# Long-term oral bisphosphonate use in relation to fracture risk in postmenopausal women with breast cancer: findings from the Women's Health Initiative

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## Abstract

*Objective:* The aim of the study was to examine the association of long-term oral bisphosphonate use, compared with short-term use, with fracture risk among postmenopausal women with breast cancer.

*Methods:* We studied 887 postmenopausal women who were enrolled to the Women's Health Initiative from 1993 to 1998, diagnosed with breast cancer after enrollment, and reported current oral bisphosphonate use of 2 years or more on a medication inventory administered in 2008 to 2009. The outcome of any clinical fracture was ascertained by self-report on an annual study form; a subset of fractures was confirmed with medical records. Women were followed from completion of the medication inventory until 2014. The association between duration of bisphosphonate use reported on the medication inventory and fracture was estimated using multivariate Cox proportional hazards survival models that compared 4 to 7 years and 8 or more years of bisphosphonate use with 2 to 3 years of use.

*Results:* On average, women were 76 years of age and were followed for 3.7 (SD 1.1) years. There were 142 clinical fractures. In the multivariate-adjusted analysis for fracture risk factors, 8 or more years of bisphosphonate use was associated with higher risk of fracture compared with 2 to 3 years of use (hazard ratio, 1.67 [95% CI, 1.06-2.62]). There was no significant association of 4 to 7 years of use with fracture.

*Conclusions:* Bisphosphonate use of 8 or more years was associated with higher risk of any clinical fracture compared with 2 to 3 years of use. Our findings raise concern about potential harm or decreased effectiveness of long-term bisphosphonate use on fracture risk. The findings warrant confirmatory studies.

*Key Words:* Breast cancer – Fracture – Oral bisphosphonate – Postmenopausal.

T he risks of breast cancer and osteoporotic fracture both increase with age.[1-3] One in eight women will be diagnosed with breast cancer in their lifetime,[3] and one in two women will experience an osteoporotic fracture after age 50.[1] Owing to some cancer treatments, women with breast cancer experience osteoporotic fracture at higher rates than women without cancer.[4] An estimated 232,670 new cases of breast cancer occurred in 2014 and 90% of women with

breast cancer survive at least 5 years after diagnosis.[3] Thus, fracture risk management is an important aspect of continuing care for postmenopausal women with breast cancer.[5]

Bisphosphonates, the most commonly prescribed osteoporosis medication, have been shown in randomized clinical trials (RCTs) to increase bone mineral density (BMD) among women with low BMD.[5-8] A Cochrane Collaboration meta-analysis of 11 RCTs of alendronate, the most commonly prescribed bisphosphonate, concluded that 1 to 4 years of therapy may prevent fractures in a subgroup of women with higher fracture risk at commencement of treatment.[9] In 2011, based on findings of harms and lack of evidence for efficacy after review of all RCTs of long-term bisphosphonate use (>3-5 y), the Food and Drug Administration (FDA) recommended that long-term bisphosphonate users be routinely evaluated for the appropriateness of continued therapy.[10-13] The 2011 FDA review included women who had used bisphosphonates for up to 10 years and noted that fracture rates were similar during earlier and later periods of bisphosphonate use.[10] The FDA, however, did not examine differences in fracture risk by duration of bisphosphonate exposure in many subgroups, and called for more research in particular populations at higher risk.[10] Specifically, there is a lack of information about long-term bisphosphonate use in postmenopausal women with breast cancer.[9-11,14]

The relationship of long-term bisphosphonate use with fracture risk requires specific research in the postmenopausal breast cancer population, because many women with breast cancer have used endocrine therapy including tamoxifen, a selective estrogen receptor modulator (SERM), and aromatase inhibitors, both of which affect fracture risk.[4,5,15,16] Tamoxifen prevents breast cancer recurrence by blocking estrogen from binding with estrogen receptors and has an estrogenic effect in bone, leading to lower fracture risk.[17,18] Aromatase inhibitors prevent recurrence by inhibiting the conversion of androgen to estrogen, but also deprive bone of estrogen, which increases fracture risk; however, risk following aromatase inhibitor termination rapidly returns to baseline.[5,19]

To date, the association of long-term bisphosphonate use with fracture has not been studied in this high-risk population.[20] In 2008 to 2009, 21% of 5,689 postmenopausal Women's Health Initiative (WHI) participants with breast cancer reported current use of oral bisphosphonates. Using data from the WHI, we examined the use of long-term compared with short-term bisphosphonate therapy in relationship to fracture among postmenopausal women with breast cancer.

## METHODS

### Study population

The WHI is an ongoing longitudinal research study with primary aims to develop strategies that reduce cardiovascular disease, cancer, and bone fracture occurrence in postmenopausal women who were aged 50 to 79 years at enrollment. In 1993 to 1998, the WHI recruited 68,132 women to participate in RCTs and 93,676 women to participate in an observational study (OS). The RCTs included studies evaluating estrogen alone, estrogen and progestin, dietary modification, and calcium and vitamin D supplementation. The RCTs and OS were conducted between 1993 and 2005.[21] The WHI study design and methods have been described in detail elsewhere.[22-24] Of 150,076 participants who were active at the end of the RCTs and OS, 115,407 consented to participate in the WHI Extension Studies that began in 2005. Breast cancers were initially identified by self-report on an annual health events form and confirmed by physician review of medical records.[24] In 2008 to 2009, the WHI administered a mailed current medication inventory form and a breast health form, which asked about the history of endocrine therapy for breast cancer, to all active WHI participants with a breast cancer diagnosis made after WHI enrollment. A total of 5,689 women completed both forms (see flowchart, Supplemental Digital Content 1, http://links.lww.com/MENO/A175, that presents the timeline for enrollment, active phase of the studies, and collection of the 2008-2009 medication inventory and breast health questionnaires).

In the subset of women who completed both forms and reported current oral bisphosphonate use of 2 years or more, we analyzed the association of longer duration of use (4-7, ≥8 y) with fracture, using shorter duration of use (2-3 y) as the referent group. We included only women who reported at least 2 years of oral bisphosphonate use to limit the analysis to women who persisted in medication use and whom we presume had a clinical indication for oral bisphosphonate use. To compare long-term use with short-term use, we chose 2 to 3 years as the referent group because shorter duration of use has been associated with lower fracture risk and we chose 4 to 7 and 8 or more years of use because longer duration of use may be associated with higher fracture risk.[9,10] We excluded one woman who had used parathyroid hormone, a medication that affects bone metabolism. In addition, we excluded 22 women who had stopped and then resumed bisphosphonate use before the 2008-2009 medication inventory. After exclusions, 887 women were included in the analysis of long-term bisphosphonate use in relation to fracture.

### Exposure ascertainment

Duration of bisphosphonate use was self-reported on the 2008-2009 medication inventory form that instructed participants to record information from the labels of all current medication prescription labels including the drug name, strength, and type (capsule, tablet, etc), and to report the duration of use (<1 mo, 1-12 mo, or number of years).[25]

### Covariates

Covariates were selected a priori based on literature review to include factors that are associated with bisphosphonate use or with the risk of fracture. Participants self-reported age, race, education level, history of fracture after age 54, diabetes mellitus treated with shots or pills, recreational physical activity, general health rating (excellent, very good, good, fair, poor),[26] parental hip fracture, smoking status, alcohol

intake, and rheumatoid arthritis diagnosis. Recreational physical activity was assessed by self-report on a validated study questionnaire[27] and categorized in metabolic equivalent hours per week.[28] Medication use and body mass index (BMI [kg/m$^2$]) were collected at clinical examinations at years 0, 3, 6, and 9 for RCT participants and at years 0 and 3 for OS participants. For OS participants, estrogen use was also collected by self-report annually in years 3 to 9, SERM use was collected at years 6, 7, and 8, and calcitonin use was collected at years 6 and 9 after enrollment. For participants of the estrogen RCTs, estrogen and calcitonin use was collected at annual clinic visits in all study years and SERM use was also collected annually in the years 2005 to 2008. Duration of ever use of aromatase inhibitors and SERMs was collected on the 2008-2009 breast health form. Calcium supplement use was self-reported on study forms annually in 2005 to 2010. Breast cancer diagnoses were confirmed and tumor characteristics (stage, estrogen receptor status, and diagnosis date) were obtained from medical record review. As a surrogate for BMD, we included the predicted risk of hip fracture within 5 years calculated as a risk score from an 11-item fracture risk prediction algorithm developed and validated in the WHI.[29] This analysis used the most recent value collected at or before the medication inventory for all characteristics except for medication use (SERMs, aromatase inhibitors, calcitonin, estrogens, and glucocorticoids), which used all measurements collected at or before the medication inventory.

### Outcome ascertainment

The outcome of interest for this analysis was any clinical fracture. Outcomes were ascertained by self-report on a form and administered annually during all years of follow-up, which asked women to report new fractures and other medical events that occurred since completion of the previous study form.[24] In addition, a subset of fractures was confirmed by review of medical records. As per the WHI protocol, clinical fracture excluded fractures of the finger, toe, jaw, nose, face, skull, rib, sternum, and cervical spine.

### Statistical analysis
#### Descriptive analysis

We described the 887 women included in the fracture analysis grouped by the duration of bisphosphonate use reported on the medication inventory categorized in approximate tertiles (2-3, 4-7, ≥8 y).

#### Statistical analysis of fracture incidence

Participants contributed follow-up time from the date of completing the 2008-2009 medication inventory until the occurrence of fracture, death, loss-to-follow-up, or end of study follow-up in 2013 to 2014, whichever occurred first.[24] We presented the fracture incidence per 1,000 person-years during follow-up. The association between duration of bisphosphonate exposure and fracture was estimated using three multivariate Cox proportional hazards survival models

that compared 4 to 7 and 8 or more years of bisphosphonate use with 2 to 3 years of use (reference group). Model 1 estimated hazard ratios (HRs) adjusted a priori for age and race. Model 2 estimated HRs adjusted a priori for characteristics associated with bisphosphonate use or fracture risk: age, race, BMI, parental hip fracture, smoking status, alcohol intake (≥3 units/d), rheumatoid arthritis, glucocorticoid use (≥3 mo), risk of hip fracture within 5 years calculated by WHI hip fracture risk algorithm, diabetes mellitus treated with pills or shots, recreational physical activity, general health rating, SERM use (ever/never), aromatase inhibitor use (ever/never), stage of cancer, current calcium supplement use, calcitonin use (use within 10 y before medication inventory), and estrogen use (use within 10 y before medication inventory) and stratified by history of fracture after age 54. To develop Model 2, we first tested the model including all the a priori variables with the addition of interaction terms for duration of bisphosphonate use with the use of SERMs, aromatase inhibitors, and calcitonin. The interaction terms were not significant ($P > 0.05$) and, thus, were not included in Model 2. Model 3 was adjusted for the variables that were significantly associated with fracture in Model 2 (history of rheumatoid arthritis and recreational physical activity) and a priori for age, race, stage of cancer, SERM use, and aromatase inhibitor use, and stratified by history of fracture after age 54. Women with missing covariate data were excluded from Cox models including that covariate (n = 27, 3% of women). All statistical tests were two-tailed (α = 0.05) and performed in Stata version 13.

### Additional analyses

We also modeled bisphosphonate use as a continuous variable (1-y increments of use) with results presented as the predicted HR associated with a 5-year increase in duration of bisphosphonate use, equivalent to the interquartile range of duration of bisphosphonate use. To examine fracture risk among women with high fracture risk, we conducted a subgroup analysis of women with a predicted 5-year hip fracture risk of 1.5% or greater (n = 582), calculated using a fracture risk prediction algorithm developed and validated in the WHI.[29]

### RESULTS
#### Descriptive characteristics

Characteristics of all 5,689 women who completed the medication inventory and breast health form are described in a supplemental table (see Table, Supplemental Digital Content 2, http://links.lww.com/MENO/A176). We observed a change over time in endocrine therapy use by WHI participants with breast cancer. Tamoxifen use decreased, whereas aromatase inhibitor use increased between 1993 and 2009; by 7 years before the 2008-2009 breast health form, aromatase inhibitor use surpassed tamoxifen use (see Figure, Supplemental Digital Content 3, http://links.lww.com/MENO/A177, which illustrates the change in medication use).

Among the 887 women in the fracture analysis, 270 (31%) had used bisphosphonates for 2 to 3 years, 323 (36%) for 4 to 7 years, and 294 (33%) for 8 or more years (Table 1). The

average age was 76.4 years (SD 6.4) and did not differ by exposure group. White race was most common among women who had used bisphosphonates for 4 to 7 years and least common among women who had used bisphosphonates for 2 to 3 years. Among women with 8 or more years of bisphosphonate use, BMI was lower and current smoking and history of aromatase inhibitor use were less common. Other characteristics including history of fracture after age 54 before the medication inventory were similar between groups.

### Fracture outcomes

The average follow-up was 3.7 (SD 1.1) years; follow-up time did not differ across bisphosphonate groups. During all years of follow-up, there were 142 clinical fractures (Table 2). Women with 8 or more years of bisphosphonates use had the highest unadjusted fracture rate (76.6 per 1,000 person-years) and women with 2 to 3 years of use had the lowest (47.4); the rate was intermediate among women with 4 to 7 years of use (51.8). In Model 2 after multivariate adjustment for all a priori variables and in Model 3 after multivariate adjustment for age, race, history of endocrine therapy use, stage of cancer, and variables significantly associated with fracture, 8 or more years of bisphosphonate use was associated with higher risk of any clinical fracture (HR, 1.67 [95% CI, 1.06-2.62] and HR, 1.65 [95% CI, 1.07-2.55]). Bisphosphonate use of 4 to 7 years, compared with 2 to 3 years, was not associated with fracture risk in any multivariate-adjusted model.

In the sensitivity analysis that modeled bisphosphonate exposure as a continuous variable, a 5-year increase in bisphosphonate use was associated with a 29% (95% CI, 1.00-1.66) increase in fracture risk in Model 2 and a 28% (95% CI, 1.00-1.63) increase in Model 3 (Table 3). In the analysis limited to 582 women at high fracture risk as defined by a 5-year hip fracture risk of 1.5% or greater, the HR for fracture associated with 8 or more years of bisphosphonate use, compared with 2 to 3 years, was the same as the HRs for Model 1 and Model 2 in the main analysis, but the confidence intervals were wider due to the smaller sample size (HR, 1.67 [95% CI, 094-2.96] and HR, 1.65 [95% CI, 0.95-2.86]; Table 4).

**TABLE 1.** *Characteristics of 887 postmenopausal bisphosphonate users with breast cancer categorized by years of bisphosphonate use at 2008-2009 medication inventory*

| | Duration of bisphosphonate use | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | 2-3 y (n = 270) | | 4-7 y (n = 323) | | 8+ y (n = 294) | |
| Characteristic | No. (%) | | No. (%) | | No. (%) | |
| Bisphosphonate use, y[a] | 2.5 (0.5) | | 5.2 (1.0) | | 10.3 (1.8) | |
| Age, y[a] | 76.1 (6.3) | | 76.3 (6.4) | | 76.9 (6.4) | |
| White race | 235 | 87.0 | 304 | 94.1 | 266 | 90.5 |
| Education | | | | | | |
| ≤ High school diploma or GED | 32 | 11.9 | 51 | 15.8 | 42 | 14.3 |
| Some education after high school | 96 | 35.6 | 89 | 27.6 | 86 | 29.3 |
| College/postgraduate/professional | 139 | 51.5 | 182 | 56.3 | 163 | 55.4 |
| History of fracture after age 54 y | 107 | 39.6 | 131 | 40.6 | 125 | 42.5 |
| Parent had hip fracture | 52 | 19.3 | 53 | 16.4 | 44 | 15.0 |
| Rheumatoid arthritis | 24 | 8.9 | 29 | 9.0 | 21 | 7.1 |
| Glucocorticoids ≥3 mo | 11 | 4.1 | 7 | 2.2 | 7 | 2.4 |
| Current smoker | 14 | 5.2 | 15 | 4.6 | 3 | 1.0 |
| Alcohol intake ≥3 units/d | 8 | 3.0 | 10 | 3.1 | 5 | 1.7 |
| Body mass index, kg/m$^2$ | 26.7 (4.8) | | 26.5 (4.9) | | 25.4 (4.4) | |
| Diabetes mellitus treated with pills or shots[a] | 19 | 7.0 | 25 | 7.7 | 24 | 8.2 |
| Hip fracture risk score[a,b] | 20.6 (4.4) | | 20.9 (4.2) | | 21.1 (4.2) | |
| Recreational physical activity[a,c] | 13.1 (12.9) | | 13.6 (13.8) | | 13.3 (12.4) | |
| General health rating | | | | | | |
| Fair or poor | 20 | 7.4 | 36 | 11.1 | 24 | 8.2 |
| Good | 110 | 40.7 | 111 | 34.4 | 100 | 34.0 |
| Very good or excellent | 140 | 51.9 | 176 | 54.5 | 170 | 57.8 |
| Stage of cancer | | | | | | |
| 1-In situ | 44 | 16.3 | 45 | 13.9 | 55 | 18.7 |
| 2-Localized | 174 | 64.4 | 206 | 63.8 | 198 | 67.3 |
| 3-Regional | 51 | 18.9 | 71 | 22.0 | 38 | 12.9 |
| 4-Distant | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 |
| Breast cancer tumor estrogen-receptor positive | 199 | 73.7 | 241 | 74.6 | 212 | 72.1 |
| Years from cancer diagnosis to medication inventory[a] | 7.4 (3.4) | | 7.6 (3.3) | | 8.0 (3.4) | |
| Ever-used SERMs | 155 | 57.4 | 188 | 58.2 | 168 | 57.1 |
| Ever-used aromatase inhibitors | 138 | 51.1 | 174 | 53.9 | 119 | 40.5 |
| Current calcium supplement use | 256 | 94.8 | 305 | 94.4 | 277 | 94.2 |
| Estrogen use ≤10 y before medication inventory | 119 | 44.1 | 138 | 42.7 | 125 | 42.5 |
| Calcitonin use ≤10 y before medication inventory | 7 | 2.6 | 11 | 3.4 | 14 | 4.8 |

GED, General Education Development; SERM, selective estrogen-receptor modulator.
[a]Values expressed as mean (SD).
[b]Probability of hip facture within 5 years by score calculated from an 11-item algorithm.
[c]Recreational physical activity categorized in metabolic equivalent hours per week.

**TABLE 2.** *Among 887 postmenopausal bisphosphonate users with breast cancer, fracture incidence, adjusted hazard rate, and 95% CI of fracture by duration of bisphosphonate use at 2008-2009 medication inventory*

| Duration of bisphosphonate use, y | Women (no.) | Fractures | | Model 1: adjusted for age and race HR (95% CI)[b,c] | Model 2: adjusted for a priori variables HR (95% CI)[b,d] | Model 3: adjusted for age, race, endocrine therapy, and significant variables HR (95% CI)[b,e] |
|---|---|---|---|---|---|---|
| | | No.[a] | Incidence per 1,000 person-years | | | |
| 2-3 | 270 | 36 | 47.4 | 1.00 | 1.00 | 1.00 |
| 4-7 | 232 | 46 | 51.8 | 1.15 (0.74-1.79) | 1.14 (0.72-1.81) | 1.17 (0.75-1.84) |
| 8+ | 294 | 60 | 76.6 | 1.44 (0.95-2.19) | 1.67 (1.06-2.62) | 1.65 (1.07-2.55) |

HR, hazard ratio.
[a]Number of fractures during all follow-up years.
[b]Follow-up period is from completion date of 2008-2009 medication inventory to end of study in 2013 to 2014.
[c]Model 1: Cox proportional hazards model adjusted for age and race.
[d]Model 2: Cox proportional hazards model adjusted for selective estrogen-receptor modulator use, aromatase inhibitor use, stage of cancer, age, race, parental hip fracture, body mass index, current smoking, alcohol intake at least 3 units/d rheumatoid arthritis, glucocorticoid use at least 3 months, risk of hip fracture within 5 years calculated by Women's Health Initiative 11-item fracture risk algorithm, current calcium supplement use, calcitonin use in past 10 years, estrogen use in past 10 years, diabetes mellitus treated with shots or pills, recreational physical activity, and general health rating and stratified by history of fracture after age 54.
[e]Model 3: Cox proportional hazards model adjusted for characteristics that were significantly associated with incident fracture after adjustment for duration of bisphosphonate use (rheumatoid arthritis, recreational physical activity) and a priori adjusted for age, race, history of selective estrogen-receptor modulator use, history of aromatase inhibitor use, and stage of cancer and stratified by history of fracture after age 54.

## DISCUSSION

In our analysis of long-term bisphosphonate use and fracture among postmenopausal women with breast cancer, 8 or more years of bisphosphonate use, compared with 2 to 3 years, was associated with higher risk of clinical fracture after multivariate adjustment for SERM use, aromatase inhibitor use, and other characteristics. In addition, we found an association between additional years of bisphosphonate use and higher fracture risk when we modeled bisphosphonate exposure as a continuous variable in multivariate-adjusted models. When we limited the analysis to women with a high risk of fracture as defined by a 5-year hip fracture risk of 1.5% or greater, the point estimate suggested a higher risk of clinical fracture for women with 8 or more years of bisphosphonate use, compared with 2 to 3 years, but the association was not significant. We found no significant association between 4 to 7 years of bisphosphonate use, compared with 2 to 3 years, and the risk of clinical fracture.

There are few studies of long-term bisphosphonate use compared with short-term use in the general population, and to our review, this is the first study of this type among postmenopausal women with breast cancer.[10,11,30] Mellstrom et al[30] in an open-label 2-year extension of an RCT of risedronate found no association with fracture for 6 to 7 years of bisphosphonate use compared with 1 to 2 years of use among women without breast cancer. Our findings in women with breast cancer for bisphosphonate exposure of less than 8 years are similar to those of Mellstrom et al, but Mellstrom et al did not examine bisphosphonate use beyond 7 years. In a case control study of 14,760 women, Meijer et al[31] found 1 to 2 and 3 to 4 years of bisphosphonate use were associated with lower fracture risk compared with less than 1 year of use, but

**TABLE 3.** *Among 887 postmenopausal bisphosphonate users with breast cancer, fracture incidence, adjusted hazard rate, and 95% CI of fracture associated with a 50-year increase in duration of bisphosphonate use[a]*

| Exposure | Women (no.) | Fractures | | Model 1: adjusted for age and race HR (95% CI)[c,d] | Model 2: adjusted for a priori variables HR (95% CI)[c,e] | Model 3: adjusted for age, race, endocrine therapy, and significant variables HR (95% CI)[c,f] |
|---|---|---|---|---|---|---|
| | | No.[b] | Incidence per 1,000 person-years | | | |
| Bisphosphonate use (5-y increase) | 887 | 142 | 58.4 | 1.21 (0.95-1.53) | 1.29 (1.00-1.66) | 1.28 (1.00-1.63) |

HR, hazard ratio.
[a]Five years is equivalent to the interquartile range.
[b]Number of fractures during all follow-up years.
[c]Follow-up period is from completion date of 2008-2009 medication inventory to end of study in 2013 to 2014.
[d]Model 1: Cox proportional hazards model adjusted for age and race.
[e]Model 2: Cox proportional hazards model adjusted for selective estrogen-receptor modulator use, aromatase inhibitor use, stage of cancer, age, race, parental hip fracture, body mass index, current smoking, alcohol intake of at least 3 units/d rheumatoid arthritis, glucocorticoid use at least 3 months, risk of hip fracture within 5 years calculated by Women's Health Initiative 11-item fracture risk algorithm, current calcium supplement use, calcitonin use in past 10 years, estrogen use in past 10 years, diabetes mellitus treated with shots or pills, recreational physical activity, and general health rating and stratified by history of fracture after age 54.
[f]Model 3: Cox proportional hazards model adjusted for characteristics that were significantly associated with incident fracture after adjustment for duration of bisphosphonate use (rheumatoid arthritis, recreational physical activity) and a priori adjusted for age, race, history of selective estrogen-receptor modulator use, history of aromatase inhibitor use, and stage of cancer and stratified by history of fracture after age 54.

**TABLE 4.** *Among 582 postmenopausal bisphosphonate users with breast cancer and high fracture risk,[a] fracture incidence, adjusted hazard rate, and 95% CI of fracture by duration of bisphosphonate use at 2008-2009 medication inventory*

| Duration of bisphosphonate use, y | Women (no.) | Fractures | | Model 1: adjusted for age and race HR (95% CI)[c,d] | Model 2: adjusted for a priori variables HR (95% CI)[c,e] | Model 3: adjusted for age, race, endocrine therapy, and significant variables HR (95% CI)[c,f] |
|---|---|---|---|---|---|---|
| | | No.[b] | Incidence per 1,000 person-years | | | |
| 2-3 | 171 | 21 | 45.2 | 1.00 | 1.00 | 1.00 |
| 4-7 | 212 | 33 | 56.3 | 1.24 (0.71-2.14) | 1.12 (0.63-1.98) | 1.25 (0.71-2.19) |
| 8+ | 199 | 43 | 81.1 | 1.49 (0.88-2.52) | 1.67 (0.94-2.96) | 1.65 (0.95-2.86) |

HR, hazard ratio.
[a]High risk defined as a 5-year hip fracture risk at least 1.5% using a fracture risk model developed in the Women's Health Initiative.
[b]Number of fractures during all follow-up years.
[c]Follow-up period is from completion date of 2008-2009 medication inventory to end of study in 2013 to 2014.
[d]Model 1: Cox proportional hazards model adjusted for age and race.
[e]Model 2: Cox proportional hazards model adjusted for selective estrogen-receptor modulator use, aromatase inhibitor use, stage of cancer, age, race, parental hip fracture, body mass index, current smoking, alcohol intake at least 3 units/d rheumatoid arthritis, glucocorticoid use at least 3 months, risk of hip fracture within 5 years calculated by Women's Health Initiative 11-item fracture risk algorithm, current calcium supplement use, calcitonin use in past 10 years, estrogen use in past 10 years, diabetes mellitus treated with shots or pills, recreational physical activity, and general health rating and stratified by history of fracture after age 54.
[f]Model 3: Cox proportional hazards model adjusted for characteristics that were significantly associated with incident fracture after adjustment for duration of bisphosphonate use (rheumatoid arthritis, recreational physical activity) and a priori adjusted for age, race, history of selective estrogen receptor modulator use, history of aromatase inhibitor use, and stage of cancer and stratified by history of fracture after age 54.

that 5 to 6 years of use was not associated with lower risk. In a study of 1,835,116 participants over age 45 years, Dell et al[32] found that risk of atypical femur fracture was higher during 8 to 9.9 years of use than during 0.1 to 1.9 years of bisphosphonate use. In contrast, Pazianas et al[33] studied a large database and found persistence of hip fracture protection up to 8 years of bisphosphonate use. Our findings of higher fracture risk during 8 or more years of use suggest the need for more confirmatory studies of long-term bisphosphonate exposure that can account for additional indicators of severity of disease, such as timing of detection of low BMD, and for lower bisphosphonate adherence, which has been associated with more fractures,[34] that may further explain the relationship between long-term bisphosphonate use and fracture risk. In particular, the long-term users may have had earlier onset of severely low BMD.

In the postmenopausal breast cancer population, the relationship of bisphosphonate use with fracture risk is complex because of the use of endocrine therapy to help prevent hormone-receptor positive breast cancer recurrence. Current clinical guidelines for breast cancer treatment recommend aromatase inhibitor or tamoxifen use to prevent the recurrence of hormone-receptor positive cancer.[35,36] Approximately 75% of breast cancers are hormone-receptor positive, and as the US population ages, clinicians will increasingly provide fracture risk management counseling to women with a history of endocrine cancer treatment. Although tamoxifen is beneficial to bone[17,18] and aromatase inhibitors are detrimental to bone,[5,19] our findings suggest that 8 or more years of bisphosphonate use is associated with higher fracture risk or with a decrease in effectiveness irrespective of history of SERM or aromatase inhibitor use. Even though analysis was stratified by prior fracture before the medication inventory and adjusted for history of aromatase inhibitor use, our analysis did not account for whether

aromatase inhibitor use started before or after bisphosphonates or prior fracture.

Beyond the role of bisphosphonates in fracture risk management, continuing care for women with breast cancer must consider the potential for bisphosphonates to prevent cancer recurrence. Zoledronic acid use compared with placebo among women receiving aromatase inhibitors or SERMs was associated with higher disease-free survival in the Austrian Breast and Colorectal Cancer Study Group Trial-12.[37] A 2015 meta-analysis of trials of bisphosphonates with primary outcomes of cancer recurrence and mortality found adjuvant intravenous bisphosphonate use significantly reduced breast cancer recurrence and mortality among postmenopausal women with breast cancer.[38] Clinical decision-making must also consider the elevated risk of osteonecrosis of the jaw, which is higher among women who have received intravenous bisphosphonates at high doses for cancer treatment than among women who have not used bisphosphonates or used bisphosphonates at lower doses.[39,40] The present study findings should not be generalized to intravenous bisphosphonate users or to women with distant stage breast cancer who are more likely to receive intravenous bisphosphonates, rather than oral bisphosphonates.

Our study has limitations. Although only a subset of fractures was confirmed by medical record review, good to excellent correlation between self-reported fracture and medical record review has been reported in the WHI with 78% confirmation for hip fracture, 81% for lower arm/wrist, 51% for clinical spine, and a 76% confirmation when including adjacent fracture sites.[41] Nonetheless, underestimation of true fracture incidence could have attenuated associations and decreased our ability to detect an association. Although medication use was by self-report, a validity study of the 2008-2009 WHI medication inventory found near perfect agreement between self-reported duration of current

medication use and pharmacy records for four chronically used medications, including bisphosphonates.[42] Our study also did not examine intravenous bisphosphonate use, which was not reliably captured in the WHI. Intravenous bisphosphonates are not commonly given together with oral bisphosphonates and this study cannot account for intravenous bisphosphonate use initiated during study follow-up. Study findings cannot account for pathological fractures or progression of the breast cancers. In addition, the study cohort may be healthier than the general population, because participants had survived 7.5 years on average after their cancer diagnosis up to the time of the medication inventory. In the United States over 90% of women diagnosed with breast cancer survive for 5 years or longer.[3] Although the analysis was stratified by prior fracture, it did not adjust for rates of prior fracture. This analysis lacked data on BMD, but incorporated a predicted 5-year hip fracture risk score. There is a significant correlation between the fracture risk score and BMD in the WHI that supports its use to adjust for potential BMD difference among participants.[29,43] Furthermore, the study had limited power to detect small associations.

There are several strengths of this analysis. Age is the strongest predictor of osteoporotic fracture and women in this analysis were 76 years of age on average.[2] The racially and ethnically diverse WHI study population included women with varying durations of bisphosphonate use. In addition, our analyses are adjusted for many characteristics predictive of fracture risk and breast cancer diagnosis was confirmed by medical record review.

## CONCLUSIONS

Among postmenopausal women with breast cancer, after adjustment for history of endocrine therapy and fracture risk factors, longer duration of bisphosphonate use was associated with higher risk of clinical fracture compared with shorter duration. Study findings should be interpreted with caution. Higher fracture risk during long-term use may represent loss of effectiveness over time, lower long-term bisphosphonate adherence, or residual confounding factors. Thus, further study is needed. Pending the results of confirmatory studies, the FDA safety recommendation for periodic reevaluation of long-term bisphosphonate users for the appropriateness of continuing therapy would seem particularly important for this population.

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