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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–

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CONFLICT OF INTEREST

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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.

Keywords

Femur Fracture; Subtrochanter; Femoral Shaft; Atypical Fracture; Bisphosphonates

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 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.

METHODS

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.

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 (821.0x), excluding open fractures (820.32, 821.1x) 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 5cm 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 2002–2004 during which access to radiologic images were 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.

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 (excluding over-the-counter use of proton pump inhibitors which could not be examined using pharmacy databases).

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.

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.

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 (2.6%) received intravenous BP and were subsequently excluded. The final study cohort included 48,390 women, mean age 69.5±10.0 years; 65.3% were white, 17.1% Asian and the remaining 17.6% were comprised

of Hispanic (9.5%), black (4.1%) or other/unknown (4.0%) race/ethnicity. Women were followed for a median duration of 7.7 years (interquartile range 5.9–9.3 years), with 88.2% having follow-up at least five years following BP initiation. Table 1 examines the baseline characteristics of women initiating BP and subsequent BP exposure by race/ethnicity. Compared to whites, Asians were more likely to be <65 years old and have diabetes mellitus, but less likely to have a prior fracture or pharmacologic treatment with glucocorticoids, aromatase inhibitor or proton pump inhibitor drugs at baseline. Almost all women received alendronate (96.6%), with only 0.9% receiving (any) ibandronate and 2.5% receiving risedronate. Most alendronate prescriptions (86.2%) were for a daily dose equivalent of 10 mg/day, while the remainder received alendronate at an equivalent dose of 5–6 mg/day (13.3%) or other dose (0.5%). By race/ethnicity, the proportion of alendronate prescriptions equivalent to 10 mg/day was 85.4%, 90.7%, 87.1% and 87.5% among whites, blacks, Hispanics and Asians, respectively.

There were 290 women with 298 fractures identified by ICD-9 diaphyseal fracture codes (820.22, 821.0x); 102 were classified as confirmed diaphyseal fracture, 183 classified as other fracture (periprosthetic, proximal or distal femur fracture) and 13 not classified due to lack of accessible images and radiologic reports (Figure). Among the 102 incident confirmed diaphyseal fractures (among 97 women), 73 fractures were classified as AFF (68 women) and the remaining 29 fractures were classified as non-AFF. The incidence of AFF among non-Asian women initiating BP therapy was 9.0 per 100,000 person-years of cohort follow-up, whereas among Asians, the incidence was 64.2 per 100,000 person-years (Table 2). Further examination of ethnic origin among the 41 (60.3%) women identified by Asian race demonstrated that the majority were of Chinese (31%) and Filipino (49%) ethnicity. All 68 women experiencing AFF received alendronate, including two who also received ibandronate or risedronate during the study period; 64 (94.1%) received BP therapy within three months prior to AFF and the remainder received their last BP within 4–13 months prior to AFF. The median BP treatment duration prior to AFF was 5.5 years (interquartile range, IQR 4.2–7.0), over a window of 6.3 years (IQR 4.8–8.1). By race/ethnicity, the median treatment duration was 5.7 (IQR 4.2–6.5) for women of white race, 5.4 (IQR 4.4–7.1) for women of Asian race and 5.1 (IQR 2.3–6.5) for all others. Among AFF cases, most (92.9%) alendronate prescriptions had a dose equivalent of 10 mg/day.

In unadjusted analyses, prior fracture, diabetes, rheumatoid arthritis and recent glucocorticoid, aromatase inhibitor and proton pump inhibitor exposure at baseline were not associated with an increased rate of AFF ($p>0.1$). However, as shown in Table 2, race/ethnicity was strongly associated with risk of AFF, with only modest attenuation after adjusting for differences in current or prior BP exposure. In the adjusted analysis, Asian women had more than 6-fold greater hazard of AFF compared to women of white race. These results were unchanged when using a stricter definition of BP exposure, requiring treatment at least 80% of each follow-up quarter to define ongoing therapy (Table 2 footnote).

DISCUSSION

Our analyses, conducted within a large multiethnic cohort of women initiating BP therapy, demonstrate that Asians are at substantially higher risk of AFF when compared to women of white race. This association was not substantially modified by putative clinical risk factors and remained after adjusting for differences in BP exposure. Dell and colleagues examined 2007–2011 data from Kaiser Permanente Southern California and identified 142 (137 women) AFF cases, where 49% were Asian [2]. This proportion exceeds the overall percentage of Asians reported in California (13–15%), including counties located in Southern California where Asians contributed <25% of the county population for the 2010 U.S. Census [13]. Our prior study in Kaiser Permanente Northern California (where Asians were estimated to contribute ~12% of older female health plan members), similarly found that Asians accounted for half of AFF cases [10]. Marciano et al. [11] examined data from a New York City academic treatment center and found that among women receiving 3 years BP therapy, those sustaining an AFF were several-fold more likely to be Asian (18% vs 4%). Consistent with these findings, Asian race is an increasingly recognized risk factor for AFF [14].

There may be several reasons that Asians are at higher risk for an atypical fracture of the femoral shaft. First, Asians are known to have unique femur geometry compared to women of white race. Both in the U.S. [15] and Asia [16], femur geometry has been suggested as a factor in the risk of both femur stress fractures and completed AFFs. These geometric factors may include smaller bone size, shorter hip axis length, larger femur varus angle and bowing, all contributing to increased tensile stresses on the lateral femur [7, 15–19]. Biomechanical forces affecting both femurs might further explain the predisposition for bilateral symmetric femur pathology in reported cases [10, 16, 18]. Future studies should examine the role of osteometry and potentially relevant nutritional factors (e.g. vitamin D and other metabolic deficiencies that may affect femoral bowing) in the observed disparities by race. In this study, baseline femur imaging was not available for most patients receiving bisphosphonate therapy and radiographs prior to complete fracture were not systematically available for AFF cases.

A second contributing factor may relate to BP pharmacology or the delivered BP dose. The standard alendronate dose equivalent (10 mg/day) has been used for treatment of osteoporosis in the United States and several other Asian countries. However, in Japan, a lower 5 mg/day alendronate dose is approved for osteoporosis treatment [20]. Nonetheless, AFF events have been reported in Japan with an incidence of AFF similar to that of predominantly white populations and BP exposure noted in 90% of affected cases [9]. In our study of 68 cases (60.3% Asian), more than 90% of alendronate prescriptions were at a dose equivalent of 10 mg/day. Whether the high proportions of affected Asians noted in U.S. and California-based studies reflect greater suppression of bone turnover with an alendronate dose equivalent of 10 mg/day is unknown. Unfortunately, no studies have directly compared the pharmacologic effects of alendronate across different race/ethnicities.

A third contributing factor is the possibility that treatment patterns and drug adherence vary by race/ethnicity. In our current analyses, we adjusted for differences in ongoing BP

treatment and the proportion of prior periods with BP exposure, but did not examine race-specific differences in drug adherence and dosing pattern.

Fourth, Asian women were younger than others at treatment initiation. As such, they may have been more active, with femurs susceptible to greater every day mechanical forces. In the face of potentially impaired bone remodeling resulting from BP therapy, these activities could contribute to the initial stress lesions in the lateral femoral cortex that ultimately progress to complete fracture [6, 16, 21]. Although we adjusted for age, we did not have systematic information pertaining to physical activity, body size or stature, and bone mineral density (BMD) for this BP initiation cohort. However, a specific association of AFF and low BMD has not been consistently observed. Since T scores for Asian women are derived from Caucasian reference populations, Asian women with smaller bone size (and hence lower areal BMD) may be more likely than their Caucasian counterparts to receive a BMD-based diagnosis of osteoporosis and treatment, despite lower prevalence of prior fracture.

This study has some additional limitations to consider. First, our study focused on racial disparities in outcome and did not specifically address the risk of AFF associated with continued BP therapy and reduction in risk with BP cessation. Second, while we saw no relationship with diabetes mellitus, rheumatoid arthritis or baseline exposure to glucocorticoids, proton pump inhibitors or aromatase inhibitor therapy, information on over-the-counter use of proton pump inhibitors was lacking and we did not evaluate other putative risk factors such as vitamin D deficiency and other disorders affecting bone metabolism or fracture risk [1]. Third, it is possible that we may have missed a few AFF cases that were miscoded as other fracture types (including pathologic, proximal femur, distal femur or open fractures), although it is unlikely that systematic fracture miscoding occurred differentially by race. Because of the limitations of diagnostic codes prior to 2009, we did not ascertain incomplete AFF cases among women identified only by femur stress fracture (ICD-9 733.97). Finally, we did not have complete data on race/ethnicity and ethnic origin, so the specific risk of AFF among Asian subgroups could not be examined. Chinese and Filipina women represent the two largest Asian subgroups within the state of California [13, 22] and within our KPNC health plan membership. As estimated from the 2011 KPNC senior female membership [23], these two ethnicities account for approximately 70% of KPNC Asians. Although the total number of AFF cases was small, Chinese and Filipina women similarly comprised 80% of the Asian AFF subset.

The strengths of our study include the availability of an extremely large and ethnically diverse population of BP-treated women of whom nearly one-fifth were Asian. Furthermore, centralized tracking of pharmacologic exposures, hospital admissions and radiologic imaging, as well as high rates of observational follow-up within the health plan, enabled comprehensive assessment and adjudication of relevant fracture outcomes. To our knowledge, this is the first study to examine the independent association of Asian race and risk of AFF by following patients longitudinally after BP initiation, adjusting for differences in exposure during follow-up. Our findings support and extend previous observations of greater AFF risk among Asians, based on cross-sectional data among patients with bisphosphonate exposure and diaphyseal fracture [11].

In conclusion, among older women who initiated oral BP therapy, we found a more than 6-fold increase in the relative risk of AFF among Asians compared to white women. This higher risk does not appear attributable to a number of putative risk factors, including timing and duration of drug exposure. Whether this risk differs across Asian subgroups is currently unknown. Future studies should also evaluate racial/ethnic disparities in the pharmacologic effect of BP drugs and the differential risks of AFF associated with BP dosage, adherence, cessation or temporary interruption of long-term therapy. In the interim, counseling and risk-benefit considerations specific to Asian women receiving long-term BP therapy should include consideration of known disparities in osteoporotic fracture risk and the potential for an increased risk of atypical fracture.

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ABBREVIATIONS

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

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HIGHLIGHTS

- Among a large cohort of women initiating bisphosphonate therapy, the rate of atypical femur fracture was 64.2 per 100,000 person years among Asian women compared to 7.6 per 100,000 person years among white women.
- Adjusting for differences in age and bisphosphonate exposure, the relative risk of atypical femur fracture was more than 6-fold higher among Asian compared to white women.
- These findings underscore the need to further examine the association of bisphosphonate duration and atypical femur fracture risk in women of Asian race, as well as differences by Asian subgroup.

Figure.

Identification of diaphyseal and atypical femur fracture (median follow-up time 7.7 years)

ST/FS = subtrochanteric or femoral shaft fracture

AFF = atypical femur fracture

Table 1

Characteristics and subsequent treatment profile of women initiating bisphosphonate (BP) therapy

	OVERALL N = 48390	White N = 31601	Asian N = 8272	All Others N = 8517
Age (mean±SD)	69.5 ± 10.0	70.6 ± 10.2	66.4 ± 8.8 ^{†‡}	68.9 ± 9.6 [†]
Age category			^{†‡}	[†]
50 – 64 years	17079 (35.3%)	10254 (32.5%)	3754 (45.4%)	3071 (36.1%)
65 – 74 years	15744 (32.5%)	9693 (30.7%)	3028 (36.6%)	3023 (35.5%)
75 – 84 years	12455 (25.7%)	9141 (28.9%)	1311 (15.9%)	2003 (23.5%)
85 years	3112 (6.4%)	2513 (8.0%)	179 (2.2%)	420 (4.9%)
Prior fracture	12210 (25.2%)	9188 (29.1%)	1069 (12.9%) ^{†‡}	1953 (22.9%) [†]
Diabetes mellitus	3738 (7.7%)	1785 (5.7%)	839 (10.1%) ^{†‡}	1114 (13.1%) [†]
Rheumatoid arthritis	1718 (3.6%)	1028 (3.3%)	234 (2.8%) ^{†‡}	456 (5.4%) [†]
Glucocorticoid exposure	1685 (3.5%)	1150 (3.6%)	155 (1.9%) ^{†‡}	380 (4.5%) [†]
Aromatase inhibitor exposure	573 (1.2%)	421 (1.3%)	75 (0.9%) [†]	77 (0.9%) [†]
Proton pump inhibitor exposure	4552 (9.4%)	3203 (10.1%)	415 (5.0%) ^{†‡}	934 (11.0%) [†]
<i>BP exposure following Treatment Initiation</i>				
BP duration			^{†‡}	[†]
< 1 year	13895 (28.7%)	9316 (29.5%)	1853 (22.4%)	2726 (32.0%)
1–2.9 years	11130 (23.0%)	7409 (23.5%)	1657 (20.0%)	2064 (24.2%)
3–4.9 years	9731 (20.1%)	6461 (20.5%)	1671 (20.2%)	1599 (18.8%)
5 years	13634 (28.2%)	8415 (26.6%)	3091 (37.4%)	2128 (25.0%)
BP duration, median (IQR)	2.8 (0.8–5.3)	2.7 (0.7–5.2)	3.8 (1.2–6.1) ^{†‡}	2.4 (0.7–5.0) [†]
BP years supply, median (IQR)	2.6 (0.7–4.9)	2.5 (0.7–4.8)	3.5 (1.1–5.6) ^{†‡}	2.1 (0.7–4.5) [†]

column percentages presented

The bisphosphonate (BP) treatment duration was based on the sum of the individual continuous treatment intervals (defined based on less than 60-day gap between completed prescription to the next prescription or refill). The BP years supply was based on the sum of BP days supply covered, not including any treatment gaps.

SD = standard deviation; IQR = interquartile range

[†] p < 0.05 compared to whites;^{†‡} p < 0.05 compared to all others

Table 2
The association of race and risk of incident atypical femur fracture (AFF) in women receiving bisphosphonate (BP) therapy

	Number of women with incident AF	Atypical Femur Fracture Incidence (AFF) per 100,000 person-years of follow-up (95% CI)	Hazard Ratio (HR) and 95% Confidence Interval (CI) for AFF Outcome adjusted for age and BP exposure		
			Age-adjusted	Age-adjusted + current BP*	§ Age-adjusted + current BP* + prior BP*
All BP Initiators	68	18.7 (14.5–23.7)			
White	18	7.6 (4.5–12.0)	Referent	Referent	Referent
Asian	41	64.2 (46.1–87.1)	8.52 (4.86–14.94)	7.01 (3.99–12.31)	6.57 (3.75–11.51)
All others or unknown	9	14.3 (6.5–27.1)	1.93 (0.86–4.29)	1.89 (0.85–4.21)	2.08 (0.93–4.64)

* For each follow-up quarter, women were considered to have current BP exposure if at least 50% of the follow-up quarter was within a BP treatment interval (or if they were currently taking BP on the censor date), allowing up to a 60-day gap between prescription and refills when defining a continuous treatment interval. Prior BP was defined by the proportion of prior time periods meeting criteria for current BP exposure.

§ In sensitivity analyses, results were similar when women were considered to have current BP if at least 80% of the follow-up quarter was within a BP treatment interval as previously defined.