)	0.82 (0.62–1.08)
Dopamine	4 (0.02%)	6 (0.01%)	2.64 (0.74–9.36)	2.95 (0.83–10.50)	2.81 (0.79–10.00)
Dopamine agonists	13 (0.06%)	71 (0.08%)	0.67 (0.37–1.21)	0.73 (0.40–1.33)	0.74 (0.40–1.34)
Other/combined therapy	37 (0.2%)	165 (0.2%)	0.82 (0.58–1.18)	0.87 (0.61–1.25)	0.87 (0.61–1.25)

* Adjusted to obesity (BMI>30), smoking (ever), alcohol consumption, diabetes mellitus, chronic aspirin/NSAIDs use, hormone replacement therapy and previous screening colonoscopy.

** In addition to the adjustment above, number of previous antibiotic courses with penicillin more than one year before cancer diagnosis (0,1,2–5,>5).

Table 3

Association between Parkinson's disease and CRC risk among males (12,142 CRC cases and 47,113 matched controls)

Parameter	Cases N (%)	Controls N (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95% CI)
Parkinson's disease	79 (0.7%)	343 (0.7%)	0.86 (0.67–1.11)	0.90 (0.70–1.16)	0.90 (0.70–1.15)
Duration of Parkinson's disease before CRC diagnosis					
No disease	12,063 (99.4%)	46,770 (99.3%)	Ref.	Ref.	Ref.
0–1 years	21 (0.2%)	54 (0.1%)	1.38 (0.83–2.31)	1.34 (0.80–2.24)	1.35 (0.81–2.26)
>1–5 years	32 (0.3%)	182 (0.4%)	0.68 (0.47–0.99)	0.73 (0.50–1.06)	0.72 (0.49–1.05)
>5 years	26 (0.2%)	107 (0.2%)	0.90 (0.59–1.39)	0.95 (0.62–1.47)	0.94 (0.61–1.45)
Age at diagnosis of Parkinson's disease					
No disease	12,063 (99.4%)	46,770 (99.3%)	Ref.	Ref.	Ref.
40–49 years	3 (0.02%)	2 (<0.01%)	6.0 (1.00–35.91)	6.77 (1.12–40.69)	6.99 (1.15–42.15)
50–75 years	36 (0.3%)	189 (0.4%)	0.73 (0.51–1.05)	0.77 (0.54–1.10)	0.76 (0.53–1.09)
>75 years	40 (0.3%)	152 (0.3%)	0.96 (0.67–1.37)	0.99 (0.70–1.42)	0.99 (0.69–1.42)
Therapy for Parkinson's disease					
No disease	12,063 (99.4%)	46,770 (99.3%)	Ref.	Ref.	Ref.
No medical therapy	37 (0.3%)	188 (0.4%)	0.76 (0.53–1.09)	0.77 (0.54–1.11)	0.77 (0.54–1.10)
Dopamine	3 (0.02%)	3 (0.01%)	3.92 (0.79–19.42)	4.31 (0.87–21.42)	4.04 (0.81–20.12)
Dopamine agonists	10 (0.08%)	41 (0.09%)	0.86 (0.43–1.73)	0.94 (0.47–1.90)	0.95 (0.47–1.92)
Other/combined therapy	29 (0.2%)	111 (0.2%)	0.95 (0.63–1.44)	1.03 (0.68–1.55)	1.02 (0.68–1.55)

* Adjusted to obesity (BMI>30), smoking (ever), alcohol consumption, diabetes mellitus, chronic aspirin/NSAIDs use, hormone replacement therapy and previous screening colonoscopy.

** In addition to the adjustment above, number of previous antibiotic courses with penicillin more than one year before cancer diagnosis (0,1,2–5,>5).

Table 4

Association between Parkinson's disease and CRC risk among females (9,951 CRC cases and 38,720 matched controls)

Parameter	Cases N (%)	Controls N (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95% CI)
Parkinson's disease	38 (0.4%)	198 (0.5%)	0.73 (0.51–1.03)	0.75 (0.53–1.07)	0.75 (0.53–1.06)
Duration of Parkinson's disease before CRC diagnosis					
No disease	9,913 (99.6%)	38,522 (99.5%)	Ref.	Ref.	Ref.
0–1 years	11 (0.1%)	30 (0.1%)	1.41 (0.70–2.82)	1.39 (0.69–2.80)	1.41 (0.70–2.83)
>1–5 years	18 (0.2%)	95 (0.3%)	0.71 (0.43–1.18)	0.74 (0.44–1.23)	0.73 (0.44–1.22)
>5 years	9 (0.1%)	72 (0.2%)	0.48 (0.24–0.96)	0.50 (0.25–1.01)	0.50 (0.25–1.01)
Age at diagnosis of Parkinson's disease					
No disease	9,913 (99.6%)	38,522 (99.5%)	Ref.	Ref.	Ref.
40–49 years	0 (0%)	2 (0.01%)	NA	NA	NA
50–75 years	16 (0.2%)	98 (0.3%)	0.62 (0.37–1.06)	0.66 (0.39–1.12)	0.66 (0.39–1.13)
>75 years	22 (0.2%)	97 (0.3%)	0.86 (0.54–1.37)	0.86 (0.54–1.37)	0.86 (0.54–1.37)
Therapy for Parkinson's disease					
No disease	9,913 (99.6%)	38,522 (99.5%)	Ref.	Ref.	Ref.
No medical therapy	26 (0.3%)	111 (0.3%)	0.89 (0.58–1.37)	0.90 (0.58–1.39)	0.90 (0.59–1.39)
Dopamine	1 (0.01%)	3 (0.01%)	1.33 (0.14–12.82)	1.50 (0.16–14.44)	1.46 (0.15–14.11)
Dopamine agonists	3 (0.03%)	30 (0.08%)	0.39 (0.12–1.26)	0.43 (0.13–1.40)	0.43 (0.13–1.40)
Other/combined therapy	8 (0.1%)	54 (0.1%)	0.55 (0.26–1.16)	0.57 (0.27–1.21)	0.57 (0.27–1.20)

* Adjusted to obesity (BMI>30), smoking (ever), alcohol consumption, diabetes mellitus, chronic aspirin/NSAIDs use, hormone replacement therapy and previous screening colonoscopy.

** In addition to the adjustment above, number of previous antibiotic courses with penicillin more than one year before cancer diagnosis (0,1,2–5,>5).