# Multiple Myeloma and IV Bisphosphonate Are Risk Factors for Osteonecrosis of the Jaw

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## BACKGROUND

Osteonecrosis of the jaw (ONJ) is exposed, necrotic bone in the maxillofacial region lasting longer than 8 weeks.[1] Risk factors include radiation to the head or neck, intravenous (IV) bisphosphonate use, and age. A number of United States (US) claims-based studies have evaluated the incidence of and potential risk factors for ONJ, but very few have validated the outcome.[2-5]

## OBJECTIVE

To measure the incidence and identify risk factors of ONJ among two cohorts:

- Individuals with breast cancer, prostate cancer, or multiple myeloma
- Individuals with osteopenia or osteoporosis

## METHODS

### Inclusion Criteria

Study cohorts were identified using a large commercially insured population in the US. Participants met the following criteria:

- Complete medical claims
- Complete pharmacy claims
- Plan eligibility dated January 1, 2000, through March 31, 2007
- Claim(s) for a cohort index diagnosis associated with at least one of the following:
  - At least two outpatient physician visits
  - One overnight emergency department claim
  - One inpatient hospital claim
  - Enrollment at least 1 year before index diagnosis

***Cancer Cohort***

Males and females aged ≥ 40 years with selected cancers (Table 1)

***Osteoporosis Cohort***

Women aged ≥ 50 years and men ≥ 60 years with selected claims (Table 2)

**Table 1. ICD-9 Codes for Cancer Cohort Index Diagnosis**

| Diagnosis Description | ICD-9 Code |
|---|---|
| Breast cancer | |
| Malignant neoplasm of breast | 174.xx |
| Breast carcinoma in situ | 233.0x |
| Uncertain neoplasm of breast | 238.3x |
| Breast neoplasm of uncertain nature | 239.3x |
| Prostate cancer | |
| Malignant neoplasm of prostate | 185.xx |
| Multiple myeloma | |
| Multiple myeloma, Kahler's disease, myelomatosis | 203.0x |

ICD-9 = International Classification of Diseases, 9th edition.

**Table 2. ICD-9 Codes for Osteoporosis Cohort Index Diagnosis**

| Diagnosis Description | ICD-9 Code |
|---|---|
| Osteoporosis | 733.0x |
| Disorder of bone and cartilage, unspecified | 733.90 |
| Vertebrae fracture | 733.13, 805.xx |
| Hip fracture | 733.14, 820.xx |
| Wrist fracture | 733.12, 813.xx, 814.xx |

### ONJ Cases

- We identified potential ONJ cases diagnosed after the index date with the following codes:
  - ICD-9 diagnosis codes: 522.7, 526.4, 526.5, 526.89
  - CPT codes: 21035, 21045, 21047, 21127, 21210, 21215, 41800, 41830, 42120, 21081, 21193.
- We excluded all potential ONJ cases with history of radiation to the head or neck.
- We abstracted medical records for medical services that occurred within 6 months of first potential ONJ claim date.
- Two clinicians blinded to bisphosphonate exposure independently reviewed the results of abstraction and classified each potential ONJ case as:
  - Probable ONJ
  - Possible ONJ
  - Not ONJ.
- Differences between the two reviewers were discussed and resolved.
- All probable ONJ cases and possible ONJ cases were included in analyses.

### Exposures

- By definition, ONJ diagnosis can be made only after 8 weeks of exposed bone.
- We assumed at least 6 weeks exposure to bisphosphonate for risk of ONJ.
- Because of the long half lives of bisphosphonates, exposure definitions for time at risk of ONJ were as follows:
  - **IV bisphosphonate exposure:** started 14 weeks after first infusion and continued until end of follow-up
  - **Oral bisphosphonate exposure:** started 14 weeks after first prescription and continued until end of follow-up
  - **No exposure to bisphosphonates:** started at index date and ended 14 weeks after first IV or oral bisphosphonate exposure.
  - **Corticosteroid use:** sum of the days' supply of corticosteroid prescription fills.

### Analysis

- ONJ incidences were estimated as number of ONJ cases divided by total person-years and derived for the following:
  - **Unadjusted incidences** were stratified by cohort and bisphosphonate exposure and weighted for cohort-specific abstraction percentages. Minimum incidence was based on probable ONJ cases, and maximum incidence was based on probable and possible ONJ cases.
  - **Sex and age-adjusted incidences** were stratified by cohort and bisphosphonate exposure, and were adjusted to person-year distribution of all exposure time by sex and age.
- To model risk factors for ONJ and adjust for variables that could change over time, we included all abstracted probable plus possible cases in a logistic regression model by modeling each 30-day follow-up period of person-time as a separate observation and accounting for the correlation between periods contributed by the same patient.[6]

## RESULTS

Crude Incidence of ONJ (Figures 1 and 2)

**Figure 1. Potential ONJ Cases in the Cancer Cohort**

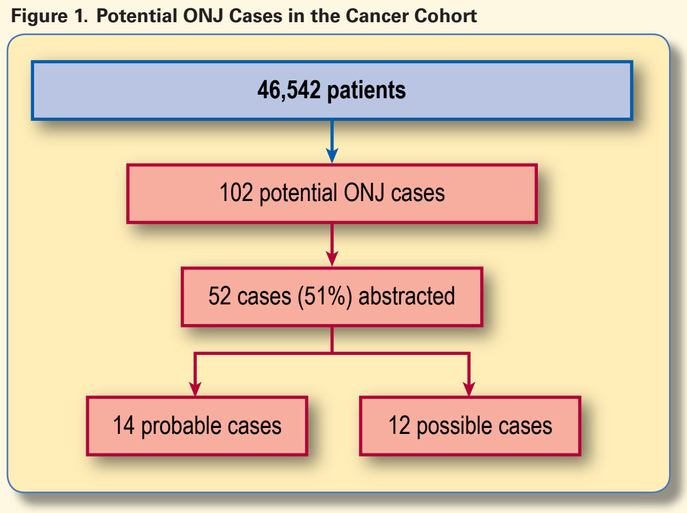


**Figure 2. Potential ONJ Cases in the Osteoporosis Cohort**

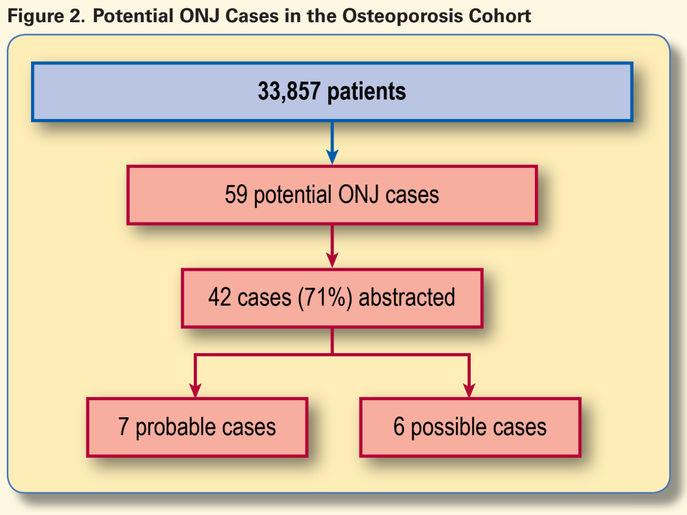


**Table 3. Crude Incidence, Adjusted for Abstraction Percentage, of ONJ in Each Cohort, by Bisphosphonate Use**

| | Cancer Cohort (N = 46,452) | | | Osteoporosis Cohort (N = 33,857) | | |
|---|---|---|---|---|---|---|
| Exposure Category | Range in Confirmed Cases[a] | Person-Years | Range of Incidence[b] of ONJ cases per 1,000 Person-Years | Range in Confirmed Cases[a] | Person-Years | Range of Incidence[b] of ONJ cases per 1,000 Person-Years |
| Unexposed | 2-10 | 87,677 | 0.045-0.22 | 4-9 | 42,358 | 0.13-0.30 |
| Oral bisphosphonate use | 2-2 | 12,638 | 0.31-0.31 | 1-2 | 18,657 | 0.075-0.15 |
| IV bisphosphonate use | 11-15 | 4,451 | 4.8-6.6 | 2-2 | 512 | 5.5-5.5 |

IV = intravenous.
Note: Estimates are adjusted to account for potential cases missed due to lack of access to medical chart review.
[a] Range is expressed as observed probable cases to probable plus possible cases; includes one case exposed to both oral and IV bisphosphonate in the cancer cohort.
[b] Incidence adjusted for abstraction percentage.

### Cancer Cohort

- Table 4 shows the characteristics of the cancer cohort, stratified by exposure. Table 5 shows the crude and age-sex-adjusted incidence ratios. Table 6 outlines the results of multiple regression analysis.

**Table 4. Cancer Cohort: Percentage of Person-Years, Number of Person-Years, and Number of Individuals in Each Covariate Stratum, by Exposure Category**

| Stratification Variable | Unexposed | | IV Bisphosphonate Use | | Oral Bisphosphonate Use | |
|---|---|---|---|---|---|---|
| | Person-Years | Percentage | Person-Years | Percentage | Person-Years | Percentage |
| Overall | 87,677 | 100 | 4,451 | 100 | 12,638 | 100 |
| Males | | | | | | |
| 40-69 years | 23,951 | 27 | 986 | 22 | 595 | 5 |
| ≥ 70 years | 16,382 | 19 | 628 | 14 | 1,162 | 9 |
| Females | | | | | | |
| 40-69 years | 38,200 | 44 | 2,175 | 49 | 7,370 | 58 |
| ≥ 70 years | 9,144 | 10 | 663 | 15 | 3,510 | 28 |
| Cohort diagnosis | | | | | | |
| Breast cancer | 46,933 | 54 | 2,199 | 49 | 10,679 | 85 |
| Multiple myeloma | 1,306 | 1 | 1,427 | 32 | 268 | 2 |
| Prostate cancer | 39,439 | 45 | 825 | 19 | 1,691 | 13 |
| Cumulative corticosteroid use | | | | | | |
| < 90 days | 85,772 | 98 | 3,322 | 75 | 11,715 | 93 |
| ≥ 90 days | 1,903 | 2 | 1,129 | 25 | 923 | 7 |

**Table 5. Cancer Cohort: Crude and Age-Sex-Adjusted Incidence Ratios for Comparison of Each Bisphosphonate Exposure Category With the Unexposed Group, by Diagnosis, Duration of Bisphosphonate Use, and Duration of Corticosteroid Use**

| Stratification Variable | IV Bisphosphonate Use | | Oral Bisphosphonate Use | |
|---|---|---|---|---|
| | BPN $IR_{crude}$ (95% CI) | BPN $IR_{adj}$[a] | BPN $IR_{crude}$ (95% CI) | BPN $IR_{adj}$[a] |
| Overall | 29.5 (13.3-65.8) | 20.2 | 1.4 (0.30-6.3) | 1.1 |
| Diagnosis | | | | |
| Breast cancer | 17.1 (4.6-63.6) | 11.7 | 0.88 (0.10-7.5) | 0.70 |
| Multiple myeloma | 3.1 (0.84-11.1) | 3.1 | 1.6 (0.17-16) | 1.1 |
| Prostate cancer | 23.9 (2.2-264) | 28.5 | 0.00 (0.00-124) | 0.00 |
| Duration of bisphosphonate use | | | | |
| < 2 years | 22.5 (9.4-54.1) | 14.2 | 0.90 (0.11-7.0) | 0.69 |
| ≥ 2 years | 78.5 (26.8-230) | 60.9 | 3.1 (0.39-24) | 1.8 |
| Corticosteroid use | | | | |
| < 90 days | 20.1 (7.5-53.9) | 13.2 | 0.81 (0.10-6.4) | 0.58 |
| ≥ 90 days | 13.5 (1.7-108) | 27.1 | 2.1 (0.13-33) | 4.0 |

adj = adjusted; BPN = bisphosphonate; CI = confidence interval; IR = incidence ratio.
[a] Standardized for age (< 70 years vs. ≥ 70 years) and sex.

**Table 6. Cancer Cohort: Results of Multiple Regression Analysis Evaluating the Association of Bisphosphonate Exposure With Incident ONJ**

| Variable | Adjusted Rate Ratio (95% CI) |
|---|---|
| Bisphosphonate exposure | |
| None | 1.0 |
| Oral | 0.6 (0.08-5.0) |
| IV | 8.3 (2.0-34) |
| Cancer cohort diagnosis | |
| Breast cancer | 1.0 |
| Multiple myeloma | 4.5 (0.7-28) |
| Prostate cancer | 0.4 (0.06-2.3) |
| Sex | |
| Male | 1.0 |
| Female | 0.8 (0.3-2.4) |
| Corticosteroid use | |
| < 90 days | 1.0 |
| ≥ 90 days or more | 1.9 (0.7-5.6) |
| Age (per additional 5 years) | 0.98 (0.8-1.2) |

Note: Adjustment was simultaneous for all listed variables.

### Osteoporosis Cohort

- Table 7 presents the characteristics of the osteoporosis cohort. Numbers of probable or possible ONJ cases were too small for stratified analysis or modeling.
- Overall, 44% of IV-bisphosphonate-exposed patients had regimens consistent with labeling for osteoporosis or off-label guidances for osteoporosis, and 56% were consistent with dosing for treatment of malignancy sequelae.

**Table 7. Osteoporosis Cohort: Percentage of Person-Years, Number of Person-Years, and Number of Individuals in Each Covariate Stratum, by Exposure Category**

| Stratification Variable | Unexposed | | IV Bisphosphonate Use | | Oral Bisphosphonate Use | |
|---|---|---|---|---|---|---|
| | Person-Years | Percentage | Person-Years | Percentage | Person-Years | Percentage |
| Overall | 42,358 | 100 | 512 | 100 | 18,657 | 100 |
| Males | | | | | | |
| 40-69 years | 2,505 | 6 | 33 | 7 | 315 | 2 |
| ≥ 70 years | 4,417 | 10 | 75 | 15 | 990 | 5 |
| Females | | | | | | |
| 40-69 years | 17,066 | 40 | 181 | 35 | 8,223 | 44 |
| ≥ 70 years | 18,370 | 43 | 223 | 44[a] | 9,129 | 49 |
| Cohort diagnosis | | | | | | |
| Fracture | 23,300 | 55 | 198 | 39 | 5,750 | 31 |
| Osteoporosis | 18,156 | 43 | 305 | 60 | 12,330 | 66 |
| Osteoporosis/ Fracture | 902 | 2 | 9 | 2 | 577 | 3 |
| Cumulative corticosteroid use | | | | | | |
| < 90 days | 40,925 | 97 | 427 | 83 | 16,652 | 89 |
| ≥ 90 days | 1,430 | 3 | 85 | 17 | 2,005 | 11 |

## CONCLUSIONS

- In the cancer cohort, there was no evidence to suggest that oral bisphosphonate use was associated with increased risk of ONJ compared with nonuse. Oral bisphosphonate use was likely for concomitant osteoporosis as there were no approved indications in cancer for any oral bisphosphonates during the study period.
- In the cancer cohort, after controlling for age, sex, types of bisphosphonate exposure, and corticosteroid use:
  - Multiple myeloma was associated with an incidence ratio of 4.5 compared with breast cancer.
  - Corticosteroid use for more than 90 days was associated with an incidence ratio of 1.9.
- There are a number of hypotheses about the causes of the increased risk of ONJ among multiple myeloma patients:
  - Changes in bone associated with multiple myeloma
  - Differential ascertainment of ONJ by treating physicians
  - Potential bias by reviewing physicians who also reviewed the medical claims.
- ONJ incidence ratios for IV bisphosphonate use compared with nonuse was comparable with that reported in the literature.[3,5,7] However, published clinical studies have not estimated absolute incidences and frequency measures from them cannot be directly compared with these results.

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## DISCLOSURE

This project was funded by Amgen. One co-author (MA) is an employee of Amgen, and all content was agreed by consensus of co-authors.

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