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Original Article

Association between sedative-hypnotic medication use and incidence of cancer in Korean Nation Health Insurance Service data

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ABSTRACT

Objectives: We aimed to investigate the association between the use of various sedative-hypnotics and the incidence of overall and individual cancers in a large, population-based, retrospective cohort study.
Methods: We selected a 5% random sample of individuals aged 50 years or older from data maintained by the Korean National Health Insurance Service for the years 2002–2015, excluding individuals with a prior diagnosis of cancer and with any sedative-hypnotic use in the initial two years of follow-up, leaving 236,759 participants for the final analysis. Exposure to sedative-hypnotics was defined by type of drug, standardized to a defined daily dose, and coded as a time-varying variable. Cox proportional hazard models were applied after adjusting for sex, socio-economic status, and comorbidities.
Results: We observed increased risk for overall cancer among men and women who used sedative-hypnotics (hazard ratio (HR) = 1.07, 95% confidence interval (CI) = 1.01–1.13 for men; HR = 1.21, 95% CI = 1.09–1.25 for women) compared with non-users after full adjustment. In the fully adjusted model, women with any sedative-hypnotic use had significantly increased risk for thyroid (HR = 1.53, 95% CI = 1.24–1.87), breast (HR = 1.29, 95% CI = 1.04–1.61), ovarian (HR = 1.65, 95% CI = 1.10–2.46), and lung cancer (HR = 1.40, 95% CI = 1.17–1.69) compared with non-users. Men with sedative-hypnotic use had increased risk for prostate (HR = 1.36, 95% CI = 1.16–1.58), brain (HR = 1.67, 95% CI = 1.04–2.69), and lung cancer (HR = 1.20, 95% CI = 1.07–1.35) compared with non-users.
Conclusion: We found a significant increase in overall cancer incidence among participants who used sedative-hypnotics, and both male and female sedative-hypnotic users had significantly increased risk for certain types of cancer.

1. Introduction

In chronic insomnia patients, several sedative-hypnotic medications are prescribed for an average of five years [1]. Commonly prescribed medications include benzodiazepines, zolpidem, low-dose anti-psychotics, and anti-depressants. Benzodiazepines were prescribed to approximately 9% of the elderly population in the United States in 2008 [2], and 24% in Korea between 2007 and 2011 with increasing rate [3].

Among the issues related to the side-effects of sedative-hypnotics [1], the association between the use of sedative-hypnotic medications and various types of cancers has been under continuous debate. Initially, breast cancer was assessed in relation to sedative-hypnotic medication use in several studies, but no significant results were found [4,5]. Hardell et al., reported a null association between use of these medications and colon cancer [6]. However, in recent studies, sedative-hypnotic

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medication use was associated with increased risk of several cancers, such as liver cancer, prostate cancer, bladder/kidney cancer, esophageal, and stomach cancer, lung cancer, and pancreatic cancer [7–9].

Notably, all of the studies showing an increased risk of specific cancers assessed benzodiazepines only [7–9]. Even the study conducted by Kripke et al. [10], which evaluated the effect of other sedative-hypnotics rather than benzodiazepines alone, observed no effect for non-benzodiazepine medications or for benzodiazepines on specific cancers. In addition, most previous work has been conducted using a case–control design, which inevitably possesses limitations on distinguishing the temporal sequence between use of sedative-hypnotics and cancer.

Therefore, we aimed to investigate the effects of the use of various sedative-hypnotics on different cancers in a large population-based cohort with long-term follow-up.

2. Materials and methods

2.1. Study population and design

We utilized data from the Korean National Health Insurance Service (NHIS) that was collected from January 2002 to December 2015. The Korean health insurance system officially started in 1977 and gradually expanded to the NHIS system to achieve nationwide health insurance that covered 97% of the population of South Korea by 1989 [11]. The NHIS collects individuals' medical claims data, such as disease diagnosis and medication prescription, as well as demographic factors. From the initial data, we designed a retrospective cohort study of individuals by randomly selecting 5% of adults in the NHIS database who were aged 50 years or older and followed up at least five years during the period 2 January 2002 to 31 December 2015 ($N = 431{,}454$). We mutually excluded individuals who had been diagnosed with cancer ($N = 13{,}038$), and individuals who had any record of sedative-hypnotic prescription ($N = 188{,}928$) during the initial two years. A total of 236,759 participants were included in the final analysis.

2.2. Definition of exposures

We pre-defined types of sedative-hypnotic medications which included benzodiazepines, zolpidem, and other medications prescribed for off-label uses (antidepressants (amitriptyline, imipramine, low-dose formulation mirtazapine, nortriptyline, trazodone) and low-dose anti-psychotics (chlorpromazine, levomepromazine, quetiapine)). We tracked the total amount of sedative-hypnotic medication use per person from 2004 and standardized it by a defined daily dose (DDD) [12]. We only included the participants whose cumulative dose of sedative-hypnotic medication exceeded 30 DDD in the exposure group. The total cumulative dose was categorized into three ranges: 30–179 DDD, 180–359 DDD, and over 360 DDD.

For subgroup analyses, we classified the sedative-hypnotic medications into two groups: the gamma-aminobutyric acid (GABA) receptor agonist ($GABA_A$) group, which included the benzodiazepines and zolpidem, and the non-GABA group, which included the antidepressants and low-dose antipsychotics. When a participant's cumulative dose exceeded 30 DDD for one of the groups, the participant was considered as exposed to a specific group. If a participant reached 30 DDD for $GABA_A$-group exposure and 30 DDD for non-GABA-group exposure or vice versa during follow-up, they were analysed as having exposure to both groups; such cases were referred to as 'combination exposure.' In such cases, the cumulative dose for $GABA_A$-group medications and non-GABA-group medications both had to exceed 30 DDD for the participant to be considered as exposed to sedative-hypnotic medications.

2.3. Definition of outcomes

We used the classification codes from the Korean Standard Classification of Diseases, sixth version [13] (KCD-6; Appendix I) to classify cancer diagnoses, as this was the standard code used for disease coding in the NHIS. The KCD-6 uses a coding system identical to the World Health Organization International Classification of Diseases, 10th version (ICD-10) [14].

For the definition of cancer cases, we used a working definition of the 'major disease' and 'first minor disease' items in the claims data. If either one of these items reported a pre-defined cancer code (Appendix I) between 1 January 2004 and 31 December 2015 with a confirmed hospitalization, the participant was considered to be a case. The first date that the cancer code was reported was considered to be the index date. For external validity, we compared the incidence of cancer in our study with cancer statistics from the Korean Central Cancer Registry [15].

2.4. Covariates

Age, sex, comorbidities, and insurance premium were included as possible confounders in the final models. Insurance premium was used as a proxy for socio-economic status [16], because it was determined by the economic status of the beneficiary, and grouped into three categories by distribution. To measure comorbidities of each participant, we utilized a previously developed algorithm applying the Charlson Comorbidity Index [17] using ICD-10-CM codes with pre-designated weights. We counted any disease listed in the Charlson Comorbidity Index which was reported more than twice during the study period. As we coded the covariates with operational definition, there were no missing data for these variables.

2.5. Statistical analysis

We compared baseline characteristics by exposure status. For exposure status, we applied a time-varying analysis to capture various exposure conditions over time. Because there was a chance of reverse causation, we considered the lag effect in our model. A five-year lag period was applied between exposure and outcome. A Cox proportional hazard model was applied to calculate hazard ratios (HRs) and 95% confidence intervals (Cis) between sedative-hypnotic medication use and cancer incidence. Person-time was measured from January 2002 until the first occurrence of cancer diagnosis, loss to follow-up, or the end of follow-up in December 2015. For individual cancers, we did not consider the presence of other types of cancer; eg, when calculating the risk of incident lung cancer, a diagnosis of colon cancer before the lung cancer diagnosis did not change the analyses. All analyses were conducted after stratification by sex. We applied the Bonferroni correction for multiple comparisons for the analysis by different cancer sites. Age was used as the time scale. For covariates, insurance premium at baseline and comorbidity status calculated with the Charlson Comorbidity Index was added into the model. All statistical analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The baseline characteristics of participants included in the final analysis are described in Table 1. A larger portion of women used any sedative-hypnotic medication compared with men; among women, 53% were prescribed any one of the sedative-hypnotics

Table 1
General characteristics of 236,759 participants included in the analysis.

	Non-users[a]	By dose				By hypnotic groups		
		Any hypnotic use[b]	Low dose (30–180 DDD)	Medium dose (180–360 DDD)	High dose (≥360 DDD)	Use of $GABA_A$[c] or non-GABA group[d] less than 30 DDD	$GABA_A$[c] hypnotic use ≥30 DDD	Non-GABA hypnotic[d] use ≥30 DDD
Total	130,217 (100)	106,542 (100)	53,389 (100)	15,743 (100)	37,410 (100)	131,734 (100)	80,524 (100)	6245 (100)
Sex								
Male	78,328 (60.15)	49,799 (46.74)	25,678 (48.10)	7245 (46.02)	16,876 (45.11)	79,059 (60.01)	37,331 (46.36)	3622 (58.00)
Female	51,889 (39.85)	56,743 (53.26)	27,711 (51.90)	8498 (53.98)	20,534 (54.89)	52,675 (39.99)	43,193 (53.64)	2623 (42.00)
Age (years, mean ± SD)	59.56 ± 8.40	61.17 ± 8.15	60.20 ± 7.95	61.23 ± 8.03	62.52 ± 8.29	59.56 ± 8.40	60.91 ± 8.12	61.19 ± 8.19
CCI (score, mean ± SD)	0.50 ± 1.02	0.90 ± 1.30	0.66 ± 1.12	0.87 ± 1.26	1.26 ± 1.47	0.50 ± 1.02	0.81 ± 1.22	1.03 ± 1.46
Insurance premium								
High	44,801 (34.40)	42,269 (39.67)	20,072 (37.60)	6164 (39.15)	16,033 (42.86)	45,387 (34.45)	31,473 (39.09)	2321 (37.17)
Medium	43,338 (33.28)	32,561 (30.56)	16,760 (31.39)	4818 (30.60)	10,983 (29.36)	43,830 (33.27)	24,893 (30.91)	1953 (31.27)
Low	42,078 (32.31)	31,712 (29.76)	16,557 (31.01)	4761 (30.24)	10,394 (27.78)	42,517 (32.27)	24,158 (30.00)	1971 (31.56)

DDD, defined daily dose; GABA, gamma-aminobutyric acid; $GABA_A$, GABA receptor agonist; SD, standard deviation.
[a] Non-users: <30 DDD of any sedative-hypnotic medication.
[b] Any hypnotic use: −30 DDD of any sedative-hypnotic medication.
[c] $GABA_A$ group: GABA agonist group including benzodiazepine and zolpidem.
[d] Non-GABA group: Including antidepressants and antipsychotics.

included in the analysis, whereas 47% of men were prescribed any sedative-hypnotic. Compared with non-users, more participants with hypnotic use were in the low-insurance-premium group and participants in the low-insurance-premium group were prescribed relatively higher doses of sedative-hypnotics. In addition, participants with higher doses of sedative-hypnotic use showed increased numbers of comorbidities. Both men and women showed a higher frequency of prescription of $GABA_A$ group medications compared with non-GABA group medications; the difference ranged from 10-times higher among men to 16.5-times higher among women.

Overall cancer incidence and HRs in relation to sedative-hypnotic use are presented in Table 2. Participants who were exposed to sedative-hypnotics had an 8% higher incidence of overall cancer after adjusting for sex, comorbidities, and socio-economic status (results not shown). When stratified by sex, only women had a statistically significant increase in risk for new-onset cancer before and after full adjustment (adjusted HR = 1.21, 95% CI = 1.13–1.29). When considering types of sedative-hypnotics, both men and women in the $GABA_A$ group (HR = 1.38, 95% CI = 1.16–1.64 in men; HR = 1.60, 95% CI = 1.27–2.03 in women) had statistically significant higher HRs for overall cancer incidence. Among women, exposure to sedative-hypnotics with a dosage in the 180- to 360-DDD range increased the incidence for overall cancer by a statistically significant 30%. However, there was not a

Table 2
Sedative-hypnotic medication use and overall incidence of cancer.

	Person-year	Case (*N*)	Incidence rate (%)	Crude HR		Adjusted HR*	
Men							
Sedative-hypnotic use				HR (95% CI)	*p*	HR (95% CI)	*p*
No hypnotic use[a]	1,401,376.3	17,343	(1.24)	1.00 (reference)		1.00 (reference)	
Any hypnotic use[b]	78,590.4	1373	(1.75)	1.04 (0.98–1.10)	0.181	1.07 (1.01–1.13)	0.014
By dose							
<30 DDD	1,401,376.3	17,343	(1.24)	1.00 (reference)		1.00 (reference)	
30–180 DDD	52,762.7	921	(1.75)	1.06 (0.99–1.13)	0.106	1.08 (1.01–1.15)	0.035
180–360 DDD	10,665.6	179	(1.68)	0.99 (0.85–1.14)	0.854	1.03 (0.89–1.19)	0.715
360 + DDD	15,162.1	273	(1.80)	1.02 (0.90–1.15)	0.775	1.10 (0.97–1.24)	0.136
By type							
Either of both groups <30DDD	1,402,653.9	17,371	(1.24)	1.00 (reference)		1.00 (reference)	
$GABA_A$ group[c] 30 + DDD	65,434.5	1168	(1.78)	1.29 (1.09–1.54)	0.004	1.38 (1.16–1.64)	0.000
Non-GABA group[d] 30 + DDD	5936.7	128	(2.16)	1.09 (0.90–1.31)	0.385	1.16 (0.96–1.40)	0.117
Women							
Sedative-hypnotic use							
No hypnotic use[a]	1,189,902.2	7677	(0.65)	1.00 (reference)		1.00 (reference)	
Any hypnotic use[b]	119,667.6	1035	(0.86)	1.16 (1.09–1.24)	<0.001	1.21 (1.13–1.29)	<0.001
By dose							
<30 DDD	1,189,902.2	7677	(0.65)	1.00 (reference)		1.00 (reference)	
30–180 DDD	77,904.9	659	(0.85)	1.15 (1.06–1.25)	0.001	1.17 (1.08–1.27)	<0.001
180–360 DDD	16,401.7	151	(0.92)	1.23 (1.04–1.44)	0.013	1.30 (1.10–1.53)	0.002
360 + DDD	25,361.0	225	(0.89)	1.14 (1.00–1.31)	0.048	1.27 (1.11–1.46)	0.000
By type							
Either of both group <30 DDD	1,191,905.8	7691	(0.65)	1.00 (reference)		1.00 (reference)	
$GABA_A$ group[c] 30 + DDD	101,174.4	922	(0.91)	1.52 (1.20–1.92)	0.001	1.60 (1.27–2.03)	<0.001
Non-GABA group[d] 30 + DDD	6205.1	71	(1.14)	1.02 (0.81–1.27)	0.895	1.11 (0.89–1.39)	0.342

DDD, defined daily dose; GABA, gamma-aminobutyric acid; $GABA_A$, GABA agonist; HR, hazard ratio.
*Adjusted for socio-economic status and comorbidity status using the Charlson Comorbidity Index. Age was considered as the time scale.
[a] <30 DDD of any sedative-hypnotic medication.
[b] 30 DDD of any sedative-hypnotic medication.
[c] $GABA_A$ group: GABA agonist group including benzodiazepine and zolpidem.
[d] Non-GABA group: Including antidepressants and antipsychotics.

statistically significant dose–response pattern for overall cancer incidence as sedative-hypnotic dosage increased.

When assessing the association between hypnotic use and incidence of individual cancers, the incidence of lung cancer increased significantly among both men and women (adjusted HR = 1.20, 95% CI = 1.07–1.35 for men; adjusted HR = 1.40, 95% CI = 1.17–1.69 for women) (Table 3). The risk of prostate and brain cancer among men (HR = 1.36, 95% CI = 1.16–1.58 for prostate cancer; HR = 1.67, 95% CI = 1.04–2.69 for brain cancer) and thyroid cancer (adjusted HR = 1.53, 95% CI = 1.24–1.87), breast cancer (adjusted HR = 1.29, 95% CI = 1.04–1.61), and ovarian cancer (adjusted HR = 1.65, 95% CI = 1.10–2.46) among women increased significantly even after adjustment for age, socio-economic status, and comorbidities. Inversely, the incidence ratio for stomach cancer among men showed a statistically significant decrease (adjusted HR = 0.86, 95% CI = 0.76–0.98). Incidence of colorectal cancer in men decreased with marginal significance.

In subgroup analyses that restricted the exposure to the $GABA_A$ group only, a statistically significant, elevated HR for overall cancer was found for women (results not shown). In addition, we observed a statistically significant, increased HR for participants exposed to sedative-hypnotics in the 180- to 360-DDD range group (HR = 2.24, 95% CI = 1.60–3.14).

4. Discussion

We examined the relationship between exposure to sedative-hypnotic medications and risk of cancer using data from 236,759 participants selected from Korea's nationwide health insurance database. We observed an increased risk for overall cancer; however, we found no dose–response relationship with the dosage of the sedative-hypnotic medications under study. Participants exposed to $GABA_A$ sedative-hypnotics showed a larger increase in HR compared with non-GABA sedative-hypnotics. In this study, women with any sedative-hypnotic use had a significantly increased risk for thyroid, breast, ovarian and lung cancer, and marginally decreased risk for cervical cancer. Among men with any sedative-hypnotic use, we observed increased risk for prostate, brain and lung cancer, and decreased risk of stomach cancer.

However, our results should be interpreted with caution. Although we adjusted the comorbidity status using the Charlson Comorbidity Index in the final model, it is not clear whether the sedative-hypnotic medication or conditions related to poor sleep affects cancer incidence.

Early case–control studies [4–6,18–20] that evaluated the association between sedative-hypnotic use and certain cancers observed no significant results. These studies were conducted with relatively small sample sizes, and thus lacked sufficient power to observe significant associations. More recent studies [7–10,21] that were conducted with a prospective or retrospective cohort design in large populations have reported several significant results between sedative-hypnotic use and cancer incidence. Recent meta-analysis including four cohort studies and 18 case–control studies found statistically significant increased association between benzodiazepine use and cancer incidence [22]. For specific cancer sites, one cohort study [21] and one large case–control study [9] found significant associations between benzodiazepine use and increased prostate cancer risk. In our study, we also found a significantly increased risk for prostate cancer in the $GABA_A$ group, which included benzodiazepine and zolpidem, but not in the non-GABA group. In our sample, both men and women showed increased incidence of lung cancer; two large case–control studies [7,9] reported increased lung cancer risk in their benzodiazepine-prescribed group. We could not find an increased risk of liver cancer among both men and women who were prescribed sedative-hypnotics, which is inconsistent with results from Kao et al. [21], and two other previous studies [7,9] that reported increased risk for liver cancer among both men and women sedative-hypnotic users. Contrary to our results, female cancers, such as breast and ovarian cancer, have shown no significant results in several other studies [4,5,20,23,24]. However, three studies [25–27] did show an increased risk for breast and ovarian cancer in benzodiazepine-prescribed groups. Cervical cancer showed a marginally decreased risk in one study [9], which is consistent with our findings; however, a recent study conducted in large Taiwanese population reported the opposite results for cervical cancer [21]. Thyroid cancer was assessed in only one other study [25], which reported non-significant results for sedative-hypnotic users, whereas our study found an increased risk for thyroid cancer among women.

Use of hypnotic-sedative medications can be a proxy for interrupted circadian rhythm, which is related to decreased length of nightly fasting. Shortened time of night fasting can disrupt metabolic factors, including glucoregulation [28]. Increases in the insulin/insulin-like growth factor system may increase the risk for a majority of cancers [29]. In addition, a number of adverse psychiatric symptoms, including insomnia and depression, which are known to be associated with overuse of alcohol [30], and cigarette

Table 3
Sedative-hypnotic use and incidence of individual cancers.

Outcomes: individual cancers	Exposure: any hypnotic use (ref.: no hypnotic use)					
	Men			Women		
	Case (*N*)	Crude HR	Adjusted[a] HR	Case (*N*)	Crude HR	Adjusted[a] HR
		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Esophageal cancer	41	1.03 (0.75–1.42)	1.10 (0.80–1.52)	2	0.39 (0.09–1.62)	0.46 (0.11–1.91)
Stomach cancer	246	0.81 (0.71–0.92)	0.86 (0.76–0.98)	153	1.00 (0.85–1.19)	1.07 (0.90–1.27)
Colon cancer	207	0.89 (0.77–1.02)	0.93 (0.81–1.08)	171	0.98 (0.84–1.15)	1.04 (0.88–1.22)
Thyroid cancer	22	1.31 (0.85–2.04)	1.36 (0.88–2.11)	106	1.44 (1.17–1.77)	1.53 (1.24–1.87)
Liver cancer	143	0.98 (0.82–1.16)	0.91 (0.77–1.08)	90	1.21 (0.96–1.51)	1.11 (0.89–1.39)
Brain cancer	20	1.58 (0.99–2.54)	1.67 (1.04–2.69)	14	1.07 (0.61–1.89)	1.11 (0.63–1.96)
Lung cancer	320	1.16 (1.03–1.30)	1.20 (1.07–1.35)	137	1.34 (1.12–1.61)	1.40 (1.17–1.69)
Renal cancer	30	1.07 (0.73–1.56)	1.11 (0.76–1.63)	18	1.45 (0.87–2.41)	1.51 (0.91–2.51)
Prostate cancer	187	1.33 (1.14–1.55)	1.36 (1.16–1.58)	NA		
Ovarian cancer	NA			29	1.56 (1.04–2.33)	1.65 (1.10–2.46)
Breast cancer	NA			92	1.23 (0.99–1.53)	1.29 (1.04–1.61)
Cervical cancer	NA			27	0.70 (0.47–1.04)	0.73 (0.49–1.08)

CI, confidence interval; HR, hazard ratio; NA, not applicable.
[a] Adjusted for socio-economic status and comorbidity status using the Charlson Comorbidity Index. Age was considered as the time scale.

smoking [31], can be relieved after administration of sedative-hypnotics. It is possible that people with diminished symptoms consume less alcohol and fewer cigarettes compared to patients without a prescription, which can lead to decreased incidence of certain cancers, such as gastric or colon cancer. In addition, people who visit a psychiatric clinic to get sedative-hypnotic prescriptions may be more sensitive to their health, use medical facilities frequently, or have been exposed more to early screening for precancerous lesions using endoscopy, resulting in an overall diminished incidence rate for gastric and colon cancers.

Circadian rhythms are also known to affect androgen levels and modulate the development and progression of prostate cancer [32], and an interrupted circadian rhythm can break the expression of related genes, altering breast biology and advancing cancer [33]. Individuals who use sedative-hypnotics, especially benzodiazepines, tend to have multiple psychiatric comorbidities, including substance use disorders [34], and possibly have altered immune function [35]. With regard to decreased immune function, several studies have suggested an association between infection and use of various sedative-hypnotics [36,37], as medications such as benzodiazepines worsen sleep apnea and provoke hypoxia followed by inflammation, which increases the risk of cancer [38]. Certain behavioral conditions, such as cigarette smoking and high alcohol consumption, co-exist with the use of sedative-hypnotics, resulting in increased risk of lung and liver cancers. A few studies have discussed the direct independent effect of sedative-hypnotics, including benzodiazepines, on individual disease onset; two early animal studies proposed an interaction between benzodiazepines and liver cancer [39–41].

This study has several strengths. First, we utilized a large, representative population-based sample, as the NHIS covers almost every population in South Korea. This granted sufficient power to observe increased risk for certain cancers that were not found in previous studies. This study was also able to assess the sedative-hypnotics categorized by drug mechanisms. Detailed information about participant sedative-hypnotic prescriptions was also employed in the analyses. We considered the effect of other comorbidities in the association between sedative-hypnotics and overall/specific cancers, and we were also able to assess specific types of cancer in relation to sedative-hypnotic use. In this way, we found the use of sedative-hypnotics to increase the likelihood of sex-specific cancers, such as breast and ovary cancer among women and prostate cancer among men. For example, the effect of abnormal circadian rhythm ion androgen levels has been investigated, inducing a carcinogenetic change in the prostate [32].

However, this study also has some limitations. Because we used only national insurance claims data, we could not obtain information on other demographic or lifestyle factors, such as body mass index, physical activity, alcohol consumption habits, or cigarette smoking habits and, thus, could not consider these factors as covariates. In addition, the diagnosis codes in the NHIS data are entered with the primary purpose of administrative billing, which can be different from the actual clinical diagnosis, further requiring validation. To address this concern, we compared incidence of cancer as defined in our data with Korean Central Cancer Registry data (results not shown). The overall cancer incidence rate in the current study exceeded the reported rate from the cancer registry, although the differences decreased as age increased, regardless of sex. If the cancer code in the NHIS dataset was inaccurate, the incidence of cancer and/or associations between sedative-hypnotic use and overall cancer may have been overestimated. However, certain cancers such as breast, lung, prostate, and thyroid cancer showed very similar incidence rates between the current study and the cancer registry, which provides external validity for our analyses. Additionally, we could not find a significant dose–response pattern for total cancer incidence because the individuals using 180–360 DDD sedative-hypnotics showed the highest HR for overall cancer. It is possible that the use of extreme levels of sedatives might result in different health outcomes such as death. Lastly, in this analysis, we used prescription data; this may not exactly reflect the actual amount of drug use.

In conclusion, we found a significantly increased incidence of overall cancer among women who used sedative-hypnotic medications, and several specific cancers showed increased risk among both men and women who used sedative-hypnotics. Men who used sedative-hypnotics had increased incidence of lung, brain, and prostate cancer and decreased incidence of stomach and colon cancer. Women who used sedative-hypnotics had increased incidence of thyroid, breast, ovarian, liver, and lung cancer. Further large-population studies that include data on potential covariates are needed to confirm the relationship of overall cancer risk and risk for specific types of cancer with use of various sedative-hypnotic medications.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix I
KCD-6 codes for cancers included in the current study

Code	Type of cancer
Cxx	Overall cancer
C15	Esophageal cancer
C16	Gastric cancer
C18–C20	Colorectal cancer
C22	Liver cancer
C33–C34	Lung cancer
C50	Breast cancer
C53	Utero-cervix cancer
C56	Ovarian cancer
C61	Prostate cancer
C64	Renal cancer
C70–C71	Brain cancer
C73	Thyroid cancer

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