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Cancer incidence among Parkinson's disease patients in a 10-yrs time-window around disease onset: A large-scale cohort study

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ABSTRACT

Objective: To compare the incidences of any cancer and specific types among patients with Parkinson's disease (PD) in a 10-yrs time window around diagnosis, to that of the general population.
Methods: We conducted a population-based, retrospective large-scale cohort study on 7125 newly diagnosed PD patients who had just initiated anti-parkinsonian medications between 1.1.2000 and 12.31.2012; all members of Maccabi Health Services (MHS), a large Israeli HMO. Cancer incidence during the same period was collected from MHS cancer-registry. Standardized-Incidence-Ratio (SIR) accounting for age, chronological-year and sex were calculated to compare cancer risks of PD patients to that of MHS population.
Results: The PD cohort (54% males) had a mean age at initiation of anti-parkinsonian medications of 71.2 ± 10.3years. In a time-window of 6.6 ± 3.4years before and 4.0 ± 3.9years after PD was first treated, 21% of the men and 15% of the women were diagnosed with incident-cancer. We found no-difference in any cancer risk for the PD cohort compared to the reference population: SIR = 0.99 (95%CI: 0.92–1.06) for males and 0.98 (95%CI: 0.89–1.07) for females. Risks for lung and colon cancers in the PD cohort were significantly lower for both sexes compared to the reference population. Risks for breast, central nervous system, kidney, leukemia, lymphoma, melanoma, ovarian, pancreatic, prostatic, rectal and thyroid were similar for the two populations. The SIRs did not differ between the sexes.
Conclusions: We found no difference in the risk of any-type of cancer among PD patients compared to the general population, focusing on 10yrs time-window around the initiation of anti-parkinsonian medications.

1. Introduction

The global prevalence and incidence rates of Parkinson's disease (PD) are 60–350 and 5–26 per 100,000 population, respectively, and approximately 256 and 33 cases per 100,000 population, respectively, in Israel [1]. The high incidence in Israel is probably due to the common genetic PD among Ashkenazi Jews [2]. The relationship between cancer risk and PD has been of interest for over two decades because of some clinical observations that suggest specific interactions [3–6]. Most studies that investigated the risk of cancer in patients with PD suggested a decreased lifetime risk compared to non-PD subjects [3,4]. There are several biological explanations in the literature that were proposed to explain the decreased association between PD and cancer. One is the inverse relations between apoptosis and PD, which is a disease of premature cell death, while cancer is a disease of cell overgrowth and lack of apoptosis [7]. It was also suggested that the elevated levels of circulating melatonin in PD patients may contribute to a lower cancer risk [8].

Melanoma is an exception to the overall decreased rates of

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cancer, and it has been reported to be more frequent among PD patients, including those in Israel [4,9–11]. Biochemical pathways shared between dopamine and melanin have been suggested to underlie that association [12]. Some studies have also found PD patients to be at higher risk of developing non-melanoma skin cancer [10,11] and breast cancer [4,11], but the evidence for those observations is less consistent. The methodological limitations of many studies include enrollment of prevalent PD cases without knowledge of the temporal relationship between cancer diagnosis and PD diagnosis, small samples (n = 200–500) of PD patients, and measures of cancer-comorbidity having been taken from clinical records rather than from validated and comprehensive cancer registries.

The 21st century is an era of big data in medicine. The availability of massive amounts of data in the era of computerized collection and storage has not been fully exploited for epidemiological studies in PD. Only 3 studies, each on PD and cancer from Denmark [6], England [4] and Taiwan [10] were conducted on large-scale PD cohorts (~12,000, 220,000, and 62,000 cases, respectively), and their results are inconsistent. Large-scale studies in different geographical areas worldwide are needed for establishing the validity of risk estimators for specific cancers (especially the rare ones). In addition, cancer comorbidity may present at different time windows in relation to the primary PD diagnosis. Considering the fact that the neuropathology of PD starts 10–30 years prior to diagnosis and the treatment is initiated later, the association between PD and cancer needs to be refined to the stage of the disease.

In Israel, the age-standardized incidence rate for cancer in 2008 was 288.3:100,000, ranking Israel 13th among the OECD countries. The three most common types of cancer in Israel, as in other western countries, are prostate/breast, lung and colon [13]. The rate of PD in Israel is higher than in other western countries, probably due to a high occurrence of the G2019S mutation in the leucine-rich repeat kinase 2 gene (LRRK2) and 8 mutations in the GBA gene which are frequently present in the Ashkenazi Jewish population [14]. The role of the LRRK2 mutation in cancer, however, is unknown [15]. This study focused on an incident, all-site and specific-site, cancer risk among PD patients in a time-window of 10 years around the initiation of anti-parkinsonian treatment. This time generally reflects the onset of motor symptoms and diagnosis.

Specifically, we aimed to evaluate all-site and site-specific new cancer (colon, rectum, pancreas, lung, melanoma, leukemia, lymphoma, kidney, central nervous system [CNS], thyroid) risks in a large-scale, population based PD cohort by sex, and to compare those risks to the same ones in the general Israeli population.

2. Methods

2.1. Ethics

The study was approved by the Helsinki ethical committee of Maccabi Health Services (MHS) and the ethical committee of Tel-Aviv University. ID numbers of participants were encrypted and secret.

2.2. The PD cohort

A population-based cohort of PD patients, all members of MHS, the second largest Health Maintenance Organization (HMO) in Israel (~25% of the population of Israel). An incident cohort of 5288 PD patients, members of MHS, firstly treated between 1.1.2000 and 12.31.2008, was recently established based on MHS drugs purchase data, a well-maintained pharmaceutical registry [1]. Each subject was assessed as having definitive, possible or probable PD. An algorithm was built to diagnose PD based on a purchasing profile of anti-parkinsonian drugs (APD). Age at first purchase of APD (is considered time of PD diagnosis), and purchase density with follow-up time were used to establish three levels of confidence of the diagnosis of PD (definite, probable and possible). The algorithm was validated against the clinical diagnoses in a specialist outpatient clinic in a tertiary medical center (the Movement Disorders Unit in the Tel Aviv Sourasky Medical Center) and was found to have a sensitivity of 96% for detecting PD cases. The current cohort is based on an extension of the earlier one up to 12.31.2012 and it includes 7125 incident PD patients.

The cohort was linked to other MHS databases for information on demographic characteristics, status at the MHS (active, deceased, transferred to another HMO), and comorbidities. Study period was 1.1.2000–31.12.2012.

2.3. Cancer assessment

The PD cohort members were linked to of MHS cancer registry, which records type of cancer and date of diagnosis for each patient and draws its data from the National Cancer Registry (completeness of 95%). The occurrence of incident cancer r during the study period (1.1.2000–12.31.2012 was recorded.

2.4. Statistical analysis

Follow-up time for each patient was measured from study initiation (a fixed date for all patients) until cancer diagnosis, death, leaving HMO or study closure, whichever occurred first. Patients with secondary or primary cancer but as a second or more cancer event (n = 464) were followed until death, leaving HMO or study closure, whichever occurred first. We estimated the risk of incidence cancer: of any cancer and of a specific cancers in our PD cohort by sex. We used Cox regression to compare time-to-cancer of the PDs males and females. We compared risk of any incident cancer and specific cancer in our PD cohort to that of the general MHS population by calculating the expected number of cancer cases in our PD cohort accounting for age-group (, 10-year interval, range 20–79yrs, 80+) and sex. Thus, by multiplying person years in risk (according to follow-up time) by the cancer incidence rates of MHS population for every age group, calendar year by sex. Standardized incidence ratios (SIRs) were calculated by dividing the observed number of cancer cases by the expected number. Analyses were performed using PAMCOMP. Comparison of SIRs was performed using Poisson regression.

3. Results

3.1. Characteristics of the PD cohort

Table 1 presents general characteristics of the PD cohort. The 7125 subjects (53.7% males) had a mean age of 71.1 ± 10.6 years at the time of first purchase of APD, similar to the 71.5 ± 10.7 years for the females. During the follow-up period of 10.5 ± 3.3 years, 1301 PD patients 18.3% (95% CI: 17.4%–19.2%) were first diagnosed as also having cancer (71.9% before PD diagnosis and the rest after). Cancer rates among PD males and females were 21.0% (95% CI: 20.7%–22.3%) and 15.1% (95%CI: 13.9%–16.3%) respectively.

3.2. Cancer risk in the PD males compared to females

The risk for any cancer differed significantly between males and females, with a higher one among the males (HR = 1.48 (95% confidence interval [CI]: 1.32–1.65). There was also a significantly higher risk among males for kidney cancer (HR = 4.21, 95% CI:

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