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Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Brief Communication

Use of sleep medications and risk of cancer: a matched case-control study

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ARTICLE INFO

Article history:

Received 25 March 2015

Received in revised form 29 April 2015

Accepted 5 May 2015

Available online

Keywords:

Malignant neoplasm

Sleep medication

Hypnotics and sedatives

Epidemiology

SUMMARY

Background: Previous research suggests a possible link between sleep-medication use and mortality, especially cancer deaths, but findings are mixed, and large population-based studies are lacking.

Methods: Data from the Finnish Public Sector study were linked to the Finnish Cancer Register and the Drug Prescription Register of Finland. A total of 5053 cancer cases (mean age of 57.4 years) diagnosed in 2002–2011, and their 24,388 controls free of cancer and matched for sex, age, socioeconomic status, employer, and geographical area, were identified. The use of sleep medications was defined as purchases of prescribed sleep medications.

Results: Both quantity and duration of prior sleep-medication use during the seven years studied were associated with increased odds of having cancer. Compared with participants not using sleep medications, the odds ratio was 1.18-fold (95% confidence interval (CI): 1.01–1.39) for those who used >100 defined daily doses per year and 1.16-fold (95% CI: 1.01–1.34) for those who had such a medication for >3 years. Site-specific analyses showed a more pronounced association of quantity and duration of sleep-medication use with subsequent cancer of the respiratory system (odds ratio for >100 defined daily doses per year vs. no use: 3.47; 95% CI: 1.97–6.11). No associations were found with other cancer sites.

Conclusion: In this register-based study, sleep-medication use was associated with an increased cancer incidence of the respiratory system. Further studies are needed to examine potential carcinogenic mechanisms associated with hypnotic medications.

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1. Introduction

It has been estimated that 6–10% of the US adult population use hypnotic medication regularly, and similar rates of medication use have been observed in European countries [1,2]. The association between the use of sleep medications and an increased mortality risk has been documented in >20 studies. Although most research has focused on all-cause mortality, a few studies have found that

sleep medications are specifically associated with cancer deaths [3–7]. A review of both epidemiological and laboratory studies suggests that the use of sleep medication may increase cancer risk, but it also emphasizes the need for more research due to limitations, such as small sample size and short exposure period, in available data [8]. We examined this association in a large cohort study using records from prescription and health registers over a 7-year period.

2. Methods

2.1. Study population and design

In this report from the Finnish Public Sector study of public sector employees from Finland, records from the national health and prescription registers from 1994 to 2011 were available for 151,618 employees who were employed for at least six months during 1994–2005 in the participating organizations. Using the Finnish

Author contribution: Authors BS and PS drafted the manuscript. Authors MK and JV were responsible for the conception and design of the study and they were involved in the acquisition of data. JP conducted the statistical analysis. Authors MK JV and JP gave critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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<http://dx.doi.org/10.1016/j.sleep.2015.05.003>

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Cancer Register records covering virtually all diagnosed malignant tumors in Finland, we identified 5053 incident cancer cases that had been diagnosed after entry to the cohort in between 2002 and 2011. For each cancer case, we selected randomly five controls not diagnosed with cancer during the study. The controls were matched for sex, age (<40, 40–46, 47–52, or >52 years, based on quartiles of age among the cases), socioeconomic status (SES; upper-grade nonmanual, lower-grade nonmanual, or manual), employer (municipality or hospital district), and geographical area (Southern, Middle, or Northern Finland) of the year they entered the study. The matching procedure was successful, and the analytic sample included thus 5053 cancer cases and 24,388 controls free of cancer. Exposure to hypnotic-medication use during a 2–7-year period was assessed using the national Drug Prescription Register and leaving a 1-year lag before cancer diagnosis (exposure period: years –1 to –8 from the time of diagnosis). Approval for the study was obtained from the ethics committee of the Hospital District of Helsinki and Uusimaa.

2.2. Sleep medication

Sleep-medication use was defined as purchases of prescribed sleep medications (Anatomical Therapeutic Chemical (ATC) code N05C), drawn from the Drug Prescription Register of the Social Insurance Institution of Finland, and measured by defined daily doses (DDDs). There were 4334 (15%) participants who had at least one purchase during the years –1 to –8 from the time of cancer diagnosis (or corresponding period among controls). Altogether, 792 (16%) of the cancer cases and 3542 (15%) of the controls had used sleep medication. Yearly prevalence rates of sleep-medication use for cases and controls are presented in Fig. 1.

2.3. Cancer

Information about the date and type of diagnosed malignant tumors was obtained from the Finnish Cancer Register. Specific cancer types analyzed were leukemia (International Classification of Disease (ICD)-10 code C42), gastrointestinal cancer (C15–C26), cancer of the respiratory system (C30–C34), breast cancer (C50), cancer of the ovaries, uterus, or cervix (C51–C58), prostate cancer (C61), cancer of the urinary organs (C64–C68), skin cancer (C44), cancer of the thyroid gland (C73), and other cancer (other C-codes).

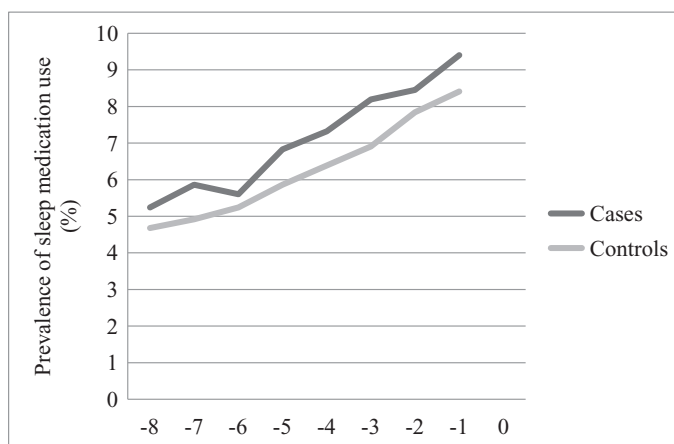


Fig. 1. The prevalence of sleep-medication use during 8 years before the year of cancer diagnosis (year 0) in cases and corresponding period in controls free of cancer.

2.4. Statistical analyses

Conditional logistic regression analysis was used to examine the association between sleep-medication use and cancer in a case-control design. To explore the effects of quantity and duration of exposure, we analyzed separately the mean sleep-medication use per year during years –1 to –8 and the duration of treatment. The mean sleep-medication use per year was categorized into 0, 1–100, or >100 DDDs per year. Treatment duration was categorized into 0 year, 1–3 years, or 4–7 years during years –1 to –8 from the time of cancer diagnosis (or corresponding period among controls). The results were quantified by odds ratios (ORs) and their 95% confidence intervals (CIs).

3. Results

The sample comprised 29,441 participants (5053 cancer cases and 24,388 controls), of whom 22,699 were women (75% of cases and 77% of controls). The mean age of the cancer cases was 57.4 years (standard deviation: 10.5; range: 20–89) and 55.9 years (10.9, 25–73) for the controls. Socio-demographical and occupational characteristics did not differ between the groups, confirming the success of matching.

Both quantity and duration of sleep-medication use during the 7-year exposure window were associated with an increased risk of any cancer (Table 1). The risk was 1.18-fold (95% CI: 1.01–1.39) for those who used >100 DDDs per year and 1.16-fold (95% CI: 1.01–1.34) for those who had been using sleep medication for >3 years, compared with those who had used no sleep medication during years –1 to –8 from the time of cancer diagnosis (or corresponding period in controls). Using sleep medication up to 100 DDDs per year or up to 3 years was not associated with an increased risk when all cancer sites were analyzed together.

Site-specific analyses revealed a dose–response relationship between quantity and duration of prior sleep-medication use and incident cancer of the respiratory system (ICD-10 codes C30–C34, Table 1). Using 1–100 DDDs per year was associated with a 1.53 (95% CI: 1.04–2.24) times higher OR for respiratory cancer compared with no sleep medication. The corresponding OR for using >100 DDDs per year was 3.47 (95% CI: 1.97–6.11). The risk of cancer of the respiratory system was 1.70 (95% CI: 1.14–2.52) for those who had used sleep medication for 1–3 years and 2.32 (95% CI: 1.41–3.83) for those who had used >3 years, compared with those who had not used sleep medication (test for trend $p < 0.0001$). The analysis included 264 cases with cancer of the respiratory system and 1255 matched controls. No association was found between sleep-medication use and any other cancer sites (test for trend; all p -values >0.10).

4. Discussion

The current study found that patients who used sleep medications had 16–18% increased risk of being diagnosed with any cancer during the follow-up period as compared with non-users. The association of sleep medications was most pronounced with cancer in the respiratory system; using >100 DDDs per year was associated with a 3.5-fold increased risk of cancer. The quantity or duration of sleep-medication use was not associated with other cancer sites, including skin cancer that has previously been linked to sleep-medication use [8].

The finding of the associations between sleep medications and respiratory cancer should be interpreted cautiously due to some important methodological limitations to this study. The lack of control for potential confounding risk factors not available at baseline is an important source of potential bias. For example, previous studies, including those from Finland, have shown a higher prevalence of smoking and obesity in individuals who use sleep medication

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