BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12001

Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study

Anton Pottegård,[1] Søren Friis,[2] Morten Andersen[3] & Jesper Hallas[1]

[1]Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, DK-5000 Odense C, Denmark, [2]Danish Cancer Society Research Center, Danish Cancer Society, DK-2100 Copenhagen Ø, Denmark and [3]Centre for Pharmacoepidemiology, Karolinska Institutet, Unit of Clinical Epidemiology, Karolinska University Hospital, SE-17177 Stockholm, Sweden

Correspondence
Mr Anton Pottegård, MSc Pharm,
J.P. Winsløws Vej 19, 2. DK-5000 Odense C,
Denmark.
Tel.: +45 2891 3340
Fax: +45 6591 6089
E-mail: apottegaard@health.sdu.dk

Keywords
benzodiazepines, cancer, case–control study, pharmacoepidemiology, population based

Received
3 August 2012
Accepted
30 September 2012
Accepted Article Published Online
9 October 2012

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The association between benzodiazepines and benzodiazepine related drugs (BZRD) and cancer risk is disputed.
- A recent cohort study has shown a 35% increased risk, even with a very low BZRD exposure.

WHAT THIS STUDY ADDS

- Long term BZRD use was not associated with cancer risk.
- No dose–response association was seen, either in terms of duration or cumulative amount of BZRD.

AIM

Studies of the carcinogenic potential of benzodiazepines and related drugs (BZRD) have been equivocal. A recent study reported a 35% excess cancer risk among users of hypnotics, including benzodiazepines.

METHOD

Using Danish nationwide registers, we conducted a matched case–control study of the association between BZRD and cancer risk. During 1 January 2002 and 31 December 2009, we identified 152 510 cases with a first time cancer who were matched (1:8) by age and gender to 1 220 317 cancer-free controls. A new-user design was applied by excluding all subjects who had used anxiolytics, hypnotics or sedatives during the first 2 years of available prescription data (1995–6). Odds ratios (ORs) with 95% confidence intervals (CI) were estimated using conditional logistic regression, adjusting for potential confounders. In the primary analysis, long term use of BZRD was defined by a cumulative amount of ≥500 defined daily doses of BZRD within a period of 1 to 5 years prior to the index date.

RESULTS

The adjusted OR for cancer associated with BZRD use was 1.09 (95% CI 1.04, 1.14). ORs were close to unity for most cancer sites, except stomach 1.40 (95% CI 1.05, 1.88), oesophagus 1.43 (95% CI 1.01, 2.02), liver 1.81 (95% CI 1.18, 2.80), lung 1.38 (95% CI 1.23, 1.54), pancreas 1.35 (95% CI 1.02, 1.79) and kidney 1.39 (95% CI 1.01, 1.91). For tobacco-related cancers, the OR was 1.15 (95% CI 1.09, 1.22) and for the remaining cancer sites 1.01 (95% CI 0.94, 1.08). Sub-group analyses revealed only small differences between different levels of exposure or different patient subgroups.

CONCLUSION

BZRD use was not associated with an overall increase in cancer risk, except for what is likely explained by minor lifestyle confounding, e.g. smoking.

Introduction

Benzodiazepines and benzodiazepine related drugs (BZRD) are among the most widely used drugs in western countries, mainly to treat anxiety and insomnia. Among the elderly, user prevalences as high as 25% have been reported [1].

Even a moderate relative increase in cancer risk for a drug class as widely used as BZRD would have major public health implications. However, the question of the carcinogenic potential of BZRD is unresolved. Studies on rodents have suggested links between clobazam and thyroid cancer [2], diazepam and breast cancer [3] and oxazepam and liver cancer [4]. In 1996, the International Agency for Research on Cancer (IARC) evaluated seven frequently used types of benzodiazepines and did not find evidence for carcinogenic effects, except for oxazepam for which animal, but not human, studies indicated an association with liver cancer [5]. Subsequently, cumulative data from FDA-approved clinical trials have suggested an excess of non-melanoma skin cancers among patients treated with benzodiazepine related drugs [6], and a small case–control study has reported an increased risk of acute myeloid leukaemia associated with benzodiazepine use [7]. Large observational studies, however, of breast cancer [8–10], ovarian cancers [10–12] and nine other cancer types [10] have consistently failed to show a link between BZRD use and cancer risk.

The controversy of BZRD and cancer risk was resumed recently after a cohort study had reported a 35% increased cancer risk among users of BZRD compared with non-users, even among users with low cumulative exposure [13].

The national Danish registries offer unique possibilities for addressing such research issues, by virtue of their high coverage, long follow-up and generally high validity [14, 15]. We used the Danish Cancer Registry and the Danish National Prescription Registry to conduct a case–control study of all incident cancers in Denmark during 2002–2009, addressing the potential association between BZRD use and cancer risk. Since we also aimed to evaluate the effect of small quantities of BZRD, we applied the new user approach in our study [16].

Methods

The study was designed as a population-based case–control analysis. By comparing the prevalence of BZRD use among persons diagnosed with cancer (cases) and cancer-free persons (controls), we estimated the odds ratio (OR) for cancer associated with use of BZRD.

We used data from four Danish nationwide registries: the Danish Cancer Registry, the Danish National Patient Register, the Danish National Prescription Registry and the Danish Civil Registration System. Data were obtained for the period of 1 January 1995 to 31 December 2009.

Data sources

The Danish Cancer Registry [17, 18] has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have an accurate and almost complete ascertainment of cancer cases [17, 19]. Cancer diagnoses in this register were recorded according to the International Classification of Diseases (ICD) for Oncology from 1977 to 2003 (ICD-O-1–3), and ICD-10 since 2004.

The Danish National Patient Register contains data on all non-psychiatric hospitalizations in Denmark since 1978 and out-patient visits since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1978 to 1993 and ICD-10 since 1994 [20]. Virtually all medical care in Denmark is furnished by the national health authorities, whereby this data resource allows true population-based studies, covering all inhabitants of Denmark.

The Danish National Prescription Registry [21] contains data on all prescription drugs redeemed by Danish citizens since 1995. Prescription data includes the type of drug, date of dispensing and quantity. The dosing information and the indication for prescribing are not available. Drugs are categorized according to the Anatomic Therapeutic Chemical index, a hierarchical classification system developed by the WHO for the purposes of drug use statistics [22], and the quantity dispensed for each prescription is expressed by the defined daily dose (DDD) measure, also developed by the WHO [22].

The Danish Civil Registration System [23] contains data on vital status (date of death) and migration to and from Denmark, which allowed us to extract controls and to keep track of all subjects.

All data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish residents since 1968 that encodes gender and date of birth [23]. All linkages were performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes [21, 24, 25].

Study base

Our study base initially consisted of all Danish residents alive on 1 January 2002. However, we applied a new user design by excluding all persons from our study base who redeemed a prescription for any anxiolytic, hypnotic or sedative (ATC-codes, N05B and N05C) during the first 2 running years of the prescription database, i.e. 1995 and 1996 [16, 21]. The rationale behind this approach was based on the assumption that users of BZRD drugs within these 2 years were likely to have used the drugs prior to 1995 as well. Inclusion of individuals with a long term exposure history prior to 1995 would potentially cause substantial misclassification in dose/intensity/duration sub-analyses. Since the possibility of a carcinogenic effect

of small amounts of BZRD were raised recently [13], it was considered vital to minimize misclassification of small volume exposure.

For a subject to be eligible for sampling at a given date (index date) as either case or control, we required that the subject had lived in Denmark continuously from 1995 to the index date. Furthermore, the subject was required to be without any history of cancer (except non-melanoma skin cancer) prior to the index date.

Cases and controls

Eligible cases were all Danish individuals in the final study base with a histologically verified primary cancer diagnosis (except non-melanoma skin cancer) between 1 January 2002 and 31 December 2009, using the date of the cancer diagnosis as the index date.

Controls were selected by use of a risk set sampling strategy. For each case, we selected eight controls randomly among all individuals in the study base, matched by gender, birth year and birth month. Controls were assigned an index date identical to the date of diagnosis for the corresponding case. Subjects were eligible to be sampled as controls before they became cases. Thereby, the calculated OR is an unbiased estimate of the incidence rate ratio (IRR) that would have emerged from a cohort study in the source population [26].

Exposure definition

BZRD were defined as any drug within the ATC groups N05BA or N05CD (benzodiazepine derivates), or N05CF (benzodiazepine related drugs).

Cases and controls were considered long term users of BZRD if they had redeemed a cumulative amount of BZRD equal to or greater than 500 DDD within a period of 5 to 1 year prior to the index date. The 1 year latency period was introduced since the use of certain drugs is known to increase within the last year prior to a cancer diagnosis, most likely because of early symptoms related to a yet undetected cancer [27]. This would inflate the drug prevalence among cases and thereby introduce reverse causation bias [28], i.e. an artificial association between the use of BZRD and cancer. Another reason for requiring this latency was that we considered it very unlikely that recent exposure within the last year would contribute to the cancer risk.

One problem with studies on the use of BZRD is that treatment can be either chronic or episodic. We therefore performed exploratory analyses to define the duration that should be assigned to each prescription. An analysis of waiting time distributions [29] revealed that prescriptions for BZRD that were more than 15 weeks apart were unlikely to pertain to the same treatment episode. We thus assigned each prescription an exposure period of 15 weeks, i.e. 105 days. If the next prescription for a BZRD occurred within this exposure period, we assumed that the treatment episode had continued. If it occurred later, we assumed that treatment had been paused. No adjustment was made for overlap between prescriptions. Similarly, the exposure period assigned to single prescriptions or the last prescription in a treatment episode was 105 days.

Data analysis

The analysis was performed as a conventional matched case–control study based on a new user design. Odds ratios (ORs) for cancer associated with use of BZRD were calculated using conditional logistic regression adjusting for potential confounders. In all analyses, use of BZRD within a given time window was compared with no use, i.e. in our main analysis we compared use of more than 500 DDD of BZRD within a period of 5 to 1 year prior to the index date with no use (0 DDD) within the same period.

The following potential confounders were included in the regression model: a) use of drugs known or suspected to modify the risk of some cancers, including aspirin (ATC: B01AC06, N02BA01, N02BA51), non-aspirin NSAIDs (M01A, excluding M01AX), 5-α-reductase inhibitors (G04CB), statins (C10AA), angiotensin-II antagonists (C09C and C09D), antidepressants (N06A), antipsychotics (N05A, excluding lithium N05AN) and oral contraceptives and hormone supplements (G02BB01, G03AA07, G03AA09, G03AA10, G03AA11, G03AA12, G03AA13, G03AB, G03C, G03D, G03F, G03HB01). Exposure to a confounder drug was defined by a cumulated dose of at least 500 DDD within a period of 5 to 1 year prior to the index date; b) prior diagnoses of diseases known or suspected to modify the risk of some cancers, established more than 1 year prior to the index date, including inflammatory bowel disease (IBD) (ICD-8: 563.01, 563.19, 569.04; ICD-10: K50, K51.0-K51.3), chronic obstructive pulmonary disease (COPD) (as a crude marker of heavy smoking) [composite measure of diagnoses (ICD-8: 490.00, 491.00, 491.01, 491.03; ICD-10: J42, J43, J44) or more than 500 DDD for drugs for obstructive airway diseases (ATC-group R03)], alcohol abuse [composite measure of diagnoses (ICD-8: 291, 303, 577.10, 979, 980; ICD-10: F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, R78.0, T51, Z72.1) or any prescription for a drug used to treat alcoholism (N07BB01, N07BB03, N07BB04)] and diabetes [composite measure of diagnoses (ICD-8: 249.00, 249.09, 250.00, 250.09; ICD-10: E10-E14) or any prescription for an anti-diabetic (A10)]; c) Charlson Comorbidity Index (CCI) score [30, 31], in which each disease category has an associated weight based on the adjusted risk of 1 year mortality. We disregarded diagnoses included in the CCI score established less than 1 year prior to the index date. We defined the level of comorbidity as none (CCI score: 0), low (CCI score: 1) and medium/high (CCI score: ≥2).

To evaluate the potential influence from confounding by lifestyle factors, we categorized cancers as related to tobacco smoking, alcohol consumption or obesity. Cancers related to tobacco smoking were defined as cancers of the buccal cavity and pharynx, oesophagus, stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses,

larynx, lung, cervix, ovary, kidney, renal pelvis or ureter, urinary bladder or myeloid leukaemia [32]. Cancers related to alcohol were defined as cancers of mouth, pharynx, oesophagus, colorectum, liver, larynx or breast [33]. Cancers related to obesity were defined as cancers of the oesophagus, colorectum, pancreas, breast, endometrium or kidney [34].

We performed sub-group analyses, specified by (i) age and gender; (ii) various exposure measures, including cumulative use, intensity and duration of use; (iii) comorbidity; and (iv) type of BZRD. In addition, we performed some pre-planned sensitivity analyses. First, the main analysis was repeated with exposure limits of 100 or 250 DDD, instead of 500 DDD. Secondly, we performed the analyses according to separate exposure groups of either benzodiazepines or BZRD. Lastly, the 1 year latency period, i.e. the exclusion of exposure to BZRD or confounders within the last year prior to the index date, was varied from 0 to 2 years.

In the recent cohort study of hypnotic use and cancer risk or mortality [13], the authors excluded all individuals from the unexposed population who at any time during the complete observation period redeemed a prescription for a hypnotic drug. Thereby, cancer cases among unexposed individuals who redeemed a prescription for a hypnotic after their cancer diagnosis were excluded from all analyses. This potentially created a spurious association between hypnotic use and cancer risk [35]. To evaluate the magnitude of this error, we performed a biased analysis, mimicking this approach by repeating our analysis, only this time excluding all unexposed cases or controls who redeemed a prescription for a BZRD at any time after their index date.

All analyses were performed using Stata Release 12.0 (StataCorp, College Station, TX, USA).

Results

We identified 149 360 cancer cases (excluding non-melanoma skin cancers) and 1 194 729 controls during the period 1 January 2002 to 31 December 2009. Characteristics of cases and controls are presented in Table 1. As expected, some categories of comorbidity were more prevalent among the cases, e.g. having diabetes, COPD or a Charlson score above 0.

Long term use of BZRD was seen in 2527 (1.7%) of cases and 17 870 (1.5%) of controls, yielding a crude OR of 1.14 (95% CI 1.09, 1.19), and an adjusted OR of 1.09 (95% CI 1.04, 1.14) (Table 2).

Table 2 shows the association with BZRD for each distinct cancer site. Nearly all cancer sites showed ORs close to unity with confidence intervals overlapping 1. Exceptions were cancer of the stomach 1.40 (95% CI 1.05, 1.88), oesophagus 1.43 (95% CI 1.01, 2.02), liver 1.81 (95% CI 1.18, 2.80), lung 1.38 (95% CI 1.23, 1.54), pancreas 1.35 (95% CI 1.02, 1.79), kidney 1.39 (95% CI 1.01, 1.91), corpus uteri 0.74 (95% CI 0.54, 1.01) and rectum 0.47 (95% CI 0.24, 0.93). The analysis examining risk of tobacco-related cancers showed an OR of 1.15 (95% CI 1.09, 1.22) with a lower OR of 1.01 (95% CI 0.94, 1.08) for the remaining cancer sites.

Table 3 presents dose–response associations, including data on cumulative use of BZRD during the entire follow-up before the index date. Overall, there were only small differences in ORs between different levels of exposure, i.e. between 1.03 to 1.09 for cumulative exposure, 1.03 to 1.11 for duration of exposure and 1.02 to 1.08 for average daily dose.

The OR for benzodiazepines was higher than the risk estimate for benzodiazepine related drugs, 1.17 (95% CI 1.09, 1.25) *vs.* 1.06 (95% CI 1.00, 1.12) (Table 4). For the

Table 1

Characteristics of cancer cases and their matched controls

	Cases (n = 149 360)	Controls (n = 1 194 729)
Men	78 817 (52.8%)	630 453 (52.8%)
Women	70 543 (47.2%)	564 276 (47.2%)
Age, median (IQR, years)	65 (56–74)	65 (56–74)
All BZRD		
Never use	118 067 (79.0%)	957 778 (80.2%)
Ever use	31 293 (21.0%)	236 951 (19.8%)
Long term use*	2527 (1.7%)	17 870 (1.5%)
Benzodiazepines†		
Never use	128 342 (85.9%)	1 037 132 (86.8%)
Ever use	21 018 (14.1%)	157 597 (13.2%)
Long term use*	1007 (0.7%)	6558 (0.5%)
Benzodiazepines related drugs†		
Never use	132 729 (88.9%)	1 067 910 (89.4%)
Ever use	16 631 (11.1%)	126 819 (10.6%)
Long term use*	1528 (1.0%)	11 095 (0.9%)
Charlson Comorbidity Index (CCI)		
CCI score = 0	109 383 (73.2%)	905 997 (75.8%)
CCI score = 1	25 812 (17.3%)	188 801 (15.8%)
CCI score ≥ 2	14 165 (9.5%)	99 931 (8.4%)
Drugs		
Aspirin	19 542 (13.1%)	150 964 (12.6%)
Non-aspirin NSAIDs	5234 (3.5%)	39 957 (3.3%)
5-α-reductase-inhibitors	776 (0.5%)	6023 (0.5%)
Statins	10 811 (7.2%)	83 501 (7.0%)
AT-II antagonists	8637 (5.8%)	65 468 (5.5%)
Contraceptives and hormone supplements	11 484 (7.7%)	80 772 (6.8%)
Antidepressants	5148 (3.4%)	42 763 (3.6%)
Antipsychotics	552 (0.4%)	4218 (0.4%)
Diagnoses		
Inflammatory bowel disease	1186 (0.8%)	8525 (0.7%)
COPD	11 069 (7.4%)	71 952 (6.0%)
Diabetes	10 089 (6.8%)	73 559 (6.2%)
Alcohol abuse	6197 (4.1%)	33 665 (2.8%)

BZRD, benzodiazepine and benzodiazepine related drugs; IQR, interquartile range. *Long term use was defined as ≥500 DDD within a period of 5 to 1 year prior to the index date. †Benzodiazepines were defined as the ATC-groups N05BA and N05CD. Benzodiazepines related drugs were defined as the ATC-group N05CF.

Table 2

Association between long term exposure* to benzodiazepines or benzodiazepine related drugs and cancer risk, overall and stratified by cancer type

Cancer type	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR (95% CI)	Adjusted OR† (95% CI)
All malignancies	2 527/126 862	17 870/1 025 216	1.14 (1.09, 1.19)	1.09 (1.04, 1.14)
Buccal cavity and pharynx	82/3 253	410/27 637	1.63 (1.28, 2.09)	1.04 (0.79, 1.36)
Oesophagus	48/1 755	219/14 211	1.76 (1.27, 2.44)	1.43 (1.01, 2.02)
Stomach	60/2 418	366/19 451	1.35 (1.01, 1.78)	1.40 (1.05, 1.88)
Colon	248/11 059	1 980/87 994	0.99 (0.87, 1.14)	1.03 (0.89, 1.18)
Rectum	9/1 427	147/11 395	0.52 (0.26, 1.02)	0.47 (0.24, 0.93)
Liver	35/874	121/7 569	2.48 (1.67, 3.69)	1.81 (1.18, 2.80)
Pancreas	65/2 746	372/22 688	1.42 (1.08, 1.86)	1.35 (1.02, 1.79)
Lung, bronchus and pleura	462/14 860	2 195/123 083	1.74 (1.57, 1.93)	1.38 (1.23, 1.54)
Melanoma of skin	81/7 251	715/58 131	0.91 (0.72, 1.15)	1.00 (0.78, 1.27)
Breast	358/19 176	2 805/154 144	1.02 (0.92, 1.15)	1.01 (0.90, 1.14)
Cervix uteri	25/1 953	214/15 660	0.93 (0.61, 1.42)	0.81 (0.52, 1.26)
Corpus uteri	49/2 926	534/23 154	0.74 (0.54, 0.99)	0.74 (0.54, 1.01)
Ovary, fallopian tube etc.	43/2 340	339/18 690	1.00 (0.72, 1.39)	1.03 (0.73, 1.45)
Prostate	234/14 220	2 002/114 566	0.95 (0.83, 1.09)	1.06 (0.92, 1.22)
Kidney	52/2 375	281/19 451	1.50 (1.11, 2.04)	1.39 (1.01, 1.91)
Urinary bladder	161/7 792	1 223/63 000	1.07 (0.90, 1.27)	1.00 (0.84, 1.19)
Brain	27/2 548	200/20 379	1.04 (0.69, 1.56)	0.95 (0.62, 1.45)
Non-Hodgkin lymphoma	80/3 989	556/32 250	1.18 (0.93, 1.50)	1.09 (0.85, 1.40)
Multiple myeloma	29/1 611	259/12 852	0.88 (0.59, 1.31)	0.95 (0.63, 1.42)
Leukaemia	54/3 375	461/26 965	0.95 (0.71, 1.27)	1.01 (0.75, 1.37)
Other	325/18 914	2 471/151 946	1.05 (0.93, 1.18)	0.99 (0.87, 1.11)
Tobacco-related cancers‡	1 431/60 083	9 035/488 073	1.28 (1.21, 1.36)	1.15 (1.09, 1.22)
Remaining cancer sites	1 096/66 779	8 835/537 143	1.00 (0.94, 1.07)	1.01 (0.94, 1.08)
Alcohol-related cancers§	878/42 672	6 495/343 313	1.08 (1.01, 1.17)	1.03 (0.95, 1.11)
Remaining cancer sites	1 649/84 190	11 375/681 903	1.18 (1.12, 1.24)	1.12 (1.06, 1.18)
Obesity-related cancers¶	919/46 470	7 163/372 295	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)
Remaining cancer sites	1 608/80 392	10 707/652 921	1.22 (1.16, 1.29)	1.13 (1.07, 1.20)

*Long term use was defined as ≥500 DDD within a period of 5 to 1 year prior to the index date. †Adjusted for use of aspirin, non-aspirin-NSAIDs, 5-α-reductase inhibitors, statins, angiotensin-II antagonists, oral contraceptives and hormone supplements, antidepressants, antipsychotics, diagnoses of inflammatory bowel disease, COPD, diabetes, alcohol abuse and Charlson Comorbidity Index score. ‡Cancers of the buccal cavity and pharynx, oesophagus, stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, cervix, ovary, kidney, renal pelvis or ureter, urinary bladder or myeloid leukaemia [32]. §Cancers of the mouth, pharynx, oesophagus, colorectum, liver, larynx or breast [33]. ¶Cancers of the oesophagus, colorectum, pancreas, breast, endometrium or kidney [34].

specific types of BZRD, ORs varied between 1.01 for alprazolam and 1.29 for bromazepam. No relative excess risk for liver cancer was seen for oxazepam compared with the other benzodiazepines (data not shown).

We found only small differences in the ORs among different patient subgroups. The largest difference was seen between those aged 80 years or older (OR 0.98) and those in the two younger age groups (OR 1.11–1.12) (Table 5).

Variation of the latency period between 0 and 2 years revealed a slight inverse trend from an OR of 1.12 (95% CI 1.07, 1.16) with no latency period to 1.07 (95% CI 1.02, 1.13) with 2 years' latency period, whereas variation of the exposure limits to 100 or 250 DDD yielded virtually unaltered risk estimates (data not shown). Exclusion of non-exposed cases and controls who had redeemed prescriptions for BZRD after their index dates, thereby mimicking the design in the recent cohort study [13], increased our overall OR to 1.35 (95% CI 1.28, 1.41).

Discussion

We did not find an association between long term use of BZRD and risk of cancer, except for what is likely explained by residual confounding. We found no apparent dose–response effect, even with extensive exposure, and no convincing substance specificity or specificity with respect to the cancer sites. Also, the associations were stronger for tobacco-related cancers, which suggest that confounding by smoking may have influenced the results. The reported overall association, OR 1.09 (95% CI 1.04, 1.14), is below the limit of what can usually be addressed in observational studies such as ours, as the weak association reported in our study might be explained entirely by residual confounding [36, 37]. The finding of statistical significance for the overall OR is mainly explained by the very large dataset used.

The main strengths of the study were its size and the nationwide approach, including all diagnosed cancers in

Table 3

Association between exposure to benzodiazepine or benzodiazepine related drugs and cancer risk, specified by exposure pattern within the entire follow-up-period, excluding the last year prior to the index date

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR (95% CI)	Adjusted OR* (95% CI)
Cumulative amount of all BZRD				
1–99 DDD	21 756/118 067	167 226/957 778	1.06 (1.04, 1.07)	1.03 (1.01, 1.05)
100–199 DDD	3 206/118 067	24 378/957 778	1.08 (1.04, 1.12)	1.04 (1.00, 1.08)
200–499 DDD	3 107/118 067	22 159/957 778	1.13 (1.08, 1.17)	1.08 (1.04, 1.13)
500–999 DDD	1 628/118 067	11 722/957 778	1.13 (1.08, 1.20)	1.09 (1.03, 1.15)
>1000 DDD	1 596/118 067	11 466/957 778	1.13 (1.07, 1.19)	1.07 (1.01, 1.13)
Length of exposure				
<1 year	21 839/118 067	167 443/957 778	1.06 (1.04, 1.08)	1.03 (1.02, 1.05)
1.0–2.9 years	6 170/118 067	46 052/957 778	1.09 (1.06, 1.12)	1.05 (1.02, 1.08)
3.0–6.9 years	2 826/118 067	20 276/957 778	1.13 (1.08, 1.17)	1.07 (1.03, 1.12)
>7 years	458/118 067	3 180/957 778	1.19 (1.07, 1.31)	1.11 (1.01, 1.23)
Average amount per day within periods classified as exposed				
0.00–0.09 DDD/day	8 976/118 067	69 627/957 778	1.05 (1.02, 1.07)	1.02 (1.00, 1.05)
0.10–0.19 DDD/day	8 118/118 067	62 203/957 778	1.06 (1.04, 1.09)	1.03 (1.01, 1.06)
0.20–0.49 DDD/day	9 216/118 067	68 986/957 778	1.08 (1.06, 1.11)	1.04 (1.02, 1.07)
0.50–0.99 DDD/day	3 687/118 067	26 612/957 778	1.12 (1.09, 1.17)	1.08 (1.04, 1.12)
>1.00 DDD/day	1 296/118 067	9 523/957 778	1.11 (1.04, 1.17)	1.04 (0.98, 1.11)

BZRD, benzodiazepine and benzodiazepine related drugs. Note: All cancer sites are included. *Adjusted for use of aspirin, non-aspirin-NSAIDs, 5-α-reductase inhibitors, statins, angiotensin-II antagonists, oral contraceptives and hormone supplements, antidepressants, antipsychotics, diagnoses of inflammatory bowel disease, COPD, diabetes, alcohol abuse and Charlson Comorbidity Index score.

Table 4

Substance-specific analysis of the association between benzodiazepine or benzodiazepine related drugs and cancer. Exposure was defined by at least 500 DDD dispensed of each substance within the past 5 years, excluding the last year prior to index date

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR (95% CI)	Adjusted OR* (95% CI)
All BZRD	2 527/126 862	17 870/1 025 216	1.14 (1.09, 1.19)	1.09 (1.04, 1.14)
All benzodiazepines†	1 007/126 862	6 558/1 025 216	1.24 (1.16, 1.32)	1.17 (1.09, 1.25)
Diazepam	143/126 862	866/1 025 216	1.35 (1.13, 1.62)	1.22 (1.02, 1.47)
Oxazepam	203/126 862	1 277/1 025 216	1.31 (1.12, 1.52)	1.25 (1.07, 1.46)
Alprazolam	153/126 862	1 143/1 025 216	1.06 (0.89, 1.25)	1.01 (0.85, 1.19)
Bromazepam	31/126 862	193/1 025 216	1.33 (0.91, 1.96)	1.29 (0.87, 1.89)
Nitrazepam	228/126 862	1 386/1 025 216	1.31 (1.14, 1.51)	1.24 (1.07, 1.43)
Triazolam	109/126 862	745/1 025 216	1.17 (0.96, 1.44)	1.10 (0.90, 1.35)
All benzodiazepines related drugs†	1 528/126 862	11 095/1 025 216	1.11 (1.05, 1.17)	1.06 (1.00, 1.12)
Zopiclone	960/126 862	6 933/1 025 216	1.11 (1.04, 1.19)	1.06 (0.99, 1.14)
Zolpidem	561/126 862	4 024/1 025 216	1.13 (1.03, 1.23)	1.08 (0.99, 1.18)

BZRD, benzodiazepine and benzodiazepine related drugs. *Adjusted for use of aspirin, non-aspirin-NSAIDs, 5-α-reductase inhibitors, statins, angiotensin-II antagonists, oral contraceptives and hormone supplements, antidepressants, antipsychotics, diagnoses of inflammatory bowel disease, COPD, diabetes, alcohol abuse and Charlson Comorbidity Index score. †Benzodiazepines were defined as the ATC-groups N05BA and N05CD. Benzodiazepines related drugs were defined as the ATC-group N05CF.

the entire Danish population for a period of 8 years. This also minimized selection bias in the sampling of controls. As almost all health care service in Denmark is undertaken by the public health care system and therefore covered by our data sources, we have high population coverage. Furthermore, the use of the Danish National Prescription Registry contributed 15 years of prescription data, allowing us to apply a new-user design to minimize misclassification of cumulative exposure. Lastly, the validity of the employed databases used is generally regarded to be high [18–21, 23, 31].

Our study also had some limitations. Most importantly, our data material did not contain information on lifestyle factors that could potentially act as confounders. It is highly conceivable that users of BZRD would have a higher use of alcohol [38] and tobacco [39, 40] than BZRD non-

Table 5

Associations between long term exposure to benzodiazepine or benzodiazepine-related drugs and cancer risk, specified by patient subgroups

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR (95% CI)	Adjusted OR* (95% CI)
All	2 527/126 862	17 870/1 025 216	1.14 (1.09, 1.19)	1.09 (1.04, 1.14)
Male	1 233/68 758	8 452/556 725	1.18 (1.11, 1.26)	1.11 (1.05, 1.19)
Female	1 294/58 104	9 418/468 491	1.11 (1.04, 1.17)	1.06 (1.00, 1.13)
Age <60 years	455/43 583	2 864/353 662	1.30 (1.17, 1.44)	1.11 (1.00, 1.24)
Age 60–79 years	1 503/68 429	10 045/553 512	1.21 (1.15, 1.28)	1.12 (1.06, 1.19)
Age 80 + years	569/14 850	4 961/118 042	0.91 (0.84, 1.00)	0.98 (0.90, 1.08)
CCI† score = 0	2 149/117 419	8 663/797 627	1.11 (1.04, 1.18)	1.08 (1.01, 1.15)
No antidepressants	1 904/124 266	13 021/1 002 495	1.18 (1.12, 1.24)	1.09 (1.04, 1.15)
No antipsychotics	2 424/126 568	17 205/1 022 780	1.14 (1.09, 1.19)	1.08 (1.03, 1.13)
No known alcohol abuse	2 170/122 642	16 038/1 001 865	1.10 (1.05, 1.15)	1.09 (1.04, 1.14)
Diabetics	288/8 159	2 184/59 868	1.04 (0.83, 1.32)	1.02 (0.80, 1.30)
Non-diabetics	2 239/118 703	15 686/965 348	1.16 (1.11, 1.21)	1.10 (1.05, 1.15)

Note: All cancer sites are included. *Adjusted for use of aspirin, non-aspirin-NSAIDs, 5-α-reductase inhibitors, statins, angiotensin-II antagonists, oral contraceptives and hormone supplements, antidepressants, antipsychotics, diagnoses of inflammatory bowel disease, COPD, diabetes, alcohol abuse and Charlson Comorbidity Index score. †Charlson Comorbidity Index (CCI).

users, and thereby a higher risk of some cancers. The estimated ORs for tobacco related-cancers were slightly higher than for non-tobacco-related cancers, 1.15 *vs.* 1.01, which suggests that residual confounding by smoking may play a role. The findings for stomach (OR, 1.40), oesophagus (OR, 1.41), liver (OR, 1.81), lung (OR, 1.37), pancreas (1.34) and kidney (OR, 1.40) cancers may thus be explained by lifestyle confounding. Finally, the use of prescription data for exposure classification is associated with some misclassification, including in-hospital treatment and non-compliance. However, our main exposure was defined by quite massive exposure which invariably would require multiple out-patient prescriptions. There is no government co-payment for these drugs, and it is unlikely that a person would renew prescriptions repeatedly for a drug he did not take. In addition, such misclassification would most likely be non-differential, i.e. independent of case status, and thereby leading to a small conservative bias.

Our results differ from the cohort study by Kripke *et al*. who reported an overall hazard ratio of 1.35 for cancer when comparing users and non-users of hypnotics [13]. Kripke *et al*. were able to account for some lifestyle factors that were not covered by our data sources. However, their study was seriously hampered by some infelicitous choices in the design [35], in particular that the authors defined non-users of hypnotics as individuals with no hypnotic prescriptions throughout the entire follow-up period. We mimicked this bias in our case–control study by excluding unexposed cases or controls who redeemed BZRD prescriptions after the index date, which produced exactly the same risk estimate as in the study by Kripke *et al*. [13].

In conclusion, our findings do not support a carcinogenic effect of BZRD. Most ORs were close to unity, except a few that seemingly can be explained by lifestyle confounding. We also found that the recently reported excess of cancers among BZRD users can be explained entirely by a flawed design. For other reasons than carcinogenesis, however, use of BZRD should generally be avoided, or reserved for short term use in select patient groups [41].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare MA and JH have participated in research projects funded by Nycomed, the manufacturer of nitrazepam, and Pfizer, the manufacturer of Halcion (triazolam) and Tafil (alprazolam), with grants paid to institutions where they have been employed. JH has personally received fees for teaching from Nycomed. AP and SF declare no conflicts of interest.

The study was approved by the Danish Data Protection Agency and Statistics Denmark's Scientific Board. Approval from the Ethics Committee was not required.

REFERENCES

1 Hogan DB, Maxwell CJ, Fung TS, Ebly EM. Prevalence and potential consequences of benzodiazepine use in senior citizens: results from the Canadian Study of Health and Aging. Can J Clin Pharmacol 2003; 10: 72–7.

2 Miyawaki I, Moriyasu M, Funabashi H, Yasuba M, Matsuoka N. Mechanism of clobazam-induced thyroidal oncogenesis in male rats. Toxicol Lett 2003; 145: 291–301.

3 Karmali RA, Volkman A, Muse P, Louis TM. The influence of diazepam administration in rats bearing the R3230AC mammary carcinoma. Prostaglandins Med 1979; 3: 193–8.

4 Iida M, Anna CH, Hartis J, Bruno M, Wetmore B, Dubin JR, Sieber S, Bennett L, Cunningham ML, Paules RS, Tomer KB, Houle CD, Merrick AB, Sills RC, Devereux TR. Changes in global gene and protein expression during early mouse liver carcinogenesis induced by non-genotoxic model carcinogens oxazepam and Wyeth-14,643. Carcinogenesis 2003; 24: 757–70.

5 International Agency for Research on Cancer (IARC). IARC monograph volume 66. 1996. Available at http://monographs.iarc.fr/ENG/Monographs/vol66/mono66.pdf (last accessed 26 October 2012).

6 Kripke DF. Possibility that certain hypnotics might cause cancer in skin. J Sleep Res 2008; 17: 245–50.

7 Pogoda JM, Katz J, McKean-Cowdin R, Nichols PW, Ross RK, Preston-Martin S. Prescription drug use and risk of acute myeloid leukemia by French-American-British subtype: results from a Los Angeles County case-control study. Int J Cancer 2005; 114: 634–8.

8 Halapy E, Kreiger N, Cotterchio M, Sloan M. Benzodiazepines and risk for breast cancer. Ann Epidemiol 2006; 16: 632–6.

9 Kaufman DW, Werler MM, Palmer JR, Rosenberg L, Stolley PD, Warshauer ME, Clarke EA, Miller DR, Shapiro S. Diazepam use in relation to breast cancer: results from two case-control studies. Am J Epidemiol 1990; 131: 483–90.

10 Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Strom BL, Harlap S, Shapiro S. Relation of benzodiazepine use to the risk of selected cancers: breast, large bowel, malignant melanoma, lung, endometrium, ovary, non-Hodgkin's lymphoma, testis, Hodgkin's disease, thyroid, and liver. Am J Epidemiol 1995; 141: 1153–60.

11 Coogan PF, Rosenberg L, Palmer JR, Strom BL, Stolley PD, Zauber AG, Shapiro S. Risk of ovarian cancer according to use of antidepressants, phenothiazines, and benzodiazepines (United States). Cancer Causes Control 2000; 11: 839–45.

12 Dublin S, Rossing MA, Heckbert SR, Goff BA, Weiss NS. Risk of epithelial ovarian cancer in relation to use of antidepressants, benzodiazepines, and other centrally acting medications. Cancer Causes Control 2002; 13: 35–45.

13 Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012; 2: e000850.

14 Thygesen LC, Ersboll AK. Danish population-based registers for public health and health-related welfare research: introduction to the supplement. Scand J Public Health 2011; 39: 8–10.

15 Frank L. Epidemiology. When an entire country is a cohort. Science 2000; 287: 2398–9.

16 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003; 158: 915–20.

17 Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry – history, content, quality and use. Dan Med Bull 1997; 44: 535–9.

18 Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011; 39: 42–5.

19 Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prev 2002; 11: 359–64.

20 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011; 39: 30–3.

21 Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011; 39: 38–41.

22 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment 2011. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2010.

23 Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011; 39: 22–5.

24 Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health 2011; 39: 103–5.

25 Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health 2011; 39: 91–4.

26 Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd edn. Philadelphia, PA: Wolters Kluwer Health, Lippincott Williams & Wilkins, 2008.

27 Jørgensen T, Herrstedt J, Friis S, Hallas J. Danish cancer patients during 1996 to 2006. J Geriatr Oncol 2012; 3: 33–40.

28 Csizmadl I, Collet J-P, Boivin J. Bias and confounding in pharmacoepidemiology. In: Pharmacoepidemiology, 4th edn, ed. Strom BL. West Sussex: Wiley and Sons, 2007; 791–810.

29 Hallas J, Gaist D, Bjerrum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. Epidemiology 1997; 8: 666–70.

30 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–83.

31 Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011; 11: 83.

32 Secretan B, Straif K, Baan R, Grosse Y, El GF, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens – Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009; 10: 1033–4.

33 Baan R, Straif K, Grosse Y, Secretan B, El GF, Bouvard V, Altieri A, Cogliano V. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007; 8: 292–3.

34 World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. Washington DC: AICR, 2007.

35 Andersen M, Pottegard A, Friis S, Hallas J. Hypnotics' association with mortality or cancer: bias related to the study design and analysis. Letter to the editor. BMJ Open 2012; 2: e000850.

36 Taubes G. Epidemiology faces its limits. Science 1995; 269: 164–9.

37 Austin H, Hill HA, Flanders WD, Greenberg RS. Limitations in the application of case-control methodology. Epidemiol Rev 1994; 16: 65–76.

38 Manthey L, Lohbeck M, Giltay EJ, van Veena T, Zitman FG, Penninx BW. Correlates of benzodiazepine dependence in the Netherlands Study of Depression and Anxiety. Addiction 2012. doi: 10.1111/j.1360-0443.2012.03975.x.

39 Cheron-Launay M, Le Faou AL, Sevilla-Dedieu C, Gilbert F, Kovess-Masfety V. Smoking and the consumption of antidepressants, anxiolytics and hypnotic drugs: results of a large, French epidemiological study in 2005. Addict Behav 2011; 36: 743–8.

40 Naja WJ, Pelissolo A, Haddad RS, Baddoura R, Baddoura C. A general population survey on patterns of benzodiazepine use and dependence in Lebanon. Acta Psychiatr Scand 2000; 102: 429–31.

41 Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005; 331: 1169.