# Use of benzodiazepine and risk of cancer: A meta-analysis of observational studies

Hong-Bae Kim[1,2], Seung-Kwon Myung[3,4,5], Yon Chul Park[2,6] and Byoungjin Park[2,7]

[1] Department of Family Medicine, MyongJi Hospital, 14-55 Hwasu-ro, Deokyang-gu, Goyang, Gyeonggi-do, 10475, Republic of Korea

[2] Department of Family Medicine, School of Medicine, Yonsei University, 50-1 Yonsei-ro, Seodaemoon-gu, Seoul, 03722, Republic of Korea

[3] Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi-do, 10408, Republic of Korea

[4] Molecular Epidemiology Branch, Division of Cancer Epidemiology and Prevention, Research Institute, National Cancer Center, Goyang, Republic of Korea

[5] Department of Family Medicine and Center for Cancer Prevention and Detection, Hospital, National Cancer Center, Goyang, Republic of Korea

[6] Department of Family Medicine, Wonju Severance Christian Hospital, 20 Ilsan-ro, Wonju, Gangwon-do, 220-701, Republic of Korea

[7] Department of Family Medicine, Yongin Severance Hospital, 225 Gumhak-ro, Cheoin-gu, Yongin, Gyeonggi-do, 17046, Republic of Korea

Cancer Epidemiology

Several observational epidemiological studies have reported inconsistent results on the association between the use of benzo-diazepine and the risk of cancer. We investigated the association by using a meta-analysis. We searched PubMed, EMBASE, and the bibliographies of relevant articles to locate additional publications in January 2016. Three evaluators independently reviewed and selected eligible studies based on predetermined selection criteria. Of 796 articles meeting our initial criteria, a total of 22 observational epidemiological studies with 18 case-control studies and 4 cohort studies were included in the final analysis. Benzodiazepine use was significantly associated with an increased risk of cancer (odds ratio [OR] or relative risk [RR] 1.19; 95% confidence interval 1.16–1.21) in a random-effects meta-analysis of all studies. Subgroup meta-analyses by various factors such as study design, type of case-control study, study region, and methodological quality of study showed consistent findings. Also, a significant dose-response relationship was observed between the use of benzodiazepine and the risk of cancer (*p* for trend <0.01). The current meta-analysis of observational epidemiological studies suggests that benzodiazepine use is associated with an increased risk of cancer.

## Introduction

Benzodiazepines are prescribed to handle a variety of medical conditions such as seizures, anxiety, insomnia, and panic disorder.[1] Previous *in vitro* laboratory and animal studies have reported controversial findings on the association between

the use of benzodiazepine and the risk of cancer. Several animal studies reported that benzodiazepines increased the risk of thyroid cancer[2] or liver cancer.[3] Conversely, *in vitro* laboratory studies indicated that benzodiazepines might inhibit the proliferation of pituitary tumor cells[4] or have antitumor effects on colorectal and breast adenocarcinoma cells.[5]

In the meantime, observational epidemiological studies reported that there was no link between diazepam use and the risk[6] or progression[7] of breast cancer. However, recent cohort studies revealed that the use of temazepam, an intermediate acting benzodiazepine was associated with an increased risk of cancer,[8] and the benzodiazepine users were exposed to the risk of benign brain tumor about three times higher than the non-benzodiazepine users.[9]

To date, no quantitative meta-analysis has been published on this topic. In the current study, we investigated the associations between benzodiazepine use and the risk of cancer by using a meta-analysis of observational epidemiologic studies such as case-control studies and cohort studies.

## Materials and Methods
### Literature search

We searched PubMed and EMBASE using common keywords linked with benzodiazepine use and the risk of cancer in January 2016. The keywords were as follows: "benzodiazepine," "diazepam," "alprazolam," "clonazepam,"

**What's new?**

In recent years, the question of whether sedative-hypnotic benzodiazepine drugs increase cancer risk has emerged. Evidence for a direct association from animal studies is inconclusive, however, and cohort studies suggest that while some benzodiazepines are associated with increased cancer risk, others are not. The present meta-analysis of observational studies published between 1982 and 2014 shows that the use of various benzodiazepines, including alprazolam, clonazepam, diazepam, oxazepam, and temazepam, was consistently associated with an increased risk of cancer, overall and in subgroup analyses. The association was characterized by a dose-response relationship, with risk elevated for multiple cancer types.

"temazepam," and "oxazepam" for exposure factors; "cancer," "tumor," "carcinoma," and "neoplasm" for outcome factors. Also, we reviewed the bibliographies of relevant articles to locate additional studies. The language of publication was not restricted.

### Selection criteria

We included observational epidemiological studies that meet all of the following criteria: (1) a case-control study or a cohort study; (2) investigated the associations between the use of benzodiazepine and the risk of cancer; (3) reported outcome measures with adjusted odds ratios (OR) or relative risks (RR) and 95% confidence intervals (CI). If data were duplicated or shared in more than one study, the first published study was included in the analysis. Studies that were not published in peer-reviewed journals or only presented in academic conferences were excluded.

### Selection of relevant studies

Three authors (Kim HB, Park YC, and Park BJ) independently evaluated the eligibility of all studies searched from the two databases. If there were disagreements on the selection of studies between investigators, they were resolved by discussion.

### Assessment of methodological quality

The methodological quality of included studies was evaluated based on the Newcastle-Ottawa Scale (NOS) for assessing the quality of case-control studies and cohort studies in meta-analyses.[10] A star system of the NOS ranges from 0 to 9 and is composed of three subscales: selection of studies, comparability, and exposure. We considered a study awarded stars of more than a mean score of each study type as a high-quality study because the criteria for the high- or low-quality of a study have not been established.

### Main and subgroup analyses

We investigated the associations between the use of benzodiazepine (use versus never use) and the overall risk of all cancers by utilizing adjusted data as a main analysis. We also performed subgroup analyses by type of study design (case-control or cohort), type of cancer, gender, types of benzodiazepines, study region (US or Canada, Europe, and Asia), duration of benzodiazepine use, cumulative yearly dose, type of case-control study (population-based or hospital-based), and methodological quality of study (high vs. low). To

perform a dose-response meta-analysis, we categorized yearly cumulative doses into tertiles (low: temazepam <240 mg/year equal to <12DDDs (defined daily dose) sec/year, benzodiazepine <35 mg/year, and benzodiazepine 1–100 tablets/year; middle: temazepam 240–1640 mg/year equal to 12-82DDDs/year, benzodiazepine 35–150 mg/year, and benzodiazepine 201–499 tablets/year; high: temazepam >1,640 mg/year equal to >82DDDs/year, benzodiazepine >150 mg/year, and benzodiazepine ≥500 tablets/year). The ATC (anatomical therapeutic chemical) code for temazepam is N05CD07.

### Statistical analyses

To compute a pooled OR or RR with its 95% CI, we used the adjusted ORs or RRs and its 95% CIs in each study reporting the association between benzodiazepine use (highest use vs. never use) and the risk of cancer. We examined heterogeneity across studies using the Higgins $I^2$, which measures the percentage of total variation across studies.[11] $I^2$ was calculated as follows:

$$I^2 = 100\% \times (Q\text{–df})/Q,$$

where $Q$ is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of $I^2$ were set at zero; the $I^2$ results are between 0% (no observed heterogeneity) and 100% (maximal heterogeneity).[11] An $I^2$ value >50% was considered to indicate substantial heterogeneity.[11]

The pooled estimate calculated based on the fixed-effect model was reported using the Woolf's (inverse variance) method when substantial heterogeneity was not found. When substantial heterogeneity was found, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian and Laird method.[12]

We evaluated publication bias using Begg's funnel plot and Egger's test. When publication bias exists, Begg's funnel plot presents asymmetry or the $p$ values of less than 0.05 by Egger's test. We used the Stata SE version 13.0 software package (StataCorp, College Station, Texas, USA) for the statistical analysis.

### Results
### Identification of relevant studies

Figure 1 shows a flow diagram of how we identified appropriate studies. A total of 796 articles were found by searching two databases and hand-searching relevant bibliographies. We excluded 215 duplicated articles and additional 539
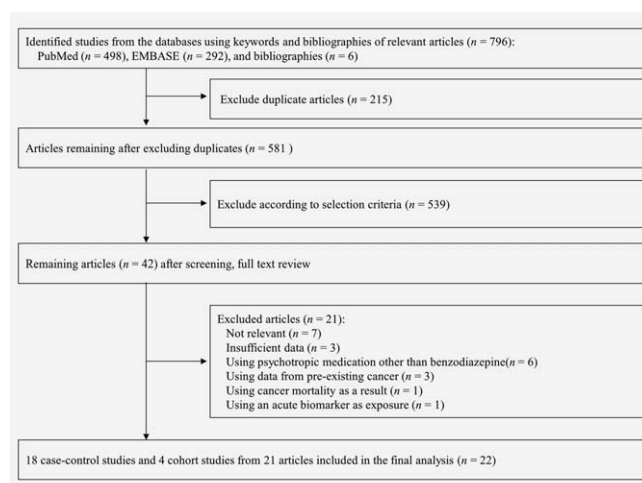
**Figure 1.** Flow diagram for identification of relevant studies.

articles that did not meet the selection criteria. We reviewed the full texts of the remaining 42 articles. Among these, 21 articles were excluded because of the following reasons: not relevant to our analysis (*n* = 7), insufficient data (*n* = 3), using psychotropic medication other than benzodiazepine (*n* = 6), data from pre-existing cancer (*n* = 3), using cancer mortality as a result, and using an acute biomarker as exposure. The remaining 21 studies including eighteen case-control studies[6,7,13–27] and four cohort studies[8,9,28,29] were included in the final analysis (the study by Kaufman et al.[13] was considered as two separate case-control studies). All of the included articles were written in English.

## Characteristics of studies included in the final analysis

A total of 22 studies published between 1982 and 2014 had 1,897,603 participants (213,823 patient cases and 1,683,780 controls). The mean age was 57.8 years (range, 18 to 95 years). Table 1 shows the general characteristics of the studies included in the final analysis. Eight studies[6,7,13,23,26–28] investigated breast cancer, three studies involved ovarian cancer,[14,19,21] two studies looked into colon cancer,[16,18] and five studies involved all types of cancer.[8,26–29] They were conducted in the following countries: US (*n* = 12),[6,7,13–15,18,19,21–25] Canada (*n* = 2),[13,23] Sweden (*n* = 3),[16,17,20] Denmark (*n* = 1),[26] France (*n* = 1),[29] and Taiwan (*n* = 3).[9,27,28] Among 18 case-control studies, 13 studies[7,13,14,17,18,20–27] were population-based studies, and five studies[6,13,15,16,19] were hospital-based case-control studies.

## Methodological quality of studies

We assessed the methodological quality of studies included in the final analysis based on the Newcastle-Ottawa Scale (NOS). The range of quality scores was 5 to 8; the average score was 6.8 for case-control studies and 7.3 for cohort studies (Table 2). The high-quality studies (scores of 7 or higher in case-control studies or 8 or higher in cohort studies) included twelve case-control study and two cohort studies.

## Benzodiazepine use and overall cancer risk

As shown in Figure 2, benzodiazepine use was significantly associated with an increased risk of cancer in the random-effects meta-analysis of all 22 studies (pooled OR/RR, 1.19; 95% CI, 1.16–1.21). In the subgroup analyses by study design, both case-control and cohort studies showed there was a significant positive association between benzodiazepine use and the risk of cancer: the pooled OR/RR was 1.18 (95% CI, 1.15–1.20) for 18 case-control studies and 1.35 (95% CI, 1.24–1.47) for 4 cohort studies, respectively. No publication bias was found in the selected studies. (Begg's funnel plot was symmetric; Egger's test, *p* for bias = 0.39; not shown in Figure).

Table 3 shows findings from subgroup meta-analyses by various factors. Benzodiazepine use was consistently associated with the increased risk of cancer in the subgroup meta-analyses by study region, type of case-control study (population-based or hospital-based), and methodological quality. Subgroup meta-analyses by gender revealed a significant positive association in the 13 studies including both gender (OR/RR = 1.20; 95% CI, 1.17–1.22), whereas no significant relationship was observed in nine studies with only female subjects. Regarding the type of benzodiazepines, intermediate-acting benzodiazepines (alprazolam, oxazepam, temazepam, and lorazepam) showed a significantly increased risk of cancer (Table 3 and Fig. 3).

## Benzodiazepine use and the risk of cancer by type of cancer

As shown in Table 3, benzodiazepine use increased the risk of breast cancer, brain cancer, esophagus cancer, renal cell cancer, prostate cancer, liver cancer, stomach cancer, pancreatic cancer, and lung cancer. However, no significant association was observed in ovarian cancer, malignant melanoma, and colon cancer.

## Overall dose-response association between benzodiazepine use and cancer risk

A statistically significant dose-response relationship was observed between benzodiazepine use and cancer risk (*p* for trend <0.01). When compared with never use of benzodiazepine, the pooled OR/RR for the risk of cancer was 0.70 (95% CI: 0.55–0.88) in a low dose, 1.59 (95% CI: 1.26–2.00) in a middle dose, and 2.93 (95% CI: 2.45–3.52) in a high dose (Table 3).

## Discussion

In the current meta-analysis of observational epidemiological studies, we found that benzodiazepine use was associated with an increased risk of cancer. Subgroup meta-analyses by various factors also showed similar findings. Additionally, these associations were observed in a dose-response manner.

There are several possible explanations for the increased risk of cancer with the use of benzodiazepine. First, some

**Cancer Epidemiology**

**Table 1.** General characteristics of the studies included in the final analysis (*n* = 22)

| Study (reference) | Type of study | Country | Years enrolled | Population (gender, age) | Type of cancer | Definition of benzodiazepine use (longest vs. shortest category) | OR/RR (95% CI) | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| 1982 Kaufman[6] | Case-control study | Canada, United States & Israel | 1976–1980 | 1,236 cases and 728 controls, (women, under 70years) | Breast cancer | Diazepam: regular-use ≥ 6 month vs. never-use | 0.9 (0.5–1.6) | Age, geographical region, years of education, religion, parity, age at first pregnancy, menopausal status, age at menopause, history of breast cancer in the mother or sisters, alcohol consumption, number of visits to a doctor in the preceding year, total number of hospital admissions, and year of interview |
| 1984 Kleinerman[7] | Case-control study | United States | 1973–1977 | 1,075 cases and 1,146 controls (women, ≥35 years) | Breast cancer | Diazepam: ever-use ≥ 6 month vs. never-use | 0.81 (0.6–1.1) | Age, Income and education, use of other tranquilizers or breast cancer risk factors such as parity, age at first birth, menarche, menopause type, age at menopause, previous breast biopsies, and family history of breast cancer. |
| 1990 Kaufman[13] | Case-control study | United States | 1981–1987 | 3,078 cases and 1,931 controls (women, 18-69 years) | Breast cancer | Diazepam: ever-use ≥ 6 month vs. never-use | 1.0 (0.6–1.7) | Age, Alcohol consumption, medical history, lifetime history of medication use, use of muscle relaxants, tranquilizers, psychiatric drugs, insomnia and pain |
| 1990 Kaufman[13] | Case-control study | Canada | 1982–1986 | 607 cases and 1,214 controls (women, median age 52 year) | Breast cancer | Diazepam: ever-use ≥ 6 month vs. never-use | 0.8 (0.5–1.3) | Age, years of education, religion, race, age at menarche, age at first birth, parity, age at menopause, history of fibrocystic breast disease, history of breast cancer in the mother or sister, alcohol consumption, lifetime number of hospital admissions, use of oral contraceptives, and use of benzodiazepiens other than diazepam |
| 1995 Harlow[14] | Case-control study | United States | 1978–1987 | 450 cases and 454 controls (women, 18-80 years) | Ovarian cancer | Benzodiazepine ever-use vs. never-use | 1.8 (1.0–3.1) | Age, race, residence, parity, prior use of oral contraceptives, religion, body mass index, prior hysterectomy, and reported therapeutic abortion |
| 1995 Rosenberg[15] | Case-control study | United States | 1977–1991 | 382 cases and 5,695 controls (men and women, 18-69 years)) | Non-Hodgkin's lymphoma | Benzodiazepine: ever-use ≥ 1 month vs. never-use | 2.1 (1.4–3.3) | Age, sex, interview year, geographic area, and years of education |

**Table 1.** General characteristics of the studies included in the final analysis (*n* = 22) (Continued)

| Study (reference) | Type of study | Country | Years enrolled | Population (gender, age) | Type of cancer | Definition of benzodiazepine use (longest vs. shortest category) | OR/RR (95% CI) | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| 1996 Hardell[16] | Case-control study | Sweden | 1984–1986 | 329 cases and 658 controls (men and women) | Colon cancer | Benzodiazepine ever-use vs. never-use | 1.7 (0.9-3.3) | Age, sex, county, and individual job-related physical activity |
| 1996 Westerdahl[17] | Case-control study | Sweden | 1988–1990 | 400 cases and 640 controls (men and women, 15-75 years) | Malignant melanoma | Benzodiazepine: ever-use vs. never-use | 1.8 (0.7–4.4) | Age, sex, parity, Family history, educational level, medical history, prescribed drugs, ultraviolet radiation exposure, smoking habits, alcohol use and endogenous and exogenous hormonal factors within in 2 months following diagnosis |
| 1998 Friedman[18] | Case-control study | United States | 1991–1994 | 1,993 cases and 2,410 controls (men and women, 30-79 years) | Colon cancer | Diazepam: ever-use $\geq$ 12 month vs. never-use | 1.2 (0.8–1.8) | Age, sex, aspirin and NSAID use, family history of colorectal cancer, body mass index, total calorie, fiber and calcium intake, physical activity, cigarette smoking and alcohol use |
| 2000 Coogan[19] | Case-control study | United States | 1976–1998 | 748 cases and 2,992 controls (women, <69 years) | Ovarian cancer | Benzodiazepine use <12month vs. never-use | 1.4 (1.0–2.1) | Age, study center, year of interview, race, religion, smoking status, parity, age at menarche, age at menopause, oral contraceptive use, body mass index, and number of physician visits in the year prior to hospitalization |
| 2000 Lagergen[20] | Case-control study | Sweden | 1995–1997 | 189 cases and 820 controls (men and women, <80 years) | Esophageal cancer | Benzodiazepine: ever-use vs. never-use | 1.5 (0.7–2.9) | Age, sex, body mass index, tobacco smoking, alcohol use, socioeconomic status (years of formal education), and intake of fruit and vegetables |
| 2002 Dublin[21] | Case-control study | United States | 1981–1997 | 314 cases and 790 controls (women, 35-79 years) | Ovarian cancer | Benzodiazepine use < 6month vs. never-use | 0.70 (0.47–1.0) | Age, parity, hysterectomy status, tubal ligation, oral contraceptive use, and number of prescription received for other medications |
| 2004 Pogoda[22] | Case-control study | United States | 1987–1994 | 412 cases and 412 controls (men and women, 25-75 years) | Acute myeloid leukemia | Benzodiazepine: ever-use $\geq$ 6 month vs. never-use | 1.5 (0.6–3.7) | Age, High-dose radiation exposure, smoking status and chemotherapy |

**Cancer Epidemiology**

**Cancer Epidemiology**

**Table 1.** General characteristics of the studies included in the final analysis ($n = 22$) (Continued)

| Study (reference) | Type of study | Country | Years enrolled | Population (gender, age) | Type of cancer | Definition of benzodiazepine use (longest vs. shortest category) | OR/RR (95% CI) | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| 2006 Halapy[23] | Case-control study | Canada | 1996–1998 | 3,133 cases and 3,062 controls (women, 25-74 years) | Breast cancer | Benzodiazepine ever-use vs. never-use | 1.06 (0.88–1.27) | Age, family history of breast cancer, personal history of breast cysts, history of anxiety and depression, use of antidepressants, use of non-steroidal anti-inflammatory drugs, hormone replacement therapy, oral contraceptives, parity, menopausal status, age at menarche, history of breast-feeding, education, income, fat intake, BMI, cigarette smoking, alcohol, and exercise |
| 2006 Landgren[24] | Case-control study | United States | 1997–2002 | 179 cases and 691 controls (women, 21-84years) | Multiple myeloma | Benzodiazepine: ever-use ≥ 6 month vs. never-use | 0.9 (0.3–2.6) | Age, race, education, and BMI |
| 2007 Fortuny[25] | Case-control study | United States | 1980–2002 | 114 cases and 3,996 controls (men and women, mean age 66.8 year) | Esophageal cancer | Benzodiazepine ever-use vs. never-use | 1.7 (0.9–3.1) | Age, sex, HMO(Health Maintenance Organization), years of enrollment in the HMO, race at HFHS(Health System's Health Alliance Plan) and use of drug classes other than the studied one |
| 2012 Kripke[8] | Prospective cohort study | United States | 2002–2007 | 2,076 cases among 25,750 people (men and women, ≥ 18 years) | All cancers | Temazepam > 1640mg/ yr vs. non-users | 1.99 (1.57–2.52) | Age, sex, ethnicity, marital status, body mass index (BMI) and self reportedalcohol use and smoking status |
| 2012 Kao[28] | Retrospective cohort study | Taiwan | 1996–2000 | 3,520 cases among 119,239 people (men and women, mean age 47.9 years) | All cancers | benzodiazepine ≥ 2 month vs. non-users | 1.19 (1.08–1.32) | Age, sex, index year of benzodiazepine cases, and urbanization level |
| 2012 Pottegard[26] | Case-control study | Denmark | 2002–2009 | 149,360 cases with a first time cancer (excluding non-melanoma skin cancers) and 1,194,729 controls (men and women, 56-74 years) | All cancers | long term use of benzodiazepine(cumulative amount ≥500 defined daily dose) vs. never-use | 1.09 (1.04–1.14) | Age, gender, use of aspirin, non-aspirin-NSAIDs, 5-a-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 1. General characteristics of the studies included in the final analysis ($n = 22$) (Continued)

| Study (reference) | Type of study | Country | Years enrolled | Population (gender, age) | Type of cancer | Definition of benzodiazepine use (longest vs. shortest category) | OR/RR (95% CI) | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| 2013 Jaussent[29] | Prospective cohort study | France | 1999–2011 | 1,454 cases among 6,696 people (men and women, 65-95 years) | All cancers | Benzodiazepine ever-use vs. never-use | 0.89 (0.66–1.19) | Age, study center, gender, high level of education, confinement, alcohol intake, smoking status, history of cardio-cerebrovascular disease, respiratory disease, Mini Mental State Examination score, body mass index, hypertension and diabetes mellitus, depressive symptoms, antidepressants use, Spielberger trait anxiety score, excessive daytime sleepiness, and number of insomnia complaints |
| 2014 Harnod[9] | Prospective cohort study | Taiwan | 2000–2009 | 274 cases among 62,050 people (men and women, 20≥ years) | Brain cancer | benzodiazepine use≥ 2 months vs. never-use | 3.15 (2.37–4.20) | Age, sex, urbanization, co-morbidities and brain CT or MRI examinations |
| 2014 Iqbal[28] | Case-control study | Taiwan | 1998–2009 | 42,500 cases and 255,000 controls (men and women, 20≥ years) | All cancers | benzodiazepine use≥ 2 months vs. never-use | 1.21 (1.18–1.24) | Age, sex, index date (ie, free of any cancer in the date of case diagnosis) by using propensity score, comorbid conditions, other drugs, regions, and socio-economic status |

Abbreviations: BMI, body mass index; OR, odd ratio; RR, relative ratio; CI, confidence interval.

**Cancer Epidemiology**

Cancer Epidemiology

**Table 2.** Methodological quality of the studies included in the final analysis based on the Newcastle-Ottawa Scale[1] for assessing the quality of case-control studies and cohort studies (n = 22[2])

| Case-control studies (n = 18) | Selection | | | | Comparability | Exposure | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Adequate definition of cases | Representativeness of cases | Selection of controls | Definition of controls | Control for important factor or additional factor | Ascertainment of exposure (blinding) | Same method of ascertainment for participants | Nonresponse rate | |
| 1982 Kaufman | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 0 | 6 |
| 1984 Kleinerman | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 1989 Kaufman | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 0 | 6 |
| 1989 Kaufman | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 1995 Harlow | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 1995 Rosenberg | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 7 |
| 1996 Hardell | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 5 |
| 1996 Westerdahl | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 1998 Friedman | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 2000 Coogan | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 0 | 6 |
| 2000 Lagergen | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 2002 Dublin | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 2004 Pogoda | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 |
| 2006 Halapy | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 7 |
| 2006 Landgren | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 6 |
| 2007 Fortuny | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 8 |
| 2012 Pottegard | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| 2014 Iqbal | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |

| Cohort studies (n = 4) | Selection | | | | Comparability | Outcome | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome of interest was not present at start of study | Control for important factor or additional factor | Assessment of outcome | Follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | |
| 2012 Kripke | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| 2012 Kao | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 6 |
| 2013 Jaussent | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| 2014 Harnold | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 |

[1]Each study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, while a maximum of two stars can be given for the comparability category.
[2]Two pooled studies with 19 case-control studies and 4 cohort studies and a cross-sectional study were excluded in this assessment of methodological quality because no required information for the methodological assessment of each study was provided.
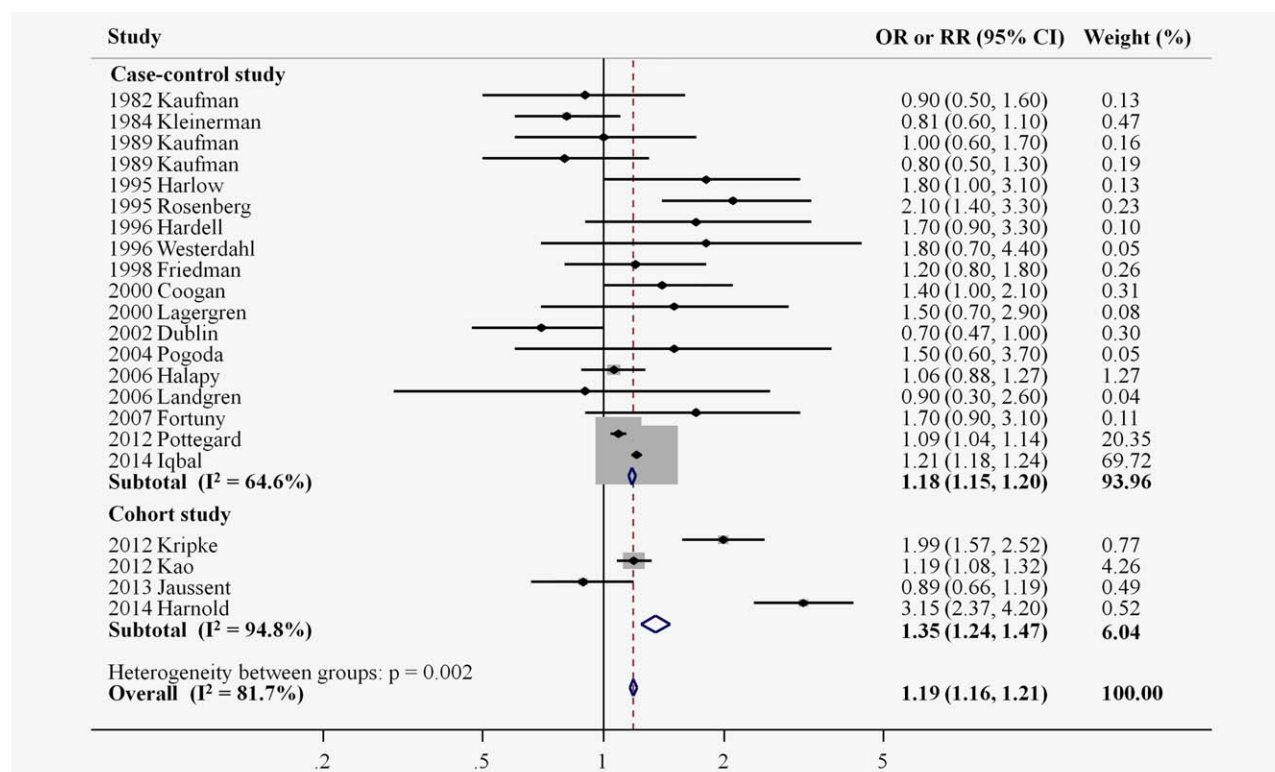
**Figure 2.** Use of benzodiazepine and the risk of cancer in a meta-analysis of observational studies by type of study design (*n* = 22). OR, odds ratio; RR, relative risk; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

studies have linked use of benzodiazepine to numerous sources of infection that can increase the occurrence of cancer. Benzodiazepines can develop several viral infections that could increase the risk of cancer. In a prospective study of the AIDS Care Cohort and Vancouver Injection Drug Users Study (VIDUS) cohorts followed-up from 1996 to 2013 in Canada,[30] there was a significant relationship between the use of benzodiazepine and seroconversion of Hepatitis C virus (HCV). A long progress of chronic hepatitis C to liver cirrhosis by HCV gives rise to hepatocellular carcinoma (HCC).[31] A 15-year prospective cohort study of 925 participants who had HCV infection reported that a cumulative risk for HCC increased from 6.4% for low levels of HCV RNA to 14.7% for high levels of HCV RNA (*p* < 0.001).[32]

Another plausible agent connecting the use of benzodiazepine to the increased risk of cancer could be human immunodeficiency virus (HIV). When a total of 1682 subjects who had no HIV at first were followed for median of about 80 months,[33] benzodiazepine use was significantly associated with an increased rate of HIV seroconversion (Adjusted Rate Ratio:1.50; 95% CI: 1.01–2.24). HIV infected people are more prone to get Human papilloma virus (HPV) infection.[34] In addition, HIV might change the natural course of immune control associated with HPV and enhance the development of squamous intraepithelial lesions of cervix.[34] In a study of 310,000 AIDS patients in the U.S. (257 605 males and 51 760 females), HIV infection tended to increase the risk of HPV

related carcinomas such as anal cancer besides cervix cancer during the 10 years of follow-up period.[35]

Benzodiazepine also seemed to promote bacterial infections that can raise the occurrence of various kinds of carcinomas. In a study of mice, diazepam aggravated a possibility of infection with Klebsiella pneumonia (K. Pneumoniae).[36] In a 11-year followed retrospective study of 2,294 subjects with pyogenic liver abscess in Taiwan, colorectal cancer incidence was 2.68 times more common (95% CI, 1.40–5.11) in patients with K. pneumoniae than patients without K. pneumoniae.[37] In vitro administration of diazepam to adult hamsters showed a detrimental effect on host protection against Mycobacterium.[38] Mycobacterium, an important respiratory pathogen, in turn could increase the development of lung cancer by DNA integration.[39] Our meta-analysis also demonstrated that lung cancer developed 20% more often among benzodiazepine-users than among non-users of benzodiazepine.

Second possible biological mechanism is inflammation. Inflammation can be an important factor as a linkage between the use of benzodiazepine and the risk of cancer risk because chronic inflammation might be associated with use of benzodiazepine. Alprazolam administration can cause chronic inflammation induced by "cotton wool granuloma".[40] Also, benzodiazepines might increase the levels of inflammation mediators such as histamine, prostaglandins or cytokines.[41] Administration of midazolam intravenously and diazepam per oral before undergoing a surgery could lead to

**Table 3.** Benzodiazepine use and the risk of cancer in the subgroup meta-analysis by various factors.

| Factors | NO. of studies | Summary OR or RR (95% CI) | Heterogeneity, $I^2$ (%) | Model used |
|---|---|---|---|---|
| All[6–9,13–29] | 22 | 1.19 (1.16–1.21) | 81.7 | Random-effects |
| Type of cancer (no. of cancer cases) | | | | |
| Breast cancer[6,7,13,23,26–28] (9,129) | 8 | 1.07 (1.01–1.14) | 17.3 | Fixed-effect |
| Ovarian cancer[14,19,21,26–28] (1,937) | 6 | 1.09 (0.94–1.26) | 59.3 | Random-effects |
| Malignant melanoma[17,26,28] (688) | 3 | 1.03 (0.72–1.48) | 0.0 | Fixed-effect |
| Brain cancer[9,26–28] (536) | 4 | 2.08 (1.77–2.44) | 86.1 | Random-effects |
| Esophagus cancer[20,25–27] (647) | 4 | 1.55 (1.30–1.85) | 0.0 | Fixed-effect |
| Renal cancer[26–28] (549) | 3 | 1.30 (1.14–1.49) | 25.7 | Fixed-effect |
| Prostate cancer[26–28] (2,421) | 3 | 1.26 (1.16–1.37) | 79.5 | Random-effects |
| Liver cancer[26,27] (618) | 3 | 1.22 (1.13–1.31) | 62.9 | Random-effects |
| Colon cancer[16,18,26,27] (5,080) | 4 | 1.05 (0.93–1.18) | 10.4 | Fixed-effect |
| Stomach cancer[26,27] (426) | 2 | 1.17 (1.03–1.32) | 45.6 | Fixed-effect |
| Pancreatic cancer[26,27] (437) | 2 | 1.39 (1.17–1.64) | 0.0 | Fixed-effect |
| Lung cancer[26,27] (4,101) | 2 | 1.20 (1.12–1.28) | 89.8 | Random-effects |
| Gender | | | | |
| Female only[6,7,13,14,19,21,23,24] | 9 | 1.00 (0.89–1.12) | 42.8 | Fixed-effect |
| Male & Female[8,9,15–18,20,22,25–29] | 13 | 1.20 (1.17–1.22) | 87.0 | Random-effects |
| Region | | | | |
| America[6–8,13–15,18,19,21–25] | 14 | 1.20 (1.09–1.33) | 73.3 | Random-effects |
| Europe[16,17,20,26,29] | 5 | 1.09 (1.05–1.14) | 35.3 | Fixed-effect |
| Asia[9,27,28] | 3 | 1.22 (1.19–1.25) | 95.3 | Random-effects |
| Duration of benzodiazepine use | | | | |
| <6 months[14,16,17,20,21,23,25,29] | 8 | 1.07 (0.94–1.22) | 55.7 | Random-effects |
| ≥6 months[6,7,13,18,24] | 6 | 0.92 (0.76–1.10) | 0.0 | Fixed-effect |
| ≥5 years[6,13,18,20,26] | 6 | 1.09 (0.99–1.20) | 0.0 | Fixed-effect |
| Cumulative yearly dose | | | | |
| Lower[8,9,21] | 3 | 0.70 (0.55–0.88) | 47.5 | Fixed-effect |
| Moderate[8,9,21] | 3 | 1.59 (1.26–2.00) | 62.8 | Random-effects |
| Highest[8,9,21] | 3 | 2.93 (2.45–3.52) | 96.6 | Random-effects |
| Types of benzodiazepine | | | | |
| Long-acting (Diazepam)[6,7,13,18,23,27] | 7 | 1.00 (0.94–1.06) | 0.0 | Fixed-effect |
| Intermediate-acting[8,23,27] | 6 | 1.20 (1.16–1.23) | 75.6 | Random-effects |
| Short-acting[23,27] | 3 | 1.05 (0.85–1.30) | 0.0 | Fixed-effect |
| Case-control study design | | | | |
| Population-based[7–9,13,14,17,18,20–29] | 17 | 1.19 (1.16–1.21) | 84.0 | Random-effects |
| Hospital-based[6,13,15,16,19] | 5 | 1.41 (1.14–1.75) | 47.4 | Fixed-effect |
| Methodological quality | | | | |
| High quality[7,8,13–15,17,18,20,21,23,25–27,29] | 14 | 1.18 (1.16–1.21) | 80.4 | Random-effects |
| Low quality[6,9,13,16,19,22,24,28] | 8 | 1.31 (1.20–1.43) | 0.0 | Fixed-effect |

inhibition of neutrophil apoptosis by affecting the depolarization of mitochondrial membrane.[42] Neutrophil apoptosis plays an essential role in retaining homeostasis of the immune system and prevent the damages of host organs by facilitating the immune response. Another experimental report of adult male rats which received alprazolam and clonazepam for 4 weeks showed that the inflammatory toxic effects of benzodiazepine could emerge through decline of anti-SRBC (Sheep
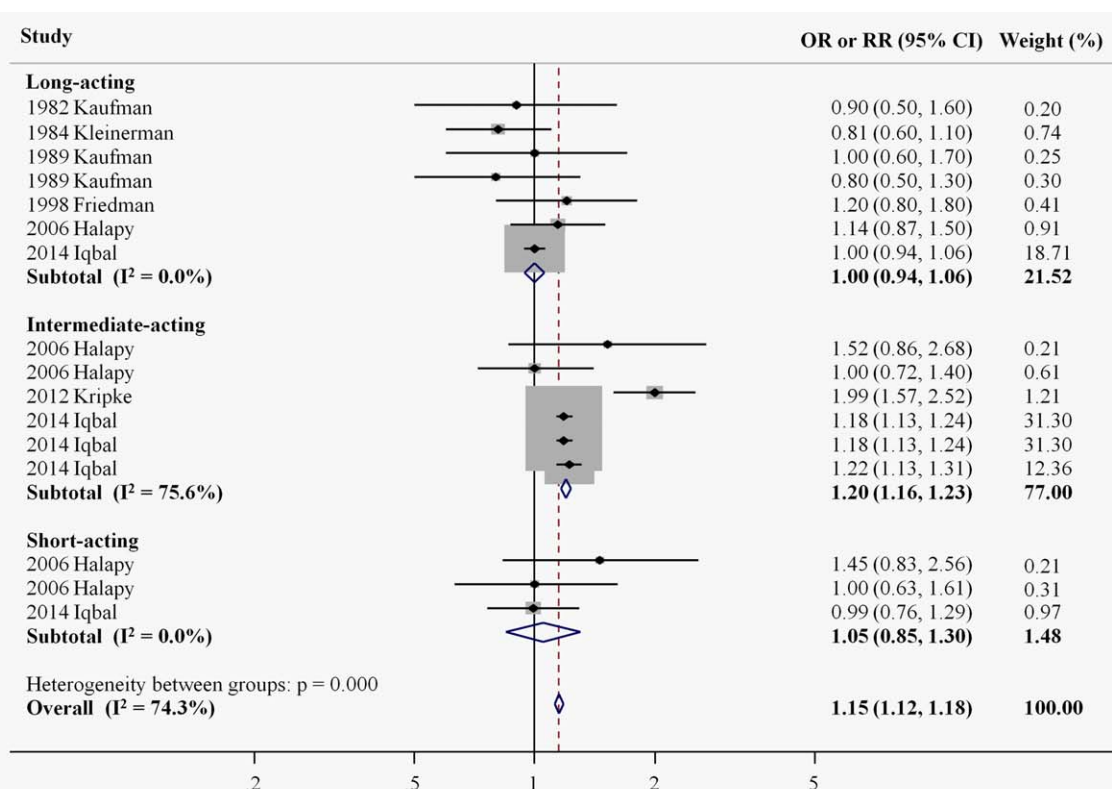
**Figure 3.** Use of benzodiazepine and the risk of cancer in a meta-analysis of observational studies by type of benzodiazepine (n = 22). OR, odds ratio; RR, relative risk; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

RBC) antibody titers and interleukin-2 (IL-2) levels.[43] Anti-SRBC antibodies are used for a sensitive tool to evaluate the degree of inflammatory changes. Natural killer (NK) cells and T-lymphocyte cells produce IL-2, and decreased levels of IL-2 indicate that suppression of the immune system could be progressing. In an Ehrlich tumor-bearing mice study, diazepam injection diminished the amount of leukocytes and the macrophage function[44] in a dose-response manner. Besides the gamma-aminobutyric acid A (GABA-A) receptor complex existing in central nervous system, peripheral-type binding sites (PBRs) of benzodiazepine have been found both in immune cells and carcinoma cells.[45] The association between PBRs density and progression of cancer cells might exist. Inflammation is a crucial factor for cancer.[46] Increased levels of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) could aggravate the course of disease in non-Hodgkin's lymphoma and gastric cancer, respectively.[47,48] Additionally, tumor associated macrophages (TAMs), which are assembled during the inflammatory reaction, are markers of a poor prognosis when they exist in the tissue of cancer.[49] Therefore, inflammation due to benzodiazepines might lead to the development of cancer.

Third, regarding esophageal cancer, benzodiazepines can loose the tone of lower esophageal sphincter (LES) by relaxation of smooth muscles in esophagus.[50] In addition to myogenic influences on LES pressure, anticholinergic effects of benzodiazepine on vagal nerve could lead to a decrease of LES pressure.[51] The LES plays a critical role in preventing gastric acid from flowing backward to esophagus. This might affect the possibility of developing esophagus carcinoma.

Another reason other than biological mechanism is that cancer patients suffer from psychiatric conditions such as insomnia, anxiety, and depression, which are frequently accompanied by the use of benzodiazepines.[52] For example, more than one third of cancer patients state anxiety.[53] While the frequency of major depressive disorders in general is 3–4%,[54] it increases to 5–26% in advanced tumor patients.[55] As a result, cancer patients are more likely to use benzodiazepines than general populations.[56]

Our study has important limitations. First, a small portion of the included studies in our analysis adjusted tobacco smoking and alcohol drinking as a confounding factor, both of which are well known important factors for developing cancer. Out of the 22 included studies, only eight studies[8,17–20,22,23,29] adjusted tobacco smoking as a confounding factor, and seven studies[8,17,18,20,22,23,29] adjusted alcohol intake as a confounding factor. Thus, we are unable to exclude the confounding effect of these important factors such as smoking or alcohol drinking regarding the association between benzodiazepine use and the risk of cancer. Another important limitation is that we only included observational epidemiological studies such as case-control studies and cohort

studies because few randomized controlled trials have been published on this topic so far. In general, case-control studies are more susceptible to biases, such as selection bias and recall bias than cohort studies. These biases might lead to spurious associations. Also, cohort studies have a lower level of evidence than randomized controlled trials. Thus, our meta-analysis does not provide the high level of evidence.

In conclusion, our meta-analysis of observational epidemiological studies found that benzodiazepine use was associated with an increased risk of cancer. Further large randomized controlled trials providing a higher level of evidence should be conducted to confirm our findings.

## Author Contributions
Dr Seung-Kwon Myung Had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Myung and Kim.

*Acquisition, analysis, or interpretation of data*: Myung, Park, Kim, and Park.

*Drafting of the manuscript*: Kim.

*Critical revision of the manuscript for important intellectual content*: Myung.

*Statistical analysis*: Myung and Kim.

## Conflict of Interest Disclosures
The authors have declared no conflicts of interest.

## References

1. Alvarenga JM, Loyola Filho AI, Firmo JO, et al. Prevalence and sociodemographic characteristics associated with benzodiazepines use among community dwelling older adults: the Bambui Health and Aging Study (BHAS). *Rev Bras Psiquiatr* 2008;30:7–11.
2. Miyawaki I, Moriyasu M, Funabashi H, et al. Mechanism of clobazam-induced thyroidal oncogenesis in male rats. *Toxicol Lett* 2003;145:291–301.
3. Iida M, Anna CH, Hartis J, et al. Changes in global gene and protein expression during early mouse liver carcinogenesis induced by nongenotoxic model carcinogens oxazepam and Wyeth-14,643. *Carcinogenesis* 2003;24:757–60. 2003
4. Kunert-Radek J, Stepień H, Pawlikowski M. Inhibition of rat pituitary tumor cell proliferation by benzodiazepines in vitro. *Neuroendocrionology* 1995;59:92–6.
5. Kim DH, LEE JT, Lee IK, et al. Comparative anticancer effects of flavonoids and diazepam in cultured cancer cells. *Biol Pharm Bull* 2008;31:255–9.
6. Kaufman DW, Shapiro S, Slone D, et al. Diazepam and the risk of breast cancer. *Lancet* 1982;6:537–9.
7. Kleinerman RA, Brinton LA, Hoover R, et al. Diazepam use and progression of breast cancer. *Cancer Res* 1984;44:1223–5. Jr.
8. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2:e000850doi: 10.1136/bmjopen-2012-000850.
9. Harnod T, Lin CL, Sung FC, et al. An association between benzodiazepine use and occurrence of benign brain tumors. *J Neurol Sci* 2014;336:8–12.
10. Wells GA, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
13. Kaufman DW, Werler MM, Palmer JR, et al. Diazepam use in relation to breast cancer: results from two case-control studies. *Am J Epidemiol* 1990;131:483–90.
14. Harlow BL, Cramer DW. Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: evidence from two combined case-control studies (Massachusetts, United States). *Cancer Causes Control* 1995;6:130–4.
15. Rosenberg L, Palmer JR, Zauber AG, et al. 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.
16. Hardell L, Fredrikson M, Axelson O. Case-control study on colon cancer regarding previous diseases and drug intake. *Int J Oncol* 1996;8:439–44.
17. Westerdahl J, Olsson H, Måsbäck A, et al. Risk of malignant melanoma in relation to drug intake, alcohol, smoking and hormonal factors. *Br J Cancer* 1996;73:1126–31.
18. Friedman GD, Coates AO, Potter JD, et al. Drugs and colon cancer. *Pharmacoepidemiol Drug Saf* 1998;7:99–106.
19. Coogan PF, Rosenberg L, Palmer JR, et al. Risk of ovarian cancer according to use of antidepressants, phenothiazines, and benzodiazepines (United States). *Cancer Causes Control* 2000;11:839–45.
20. Lagergren J, Bergström R, Adami HO, et al. Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. *Ann Intern Med* 2000;133:165–75.
21. Dublin S, Rossing MA, Heckbert SR, et al. Risk of epithelial ovarian cancer in relation to use of antidepressants, benzodiazepines, and other centrally acting medications. *Cancer Causes Control* 2002;13:35–45.
22. Pogoda JM, Katz J, McKean-Cowdin R, et al. 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.
23. Halapy E, Kreiger N, Cotterchio M, et al. Benzodiazepines and risk for breast cancer. *Ann Epidemiol* 2006;16:632–6.
24. Landgren O, Zhang Y, Zahm SH, et al. Risk of multiple myeloma following medication use and medical conditions: a case-control study in Connecticut women. *Cancer Epidemiol Biomarkers Prev* 2006;15:2342–7.
25. Fortuny J, Johnson CC, Bohlke K, et al. Use of anti-inflammatory drugs and lower esophageal sphincter-relaxing drugs and risk of esophageal and gastric cancers. *Clin Gastroenterol Hepatol* 2007;5:1154–9.
26. Pottegård A, Friis S, Andersen M, et al. Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study. *Br J Clin Pharmacol* 2013;75:1356–64.
27. Iqbal U, Nguyen PA, Syed-Abdul S, et al. Is long-term use of benzodiazepine a risk for cancer?. *Medicine (Baltimore)* 2015;94:e483. doi:10.1097/MD.0000000000000483.
28. Kao CH, Sun LM, Su KP, et al. Benzodiazepine use possibly increases cancer risk: a population-based retrospective cohort study *in Taiwan. J Clin Psychiatry* 2012;73:e555–60. doi: 10.4088/JCP.11m07333.
29. Jaussent I, Ancelin ML, Berr C, et al. Hypnotics and mortality in an elderly general population: a 12-year prospective study. *BMC Med* 2013;11:212. doi:10.1186/1741-7015-11-212.
30. Bach P, Walton G, Hayashi K, et al. Benzodiazepine use and hepatitis C seroconversion in a cohort of persons who inject drugs. *Am J Public Health* 2016;106:1067–72.
31. Blackadar CB. Historical review of the causes of cancer. *World J Clin Oncol* 2016;7:54–86.
32. Lee MH, Yang HI, Lu SN, et al. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma: long-term predictors from a community-based cohort study. *J Clin Oncol* 2010;28:4587–93.
33. Ickowicz S, Hayashi K, Dong H, et al. Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting. *Drug Alcohol Depend* 2015;155:190–4.
34. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;118:3030–44.

35. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000;92:1500–10.

36. Laschi A, Descotes J, Tachon P, et al. Adverse influence of diazepam upon resistance to Klebsiella pneumoniae infection in mice. *Toxicol Lett* 1983;16:281–4.

37. Hwang WK, Chang JW, See LC, et al. Higher rate of colorectal cancer among patients with pyogenic liver abscess with Klebsiella pneumoniae than those without: an 11-year follow-up study. *Colorectal Dis* 2012;14:e794–801.

38. Righi DA, Pinheiro SR, Guerra JL, et al. Effects of diazepam on Mycobacterium bovis-induced infection in hamsters. *Braz J Med Biol Res* 1999;32:1145–53.

39. Tian Y, Hao T, Cao B, et al. Clinical end-points associated with mycobacterium tuberculosis and lung cancer: implications into host-pathogen interaction and coevolution. *Biomed Res Int* 2015;827829. doi: 10.1155/2015/827829. Epub 2015 Oct 25.

40. Zdrîncă M, Muțiu G, Bogdan M, et al. Effects of alprazolam, zolpidem and zopiclone, and of chronic inflammation on peripheral experimental algesia in Wistar rats. *Rom J Morphol Embryol* 2011;52:471–4.

41. Levine JD, Reichling DB. Peripheral mechanisms of inflammatory pain. In: Wall PD, Melzack R, eds. Textbook of pain. Churchill Livingstone, New York, 1999. 59–84.

42. Goto Y, O'Malley C, Fanning NF, et al. Benzodiazepines inhibit the rate of neutrophil apoptosis. *Ir J Med Sci* 2003;172:191–4.

43. Elmesallamy GE, Abass MA, Ahmed Refat NA, et al. Differential effects of alprazolam and clonazepam on the immune system and blood vessels of non-stressed and stressed adult male albino rats. *Interdiscip Toxicol* 2011;4:132–43.

44. Sakai M, Fonseca ES, Dagli ML, et al. Diazepam effects on Ehrlich tumor growth and macrophage activity in mice. *Life Sci* 2006;78:1777–83.

45. Han Z, Slack RS, Li W, et al. Expression of peripheral benzodiazepine receptor (PBR) in human tumors: relationship to breast, colorectal, and prostate tumor progression. *J Recept Signal Transduct Res* 2003;23:225–38.

46. Pease NA, Wise-Draper T, Privette Vinnedge L. Dissecting the potential interplay of DEK functions in inflammation and cancer. *J Oncol* 2015;106517. doi:10.1155/2015/106517. Epub 2015 Sep 6.

47. Warzocha K, Ribeiro P, Bienvenu J, et al. Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. *Blood* 1998;91:3574–81.

48. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;404:398–402.

49. Duncan LM, Richards LA, Mihm MC. Jr. Increased mast cell density in invasive melanoma. *J Cutan Pathol* 1998;25:11–5.

50. Rushnak MJ, Leevy CM. Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. *Am J Gastroenterol* 1980;73: 127–30.

51. Brinbaum D, Ben-Menachem J, Schwartz A. The influence of oral diazepam on gastrointestinal motility. *Am J Proctol* 1970;21:263–6.

52. Pruitt AA. Medical management of patients with brain tumors. *Curr Treat Options Neurol* 2011;13: 413–26.

53. Mosher CE, Duhamel KN. An examination of distress, sleep, and fatigue in metastatic breast cancer patients. *Psychooncology* 2010;21: 100–7.

54. Waraich P, Goldner EM, Somers JM, et al. Prevalence and incidence studies of mood disorders: a systematic review of the literature. *Can J Psychiatry* 2005;49:124–38.

55. Hotopf M, Chidgey J, Addington-Hall J, et al. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. *Palliat Med* 2002;16:81–97.

56. Saarelainen LK, Turner JP, Shakib S, et al. Potentially inappropriate medication use in older people with cancer: prevalence and correlates. *J Geriatr Oncol* 2014;5:439–46.

**Cancer Epidemiology**