**Androgen-deprivation therapy and the risk of newly developed fractures in patients with prostate cancer: a nationwide cohort study in Korea**

Do Kyung Kim1, Jong Won Kim2, Hye Sun Lee3, Ju-Young Park3, Hyun Kyu Ahn2, Jee Soo Ha2, Kang Su Cho2,\*

**Affiliations**

1Department of Urology, Soonchunhyang University Hospital, Soonchunhyang University College of Medicine, Seoul, Republic of Korea

2Department of Urology, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

3Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Republic of Korea

Supplementary Table 1**.** Diagnostic codes and definitions of comorbidities

|  |  |
| --- | --- |
| Comorbidity | ICD-10-CM code and definition |
| Rheumatoid arthritis | M05 (Seropositive rheumatoid arthritis): M05.0, M05.1, M05.2, M05.3, M05.8, M05.9M06 (Other rheumatoid arthritis): M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9 |
| Diabetes mellitus | E10 (Type 1 diabetes mellitus): E10.0, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E10.9E11 (Type 2 diabetes mellitus): E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E11.9E12 (Malnutrition-related diabetes mellitus): E12.0, E12.1, E12.2, E12.3, E12.4, E12.5, E12.6, E12.7, E12.8, E12.9E13 (Other specified diabetes mellitus): E13.0, E13.1, E13.2, E13.3, E13.4, E13.5, E13.6, E13.7, E13.8, E13.9E14 (Unspecified diabetes mellitus): E14.0, E14.1, E14.2, E14.3, E14.4, E14.5, E14.6, E14.7, E14.8, E14.9 |
| Hyperthyroidism | E05 (Thyrotoxicosis [hyperthyroidism]): E05.0, E05.1, E05.2, E05.3, E05.4, E05.5, E05.8, E05.9 |
| Chronic liver disease | K73 (Chronic hepatitis): K73.0, K73.1, K73.2, K73.8, K73.9K74 (Fibrosis and cirrhosis of liver): K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6B18 (Chronic viral hepatitis): B18.0, B18.1, B18.2, B18.8, B18.9 |
| Chronic kidney disease | N18 (Chronic kidney disease): N18.1, N18.2, N18.3, N18.4, N18.5, N18.9 |
| COPD | J44 (Other chronic obstructive pulmonary disease): J44.0, J44.1, J44.8, J44.9 |
| Neurological disease |  |
| Stroke | I60 (Subarachnoid haemorrhage): I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9I61 (Intracerebral haemorrhage): I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9I62 (Other nontraumatic intracranial haemorrhage): I62.0, I62.1, I62.9I63 (Cerebral infarction): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9I64 (Stroke, not specified as haemorrhage or infarction) |
| Parkinson’s disease | G20 (Parkinson’s disease)G21 (Secondary parkinsonism): G21.1, G21.2, G21.3, G21.4, G21.8, G21.9G22 (Parkinsonism in diseases classified elsewhere) |
| Dementia | F00 (Dementia in Alzheimer’s disease): F00.0, F00.1, F00.2, F00.9F01 (Vascular dementia): F01.0, F01.1, F01.2, F01.3, F01.8, F01.9F02 (Dementia in other diseases classified elsewhere): F02.0, F02.1, F02.2, F02.3, F02.4, F02.8F03 (Unspecified dementia): F05.0, F05.1 |
| Osteoporosis | M80 (Osteoporosis with pathological fracture): M80.5, M80.8, M80.9M81 (Osteoporosis without pathological fracture): M81.5, M81.8, M81.9 |
| Fracture |  |
| Hip | S72 (Fracture of femur): S72.0, S72.1, S72.2, S72.3, S72.4, S72.7, S72.8, S72.9 |
| Spine | S22.0 (Fracture of thoracic vertebra)S22.1 (Multiple fracture of thoracic spine)S32.0 (Fracture of lumbar vertebra) |
| Upper extremity | S52.5 (Fracture of lower end of radius)S42.2 (Fracture of upper end of humerus) |

COPD, chronic obstructive pulmonary disease

Supplementary Table 2. Medication code definitions

|  |  |
| --- | --- |
| Medication | Billing Code |
| GnRH agonists or antagonist | Degarelix: 624401BIJ, 624402BIJGoserelin acetate: 167202BIJ, 167201BIJLeuprorelin acetate: 182602BIJ, 182605BIJ, 182601BIJ, 182604BIJ, 182606BIJ, 182630BIJ, 182608BIJ, 182610BIJ, 182611BIJTriptorelin acetate: 244902BIJ, 467501BIJ, 467502BIJ |
| Anti-androgen | Cyproterone acetate: 139401ATBBicalutamide: 117201ATB, 117202ATBFlutamide: 162101ATB |
| Bisphosphonate | Disodium salt of a nitrogen-free bisphosphonate analog: 136101ACH, 136102BIJ, 147401ATB, 207901ACS, 207902BIJAlendronate: 228301ATB, 228302ATB, 228303ALQ, 228303ATBZoledronic acid: 420702BIJ, 420730BIJ, 420731BIJRisedronic acid: 442301ATB, 442302ATB, 442302ATE, 442303ATB, 442330ATBIbandronic acid: 480301BIJ, 480302BIJ, 480304ATB, 480330BIJ, 641201BIJCombination: 468000ATE, 481100ATB, 500200ATB, 511200ATB, 518400ATB, 523900ATB |
| Calcium, combination with vitamin D and/or other durgs | Calcium carbonate combination: 302600ATB, 303200ATB, 387900ACS, 475200ATB, 480200ATB, 498200ATB, 498300ATB, 526100ATB, 634000ATBCalcium citrate combination: 302800ATB, 462700ATB, 462800ATB, 503100ATB, 508700ATB, 519000ATB, 665600ATB, 670000ATB |
| Parathyroid hormone | Teriparatide: 646301BIJ, 487502BIJ |

Supplementary Table 3. Age-adjusted Cox regression analysis for osteoporosis in the unmatched (A) and matched (B) cohorts after adjusting for the index date

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Univariable anlaysis** |  | **Age-adjusted Cox regression analysis** |
|  | **ADT** |  | **Duration of ADT** |
| **HR (95% CIs)** | **p-value** |  | **HR (95% CIs)** | **p-value** |  | **HR (95% CIs)** | **pairwise comparison p-value** |
| **(A) Unmatched cohorts** |  |  |  |  |  |  |  |  |  |  |  |
| Age | 1.064 (1.062-1.067) | < 0.0001 |  | 1.059 (1.057-1.062) | < 0.0001 |  | 1.059 (1.056-1.062) | < 0.0001 |  |  |  |
| ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |  |  |  |  |  |  |
| Yes | 2.069 (1.977-2.165) | < 0.0001 |  | 1.346 (1.283-1.413) | < 0.0001 |  |  |  |  |  |  |
| Duration of ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  |  |  |  | Ref. | Ref |  |  |  |
| < 1 year | 1.454 (1.320-1.601) | < 0.0001 |  |  |  |  | 1.013 (0.919-1.117) | 0.795 | Ref |  |  |
| 1~2 year | 1.987 (1.815-2.176) | < 0.0001 |  |  |  |  | 1.270 (1.158-1.393) | < 0.0001 | 0.0005 | Ref |  |
| 2~3 year | 2.048 (1.863-2.250) | < 0.0001 |  |  |  |  | 1.333 (1.211-1.467) | < 0.0001 | < 0.0001 | 0.4534 | Ref |
| > 3 year | 2.476 (2.331-2.630) | < 0.0001 |  |  |  |  | 1.572 (1.477-1.674) | < 0.0001 | < 0.0001 | < 0.0001 | 0.0023 |
| **(B) Matched cohorts** |  |  |  |  |  |  |  |  |  |  |  |
| Age | 1.036 (1.032-1.040) | < 0.0001 |  | 1.035 (1.032-1.039) | < 0.0001 |  | 1.034 (1.031-1.038) | < 0.0001 |  |  |  |
| ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |  |  |  |  |  |  |
| Yes | 1.363 (1.288-1.442) | < 0.0001 |  | 1.351 (1.277-1.430) | < 0.0001 |  |  |  |  |  |  |
| Duration of ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  |  |  |  | Ref. | Ref |  |  |  |
| < 1 year | 0.958 (0.865-1.061) | 0.413 |  |  |  |  | 0.990 (0.893-1.096) | 0.8402 | Ref |  |  |
| 1~2 year | 1.286 (1.167-1.418) | < 0.0001 |  |  |  |  | 1.262 (1.145-1.391) | < 0.0001 | < 0.0001 | Ref |  |
| 2~3 year | 1.336 (1.208-1.477) | < 0.0001 |  |  |  |  | 1.324 (1.197-1.464) | < 0.0001 | < 0.0001 | 0.6389 | Ref |
| > 3 year | 1.652 (1.542-1.771) | < 0.0001 |  |  |  |  | 1.610 (1.502-1.725) | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 |

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio

Supplementary Table 4. Age-adjusted Cox regression analysis for predicting fractures in the unmatched (A) and matched (B) cohorts after adjusting for the index date

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Univariable analysis** |  | **Age-adjusted Cox regression analysis** |
|  | **ADT** |  | **Duration of ADT** |
| **HR (95% CIs)** | **p-value** |  | **HR (95% CIs)** | **p-value** |  | **HR (95% CIs)** | **pairwise comparison p-value** |
| **(A) Unmatched cohorts** |  |  |  |  |  |  |  |  |  |  |  |
| Age | 1.078 (1.075-1.081) | < 0.0001 |  | 1.066 (1.063-1.069) | < 0.0001 |  | 1.066 (1.063-1.069) | < 0.0001 |  |  |  |
| ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |  |  |  |  |  |  |
| Yes | 2.936 (2.792-3.087) | < 0.0001 |  | 1.843 (1.746-1.944) | < 0.0001 |  |  |  |  |  |  |
| Duration of ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  |  |  |  | Ref. | Ref |  |  |  |
| < 1 year | 2.166 (1.959-2.394) | < 0.0001 |  |  |  |  | 1.470 (1.328-1.627) | < 0.0001 | Ref |  |  |
| 1~2 year | 3.034 (2.762-3.334) | < 0.0001 |  |  |  |  | 1.865( 1.694-2.053) | < 0.0001 | 0.0003 | Ref |  |
| 2~3 year | 3.255 (2.958-3.582) | < 0.0001 |  |  |  |  | 2.047 (1.857-2.256) | < 0.0001 | < 0.0001 | 0.1477 | Ref |
| > 3 year | 3.186 (2.981-3.406) | < 0.0001 |  |  |  |  | 1.944 (1.814-2.084) | < 0.0001 | < 0.0001 | 0.4437 | 0.3504 |
| **(B) Matched cohorts** |  |  |  |  |  |  |  |  |  |  |  |
| Age | 1.068 (1.064-1.073) | < 0.0001 |  | 1.068(1.063-1.072) | <.0001 |  | 1.067 (1.063-1.072) | < 0.0001 |  |  |  |
| ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |  |  |  |  |  |  |
| Yes | 1.800 (1.689-1.918) | < 0.0001 |  | 1.775(1.666-1.892) | <.0001 |  |  |  |  |  |  |
| Duration of ADT |  |  |  |  |  |  |  |  |  |  |  |
| No | Ref. |  |  |  |  |  | Ref. | Ref |  |  |  |
| < 1 year | 1.328 (1.192-1.479) | < 0.0001 |  |  |  |  | 1.415 (1.270-1.577) | < 0.0001 | Ref |  |  |
| 1~2 year | 1.850 (1.669-2.050) | < 0.0001 |  |  |  |  | 1.787 (1.613-1.980) | < 0.0001 | 0.0005 | Ref |  |
| 2~3 year | 1.988 (1.792-2.205) | < 0.0001 |  |  |  |  | 1.962 (1.769-2.177) | < 0.0001 | < 0.0001 | 0.1486 | Ref |
| > 3 year | 1.960 (1.814-2.118) | < 0.0001 |  |  |  |  | 1.874 (1.735-2.025) | < 0.0001 | < 0.0001 | 0.3878 | 0.4064 |

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio

Supplementary Table 5. Age-adjusted Cox regression analysis for osteoporosis (A) and fracture (B) in the matched cohorts according to the use of anti-androgens

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Univariable analysis** |  | **Age-adjusted Cox regression analysis** |
| **HR (95% CIs)** | **p-value** |  | **HR (95% CIs)** | **p-value** |
| **(A) Osteoporosis** |  |  |  |  |  |
| Age | 1.031 (1.018-1.045) | < 0.0001 |  | 1.031 (1.018-1.045) | < 0.0001 |
| Anti-androgen use |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |
| Yes | 1.034 (0.846-1.264) | 0.7436 |  | 1.039 (0.850-1.269) | 0.7120 |
| **(B) Fracture** |  |  |  |  |  |
| Age | 1.075 (1.060-1.091) | < 0.0001 |  | 1.076 (1.060-1.092) | < 0.0001 |
| Anti-androgen use |  |  |  |  |  |
| No | Ref. |  |  | Ref. |  |
| Yes | 1.200 (0.974-1.478) | 0.0874 |  | 1.222 (0.992-1.506) | 0.0599 |

CI, confidence interval; HR, hazard ratio