**Is Long-term use of Benzodiazepines a risk for cancer?**

**Supplementary Appendix**

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# S1. Definition of cases in this study

To clearly define all subjects with diagnosed cancers (International Classification of Disease, Clinical Modification, Ninth Revision [ICD-9-CM] codes 104 – 208) in this study who were eligible cases, we follow patients from the first diagnosis to their regular treatment. In most situations, when patients accept the diagnosis of cancer, they typically undergo regularly scheduled treatment. According to NHI reimbursement schemes, 4 main forms of cancer treatment are used:

1. Surgery (ICD\_op\_code [NHI, Taiwan coding manual], varies for different types of cancer)
2. Radiotherapy
3. Chemotherapy
4. Drugs used

Undergoing 1 of these 4 types of treatment after a diagnosis of cancer is considered regular treatment.

# Table S1. Benzodiazepine medication used by two million sampling patients in Taiwan during the period from 1998 through 2009

|  |  |  |
| --- | --- | --- |
| Benzodiazepine Medication | ATC-code | Defined Daily Dose,  mg |
| Anxiolytics (N05BA) |  |  |
| diazepam | N05BA01 | 10 |
| chloradiazepoxide | N05BA02 | 30 |
| lorazepam | N05BA06 | 2·5 |
| bromazepam | N05BA08 | 10 |
| alprazolam | N05BA12 | 1 |
| medazepam | N05BA03 | 20 |
| oxazepam | N05BA04 | 50 |
| fludiazepam | N05BA17 | 0·75 |
| oxazolam | N05BA91, N05BA22 | 30a |
| Hypnotics and sedatives (N05CD) |  |  |
| nitrazepam | N05CD02 | 5 |
| flunitrazepam | N05CD03 | 1 |
| lorametazepam | N05CD06 | 1 |
| Antiepileptics (N03AE) |  |  |
| clonazepam | N03AE01 | 8 |
| Benzodiazepine related drugs (N05CF) |  |  |
| zopiclone | N05CF01 | 7·5 |
| zolpidem | N05CF02 | 10 |

Defined daily dose is the WHO recommended dose of medication for each patient per day.

Calculation of daily statin dose: A patient was prescribed 100 tablets of 4 mg diazepam in duration 1 months. The total dose for the 30 days is thus 400 mg. This corresponds to (400 mg/30 days)/10 mg/defined daily dose = 1·33 defined daily dose per day for the period. a Taiwan used and none ATC code from WHO.

# Table S2. Detail of overall and each benzodiazepine use associated with cancer risk

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Unadjusted OR  (95% CI) | p-value | Adjusted OR  (95% CI) | p-value |
| Overall Benzodiazepines |  |  |  |  |  |  |
| No | 31576 | 202070 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 10924 | 52930 | 1·32 (1·29 - 1·35) | 1·21 (1·18 - 1·24) |
| 61 - 90 days | 1718 | 8277 | 1·33 (1·26 - 1·40)\*\*\* | p trend < 0·0001 | 1·22 (1·16 - 1·29)\*\*\* | p trend < 0·0001 |
| 91 - 180 days | 2556 | 12427 | 1·31 (1·26 - 1·37)\*\*\* | 1·20 (1·15 - 1·26)\*\*\* |
| 181 days - 1 year | 2137 | 10364 | 1·32 (1·25 - 1·38)\*\*\* | 1·20 (1·14 - 1·26)\*\*\* |
| 1 year - 2 years | 1968 | 9515 | 1·32 (1·26 - 1·39)\*\*\* | 1·22 (1·15 - 1·28)\*\*\* |
| > 2 years | 2545 | 12347 | 1·32 (1·26 - 1·38)\*\*\* | 1·23 (1·17 - 1·29)\*\*\* |
| Alprazolam |  |  |  |  |  |  |
| No | 39934 | 243140 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 2566 | 11860 | 1·32 (1·26 - 1·38) | 1·18 (1·13 - 1·24) |
| 61 - 90 days | 422 | 2025 | 1·26 (1·14 - 1·40)\*\*\* | p trend < 0·0001 | 1·12 (1·01 - 1·25)\* | p trend < 0·0001 |
| 91 - 180 days | 680 | 3084 | 1·34 (1·23 - 1·46)\*\*\* | 1·18 (1·09 - 1·29)\*\*\* |
| 181 days - 1 year | 545 | 2591 | 1·28 (1·17 - 1·41)\*\*\* | 1·15 (1·05 - 1·26)\*\* |
| 1 year - 2 years | 495 | 2218 | 1·36 (1·23 - 1·50)\*\*\* | 1·24 (1·12 - 1·37)\*\*\* |
| > 2 years | 424 | 1942 | 1·32 (1·19 - 1·47)\*\*\* | 1·23 (1·11 -1·37)\*\*\* |
| Bromazepam |  |  |  |  |  |  |
| No | 41624 | 250946 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 876 | 4054 | 1·30 (1·20 - 1·40) | 1·16 (1·08 - 1·25) |
| 61 - 90 days | 184 | 826 | 1·34 (1·14 - 1·58)\*\*\* | p trend < 0·0001 | 1·17 (1·00 - 1·38) | p trend  0·003 |
| 91 - 180 days | 233 | 1136 | 1·23 (1·06 - 1·41)\*\* | 1·08 (0·94 - 1·25) |
| 181 days - 1 year | 200 | 841 | 1·42 (1·21 - 1·66)\*\*\* | 1·26 (1·08 - 1·48)\*\* |
| 1 year - 2 years | 159 | 702 | 1·36 (1·14 - 1·61)\*\* | 1·23 (1·03 - 1·46)\* |
| > 2 years | 100 | 549 | 1·11 (0·90 - 1·38) | 1·05 (0·85 - 1·31) |
| Chlordiazepoxide |  |  |  |  |  |  |
| No | 42335 | 254239 | 1·00 | 0·001 | 1·00 | 0·097 |
| Yes | 165 | 761 | 1·32 (1·11 - 1·56) | 1·16 (0·97 - 1·37) |
| 61 - 90 days | 50 | 233 | 1·30 (0·96 - 1·76) | p trend  0·005 | 1·14 (0·83 - 1·54) | p trend  0·131 |
| 91 - 180 days | 58 | 252 | 1·41 (1·06 - 1·88)\* | 1·21 (0·91 - 1·62) |
| 181 days - 1 year | 29 | 152 | 1·15 (0·77 - 1·72) | 1·02 (0·69 - 1·53) |
| 1 year - 2 years | 23 | 74 | 1·87 (1·19 - 2·98)\*\* | 1·69 (1·05 - 2·70)\* |
| > 2 years | 5 | 50 | 0·60 (0·24 - 1·51) | 0·57 (0·23 - 1·43) |
| Clonazepam |  |  |  |  |  |  |
| No | 41534 | 250592 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 966 | 4408 | 1·32 (1·23 - 1·42) | 1·22 (1·13 - 1·31) |
| 61 - 90 days | 171 | 772 | 1·34 (1·13 - 1·58)\*\* | p trend < 0·0001 | 1·24 (1·04 - 1·46)\* | p trend < 0·0001 |
| 91 - 180 days | 247 | 1104 | 1·35 (1·18 - 1·55)\*\*\* | 1·22 (1·06 - 1·40)\*\* |
| 181 days - 1 year | 225 | 964 | 1·38 (1·19 - 1·60)\*\*\* | 1·27 (1·10 - 1·48)\*\* |
| 1 year - 2 years | 191 | 859 | 1·35 (1·15 - 1·57)\*\*\* | 1·22 (1·04 - 1·43)\* |
| > 2 years | 132 | 709 | 1·13 (0·94 - 1·37) | 1·10 (0·91 - 1·32) |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

OR, Odd ratio; CI, Confidence Interval

Table S2. (Continue.)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Unadjusted OR  (95% CI) | p-value | Adjusted OR  (95% CI) | p-value |
| Diazepam |  |  |  |  |  |  |
| No | 41227 | 248117 | 1·00 | 0·001 | 1·00 | 0·991 |
| Yes | 1273 | 6883 | 1·11 (1·04 - 1·18) | 1·00 (0·94 - 1·06) |
| 61 - 90 days | 399 | 2068 | 1·16 (1·04 - 1·29)\*\* | p trend  0·023 | 1·03 (0·92 - 1·15) | p trend  0·906 |
| 91 - 180 days | 426 | 2361 | 1·08 (0·97 - 1·20) | 0·96 (0·87 - 1·07) |
| 181 days - 1 year | 253 | 1329 | 1·13 (0·99 - 1·30) | 1·04 (0·90 - 1·19) |
| 1 year - 2 years | 135 | 741 | 1·10 (0·91 - 1·32) | 1·03 (0·85 - 1·24) |
| > 2 years | 60 | 384 | 0·94 (0·72 - 1·24) | 0·91 (0·69 - 1·20) |
| Fludiazepam |  |  |  |  |  |  |
| No | 40477 | 245912 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 2023 | 9088 | 1·35 (1·28 - 1·41) | 1·19 (1·13 - 1·25) |
| 61 - 90 days | 530 | 2246 | 1·43 (1·30 - 1·58)\*\*\* | p trend < 0·0001 | 1·25 (1·13 - 1·38)\*\*\* | p trend < 0·0001 |
| 91 - 180 days | 681 | 2965 | 1·38 (1·27 - 1·51)\*\*\* | 1·21 (1·11 - 1·32)\*\*\* |
| 181 days - 1 year | 403 | 1888 | 1·29 (1·16 - 1·44)\*\*\* | 1·14 (1·02 - 1·27)\* |
| 1 year - 2 years | 246 | 1209 | 1·23 (1·07 - 1·42)\*\* | 1·09 (0·95 - 1·26) |
| > 2 years | 163 | 780 | 1·26 (1·06 - 1·49)\*\* | 1·20 (1·01 - 1·42)\* |
| Flunitrazepam |  |  |  |  |  |  |
| No | 42105 | 253151 | 1·00 | < 0·0001 | 1·00 | 0·009 |
| Yes | 395 | 1849 | 1·29 (1·15 - 1·44) | 1·16 (1·04 - 1·30) |
| 61 - 90 days | 52 | 208 | 1·52 (1·12 - 2·06)\*\* | p trend < 0·0001 | 1·31 (0·97 - 1·79) | p trend  0·035 |
| 91 - 180 days | 87 | 368 | 1·43 (1·13 - 1·81)\*\* | 1·27 (1·01 - 1·61)\* |
| 181 days - 1 year | 89 | 398 | 1·35 (1·07 - 1·70)\* | 1·21 (0·96 - 1·53) |
| 1 year - 2 years | 84 | 380 | 1·33 (1·05 - 1·69)\* | 1·20 (0·94 - 1·52) |
| > 2 years | 83 | 495 | 1·00 (0·79 - 1·27) | 0·93 (0·74 - 1·18) |
| Lorazepam |  |  |  |  |  |  |
| No | 40074 | 243811 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 2426 | 11189 | 1·32 (1·26 - 1·38) | 1·18 (1·13 - 1·24) |
| 61 - 90 days | 524 | 2344 | 1·36 (1·24 - 1·50)\*\*\* | p trend < 0·0001 | 1·21 (1·10 - 1·33)\*\*\* | p trend < 0·0001 |
| 91 - 180 days | 708 | 3264 | 1·31 (1·21 - 1·42)\*\*\* | 1·15 (1·06 - 1·25)\*\* |
| 181 days - 1 year | 542 | 2425 | 1·36 (1·24 - 1·49)\*\*\* | 1·22 (1·11 - 1·34)\*\*\* |
| 1 year - 2 years | 367 | 1778 | 1·26 (1·12 - 1·41)\*\*\* | 1·15 (1·03 - 1·29)\* |
| > 2 years | 285 | 1378 | 1·26 (1·11 - 1·43)\*\*\* | 1·18 (1·03 - 1·34)\* |
| Lormetazepam |  |  |  |  |  |  |
| No | 42291 | 254028 | 1·00 | 0·001 | 1·00 | 0·027 |
| Yes | 209 | 972 | 1·30 (1·12 - 1·51) | 1·19 (1·02 - 1·38) |
| 61 - 90 days | 39 | 213 | 1·12 (0·79 - 1·57) | p trend  0·025 | 1·00 (0·71 - 1·41) | p trend  0·266 |
| 91 - 180 days | 59 | 268 | 1·34 (1·01 - 1·77)\* | 1·19 (0·90 - 1·59) |
| 181 days - 1 year | 57 | 244 | 1·39 (1·04 - 1·86)\* | 1·29 (0·96 - 1·72) |
| 1 year - 2 years | 35 | 158 | 1·35 (0·93 - 1·94) | 1·27 (0·88 - 1·84) |
| > 2 years | 19 | 89 | 1·28 (0·78 - 2·10) | 1·22 (0·74 - 2·01) |
| Medazepam |  |  |  |  |  |  |
| No | 42487 | 254960 | 1·00 | 0·031 | 1·00 | 0·080 |
| Yes | 13 | 40 | 2·00 (1·07 - 3·75) | 1·76 (0·94 - 3·32) |
| 61 - 90 days | 5 | 19 | 1·58 (0·59 - 4·23) | p trend  0·245 | 1·60 (0·59 - 4·30) | p trend  0·519 |
| 91 - 180 days | 5 | 12 | 2·73 (0·95 - 7·85) | 2·18 (0·75 - 6·32) |
| 181 days - 1 year | 1 | 6 | 1·00 (0·12 - 8·30) | 0·83 (0·10 - 6·92) |
| 1 year - 2 years | 1 | 2 | 3·00 (0·27 - 33·07) | 2·60 (0·23 - 28·72) |
| > 2 years | 1 | 1 | 6·00 (0·38 - 95·87) | 3·16 (0·20 - 50·62) |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

OR, Odd ratio; CI, Confidence Interval

Table S2. (Continue.)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Unadjusted OR  (95% CI) | p-value | Adjusted OR  (95% CI) | p-value |
| Nitrazepam |  |  |  |  |  |  |
| No | 42391 | 254380 | 1·00 | 0·559 | 1·00 | 0·867 |
| Yes | 109 | 620 | 1·06 (0·87 - 1·30) | 0·98 (0·80 - 1·21) |
| 61 - 90 days | 26 | 164 | 0·96 (0·63 - 1·45) | p trend  0·833 | 0·85 (0·56 - 1·29) | p trend  0·912 |
| 91 - 180 days | 41 | 205 | 1·21 (0·87 - 1·69) | 1·11 (0·79 - 1·56) |
| 181 days - 1 year | 17 | 114 | 0·90 (0·54 - 1·50) | 0·88 (0·53 - 1·47) |
| 1 year - 2 years | 17 | 83 | 1·23 (0·73 - 2·07) | 1·13 (0·67 - 1·90) |
| > 2 years | 8 | 54 | 0·91 (0·43 - 1·90) | 0·89 (0·42 - 1·88) |
| Oxazepam |  |  |  |  |  |  |
| No | 42435 | 254647 | 1·00 | 0·414 | 1·00 | 0·944 |
| Yes | 65 | 353 | 1·12 (0·86 - 1·46) | 0·99 (0·76 - 1·29) |
| 61 - 90 days | 13 | 95 | 0·83 (0·46 - 1·48) | p trend  0·360 | 0·70 (0·39 - 1·25) | p trend  0·503 |
| 91 - 180 days | 21 | 119 | 1·07 (0·67 - 1·70) | 0·97 (0·61 - 1·54) |
| 181 days - 1 year | 17 | 70 | 1·50 (0·88 - 2·55) | 1·31 (0·77 - 2·24) |
| 1 year - 2 years | 11 | 40 | 1·65 (0·85 - 3·21) | 1·47 (0·75 - 2·88) |
| > 2 years | 3 | 29 | 0·62 (0·19 - 2·04) | 0·63 (0·19 - 2·06) |
| Oxazolam |  |  |  |  |  |  |
| No | 41231 | 248820 | 1·00 | < 0·0001 | 1·00 | 0·008 |
| Yes | 1269 | 6180 | 1·23 (1·16 - 1·31) | 1·09 (1·02 - 1·16) |
| 61 - 90 days | 343 | 1670 | 1·23 (1·09 - 1·38)\*\* | p trend < 0·0001 | 1·08 (0·95 - 1·21) | p trend  0·155 |
| 91 - 180 days | 419 | 2032 | 1·25 (1·12 - 1·39)\*\*\* | 1·08 (0·97 - 1·20) |
| 181 days - 1 year | 256 | 1231 | 1·26 (1·10 - 1·44)\*\* | 1·12 (0·97 - 1·28) |
| 1 year - 2 years | 153 | 778 | 1·16 (0·97 - 1·38) | 1·05 (0·88 - 1·26) |
| > 2 years | 98 | 469 | 1·25 (1·00 - 1·55)\* | 1·19 (0·93 - 1·43) |
| Zopiclone |  |  |  |  |  |  |
| No | 41942 | 252360 | 1·00 | < 0·0001 | 1·00 | 0·006 |
| Yes | 558 | 2640 | 1·27 (1·16 - 1·39) | 1·14 (1·04 - 1·25) |
| 61 - 90 days | 99 | 501 | 1·17 (0·94 - 1·46) | p trend < 0·0001 | 1·03 (0·82 - 1·28) | p trend  0·030 |
| 91 - 180 days | 168 | 786 | 1·28 (1·09 - 1·52)\*\* | 1·12 (0·95 - 1·33) |
| 181 days - 1 year | 138 | 580 | 1·43 (1·19 - 1·73)\*\*\* | 1·29 (1·07 - 1·56)\*\* |
| 1 year - 2 years | 85 | 469 | 1·10 (0·87 - 1·38) | 1·01 (0·80 - 1·28) |
| > 2 years | 68 | 304 | 1·35 (1·04 - 1·76)\* | 1·29 (0·99 - 1·68) |
| Zolpidem |  |  |  |  |  |  |
| No | 40447 | 244926 | 1·00 | < 0·0001 | 1·00 | < 0·0001 |
| Yes | 2053 | 10074 | 1·23 (1·18 - 1·30) | 1·13 (1·07 - 1·18) |
| 61 - 90 days | 360 | 1784 | 1·23 (1·10 - 1·38)\*\*\* | p trend  < 0·0001 | 1·11 (0·99 - 1·24) | p trend  < 0·0001 |
| 91 - 180 days | 566 | 2716 | 1·26 (1·15 - 1·38)\*\*\* | 1·14 (1·04 - 1·25)\*\* |
| 181 days - 1 year | 481 | 2386 | 1·22 (1·11 - 1·35)\*\*\* | 1·12 (1·01 - 1·24)\* |
| 1 year - 2 years | 406 | 1886 | 1·30 (1·17 - 1·45)\*\*\* | 1·18 (1·06 - 1·32)\*\* |
| > 2 years | 240 | 1302 | 1·12 (0·97 - 1·29) | 1·05 (0·91 - 1·20) |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

OR, Odd ratio; CI, Confidence Interval

# Table S3. Detail of benzodiazepine class associated with cancer risk

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Unadjusted OR  (95% CI) | p-value | Adjusted OR  (95% CI) | p-value |
| Antiepileptics (N03AE) Class | | | | | | |
| No | 41534 | 250592 | 1·00 | <0·0001 | 1·00 | <0·0001 |
| Yes | 966 | 4408 | 1·32 (1·23 - 1·42) | 1·22 (1·13 - 1·31) |
| 61 - 90 days | 171 | 772 | 1·34 (1·13 - 1·58)\*\* | p trend  <0·0001 | 1·24 (1·04 - 1·46)\* | p trend  <0·0001 |
| 91 - 180 days | 247 | 1104 | 1·35 (1·18 - 1·55)\*\*\* | 1·22 (1·06 - 1·40)\*\* |
| 181 days - 1 year | 225 | 964 | 1·38 (1·19 - 1·60)\*\*\* | 1·27 (1·10 - 1·48)\*\* |
| 1 year - 2 years | 191 | 859 | 1·35 (1·15 - 1·57)\*\*\* | 1·22 (1·04 - 1·43)\* |
| > 2 years | 132 | 709 | 1·13 (0·94 - 1·37) | 1·10 (0·91 - 1·32) |
| Anxiolytics (N05BA) Class | | | | | |  |
| No | 33477 | 211631 | 1·00 | <0·0001 | 1·00 | <0·0001 |
| Yes | 9023 | 43369 | 131 (1·28 - 1·35) | 1·19 (1·16 - 1·22) |
| 61 - 90 days | 1640 | 7829 | 1·33 (1·26 - 1·40)\*\*\* | p trend  <0·0001 | 1·21 (1·15 - 1·28)\*\*\* | p trend  <0·0001 |
| 91 - 180 days | 2364 | 11359 | 1·32 (1·25 - 1·37)\*\*\* | 1·18 (1·12 - 1·23)\*\*\* |
| 181 days - 1 year | 1851 | 9112 | 1·28 (1·22 - 1·35)\*\*\* | 1·15 (1·09 - 1·22)\*\*\* |
| 1 year - 2 years | 1603 | 7681 | 1·32 (1·24 - 1·39)\*\*\* | 1·19 (1·12 - 1·26)\*\*\* |
| > 2 years | 1565 | 7388 | 1·33 (1·26 - 1·41)\*\*\* | 1·24 (1·17 - 1·31)\*\*\* |
| Hypnotics and sedatives (N05CD) Class | | | | | | |
| No | 41663 | 251041 | 1·00 | <0·0001 | 1·00 | <0·0001 |
| Yes | 837 | 3959 | 1·28 (1·19 - 1·38) | 1·16 (1·08 - 1·25) |
| 61 - 90 days | 154 | 668 | 1·41 (1·18 - 1·68)\*\*\* | p trend <0·0001 | 1·25 (1·05 - 1·50)\* | p trend  0·001 |
| 91 - 180 days | 205 | 946 | 1·31 (1·13 - 1·53)\*\*\* | 1·17 (1·01 - 1·36)\* |
| 181 days - 1 year | 175 | 874 | 1·20 (1·02 - 1·41)\* | 1·09 (0·93 - 1·29) |
| 1 year - 2 years | 164 | 695 | 1·43 (1·21 - 1·70)\*\*\* | 1·31 (1·10 - 1·56)\*\* |
| > 2 years | 139 | 776 | 1·08 (0·90 - 1·30) | 1·01 (0·84 - 1·21) |
| Related drugs (N05CF) Class | | | | | | |
| No | 39509 | 240727 | 1·00 | <0·0001 | 1·00 | <0·0001 |
| Yes | 2991 | 14273 | 1·28 (1·23 - 1·33) | 1·17 (1·12 - 1·22) |
| 61 - 90 days | 525 | 2423 | 1·33 (1·21 - 1·46)\*\*\* | p trend <0·0001 | 1·21 (1·10 - 1·33)\*\*\* | p trend  <0·0001 |
| 91 - 180 days | 773 | 3694 | 1·28 (1·18 - 1·38)\*\*\* | 1·16 (1·07 - 1·26)\*\*\* |
| 181 days - 1 year | 671 | 3142 | 1·30 (1·19 - 1·41)\*\*\* | 1·18 (1·08 - 1·28)\*\*\* |
| 1 year - 2 years | 569 | 2741 | 1·27 (1·16 - 1·39)\*\*\* | 1·16 (1·06 - 1·28)\*\* |
| > 2 years | 453 | 2273 | 1·21 (1·10 - 1·34)\*\*\* | 1·13 (1·02 - 1·26)\* |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

OR, Odd ratio; CI, Confidence Interval

# Table S4. Detail DDD of overall and each benzodiazepine associated with risk for cancers

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Adjusted Odds Ratio  (95% CI) | p-value |
| Overall Benzodiazepines |  |  |  |  |
| 0·0 (never users) | 33377 | 209926 | 1·00 | p trend < 0·0001 |
| < 0·10 | 1125 | 5204 | 1·23 (1·15 - 1·32)\*\*\* |
| 0·10 - 0·39 | 4899 | 23726 | 1·18 (1·13 - 1·22)\*\*\* |
| 0·40 - 0·69 | 2178 | 10837 | 1·18 (1·12 - 1·24)\*\*\* |
| 0·70 - 0·99 | 517 | 2712 | 1·14 (1·03 - 1·25)\*\* |
| >= 1·00 | 404 | 2595 | 0·95 (0·85 - 1·06) |
| Alprazolam |  |  |  |  |
| 0·0 (never users) | 39934 | 243140 | 1·00 | p trend < 0·0001 |
| < 0·10 | 11 | 34 | 1·64 (0·80 - 3·33) |
| 0·10 - 0·39 | 370 | 1770 | 1·18 (1·05 - 1·32)\*\* |
| 0·40 - 0·69 | 1192 | 5560 | 1·17 (1·10 - 1·25)\*\*\* |
| 0·70 - 0·99 | 508 | 2172 | 1·25 (1·13 - 1·38)\*\*\* |
| >= 1·00 | 485 | 2324 | 1·15 (1·04 - 1·27)\*\* |
| Bromazepam |  |  |  |  |
| 0·0 (never users) | 41625 | 250946 | 1·00 | p trend  0·001 |
| < 0·10 | 16 | 126 | 0·72 (0·43 - 1·22) |
| 0·10 - 0·39 | 584 | 2703 | 1·16 (1·06 - 1·27)\*\* |
| 0·40 - 0·69 | 217 | 930 | 1·26 (1·09 - 1·46)\*\* |
| 0·70 - 0·99 | 50 | 256 | 1·00 (0·73 - 1·36) |
| >= 1·00 | 8 | 39 | 0·94 (0·42 - 2·12) |
| Chlordiazepoxide |  |  |  |  |
| 0·0 (never users) | 42335 | 254239 | 1·00 | p trend  0·124 |
| < 0·10 | 1 | 10 | 0·54 (0·07 - 4·22) |
| 0·10 - 0·39 | 51 | 239 | 1·16 (0·86 - 1·58) |
| 0·40 - 0·69 | 61 | 235 | 1·38 (1·04 - 1·83)\* |
| 0·70 - 0·99 | 16 | 119 | 0·71 (0·42 - 1·20) |
| >= 1·00 | 36 | 158 | 1·19 (0·82 - 1·71) |
| Clonazepam |  |  |  |  |
| 0·0 (never users) | 41534 | 250592 | 1·00 | p trend < 0·0001 |
| < 0·10 | 518 | 2470 | 1·17 (1·06 - 1·29)\*\* |
| 0·10 - 0·39 | 423 | 1782 | 1·31 (1·17 - 1·46)\*\*\* |
| 0·40 - 0·69 | 21 | 135 | 0·86 (0·54 - 1·36) |
| 0·70 - 0·99 | 3 | 18 | 0·92 (0·27 - 3·17) |
| >= 1·00 | 1 | 3 | 1·59 (0·16 - 15·46) |
| Diazepam |  |  |  |  |
| 0·0 (never users) | 41227 | 248120 | 1·00 | p trend  0·989 |
| < 0·10 | 34 | 216 | 0·89 (0·62 - 1·28) |
| 0·10 - 0·39 | 570 | 3022 | 1·01 (0·92 - 1·11) |
| 0·40 - 0·69 | 580 | 3132 | 1·00 (0·91 - 1·10) |
| 0·70 - 0·99 | 61 | 340 | 0·98 (0·74 - 1·29) |
| >= 1·00 | 28 | 170 | 0·95 (0·63 - 1·42) |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

DDD, Define daily dose; OR, Odd ratio; CI, Confidence Interval

Table S4. (Continue.)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Adjusted Odds Ratio (95% CI) | p-value |
| Fludiazepam |  |  |  |  |
| 0·0 (never users) | 40477 | 245913 | 1·00 | p trend  < 0·0001 |
| < 0·10 | 3 | 19 | 0·94 (0·28 - 3·20) |
| 0·10 - 0·39 | 332 | 1747 | 1·07 (0·95 - 1·20) |
| 0·40 - 0·69 | 849 | 3786 | 1·20 (1·11 - 1·30)\*\*\* |
| 0·70 - 0·99 | 544 | 2102 | 1·31 (1·19 - 1·44)\*\*\* |
| >= 1·00 | 295 | 1433 | 1·11 (0·98 - 1·26) |
| Flunitrazepam |  |  |  |  |
| 0·0 (never users) | 42105 | 253151 | 1·00 | p trend < 0·0001 |
| < 0·10 | 0 | 0 | - |
| 0·10 - 0·39 | 8 | 4 | 10·83 (3·23 - 36·20)\*\*\* |
| 0·40 - 0·69 | 12 | 46 | 1·43 (0·75 - 2·71) |
| 0·70 - 0·99 | 21 | 76 | 1·50 (0·92 - 2·45) |
| >= 1·00 | 354 | 1723 | 1·16 (0·99 - 1·25) |
| Lorazepam |  |  |  |  |
| 0·0 (never users) | 40075 | 243812 | 1·00 | p trend  < 0·0001 |
| < 0·10 | 76 | 376 | 1·14 (0·89 - 1·46) |
| 0·10 - 0·39 | 1411 | 6357 | 1·21 (1·14 - 1·28)\*\*\* |
| 0·40 - 0·69 | 675 | 3243 | 1·14 (1·05 - 1·24)\*\* |
| 0·70 - 0·99 | 185 | 792 | 1·26 (1·07 - 1·49)\*\* |
| >= 1·00 | 78 | 420 | 1·01 (0·79 - 1·30) |
| Lormetazepam |  |  |  |  |
| 0·0 (never users) | 42291 | 254028 | 1·00 | p trend  0·034 |
| < 0·10 | 0 | 0 | - |
| 0·10 - 0·39 | 5 | 37 | 0·73 (0·29 - 1·86) |
| 0·40 - 0·69 | 11 | 92 | 0·71 (0·38 - 1·32) |
| 0·70 - 0·99 | 34 | 128 | 1·46 (1·00 - 2·14) |
| >= 1·00 | 159 | 715 | 1·22 (1·03 - 1·45)\* |
| Medazepam |  |  |  |  |
| 0·0 (never users) | 42487 | 254960 | 1·00 | p trend  0·202 |
| < 0·10 | 0 | 0 | - |
| 0·10 - 0·39 | 1 | 5 | 1·03 (0·12 - 8·88) |
| 0·40 - 0·69 | 1 | 9 | 0·56 (0·07 - 4·41) |
| 0·70 - 0·99 | 6 | 16 | 2·24 (0·86 - 5·81) |
| >= 1·00 | 5 | 10 | 2·58 (0·87 - 7·65) |
| Nitrazepam |  |  |  |  |
| 0·0 (never users) | 42391 | 254380 | 1·00 | p trend  0·936 |
| < 0·10 | 0 | 0 | - |
| 0·10 - 0·39 | 6 | 42 | 0·77 (0·32 - 1·81) |
| 0·40 - 0·69 | 12 | 65 | 1·00 (0·54 - 1·86) |
| 0·70 - 0·99 | 16 | 74 | 1·19 (0·69 - 2·04) |
| >= 1·00 | 75 | 439 | 0·97 (0·76 - 1·24) |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

DDD, Define daily dose; OR, Odd ratio; CI, Confidence Interval

Table S4. (Continue.)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Adjusted Odds Ratio (95% CI) | p-value |
| Oxazepam |  |  |  |  |
| 0·0 (never users) | 42435 | 254647 | 1·00 | p trend  0·485 |
| < 0·10 | 2 | 2 | 4·82 (0·65 - 35·45) |
| 0·10 - 0·39 | 33 | 163 | 1·08 (0·74 - 1·58) |
| 0·40 - 0·69 | 18 | 120 | 0·82 (0·50 -1·35) |
| 0·70 - 0·99 | 11 | 50 | 1·15 (0·60 - 2·23) |
| >= 1·00 | 1 | 18 | 0·34 (0·04 - 2·54) |
| Oxazolam |  |  |  |  |
| 0·0 (never users) | 41235 | 248839 | 1·00 | p trend  0·018 |
| < 0·10 | 12 | 30 | 2·16 (1·10 - 4·25)\* |
| 0·10 - 0·39 | 189 | 989 | 1·05 (0·90 - 1·23) |
| 0·40 - 0·69 | 434 | 2175 | 1·06 (0·95 - 1·18) |
| 0·70 - 0·99 | 323 | 1414 | 1·18 (1·04 - 1·33)\*\* |
| >= 1·00 | 307 | 1553 | 1·05 (0·93 - 1·19) |
| Zopiclone |  |  |  |  |
| 0·0 (never users) | 41861 | 251947 | 1·00 | p trend  0·019 |
| < 0·10 | 0 | 0 | - |
| 0·10 - 0·39 | 13 | 77 | 0·88 (0·49 - 1·59) |
| 0·40 - 0·69 | 86 | 355 | 1·35 (1·06 - 1·71)\* |
| 0·70 - 0·99 | 122 | 525 | 1·23 (1·01 - 1·50)\* |
| >= 1·00 | 418 | 2096 | 1·08 (0·97 - 1·20) |
| Zolpidem |  |  |  |  |
| 0·0 (never users) | 40025 | 243094 | 1·00 | p trend  < 0·0001 |
| < 0·10 | 0 | 2 | - |
| 0·10 - 0·39 | 72 | 359 | 1·17 (0·90 - 1·50) |
| 0·40 - 0·69 | 329 | 1685 | 1·09 (0·97 - 1·23) |
| 0·70 - 0·99 | 687 | 3152 | 1·20 (1·10 - 1·30)\*\*\* |
| >= 1·00 | 1387 | 6708 | 1·16 (1·09 - 1·23)\*\*\* |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

DDD, Define daily dose; OR, Odd ratio; CI, Confidence Interval

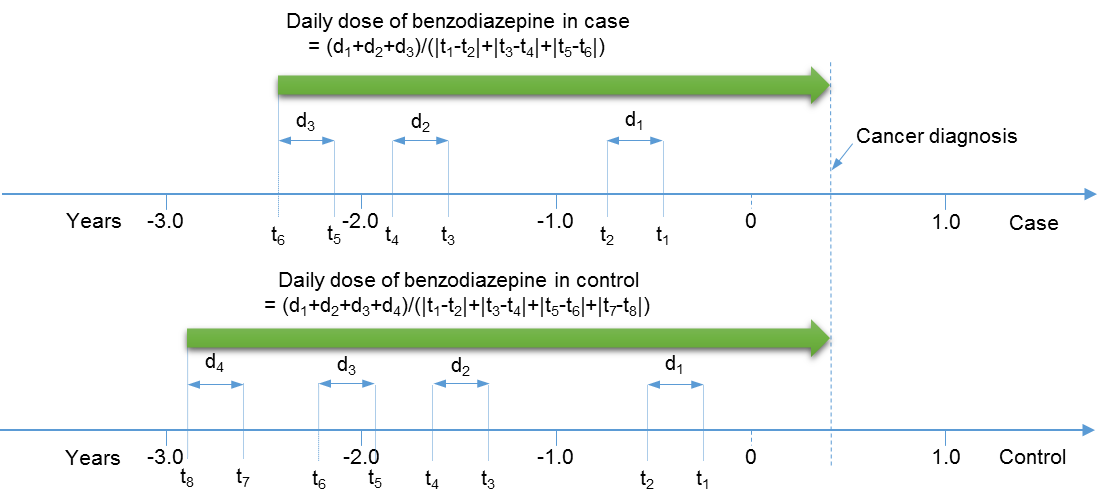
# Table S5. Detail DDD of benzodiazepine class associated with risk for cancers

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Case  (n = 42500) | Control  (n = 255000) | Adjusted Odds Ratio (95% CI) | p-value |
| Overall Benzodiazepines | | | | |
| 0·0 (never users) | 33377 | 209926 | 1·00 | p trend <0·0001 |
| < 0·10 | 1125 | 5204 | 1·23 (1·15 - 1·32)\*\*\* |
| 0·10 - 0·39 | 4899 | 23726 | 1·18 (1·13 - 1·22)\*\*\* |
| 0·40 - 0·69 | 2178 | 10837 | 1·18 (1·12 - 1·24)\*\*\* |
| 0·70 - 0·99 | 517 | 2712 | 1·14 (1·03 - 1·25)\*\* |
| >= 1·00 | 404 | 2595 | 0·95 (0·85 - 1·06) |
| Antiepileptics (N03AE) Class | | | | |
| 0·0 (never users) | 41534 | 250592 | 1·00 | p trend <0·0001 |
| < 0·10 | 518 | 2470 | 1·17 (1·06 - 1·29)\*\* |
| 0·10 - 0·39 | 423 | 1782 | 1·31 (1·17 - 1·46)\*\*\* |
| 0·40 - 0·69 | 21 | 135 | 0·86 (0·54 - 1·36) |
| 0·70 - 0·99 | 3 | 18 | 0·92 (0·27 - 3·17) |
| >= 1·00 | 1 | 3 | 1·59 (0·16 - 15·46) |
| Anxiolytics (N05BA) Class | | | | |
| 0·0 (never users) | 34906 | 217883 | 1·00 | p trend <0·0001 |
| < 0·10 | 811 | 3842 | 1·17 (1·08 - 1·27)\*\*\* |
| 0·10 - 0·39 | 4566 | 21938 | 1·17 (1·13 - 1·21)\*\*\* |
| 0·40 - 0·69 | 1678 | 8300 | 1·16 (1·10 - 1·23)\*\*\* |
| 0·70 - 0·99 | 318 | 1741 | 1·06 (0·94 - 1·20) |
| >= 1·00 | 221 | 1296 | 1·00 (0·87 - 1·16) |
| Hypnotics and sedatives (N05CD) Class | | | | |
| 0·0 (never users) | 41698 | 251160 | 1·00 | p trend 0·007 |
| < 0·10 | 1 | 4 | 1·48 (0·16 - 13·35) |
| 0·10 - 0·39 | 46 | 180 | 1·34 (0·96 - 1·85) |
| 0·40 - 0·69 | 115 | 501 | 1·25 (1·01 - 1·53)\* |
| 0·70 - 0·99 | 94 | 388 | 1·30 (1·04 - 1·64)\* |
| >= 1·00 | 546 | 2767 | 1·09 (1·00 - 1·20) |
| Related drugs (N05CF) Class | | | | |
| 0·0 (never users) | 39594 | 241043 | 1·00 | p trend <0·0001 |
| < 0·10 | 0 | 4 | - |
| 0·10 - 0·39 | 133 | 740 | 1·00 (0·83 - 1·21) |
| 0·40 - 0·69 | 679 | 3078 | 1·21 (1·11 - 1·32)\*\*\* |
| 0·70 - 0·99 | 723 | 3210 | 1·24 (1·14 - 1·34)\*\*\* |
| >= 1·00 | 1371 | 6925 | 1·12 (1·06 - 1·19)\*\*\* |

\* p < 0·05; \*\* p < 0·01; \*\*\* p < 0·001

Adjusted odd ratio were adjusted for the confounders as Comorbid conditions, other drugs, branch, and socio-economic status in Table 1.

DDD, define daily dose

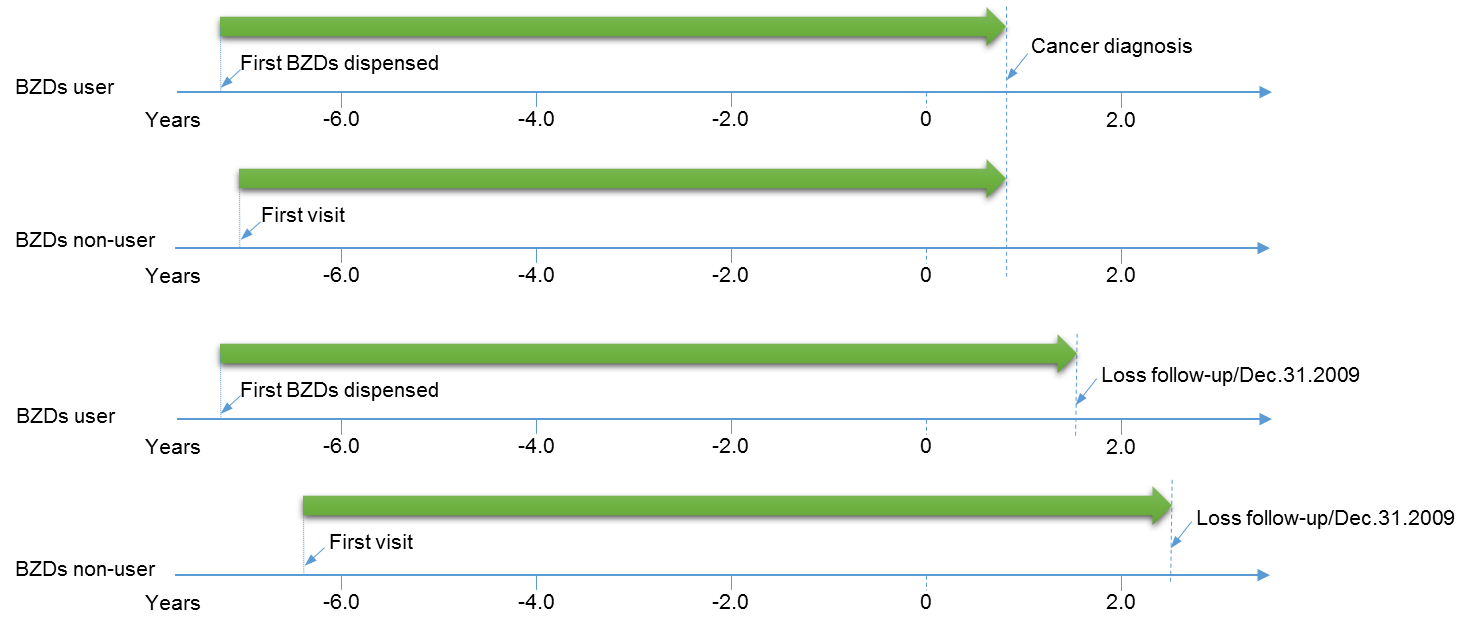


# Figure S1. The BZDs use were checked during three year before the date of cancer diagnosis for both cases and control groups. The daily dose of BZD is calculated as the collected total amount of BZD at dispenses (i.e. d1, d2, d3) divided by the total time duration of dispenses (i.e. |t1-t2|, |t3-t4|, |t5-t6|).

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# Figure S2. Distribution of BZD dispenses 3 years before and 1 year after cancer diagnosis in case and control group. For cases, the dispense pattern before and after cancer diagnosis with the increased dispense after for short duration compared with before cancer diagnosis, likely explained by anxiety or sleeplessness. After that the slightly decreased dispense of BZDs which might be of the death of some cancer patients after a cancer diagnosis. For control, the dispense pattern before and after index date was likely similar.

# Figure S3. Selection of cancer patients (case) and non-cancer patients (control) entering into the study by using propensity score (1:6) matched study



# Figure S4. The BZDs use were checked by follow-up all subjects started from the initial BZDs dispense date or the first visit date of the cohort database until a cancer diagnosis/index date or until the time subject was censored for loss to follow-up, or termination of insurance.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Benzodiazepines used** | **Number of patients**a | **Number of cancers**b | **Hazard ratio**c **(95% Confident Intervals)** | | | **p-value** |
| No used (Overall) | 99082 | 13131 | 1.00 |  |  |  |
| Benzo used (Overall) | 48975 | 7915 | 1.15 (1.11 - 1.19) |  |  | <0.0001 |
| N03AE Class | 7390 | 1315 | 1.17 (1.11 - 1.24) |  |  | <0.0001 |
| N05BA Class | 48457 | 7853 | 1.15 (1.12 - 1.19) |  |  | <0.0001 |
| N05CD Class | 11947 | 1941 | 1.08 (1.03 - 1.13) |  |  | 0.003 |
| N05CF Class | 22834 | 3836 | 1.14 (1.10 - 1.18) |  |  | <0.0001 |
| Alprazolam | 26526 | 4484 | 1.15 (1.11 - 1.19) |  |  | <0.0001 |
| Bromazepam | 14748 | 2548 | 1.15 (1.10 - 1.20) |  |  | <0.0001 |
| Chlordiazepoxide\* | 7955 | 1293 | 1.04 (0.98 - 1.10) |  |  | 0.146 |
| Clonazepam | 7390 | 1315 | 1.17 (1.11 - 1.24) |  |  | <0.0001 |
| Diazepam\* | 33802 | 5400 | 0.93 (0.89 - 0.98) |  |  | 0.003 |
| Fludiazepam | 28260 | 4786 | 1.15 (1.11 - 1.19) |  |  | <0.0001 |
| Flunitrazepam | 4129 | 685 | 1.09 (1.01 - 1.18) |  |  | 0.028 |
| Lorazepam | 31136 | 5158 | 1.14 (1.10 - 1.18) |  |  | <0.0001 |
| Lormetazepam\* | 3878 | 631 | 1.08 (0.99 - 1.17) |  |  | 0.053 |
| Medazepam\* | 782 | 116 | 0.96 (0.80 - 1.15) |  |  | 0.648 |
| Nitrazepam\* | 4793 | 775 | 1.06 (0.98 - 1.14) |  |  | 0.131 |
| Oxazepam\* | 2058 | 322 | 1.02 (0.91 - 1.14) |  |  | 0.706 |
| Oxazolam | 29151 | 4846 | 1.12 (1.08 - 1.16) |  |  | <0.0001 |
| Zopiclone | 8256 | 1428 | 1.13 (1.09 - 1.18) |  |  | <0.0001 |
| Zolpidem | 19598 | 3300 | 1.14 (1.08 - 1.21) |  |  | <0.0001 |

a Number of patient used individual and classes of benzodiazepines

b Number of patient developed cancers

c Hazard ratio were adjusted for the confounders as Comorbid conditions, other drugs, regions, and socio-economic status in Table 1

\* Defined as safer benzodiazepines

# Figure S5. Benzodiazepines (classes and individuals) and their association with overall cancer risk in Female patients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Benzodiazepines used** | **Number of patients**a | **Number of cancers** | **Hazard ratioc (95% Confident Intervals)** | | | **p-value** |
| No used (Overall) | 109371 | 14671 | 1.00 |  |  |  |
| Benzo used (Overall) | 40072 | 6783 | 1.14 (1.10 - 1.18) |  |  | <0.0001 |
| N03AE Class | 6753 | 1213 | 1.13 (1.07 - 1.20) |  |  | <0.0001 |
| N05BA Class | 39127 | 6668 | 1.15 (1.11 - 1.19) |  |  | <0.0001 |
| N05CD Class | 9125 | 1596 | 1.10 (1.05 - 1.16) |  |  | <0.0001 |
| N05CF Class | 17624 | 3118 | 1.14 (1.10 - 1.19) |  |  | <0.0001 |
| Alprazolam | 17746 | 3116 | 1.12 (1.07 - 1.16) |  |  | <0.0001 |
| Bromazepam | 10122 | 1794 | 1.11 (1.05 - 1.17) |  |  | <0.0001 |
| Chlordiazepoxide | 5021 | 892 | 1.08 (1.01 - 1.16) |  |  | 0.020 |
| Clonazepam | 6753 | 1213 | 1.13 (1.07 - 1.20) |  |  | <0.0001 |
| Diazepam\* | 24529 | 4199 | 1.00 (0.95 - 1.05) |  |  | 0.915 |
| Fludiazepam | 19775 | 3544 | 1.15 (1.10 - 1.19) |  |  | <0.0001 |
| Flunitrazepam | 3776 | 686 | 1.13 (1.05 - 1.23) |  |  | 0.001 |
| Lorazepam | 22545 | 4031 | 1.18 (1.13 - 1.22) |  |  | <0.0001 |
| Lormetazepam\* | 2726 | 474 | 1.08 (0.99 - 1.19) |  |  | 0.092 |
| Medazepam\* | 451 | 81 | 1.11 (0.90 - 1.39) |  |  | 0.336 |
| Nitrazepam\* | 3113 | 535 | 1.08 (0.98 - 1.17) |  |  | 0.110 |
| Oxazepam\* | 1376 | 251 | 1.11 (0.98 - 1.26) |  |  | 0.096 |
| Oxazolam | 19554 | 3362 | 1.09 (1.04 - 1.13) |  |  | <0.0001 |
| Zopiclone | 6830 | 1196 | 1.14 (1.09 - 1.19) |  |  | <0.0001 |
| Zolpidem | 14892 | 2646 | 1.10 (1.03 - 1.16) |  |  | 0.003 |

a Number of patient used individual and classes of benzodiazepines

b Number of patient developed cancers

c Hazard ratio were adjusted for the confounders as Comorbid conditions, other drugs, regions, and socio-economic status in Table 1

\* Defined as safer benzodiazepines

# Figure S6. Benzodiazepines (classes and individuals) and their association with overall cancer risk in Male patients