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Risk for Parkinson disease among patients with osteoarthritis: a Danish cohort study

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Abstract

It has been suggested that use of non-steroidal anti-inflammatory drugs (NSAID) protects against Parkinson disease, although the results are not consistent. We investigated the risk for Parkinson disease in patients with osteoarthritis, who are typically intensive users of NSAID.

Using the files of the National Danish Hospital Register for the period 1977–2006, we identified a cohort of 134 176 patients with osteoarthritis severe enough to have required subsequent hip or knee implant surgery. The number of first hospital contacts for Parkinson disease among cohort members in 1986–2007 was compared with that expected from the age-, gender- and period-specific hospital contact rates of the general Danish population, and standardized incidence ratios (SIRs) and associated 95% confidence intervals (CIs) were derived. Cohort members were also linked to the Danish Cancer Register to estimate the SIRs for colorectal and lung cancer. We observed a slightly increased risk for Parkinson disease among patients with osteoarthritis and subsequent implant surgery (SIR, 1.07; 95% CI, 0.99–1.16). Decreased SIRs were found for both colorectal cancer (0.92; 95% CI, 0.88–0.97), consistent with a high prevalence of NSAID use among cohort members, and for lung cancer (0.77; 95% CI, 0.73–0.80), indicating a lower prevalence of smoking than usual. Our results do not support the hypothesis that patients with prolonged use of NSAID and other analgesics are at reduced risk for Parkinson disease. A possible lower smoking prevalence among patients with osteoarthritis might explain the slightly increased risk for Parkinson disease.

Introduction

Parkinson disease is a neurodegenerative disease that affects 1–2% of the population over the age of 60 years.[1] The disease is characterized by progressive degeneration of the dopaminergic neurons in the substantia nigra of the brain, which leads to motor impairment involving tremor, bradykinesia, rigidity and postural instability.[2] Patients with Parkinson disease are also at increased risk for dementia and depression.[3] The etiology of the disease is

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largely unknown, although a small fraction of cases are due to genetic mutations.[4] No chemopreventive therapy for Parkinson disease is currently known, but it has been suggested that regular use of non-steroidal anti-inflammatory drugs (NSAID) reduces the risk.[5-8] In a recent study, we observed a 30% decrease in the risk for Parkinson disease among patients with rheumatoid arthritis,[9] and we speculated that this might be a consequence of treatment with anti-inflammatory analgesics. To explore this hypothesis further, we decided to evaluate the risk of Parkinson disease in a cohort of patients receiving long-term, often intensive treatment with NSAID, namely, patients with osteoarthritis severe enough to have required subsequent hip or knee implant surgery.

Methods

Study population

The Danish National Hospital Register contains information on all persons admitted to non-psychiatric hospitals since 1977.[10] Information on outpatient visits, including visits to emergency rooms, was added to the register on 1 January 1995. The Register contains the personal identification number of the patient, dates of admission and discharge (inpatient registration), surgical procedures performed during the admission, the dates of first and last contact (outpatient registration), a code for the primary diagnosis made at hospital discharge, and codes for up to 19 supplementary diagnoses. The personal identification number, which is unique to every Danish citizen, incorporates gender and date of birth and permits accurate linkage between registers. The diagnoses, established at discharge from hospital, were coded according to the Danish version of the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and according to the 10th revision thereafter.[10] Surgical procedures were classified according to the Danish Classification of Surgical Procedures and Therapies until the end of 1995 and according to the Danish version of the Nordic Medico-Statistical Committee classification thereafter.[11;12]

We identified 134 825 patients who were registered in the Danish Hospital Register in 1977–2007 under the combined codes of idiopathic osteoarthritis of the hip (ICD-8, 713.00; ICD-10, M16.0–M16.7, M16.9) and subsequent hip implantation (8274, 70032, 70033, KNFB, KNFC) or idiopathic osteoarthritis of the knee (ICD-8, 713.01; ICD-10, M17.0–M17.5, M17.9) and subsequent knee implantation (8280, 70042, 70043, KNGB, KNGC) and who were alive and living in Denmark on 1 January 1986. After exclusion of 245 (0.2%) patients in whom Parkinson disease was diagnosed before the date of implant surgery, 138 (0.1%) patients who died during or shortly after implant surgery, and 266 (0.2%) patients below the age of 35 years throughout the period of follow-up, 134 176 osteoarthritis patients who had undergone hip or knee implant surgery remained for study.

Ascertainment of Parkinson disease and selected types of cancers

We re-linked the study population to the Danish Hospital Register in order to identify cohort members in whom Parkinson disease (ICD–8, 342 and ICD–10, G20) developed during follow-up. Only patients with a primary diagnosis of Parkinson disease were identified, because a primary diagnosis is considered to be more reliable and accurate compared with supplementary diagnoses. In a previous study[9] we found that 65% of patients received their primary diagnosis of Parkinson disease from a neurologic department, whereas the corresponding proportion among those with a supplementary diagnosis was 7%. Follow-up for Parkinson disease began at the date of hip or knee implantation, the 35th birthday or 1 January 1986, whichever occurred last. We chose 1986 as the earliest date of follow-up in order to eliminate prevalent cases of Parkinson disease included in the Hospital Register in the first years of registration, i.e. 1977–1985. Follow-up ended at the date of first hospital contact for Parkinson disease, date of death, date of emigration or 31 December 2007,

whichever occurred first. Only cases verified by a primary diagnosis of Parkinson disease were counted.

In addition, cohort members were linked to the Danish Cancer Registry in order to identify incident cases of colorectal and lung cancer through 2006. The Cancer Registry has recorded incident cases of cancer on a nationwide scale since 1943 and has been shown to be accurate, with virtually complete ascertainment of cancer cases.[13] As previous studies have found a reduced risk for colorectal cancer among users of NSAID,[14;15] colorectal cancer was included as a secondary outcome in this study as a positive control for excess use of NSAID by cohort members. The incidence of lung cancer closely reflects smoking habits and is thus a reliable marker of smoking.

Statistical analysis

The occurrence of Parkinson disease during follow-up of cohort members was compared with that expected from the age-, gender-, and calendar period-specific rates of Parkinson disease in the general population during the period 1986–2007. The national rates were computed by dividing the number of first-time hospital contacts with a primary diagnosis of Parkinson disease by the corresponding mean person–years for men and women in the general population in 5-year age and calendar periods. Expected numbers of Parkinson disease were obtained by multiplying the age-, gender- and period-specific person–years of observation among cohort members by the national rates of Parkinson disease. The standardized incidence ratio (SIR), taken as the ratio of observed-to-expected cases, was calculated as a measure of the relative risk for Parkinson disease in the study population, and 95% confidence intervals (CIs) for the SIRs were calculated on the assumption of a Poisson distribution of the observed number of patients with Parkinson disease.[16] Similarly, the incidences of colorectal and lung cancer in the cohort were compared with those expected from the age-, gender- and calendar time-specific incidence rates in the general population, derived from the Danish Cancer Registry for the period 1986–2006.

To explore the possible effect of treatment with NSAID further, SIRs were also estimated for two subcohorts defined by the time between first hospital diagnosis of osteoarthritis and implant surgery, as < 3 years and ≥ 3 years, assuming that the latter subcohort might have been treated intensively with analgesics for at least 3 years. We also performed a subanalysis to determine whether Parkinson disease was diagnosed more frequently within the first 5 years after implant surgery than subsequently, as an indication of surveillance bias in our study. In additional subanalyses, we evaluated the risks of hip and knee implant patients separately and those of patients in whom osteoarthritis was diagnosed when they were < 65 years and ≥ 65 years. Calculations were performed with SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina, USA).

Use of analgesics

In order to characterize part of the study population with osteoarthritis and subsequent hip or knee implantation according to prescribed use of aspirin (Anatomical Therapeutical Chemical (ATC) [17] codes B01AC06, N02BA01, N02BA51) and non-aspirin NSAID (ATC code M01A), we took advantage of the existence of a prescription database in the County of North Jutland. This is one of the former (before 2006) 13 counties of Denmark, comprising approximately 10% of the total Danish population. The North Jutland Prescription Database was initiated on 1 January 1989 and contains information on prescriptions dispensed from all pharmacies in the county.[18;19] Prescription data for use in this study were available for the period 1989–2002; in this period non-aspirin NSAIDs were available by prescription only, except for low-dose ibuprofen (200 mg per tablet) which accounted for approximately 14% of the total use.[19] Aspirin could be purchased over the counter throughout the period,

but was typically not used for treatment of osteoarthritis. Thus, for 5884 cohort members with osteoarthritis diagnosed at hospitals in North Jutland during this period, we obtained complete personal prescription histories for the years 1989–2002. Use of analgesics was compared with that of the background population of the county. The study protocol was approved by the Danish Data Protection Agency (No 2002-41-2112).

Results

Table 1 lists the characteristics of the cohort, consisting of 134 176 patients (41% men and 59% women) with osteoarthritis, 67% of whom subsequently had hip implant surgery and 33% of whom had a knee implant. The cohort members accrued a total of 968 287 person–years of follow-up (average, 7.2 years; range, 0–22 years), and the mean age at hip or knee implant surgery was 67.7 years (range, 16.0–103.0 years). During follow-up, 668 cohort members had a hospital contact for Parkinson disease, while 621.6 were expected from the rates for the general population, equivalent to a 7% increase in risk for Parkinson disease after implant surgery for a diagnosis of osteoarthritis (SIR, 1.07; 95% CI, 0.99–1.16) (Table 2). Parkinson disease was diagnosed among 0.62% of the men and 0.42% of the women in the cohort. Stratification of cohort members according to gender and time between first hospital contact for implant surgery and Parkinson disease did not indicate any significant variations in risk (Table 2). In a further subanalysis, we found that the risk estimate for Parkinson disease < 5 years after implant surgery (SIR, 1.08; 95% CI, 0.96–1.21) was similar to that for ≥ 5 years after implant surgery (1.07; 0.96–1.18) (not shown in table). Age at diagnosis of osteoarthritis had no major influence on the risk for Parkinson disease (< 65 years: SIR, 1.18; 95% CI, 1.01–1.36; ≥ 65 years: SIR, 1.04; 95% CI, 0.95–1.14) (not shown in table). When we analysed data for hip and knee patients separately, we saw a modest but significant increase in risk for Parkinson disease in the subgroup of patients who had a knee implant (SIR, 1.28, 95% CI, 1.04–1.56), which was not found among patients who had a hip implant (SIR, 1.01, 95% CI, 0.96–1.18) (not shown in table).

Our analysis of cancers showed a statistically significant, 8% reduction in the risk for colorectal cancer among cohort members in general and a significant, 14% reduction among patients with ≥ 3 years between diagnosis of osteoarthritis and the date of implant surgery (Table 2). The risk estimate for colorectal cancer was further decreased in the subcohort for whom ≥ 5 or more years elapsed between the diagnosis of osteoarthritis and the date of implant surgery (SIR, 0.77; 95% CI, 0.65–0.92; n = 164) (not shown in table). We also observed a significantly decreased risk for lung cancer in the cohort (SIR, 0.77; 95% CI, 0.74–0.81), indicating a low smoking prevalence among patients with advanced osteoarthritis.

For the subcohort of 5884 patients in whom osteoarthritis was diagnosed at a hospital in North Jutland during the period 1989–2002, we obtained information on prescribed NSAID. The average follow-up period in the period 1989–2002 was 13.4 years. Among the 4658 (79%) patients who received at least two prescriptions for NSAID during this period 22 developed Parkinson disease whereas 23.9 were expected (SIR, 0.92, 95% CI, 0.58–1.40) and among the 3810 (65%) patients receiving two or more prescriptions per year 21 developed Parkinson disease during follow-up and 19.9 were expected (SIR, 1.05, 95% CI, 0.65–1.61). In comparison, 27% of the population in Northern Jutland received two or more prescriptions per year in the period 1989–2002.[20]

Discussion

In this cohort study of more than 130 000 patients with osteoarthritis and a subsequent hip or knee implant surgery, we observed a slightly increased risk for Parkinson disease over that

of the general population. Although we did not have data for the timing and duration of NSAID use among cohort members, we have several lines of evidence for intensive, prolonged use of this class of pharmaceuticals by such patients. In a previous study, we saw a 30% decrease in risk for Parkinson disease among patients with rheumatoid arthritis[9] which we speculated might be due to treatment with anti-inflammatory analgesics, as previous studies have indicated a protective effect of NSAID. [5;6;8] The results of the present study do not, however, support this interpretation, and thus our previous finding of a reduced risk in patients with rheumatoid arthritis[9] might have been caused by an underdiagnosis of Parkinson disease in these patients, possibly due to the severe physical consequences of rheumatoid arthritis. Data on prescriptions received by a subcohort of our osteoarthritis cohort showed substantial use of aspirin and non-aspirin NSAID by these patients. For the patients in Northern Jutland that we knew received NSAIDs, we saw that the risk of Parkinson disease was similar to that in the whole cohort of patients with osteoarthritis, indicating similar use of NSAIDs in the subcohort and the whole cohort. Furthermore, this estimate of the use of NSAID by osteoarthritis patients is probably an underestimate, as patients might have supplemented their prescription with aspirin or low-dose NSAID purchased over-the-counter.[21] Further, our analysis did not include a full history of NSAID use by the patients, most of whom were probably treated for long periods with these medications both before the first hospitalization for osteoarthritis and after implant surgery. In a recent cohort study of Danish men and women, long-term use of NSAID was found to be associated with a decreased risk for colorectal cancer[22], consistent with the literature[14] and with our finding of a decreased risk for colorectal cancer among patients with osteoarthritis.

Previous studies of the influence of NSAID on the risk for Parkinson disease yielded inconsistent results. A study based on the Health Professionals Follow-up study and the Nurses' Health study found a relative risk of 0.55 (95% CI, 0.32–0.96) for Parkinson disease among participants reporting regular use of non-aspirin NSAID when compared with irregular users.[5] In this study, a tendency to a further reduction in risk for Parkinson disease with increasing duration of regular use of non-aspirin NSAID was also reported.[5] Similarly, in a population-based case–control study a decreased risk for Parkinson disease was seen among regular users of non-aspirin NSAID (OR, 0.52; 95% CI, 0.35–0.79), and the lowest risk estimate was seen for those treated regularly (two pills or more per week) with non-aspirin NSAID for ≥ 2 years.[8] In the Cancer Prevention cohort study II, however, no protective effect was found for users of all types of NSAID combined, although users of ibuprofen specifically had a reduced risk for Parkinson disease (RR, 0.65; 95% CI, 0.48–0.89).[6] Two case–control studies[23;24] and one cohort study[25] based on pharmacy data reported no association overall between use of NSAID and the risk for Parkinson disease.

The major advantages of the present cohort study are the population-based approach, use of the nationwide Danish Hospital Register, the completeness of follow-up and the large size of the cohort of patients with osteoarthritis and implant surgery. Further, access to prescription data from North Jutland enabled us to evaluate the prevalence of NSAID use in a representative subgroup of cohort members and to compare the use with that of the background population. In addition, by linking cohort members to the Danish Cancer Registry, we were able to document a decreased risk for colorectal cancer in the cohort, adding further strength to the assumption of intense NSAID use by patients with osteoarthritis. A limitation of our study is the existence of a potential surveillance bias, as patients with osteoarthritis and subsequent implant surgery are under more intensive medical care, so that early signs of Parkinson disease are more likely to be detected. We addressed this possible bias in a sensitivity analysis by examining the risk for Parkinson disease during the first 5 years of follow-up after implant surgery with that during longer follow-up. The risks were similar in the two groups, indicating no major surveillance bias. We had no

information on clinical details for patients with Parkinson disease, however we included only patients with a primary diagnosis of Parkinson disease and further, we previously found that 91% of these patients had received anti-Parkinson drugs[26], indicating limited misclassification.

In our cohort of patients with osteoarthritis, the risk for lung cancer was decreased by 23%. This is probably due to a reduced prevalence of smoking, although the decrease might be explained partly by intensive use of NSAID, as indicated by a recent Danish case–control study of lung cancer[27]. Reduced smoking among study subjects is consistent with the observation of previous studies that tobacco smoking is inversely associated with the risk for osteoarthritis, i.e. tobacco smoking appears to be a protective against osteoarthritis.[28;29] As tobacco smoking is also inversely associated with Parkinson disease,[30] smoking is a potential confounding factor in the present study and might explain the slight overall excess risk for Parkinson disease observed.

In summary, in a large group of patients with severe osteoarthritis and extensive use of NSAID medications, we found no indication of a reduced risk for Parkinson disease. Rather, we saw a slight, non-significantly increased risk, possibly due to a reduced prevalence of smoking among cohort members. Thus, the results do not support the hypothesis that prolonged use of NSAID protects against Parkinson disease.

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Table 1

Descriptive characteristics of patients with osteoarthritis of the hip or knee who underwent implant surgery between 1977–2007 and who were alive on 1 January 1986

			Implant surgery			
Characteristic	**Total**	**%**	**Hip**	**%**	**Knee**	**%**
Both genders	134 176	100	90 024	67.1	44 152	32.9
Male	54 624	40.7	39 298	43.6	15 326	34.7
Female	79 552	59.3	50 726	56.3	28 826	65.3
Year of birth						
< 1900	460	0.3	392	0.4	68	0.2
1900–1920	39 087	29.1	29 438	32.5	9 649	21.9
1921–1930	36 346	27.1	24 477	27.2	11 869	26.9
1931–1940	31 459	23.4	20 029	22.2	11 430	25.9
1941–1950	19 560	14.6	11 302	12.6	8 258	18.7
1951–1960	5 627	4.2	3 292	3.7	2 335	5.3
> 1960	1 637	1.2	1 094	1.2	543	1.2
Age at cohort entry (years)						
35–49	6 963	5.2	4 813	5.3	2 150	4.9
50–64	38 320	28.6	24 705	27.4	13 615	30.8
65–79	71 334	53.2	48 197	53.5	23 137	52.4
80–94	17 491	13.0	12 243	13.6	5 248	11.9
≥ 95	68	0.1	66	0.1	2	0.0
Follow-up (years)						
0–4	59 046	44.0	35 915	39.9	23 131	52.4
5–9	38 125	28.4	26 280	29.2	11 845	26.8
10–14	21 352	15.9	15 224	16.9	6 128	13.9
15–19	10 453	7.8	8 089	9.0	2 364	5.4
≥ 20	5 200	3.9	4 516	5.0	684	1.5
Censoring of follow-up due to						
Parkinson disease	668	0.5	452	0.5	216	0.5
Death	47 023	35.0	35 460	39.4	11 563	26.2

Mov Disord. Author manuscript; available in PMC 2011 October 30.

Characteristic	Total	%	Implant surgery					
			Hip	%	Knee	%		
Emigration	198	0.1	125	0.1	73	0.2		
31 December 2007	86 287	64.3	53 987	60.0	32 300	73.2		

Table 2

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for Parkinson disease, colorectal cancer (overall and for those with < 3 years between osteoarthritis diagnosis and implant and for those with ≥ 3 years between the two events), and lung cancer among patients with osteoarthritis

Disease outcome			
Time between osteoarthritis diagnosis and implant	**Observed**	**Expected**	**SIR (95% CI)**
Both genders			
Parkinson disease	668	621.6	1.07 (0.99–1.16)
< 3 years	610	561.4	1.09 (1.00–1.18)
≥ 3 years	58	60.0	0.97 (0.73–1.25)
Colorectal cancer	2401	2603.8	0.92 (0.89–0.96)
< 3 years	2184	2350.2	0.93 (0.89–0.97)
≥ 3 years	217	253.6	0.86 (0.75–0.98)
Lung cancer	1676	2171.0	0.77 (0.74–0.81)
Men			
Parkinson disease	337	310.2	1.09 (0.97–1.21)
< 3 years	305	280.8	1.09 (0.97–1.21)
≥ 3 years	32	29.4	1.09 (0.75–1.54)
Colorectal cancer	1053	1143.3	0.92 (0.87–0.98)
< 3 years	960	1033.9	0.93 (0.87–0.99)
≥ 3 years	93	109.9	0.85 (0.68–1.04)
Lung cancer	939	1239.3	0.76 (0.71–0.81)
Women			
Parkinson disease	331	311.4	1.06 (0.95–1.18)
< 3 years	305	280.8	1.09 (0.97–1.22)
≥ 3 years	26	30.6	0.85 (0.55–1.24)
Colorectal cancer	1348	1460.0	0.92 (0.88–0.97)
< 3 years	1224	1316.4	0.93 (0.88–0.98)
≥ 3 years	124	143.7	0.86 (0.72–1.03)
Lung cancer	737	931.7	0.79 (0.73–0.85)