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The association of race/ethnicity and risk of atypical femur fracture among older women receiving oral bisphosphonate therapy

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ABSTRACT

Purpose: Several epidemiologic studies suggest that compared to white women, Asians have a greater propensity to suffer an atypical femur fracture (AFF) while taking bisphosphonate therapy. This study examines the relative risk of AFF following bisphosphonate initiation for Asian compared to white women.
Methods: Using data from a large integrated northern California healthcare delivery system, we examined diaphyseal femur fracture outcomes among women age ≥ 50 years old who initiated oral bisphosphonate therapy during 2002–2007. An AFF was defined by the 2013 American Society of Bone and Mineral Research Task Force criteria. The risk of radiographically-confirmed AFF was examined for Asian compared to white women, adjusting for differences in bisphosphonate exposure and other potential risk factors.
Results: Among 48,390 women (65.3% white, 17.1% Asian) who newly initiated bisphosphonate therapy and were followed for a median of 7.7 years, 68 women experienced an AFF. The rate of AFF was 18.7 per 100,000 person-years overall and eight-fold higher among Asian compared to white women (64.2 versus 7.6 per 100,000 person-years). Asians were also more likely to have longer bisphosphonate treatment duration compared to whites (median 3.8 versus 2.7 years). The age-adjusted relative hazard for AFF was 8.5 (95% confidence interval 4.9–14.9) comparing Asian to white women, and was only modestly reduced to 6.6 (3.7–11.5) after adjusting for bisphosphonate duration and current use.
Conclusions: Our study confirms marked racial disparity in AFF risk that should be further investigated, particularly the mechanisms accounting for this difference. These findings also underscore the need to further examine the association of bisphosphonate duration and AFF in women of Asian race, as well as differential risk across Asian subgroups. In the interim, counseling of Asian women about osteoporosis drug continuation should include consideration of their potentially higher AFF risk.

1. Introduction

The occurrence of low energy femoral diaphysis fractures among long-term bisphosphonate (BP) users is now well defined [1] and recognized world-wide [1–5]. While the precise mechanism by which chronic BP exposure increases the risk of atypical femur fracture (AFF) is not fully understood, a current hypothesis involves changes in cortical bone material properties caused by prolonged suppression of bone remodeling and impairment of micro-crack repair, with development of stress fractures that can progress to completed fracture [6]. Both treatment duration [2–4] and recent BP exposure [3] appear strongly related to AFF risk. However, the overall rare occurrence of AFF events among the vast numbers of women receiving oral BP drugs each year indicates there may be additional contributing factors.

Some of the larger AFF case series have come from Asian countries, including Singapore [7], Korea [8] and Japan [9]. In several U.S. epidemiologic studies, Asians were overrepresented and contributed 17–50% of identified AFF cases [2,10,11], compared to a much lower proportion of Asians among women with proximal femur or non-atypical diaphyseal femur fracture (2–5%) or those receiving BPs without fracture [10,11]. Recent data from northern California were notable for an increase in

Abbreviations: BP, Bisphosphonate; AFF, Atypical femur fracture; KPNC, Kaiser Permanente Northern California; ICD-9, International Classification of Diseases, Ninth Revision.

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diaphyseal femur fracture rates, greatest among Asian women, many of whom received recent BP therapy [12]. These findings suggest there are important racial/ethnic disparities in BP-related AFF, although the extent to which they reflect differences in drug exposure or comorbidity is unknown.

In the present study, we examined the relative risk of AFF for Asian women compared to women of white race following initiation of BP therapy and explored potential factors contributing to this disparity. We hypothesized that Asian women have a substantially higher risk of AFF, independent of age, comorbidity, duration and recency of BP exposure.

2. Methods

2.1. Study population

The source population included female members age ≥ 50 years within Kaiser Permanente Northern California (KPNC), a large, integrated healthcare delivery system serving >3 million members. Using pharmacy databases, we identified women who initiated oral BP therapy with alendronate, risedronate or ibandronate during 1/1/2002–12/31/2007. Women without health plan membership one year prior and at least 3 years following BP initiation and those receiving intravenous BP prior to or during the study observation period were excluded. Women were followed through 12/31/12 or until death or membership termination. The study was approved by the KPNC Institutional Review Board and the requirement for informed consent was waived due to the nature of the study.

2.2. Atypical femur fracture (AFF) classification

As previously described [12], diaphyseal femur fractures were initially identified from principal hospital discharge diagnoses (International Classification of Diseases, Ninth Revision, ICD-9 codes) for closed fractures of the femoral subtrochanter (820.22) and shaft (821.0×), excluding open fractures (820.32, 821.1×) and those associated with high energy trauma (secondary ICD-9 diagnoses E800-848). Radiologic images of identified fractures were reviewed for anatomic classification, with subtrochanteric fracture defined by location within 5 cm below the lower border of the lesser trochanter and femoral shaft fracture defined by location distal to 5 cm below the lesser trochanter and up to but not including the distal metaphyseal flare [12]. Hip, distal femur and peri-prosthetic fractures, when identified, were reclassified. Previously we found that a large number of femoral shaft-coded fractures were periprosthetic and the majority of subtrochanteric-coded fractures localized to the proximal femur [12].

Diaphyseal fracture pattern was classified as atypical (AFF) or non-atypical (non-AFF) based on the 2013 American Society for Bone and Mineral Research task force criteria [1], requiring a low-energy, primarily transverse fracture (with or without medial spike or oblique progression), focal periosteal or endosteal thickening of the lateral cortex at the fracture site and minimal or no evidence of comminution. For these analyses, incident AFF cases occurring after BP initiation were counted as study events, regardless of BP duration or ongoing therapy. Only 16 women experienced a fracture between 2002 and 2004 during which access to radiologic images was limited: 4 were periprosthetic fractures and the remaining 12 included 6 with radiographic images (identifying 5 proximal femur and 1 non-atypical diaphyseal fracture) and 6 without radiographs for fracture classification.

2.3. Patient characteristics

Age and self-reported race-ethnicity were determined using administrative databases with race/ethnicity classified as non-Hispanic white, Asian (including Pacific Islander) and all others, including those of black, Hispanic and other or unknown race/ethnicity. The Asian subgroup also included Asian women identified with Hispanic ethnicity (<0.5% of the total cohort), mostly Filipina women [12]. Prior fracture status was defined by hospitalization or ambulatory diagnoses of fracture after age 40 years involving the spine, trunk, upper or lower extremities (ICD-9 805, 807–815, 817–825, 827–829), excluding open fractures, fractures with spinal cord injury, fractures of the head or fingers/toes and hospitalized fractures associated with high energy trauma (ICD-9 E800-E848). Diabetes mellitus was defined by a prior diabetes diagnosis with pharmacologic treatment (e.g. insulin and oral agents). Rheumatoid arthritis was defined by ≥2 such ambulatory diagnoses. Recent systemic (oral) glucocorticoid exposure was categorized based on a cumulative prednisone-equivalent dose ≥1825 mg received in the prior year (approximating 5 mg/day). We also examined the use of proton pump inhibitors and aromatase inhibitors based on receipt of at least 2 qualifying filled prescriptions within the prior year (over-the-counter use of proton pump inhibitors could not be examined using pharmacy databases).

2.4. Bisphosphonate exposure

Initiation of oral BP therapy was determined by date of the first prescription for alendronate, risedronate or oral ibandronate during 2002–2007 among those without BP in the preceding ≥12 months. A continuous BP treatment interval was calculated based on the days supply dispensed, allowing up to a 60-day gap between the expected prescription end date and the start date of the next prescription/refill. The cumulative BP duration was calculated from the sum of these continuous BP treatment intervals, with prescription/refill gaps >60 days excluded. This estimate was slightly larger than the total treated days (BP years supply) which was calculated excluding all treatment gaps. For analyses in which BP exposure was updated over time after treatment initiation (hereafter referred to as "time-dependent analyses"), ongoing BP exposure was categorized based on examining successive quarters of follow-up (92-day time periods), anchored by the index BP date. For each follow-up quarter, women were considered to have received BP if at least 50% of the follow-up quarter (e.g. 46 of 92 days) was within a BP treatment interval. In sensitivity analyses, time-dependent exposure was also defined requiring at least 80% (e.g. 74 of 92 days) of the follow-up quarter to be covered within a BP treatment interval.

2.5. Statistical analyses

Standard descriptive statistics (Student's t-test for continuous variables and chi-squared or Fisher exact test for categorical variables) were used to compare subgroups by race. Cox proportional hazard analyses were used to examine the association of race and AFF, controlling for putative AFF risk factors. To control for the expected strong risk effects of BP duration and recent exposure, we employed time-dependent analyses that accounted for both current BP exposure and the proportion of prior time periods with BP exposure for each successive quarter of follow-up. Follow-up ended on the censoring date (first qualifying AFF date, death date, end of health plan membership or 12/31/12, whichever came first). Models were also adjusted for age. Other covariates that were examined for adjustment included history of fracture, diabetes mellitus, rheumatoid arthritis, systemic glucocorticoid exposure, aromatase inhibitor and pharmacologic proton pump inhibitor therapy, all assessed at baseline, with a p-value criterion of ≤0.1 required for inclusion in the regression model. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). A p-value criterion of <0.05 was chosen as the threshold for statistical significance.

3. Results

During 2002–2007, 49,658 KPNC female members age ≥ 50 years old initiated oral BP therapy and had ≥3 years of follow-up. Of these, 1268