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Adult narcoleptic patients have increased risk of cancer: A nationwide population-based study

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ABSTRACT

Background: The comorbidity profile, especially cancer risk, of narcoleptic patients has seldom been explored. We used a nationwide database to evaluate the risk of cancer among adult narcoleptic patients.
Methods: We conducted the cohort study using National Health Insurance Research Database from 2000 to 2009. Standardized incidence ratios (SIRs) of cancers were calculated to compare the cancer incidence of the study cohort with that of the general population.
Results: 2833 narcoleptic patients were identified after excluding patients with antecedent malignancy and age younger than 18 years old. The study cohort was observed for 15,913 person-years during a 10-year period. The median follow-up interval was 5.6 ± 3.0 years. Seventy-four cancers occurred in during the follow-up. The risk of all cancers was found significantly increased in adult narcoleptic patients (SIR 1.32; 95% CI, 1.04–1.66, $p = 0.0248$). Regarding sex, the overall cancer risk was increased in female patients (SIR 1.52; 95% CI, 1.05–2.13, $p = 0.026$). Furthermore, females were found to have more head and neck cancers (SIR 6.17; 95% CI, 1.66-15.80, $p = 0.009$) and gastric cancers (SIR 4.87; 95% CI, 1.31–12.48, $p = 0.02$). For males, the incidence of overall and specific cancer types was not significantly increased.
Conclusions: Adult narcoleptic patients had a higher risk for cancer. Further research is warranted to elucidate the mechanism underlying its association.

1. Introduction

Narcolepsy is a chronic disabling illness, characterized by excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations [1]. The prevalence of narcolepsy with cataplexy falls between 25 and 50 per 100,000 people, making it the second most common cause of disabling daytime sleepiness after obstructive sleep apnea [2,3]. The onset of narcolepsy has been reported to be of bimodal distribution, with a first peak occurring at 14.7 years of age, and a second at 35 years [4]. The underlying pathogenesis of narcolepsy is not very clear. Several hypotheses had been reported, including hypocretin deficiency [5], genetic predisposition of the immune system [6], the environmental triggers (e.g., flu) or the autoimmune mechanism [7]. However, the pathogeneses of narcolepsy between subpopulations of the two peaks of onset age may not be entirely the same.

The comorbidity profile of patients with narcolepsy has seldom been investigated. Given the potential great impact of comorbid diseases on the quality of life of such patients, some exploration has been attempted in recent research. Jennum et al. found that narcoleptic patients may present higher morbidity several years prior to their diagnosis and even higher morbidity thereafter, while the mortality rate was not significantly higher [8]. The close association of narcolepsy with several psychiatric and medical diseases has also been reported [8–10]. Despite diagnoses of narcolepsy having increased due to improved disease awareness in

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recent decades [11], research addressing the cancer risk among narcoleptic patients were still scarce. We thus conducted this nationwide population study to evaluate the relationship of adult narcolepsy and cancers employing an epidemiological methodology.

2. Materials and methods

2.1. Data source

In this nationwide retrospective cohort study, we used the Longitudinal Health Insurance Database (LHID) from 2000 to 2009 obtained from the National Health Insurance Research Database (NHIRD). National Health Insurance program, launched in Taiwan in 1995, contains health care data from more than 99% of the nation's population of 23 million people. The LHID consists of 1 million beneficiaries randomly sampled from the original NHI beneficiaries, which is one of the largest nationwide population-based databases in the world. The LHID consists of de-identified secondary data released for research purposes. The database comprises comprehensive information, including the entire registry and claims data from this health insurance system, ranging from demographic data to detailed orders from ambulatory and inpatient care. Numerous published researchers have used the NHIRD as the basis for their studies [12]. The diseases were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, 2001 edition.

2.2. Study subjects

From January 1, 2000 to December 31, 2009, patients with a new diagnosis of narcolepsy (ICD-9-CM 347.xx) were enrolled. Patients with the following conditions were excluded: age younger than 18 years old, and antecedent cancers before enrolment. Considering the possible introduction of surveillance bias, we excluded patients with a diagnosis of any cancer within the first year of the follow-up period. The index date was defined as 366 days after diagnosis of narcolepsy in order to avoid immortal time bias. Information regarding comorbidities including Charlson comorbidity index (CCI) score, diabetes mellitus, hypertension, chronic kidney disease, coronary artery disease, dyslipidemia, and chronic liver disease was collected for analysis. Data regarding monthly income levels were collected as a surrogate of socioeconomic status, and numbers of ambulatory visit in the past one year were also collected as a marker of health care utilization. The urbanization levels of the residential area were also gathered.

2.3. Outcomes

The endpoint of the current study was cancer occurrence of nearly all origins. To identify a patient diagnosed with cancer, we used the data from the Catastrophic Illness Registry to which patho-histologic confirmation for a diagnosis of cancer is required to be reported. All patients were followed until the occurrence of cancer, dropout from the NHI program, death, or the end of 2010.

Table 1
Characteristics of the study subjects.

	Total	Male	Female
No. of patient, (%)	2,833	1,557(54.9)	1,276(45.1)
Person-years at risk	15,913	8,541	7,372
Age at diagnosis	37.4(19.7)	36.8(19.8)	38.1(19.5)
Median follow-up, years	5.6(3.0)	5.5(3.0)	5.8(3.1)
Outpatient visits, in the past one year			
0–5 visits, *n* (%)	232	172(74.1)	60(25.9)
6–10 visits, *n* (%)	497	308(62.0)	189(38.0)
>10 visits, *n* (%)	2104	1077(51.2)	1027(48.8)
Income			
Dependent, *n* (%)	1159	569(49.1)	590(50.9)
0–19,100 NT dollars, *n* (%)	640	405(63.3)	235(36.7)
19,100–42,000 NT dollars, *n* (%)	837	438(52.3)	399(47.7)
>42,000NT dollars, *n* (%)	197	145(73.6)	52(26.4)
Urbanization			
Level 1, *n* (%)	1530	837(54.7)	693(45.3)
Level 2, *n* (%)	1076	598(55.6)	478(44.4)
Level 3, *n* (%)	205	110(53.7)	95(46.3)
Level 4, *n* (%)	22	12(54.5)	10(45.5)
Charlson comorbidity index score			
0, *n* (%)	1066	587(55.1)	479(44.9)
1, *n* (%)	758	415(54.7)	343(45.3)
2, *n* (%)	417	226(54.2)	191(45.8)
≧3, *n* (%)	592	329(55.6)	263(44.3)
No. of comorbidities (%)			
Diabetes mellitus, *n* (%)	379	194(51.2)	185(48.8)
Hypertension, *n* (%)	600	346(57.7)	254(42.3)
Chronic kidney disease, *n* (%)	210	117(55.7)	93(44.3)
Coronary artery disease, *n* (%)	396	211(53.3)	185(46.7)
Dyslipidemia, *n* (%)	475	258(54.3)	217(45.7)
Chronic liver disease, *n* (%)	665	412(62.0)	253(38.0)
Connective tissue disease, *n* (%)	98	37(37.8)	61(62.2)
Patients with incident cancer	74	40	34
Incidence of all cancer (per 1000 person-years)	4.65	4.68	4.61

Abbreviations: NT, New Taiwan