Benzodiazepine Use Possibly Increases Cancer Risk: A Population-Based Retrospective Cohort Study in Taiwan

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ABSTRACT

Objective: To evaluate the possible association between benzodiazepine use and subsequent cancer risk in Taiwan.

Method: In this population-based retrospective cohort study, we used data from 1996 to 2000 from the Taiwanese National Health Insurance system to investigate the possible association between benzodiazepine use and cancer risk. The exposure cohort (mean age = 47.9 years, standard deviation [SD] = 17.3 years) consisted of 59,647 patients with benzodiazepine use. Each patient from the exposure cohort was randomly frequency-matched by age and sex to a person from the cohort with no benzodiazepine exposure (the comparison group; mean age = 46.4 years, SD = 17.8 years). Each study subject was followed until a diagnosis of cancer was made (according to *ICD-9-CM*) or until the time the subject was censored for loss to follow-up, death, or termination of insurance—or to the end of 2009. A Cox proportional hazard regression analysis was conducted to estimate the effects of benzodiazepine use on cancer risk.

Results: In the group with benzodiazepine use, the overall risk of developing cancer was 19% higher than in the group without benzodiazepine exposure, and the difference between the groups was statistically significant (hazard ratio [HR] = 1.19; 99.6% CI, 1.08–1.32). With regard to individual types of cancer, the risk of developing liver cancer (HR = 1.45; 99.6% CI, 1.10–1.90), prostate cancer (HR = 1.72; 99.6% CI, 1.10–2.70), and bladder and kidney cancer (HR = 1.76; 99.6% CI, 1.16–2.67) was significantly higher for the benzodiazepine cohort.

Conclusions: This population-based study has shed light on a possible relationship between benzodiazepine use and increased cancer risk. Further large, thorough investigations are needed to confirm these findings.

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Benzodiazepines are psychoactive drugs that can be used to treat a variety of conditions such as insomnia, anxiety, alcohol dependence, seizures, panic, and agitation. For the general population, benzodiazepines are one of the most frequently prescribed classes of drugs, and the use of benzodiazepines ranges from 10% to 42% worldwide among the elderly.[1–4] Cheng and colleagues[5] found that the rate of benzodiazepine use among the Taiwanese elderly was even higher, and the 1-year period prevalence was approximately 43%.

The possible link between benzodiazepine use and subsequent cancer risk has been debated for some time. Some studies have indicated that benzodiazepines increase the risk of selected cancers.[6–10] A previous survey conducted by the American Cancer Society in 1982 found an increased risk of cancer among individuals who used sleeping pills, most of which were benzodiazepines.[10] There have been over a dozen epidemiologic studies suggesting that benzodiazepine or nonbenzodiazepine hypnotic drug use is associated with increased mortality in humans, mainly due to increased cancer deaths. The particular cancer sites include, but are not limited to, brain, lung, bowel, breast, and bladder. Some researchers have hypothesized that either depressed immune function or viral infections were the cause of the increased rates of cancer. Furthermore, several case-control studies[11–14] have failed to show a definite association between benzodiazepine use and cancer risk.

The US Food and Drug Administration eventually approved the clinical use of benzodiazepines with safety advice. Since benzodiazepines are used so commonly, a small risk accompanying their use could have important clinical implications—and spark interest among the general public as well. Believing that a large population-based study might help us clarify this controversy, we were interested in exploring this issue using the Taiwanese National Health Insurance system database.

METHOD

Data Sources

This study used reimbursement data from the universal National Health Insurance system in Taiwan, which has registered all medical claims since 1996. Since the end of 1996, the National Health Insurance program has covered more than 96% of the population and has contracts with 97% of clinics and hospitals. For administrative use and research, the National Health Research Institute established a randomly selected claim-file database representative of the whole population, which provides information on all medical services received by each included individual from 1996 to 2009, as well as the characteristics of the patients, hospitals, and physicians. Details of the database have been described previously.[15]

In this longitudinal retrospective cohort study, we obtained insurance claim data from 1996 to 2000 for 1,000,000 persons randomly selected from all insured persons in Taiwan. We were able to use a scrambled, anonymous identification number for each subject so as to link each subject's files, including the registry of medical services, medications prescribed, inpatient orders, and ambulatory care. Available sociodemographic information for study subjects

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Clinical Points

- This population-based study has shed light on a possible relationship between benzodiazepine use and an increased cancer risk.
- Clinicians should consider the potentially increased cancer risk of benzodiazepine use in clinical practice.

included gender, birth date, occupation, and residential area. Diagnoses were coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

Study Subjects

Subjects who were prescribed a benzodiazepine for at least 2 months during the study period (mean prescription frequency was 26.7 times [standard deviation (SD) = 34.3 times]) were identified (N = 59,647) and defined as the benzodiazepine cohort (mean age = 47.9 years, SD = 17.3 years). The initial benzodiazepine treatment date was defined as the index date. We excluded patients with a history of malignant cancer (*ICD-9-CM* codes 140–208) diagnosed before the index date or with missing information about age or sex. A nonbenzodiazepine control cohort (mean age = 46.4 years, SD = 17.8 years) was also established by randomly frequency-matching age, sex, and index year of the benzodiazepine cases to subjects from the insured population without a history of cancer or benzodiazepine treatment. Each study subject was followed until a diagnosis of cancer was made (*ICD-9-CM*) or until the time the subject was censored for loss to follow-up, death, or termination of insurance—or to the end of 2009.

We then subclassified the benzodiazepine cohort into 4 groups as follows for further analysis according to their disease status: (1) those with sleep disorders (*ICD-9-CM* codes 780.5 and 307.4 [except for sleep apnea syndrome: codes 780.51, 780.53, and 780.57]); (2) those with anxiety (*ICD-9-CM* codes 300.0, 300.2, 300.3, 308.3, and 309.81); (3) those with both sleep disorders and anxiety; and (4) those with neither.

Statistical Analysis

First, we compared the distribution of sociodemographic factors between the benzodiazepine cohort and the comparison group not exposed to benzodiazepines using χ^2 tests. Then, we calculated the sex-specific and age-specific incidence density rates of cancer with person-years in each cohort. The incidence rate ratio (IRR) of each variable was estimated by Poisson regression.

The Cox proportional hazard regression analysis was used to measure the effect of benzodiazepines on the time to cancer diagnosis. The hazard ratios (HRs) are presented with 99.6% or 99.5% confidence intervals, with the model controlling for sociodemographic factors. The Bonferroni adjustment was used in multiple comparisons.

All analyses were performed using SAS statistical software, Version 9.1 (SAS Institute Inc, Cary, North Carolina), and the significance level was set at .05.

Table 1. Comparison of Baseline Characteristics Between the Groups With and Without Benzodiazepine Use

	Group Without Benzodiazepine Use, N = 59,592		Group With Benzodiazepine Use, N = 59,647		*P*
Characteristic	n	%	n	%	Value[a]
Sex					
Women	31,286	52.5	31,341	52.5	
Men	28,306	47.5	28,306	47.5	
Age, y					
< 20	2,921	4.9	2,920	4.9	
20–39	17,237	28.9	17,240	28.9	
40–49	13,381	22.5	13,379	22.4	
50–59	10,646	17.9	10,646	17.9	
60–69	8,248	13.8	8,248	13.8	
≥ 70	7,159	12.0	7,214	12.1	
Urbanization level[b]					< .0001
1	19,075	32.0	18,674	31.3	
2	17,359	29.1	17,001	28.5	
3	10,774	18.1	10,297	17.3	
4	7,167	12.0	7,918	13.3	
5	5,215	8.8	5,757	9.7	

[a] χ^2 test. No *P* values are given for sex and age since the selection of subjects with no benzodiazepine exposure was constrained by the distribution of sex and age in the subjects with benzodiazepine use.
[b] Urbanization level: 1 indicates the highest level of urbanization, and 5 indicates the lowest. The townships within which subjects registered for insurance were grouped into 5 levels of urbanization that were based on a score calculated by incorporating variables indicating population density (people/km^2), population ratio of different educational levels, population ratio of the elderly, population ratio of agricultural workers, and number of physicians per 100,000 people.[16]

RESULTS

The frequency matching by sex and age worked well, as displayed in Table 1. Only slight differences are observed between the 2 cohorts with respect to urbanization, but the differences are statistically significant due to the large sample size and statistical power.

The incidence density and crude rate ratio of cancer by age and sex is shown in Table 2. Overall, compared with the group not exposed to benzodiazepines, subjects with benzodiazepine use were 1.29 times more likely to develop cancer (a rate of 5.08 vs 3.95 per 1,000 person-years), with the highest IRR appearing in the group aged 20–39 years (IRR = 1.95; 95% CI, 1.50–2.54). The sex-specific incidence rate of cancer shows that the benzodiazepine cohort had a higher IRR than the group not exposed to benzodiazepines for both women (IRR = 1.19; 95% CI, 1.07–1.32) and men (IRR = 1.37; 95% CI, 1.25–1.49). The IRR among men aged 20–39 years in the benzodiazepine cohort was 2.81 times higher (95% CI, 1.81–4.35) than among subjects in the same age group without benzodiazepine exposure (Table 2).

Figure 1 exhibits the Kaplan-Meier curves of freedom from cancer in the 2 cohorts—patients with versus without benzodiazepine use. There was a statistically significant

Table 2. Comparisons of Incidence Density of Cancer Between the Groups With (N = 59,647) and Without (N = 59,592) Benzodiazepine Use by Age and Sex

	Group Without Benzodiazepine Use			Group With Benzodiazepine Use				
Variable	Cancer Cases, N	Person-Years	Rate[a]	Cancer Cases, N	Person-Years	Rate[a]	IRR[b]	95% CI
All subjects, age, y								
< 20	3	19,545	0.15	4	19,683	0.20	1.32	0.30–5.92
20–39	82	112,487	0.73	167	117,539	1.42	1.95	1.50–2.54***
40–49	201	90,663	2.22	301	92,147	3.27	1.47	1.23–1.76***
50–59	281	69,559	4.04	447	70,073	6.38	1.58	1.36–1.83***
60–69	409	53,396	7.66	511	55,011	9.29	1.21	1.06–1.38*
≥ 70	532	36,336	14.60	582	41,500	14.00	0.96	0.85–1.08
Overall	1,508	381,985	3.95	2,012	395,954	5.08	1.29	1.20–1.38***
Women, age, y								
< 20	1	11,224	0.09	1	11,294	0.09	0.99	0.06–15.9
20–39	55	62,590	0.88	89	66,160	1.35	1.53	1.09–2.14*
40–49	114	51,799	2.20	141	52,881	2.67	1.21	0.95–1.55
50–59	135	37,989	3.55	194	38,601	5.03	1.41	1.14–1.76*
60–69	161	27,409	5.87	184	28,208	6.52	1.11	0.90–1.37
≥ 70	177	16,418	10.80	186	19,088	9.74	0.90	0.74–1.11
Overall	643	207,429	3.10	795	216,234	3.68	1.19	1.07–1.32*
Men, age, y								
< 20	2	8,321	0.24	3	8,388	0.36	1.49	0.25–8.90
20–39	27	49,897	0.54	78	51,379	1.52	2.81	1.81–4.35***
40–49	87	38,863	2.24	160	39,265	4.07	1.82	1.40–2.36***
50–59	146	31,570	4.62	253	31,472	8.04	1.74	1.42–2.13***
60–69	248	25,987	9.54	327	26,803	12.20	1.28	1.08–1.51*
≥ 70	355	19,918	17.80	396	22,412	17.70	0.99	0.86–1.14
Overall	865	174,556	4.96	1,217	179,720	6.77	1.37	1.25–1.49***

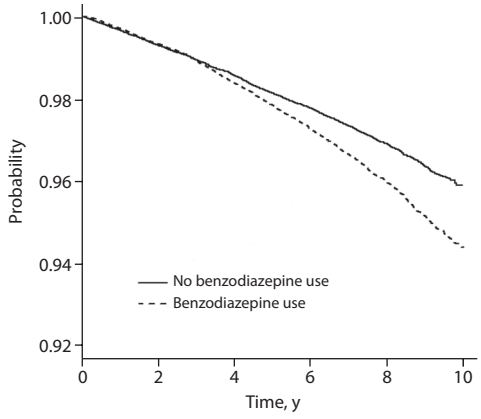
[a]Per 1,000 person-years. [b]Compared to group without benzodiazepine use.
*$P < .05$, ***$P < .0001$.
Abbreviation: IRR = incidence rate ratio.

difference in cancer occurrence between the patients with benzodiazepine use and those without benzodiazepine use (log-rank test, $P < .0001$).

The further analyses on specific cancer types are presented in Table 3. We observed that subjects with benzodiazepine use showed an increased risk of bladder and kidney cancer (HR = 1.76; 99.6% CI, 1.16–2.67), prostate cancer (HR = 1.72; 99.6% CI, 1.10–2.70), and liver cancer (HR = 1.45; 99.6% CI, 1.10–1.90). In addition, men with benzodiazepine use showed an increased risk of brain cancer (HR = 4.90; 99.5% CI, 1.05–22.8).

Furthermore, the subclassification analysis separated the benzodiazepine cohort on the basis of whether or not the patients were being treated for sleep disorders, anxiety, both, or neither. The results show that the benzodiazepine cohort without sleep disorders or anxiety had a 1.35-times greater risk (95% CI, 1.24–1.46) of cancer than the group with no benzodiazepine exposure. Additionally, those in the benzodiazepine cohort with sleep disorders alone had a 1.21-times greater risk (95% CI, 1.10–1.34) of cancer (Table 4). In contrast, the female subjects in the benzodiazepine cohort with both sleep disorders and anxiety had a decreased risk of cancer (HR = 0.80; 95% CI, 0.66–0.97).

Figure 1. Kaplan-Meier Curves of Freedom From Cancer in the Groups With (N = 59,647) and Without (N = 59,592) Benzodiazepine Use[a]



[a]Log-rank $P < .0001$.

DISCUSSION

The results of the adjusted analysis from this population-based cohort study indicated that benzodiazepine use significantly increased the risk of cancer overall and, specifically, of brain cancer in men, liver cancer, bladder/kidney cancer, and prostate cancer. In contrast, women with benzodiazepine use had a significantly lower risk of developing cervical cancer. The findings are surprising because they contradict previously held ideas. It is important to share these findings as they may have significant impact.

Since 1982, cancer has been the leading cause of death among the general population in Taiwan. The age-adjusted incidence rate has increased steadily and reached 270 new cases per 100,000 people in 2007.[17] This trend is different from the Surveillance, Epidemiology, and End Results (SEER) data, which show that overall cancer incidence rates

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Table 3. Hazard Ratios and Confidence Intervals of Cancer Associated With Benzodiazepine Use in Cox Regression Analysis in Different Cancers[a]

	All Subjects With Benzodiazepine Use[c]			Women With Benzodiazepine Use			Men With Benzodiazepine Use		
Cancer Diagnosis[b]	Cases, N	Hazard Ratio	99.6% CI	Cases, N	Hazard Ratio	99.6% CI	Cases, N	Hazard Ratio	99.5% CI
All cancers	3,520	1.19	1.08–1.32*	1,438	1.11	0.95–1.29	2,082	1.26	1.11–1.42*
Oral cancer	196	1.47	0.97–2.25	17	1.63	0.38–7.03	179	1.46	0.95–2.24
Colorectal cancer	530	1.02	0.80–1.32	196	1.10	0.72–1.66	334	0.98	0.72–1.34
Liver cancer	462	1.45	1.10–1.90*	107	1.38	0.78–2.43	355	1.47	1.08–2.00*
Lung cancer	444	1.16	0.88–1.52	129	1.26	0.75–2.10	315	1.12	0.81–1.54
Breast cancer	323	1.16	0.84–1.60	323	1.16	0.84–1.60	…[d]	…[d]	…[d]
Cervical cancer	92	0.56	0.30–1.03	92	0.56	0.30–1.03	…[d]	…[d]	…[d]
Prostate cancer	185	1.72	1.10–2.70*	…[d]	…[d]	…[d]	185	1.72	1.11–2.67*
Ovarian cancer	44	0.58	0.24–1.41	44	0.58	0.24–1.41	…[d]	…[d]	…[d]
Melanoma	14	0.66	0.14–3.12	6	0.89	0.08–9.35	8	0.52	0.07–4.01
Esophageal cancer	77	1.28	0.66–2.49	9	0.72	0.10–4.94	68	1.39	0.69–2.79
Bladder/kidney cancer	216	1.76	1.16–2.67*	79	2.27	1.10–4.68*	137	1.53	0.93–2.52
Brain cancer	35	2.75	0.90–8.38	11	1.08	0.19–6.19	24	4.90	1.05–22.8*
Other cancers	902	1.08	0.89–1.31	425	1.09	0.82–1.44	477	1.07	0.83–1.39

[a]Adjusted for age and urbanization level. [b]*ICD-9-CM* diagnosis codes: oral cancer, 140.xx, 141.xx, 143.xx–146.xx, and 148.xx–149.xx; esophageal cancer, 150.xx; colorectal cancer, 153.xx and 154.xx; liver cancer, 155.xx; lung cancer, 162.xx; breast cancer, 174.xx; melanoma, 172.xx; cervical cancer, 180.xx; ovarian cancer, 183.xx; prostate cancer, 185.xx; bladder and kidney cancer, 188.xx and 189.xx; brain cancer, 191.xx. [c]Adjusted for sex, age, and urbanization level. [d]Not applicable.
*Significant under Bonferroni correction: all $P < .005$.

Table 4. Cox Proportional Hazard Regression Analysis for the Risk of Benzodiazepine-Associated Cancer With Interaction of Comorbidity[a]

Group	N	Cancer Cases, n	Hazard Ratio	95% CI
All subjects[b]				
No benzodiazepine use	59,592	1,508	1.00	Reference
Benzodiazepine use	59,647			
Sleep disorder	15,444	577	1.21	1.10–1.34***
Anxiety	8,898	231	1.04	0.91–1.20
Sleep disorder and anxiety	11,552	272	0.91	0.80–1.04
Neither	23,753	932	1.35	1.24–1.46***
Women				
No benzodiazepine use	31,286	643	1.00	Reference
Benzodiazepine use	31,341			
Sleep disorder	8,309	231	1.14	0.98–1.32)
Anxiety	4,797	108	1.05	0.86–1.29
Sleep disorder and anxiety	6,975	120	0.80	0.66–0.97**
Neither	11,260	336	1.29	1.13–1.48***
Men				
No benzodiazepine use	28,306	865	1.00	Reference
Benzodiazepine use	28,306			
Sleep disorder	7,135	346	1.27	1.12–1.44**
Anxiety	4,101	123	1.04	0.86–1.26
Sleep disorder and anxiety	4,577	152	1.02	0.85–1.21
Neither	12,493	596	1.39	1.25–1.54***

[a]Adjusted for age and urbanization level. [b]Adjusted for sex, age, and urbanization level.
**$P < .001$, ***$P < .0001$.

in the United States for all racial/ethnic groups combined decreased by 0.7% per year between 1999 and 2006.[18] As this issue continues to be a challenge for public health in Taiwan, it has come to the attention of the government, thus resulting in population-based investigations regarding cancer-preventive epidemiology. As the Taiwanese National Health Insurance program provides comprehensive coverage, the National Health Insurance Research Database contains ambulatory service records, hospital service records, and prescription claim data. The database allows us to appropriately select matched subjects representative of the underlying population. We recently used this database to evaluate the risk of malignancy for patients with end-stage renal disease and published the article indicating some positive findings.[19] This present study used a similar design to determine the effect of benzodiazepine use on the risk of cancer development.

To our knowledge, this current study is the first population-based investigation of these 59,647 Taiwanese persons with benzodiazepine use. In order to create a comparison group, we used age, sex, and index calendar year to randomly frequency-match each individual with benzodiazepine use to a person from the cohort that had no benzodiazepine use. With regard to the cancer risk analysis, Horrobin and Trosko[20] discussed the possible effect of diazepam on cancer development and growth in 1982 and suggested that epidemiologic studies in humans were urgently required. Rosenberg et al[12] conducted a large case-control surveillance study in 1995 and investigated the relationship between benzodiazepine use and the risk of selected cancers. These authors suggested that benzodiazepines do not influence the risk of cancer as a whole, but they mentioned that the possibility of selection bias could not be excluded definitively. We were surprised to find in our results that individuals with benzodiazepine use had a significantly higher overall risk of cancer. However, this finding is consistent with a previous report,[21] which showed that the adjusted hazard of sleeping-pill usage was a statistically significantly elevated risk of cancer.

In regard to risks for individual cancers, our data showed that the risks for developing liver, prostate, and bladder/kidney cancers among patients with benzodiazepine use were significantly higher. During the literature review, we found scarce data discussing the relationship between these cancers and benzodiazepine use. For liver cancer, data from earlier animal studies[6,7] showed an interaction between benzodiazepines and hepatocarcinogenesis, although no human data are available to support the interaction. We also found that

patients with benzodiazepine use had a marginally significantly higher risk for oral cancer. Both oral and liver cancers are related to viral infections, and patients with immunocompromised status are more vulnerable to viral infections. Normally, individuals with benzodiazepine use have more psychological problems. Psychological parameters may alter immune function, and it has long been hypothesized that, through this pathway, psychosocial factors may affect the incidence of cancer.[22] The growing evidence implicates a role for the immune system as a link between the central nervous system and disease processes.[23] Various studies in this field have proven that external factors such as stress, depression, or lack of social support have significant influence on components of the immune system that, in turn, influence the onset as well as the course of cancer.[24]

Regarding bladder/kidney cancer, Kripke[11] also pointed out that bladder cancer is associated with an increased mortality caused by hypnotic drug use. The mechanism is still being studied, but the pharmacologic action and excretion of benzodiazepines may play a role. We analyzed earlier the relationship between anxiety and cancer and found that patients with anxiety disorders had a higher risk of prostate cancer—but a lower risk of cervical cancer (J.A.L., L.M.S., K.P.S., et al; unpublished data, 2011). One possible explanation is that the intrinsic personality of patients with anxiety disorders causes them to have more frequent cancer screening tests, and, therefore, more diagnoses of prostate cancer and carcinoma in situ cervical cancer can be expected. The current study also reflects similar findings, showing a significantly higher risk for prostate cancer in men with benzodiazepine use—but a marginally significantly lower risk for cervical cancer in women with benzodiazepine use. These findings imply a possible pathway: anxiety→benzodiazepine use→cancer. We are concerned about whether the increased cancer risk is actually from the underlying psychological problems instead of the benzodiazepine; however, Table 4 indicates that, among individuals with benzodiazepine use, those without anxiety or sleep disorders still had a higher risk of developing cancer.

One of the strengths of this study is the population-based design with its inherent representativeness. However, the study has some limitations. First, detailed information such as smoking habits, alcohol consumption, body mass index, socioeconomic status, and family history of cancer were not available from the National Health Insurance Research Database; all of these variables are major risk factors for multiple cancers and could plausibly be associated with benzodiazepines. However, since the National Health Insurance Research Database covers almost the whole population of Taiwan and the reimbursement policy is universally the same, it is unlikely that these factors would affect the prescription of benzodiazepines. Second, the organ-specific pattern of cancer occurrence does not appear to correspond to any biological hypothesis of benzodiazepine action. We think it most likely that our findings in part reflect a "healthy non-user effect" (ie, those with healthier lifestyles and behaviors may be less likely to have indications for benzodiazepines or may be more likely to address such problems with nonpharmacologic approaches). Third, the evidence derived from a cohort study is generally of lower quality than that derived from randomized control trials because a cohort study design is subject to many biases related to confounding adjustment. Despite our meticulous study design with adequate control of confounding factors, a key limitation is that bias could still remain if there are unmeasured or unknown confounders. Fourth, the diagnoses in the National Health Insurance claims primarily serve the purpose of administrative billing and do not undergo verification for scientific purposes. We were not able to contact the patients directly about their use of benzodiazepines because of the anonymity provided by their identification numbers. Prescriptions for these drugs before 1996 would not have been captured in our analysis. This time point cutoff could have caused underestimation of the cumulative dosage and may have weakened the observed association. However, the data for the prescription of benzodiazepines and for cancer diagnoses were very reliable.

In conclusion, this population-based retrospective cohort study unexpectedly found a significant increase in overall cancer risk as well as the risk of some individual cancers in individuals with benzodiazepine use. These findings contradict our previous thinking, and the reasons for these results are still unclear. Further large, unbiased population-based studies and randomized control trials to investigate the relative cancer risk between different benzodiazepines and specific types of cancer are needed to support our findings before any confirmatory conclusions can be made.

Drug names: diazepam (Diastat, Valium, and others).

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