Osteoporosis Medication Use and Fracture Risk in the Women's Health Initiative

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2015

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Program Authorized to Offer Degree:

Public Health - Epidemiology

University of Washington

Abstract

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BACKGROUND: Evidence is inconclusive about whether long-term (>3-5 years) bisphosphonate therapy reduces or increases fracture risk. This dissertation examined the association of long-term bisphosphonate use with fracture, using short-term use as the referent group, among older women and postmenopausal women with breast cancer. Additionally, this dissertation, which used self-reported medication data, included a validity study of self-reported medication use.

METHODS: Participants were Women's Health Initiative participants who completed a mailed medication inventory. Fracture outcomes were ascertained by self-report on an annual study form; a subset was confirmed with medical records. The analyses examined hip, wrist/forearm, clinical vertebral, and any clinical fracture among older women (n=5,137) and any clinical fracture among women with breast cancer (n=902). The association between bisphosphonate use and fracture was estimated using multivariate Cox proportional hazards models that compared 3-5, 6-9, and 10 or more years of use with 2 years among older women and

compared 4-7 and 8 or more years of use with 2-3 years among women with breast cancer. Self-reported medication use was compared with pharmacy records for four chronically-used classes of medications (statins, calcium channel blockers, beta blockers, and bisphosphonates) among 223 participants using sensitivity, specificity, and positive predictive value for current medication use and kappa statistic for duration of use (<2, 2, 3, 4, ≥5 years).

RESULTS: Among older women, 10 or more years of bisphosphonate use was associated with increased risk of any clinical fracture compared with 2 years of use (HR: 1.29 [95% CI: 1.06-1.56]). Among women with breast cancer, 8 or more years of bisphosphonate use was associated with increased risk of fracture compared with 2-3 years of use (HR: 1.65 [95% CI: 1.01-2.58]). Compared with pharmacy records, sensitivity, specificity, positive predictive value, and kappa statistic were near perfect for all medication classes, except for bisphosphonates, which had sensitivity and positive predictive value of 80%.

CONCLUSION: The longest duration of bisphosphonate use was associated with increased risk of any clinical fracture compared with short-term use among older women and women with breast cancer. The medication inventory was a highly accurate source of self-reported current medication use for chronically-used medications.

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ACKNOWLEDGEMENTS

This dissertation was completed with the help and support of many people. I would like to thank each of my dissertation committee members for their support and mentorship: Susan Heckbert, Andrea LaCroix, Shirley Beresford, Denise Boudreau, and Charles Kooperberg. Additionally, I would like to thank the faculty steering committee and fellows of the Biobehavioral Cancer Prevention and Control Training Program for providing feedback on early versions of my dissertation proposal and preliminary results. I would also like to acknowledge the WHI for use of WHI data, the WHI staff especially Doris Nodtvedt and her team for their help with participant recruitment, the WHI participants for their time and dedication, and Kelly Ehrlich and Douglas Kane at Group Health Research Institute for their help with pharmacy data retrieval. Lastly, I am grateful for the support of friends and family during this entire process.

This dissertation work was partially supported by the NCI Biobehavioral Cancer Prevention and Control Training Program (R25CA092408) at the University of Washington. The WHI programs is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts, HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C.

Disclosure: The opinions, ideas, and interpretations included in this dissertation are mine alone and do not necessarily represent those of other WHI investigators.

Chapter 1:

Long-term Bisphosphonate Therapy and Fracture Rates in Older Postmenopausal Women: Findings from the Women's Health Initiative

Long-term Bisphosphonate Therapy and Fracture Rates in Older Postmenopausal Women: Findings from the Women's Health Initiative

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Manuscript length: 3,123

Abstract length: 272

ABSTRACT

BACKGROUND: Evidence is inconclusive about whether long-term bisphosphonate therapy (>3-5 years) reduces or increases overall fracture risk. In particular, there is little research on long-term use in women over age 70. Among older women, we studied the association of long-term bisphosphonate use with fracture using shorter duration of use as the referent group.

METHODS: Retrospective cohort of 5,137 postmenopausal women enrolled in the Women's Health Initiative who reported current bisphosphonate use of two years or more on a medication inventory administered in 2008-9. Outcomes (hip, clinical vertebral, and wrist/forearm, and any clinical fracture) were ascertained annually by self-report and a subset of fractures was confirmed with medical records. The association between duration of bisphosphonate use and fracture was estimated using multivariate Cox proportional hazards models that compared 3-5, 6-9, and 10 or more years of bisphosphonate use with two years of use (reference group).

RESULTS: Participants were 81 years of age on average and 97% were over age 70. They were followed for an average of 3.7 (SD: 1.2) years. There were 128 hip fractures, 159 wrist/forearm fractures, 236 clinical vertebral fractures, and a total of 1,318 clinical fractures. In the multivariate-adjusted analysis, 10 or more years of bisphosphonate use was associated with increased risk of any clinical fracture compared with two years of use (HR: 1.29 [95% CI: 1.06-1.56]). There was no significant association of long-term bisphosphonate use with the site-specific fractures studied.

CONCLUSIONS: Among older women, 10 or more years of bisphosphonate use was associated with increased risk of any clinical fracture compared with two years of use. Additional studies are needed to confirm these findings in large population cohorts.

INTRODUCTION

Age is the strongest risk factor for osteoporotic fracture and one in two women will experience an osteoporotic fracture after age 50.[1, 2] Low bone mineral density (BMD) increases risk of osteoporotic fracture and by 2020 an estimated 61 million U.S. adults will be at increased risk of fracture from low BMD.[1] Bisphosphonates, the most commonly prescribed drug class for fracture prevention,[3, 4] increase BMD by inhibiting bone resorption in the bone remodeling process.[3-5] Since the late 1990s, dramatic uptake of bisphosphonates has led to long-term use (> 3-5 years) by diverse populations, but recent studies question the safety of long-term bisphosphonate use.[6-8] In 2011, evidence of harms, including atypical fracture, and a lack of evidence of benefit from long-term bisphosphonate use led to a Food and Drug Administration (FDA) recommendation that patients be routinely evaluated for the appropriateness of continued therapy during long-term bisphosphonate use.[9-13]

A 2011 Cochrane Collaboration review of 11 randomized controlled trials (RCTs) of alendronate, the most commonly used bisphosphonate, concluded that one to four years of therapy may prevent fractures in women with low BMD (T-score < -2.5 SD) or with a vertebral fracture prior to treatment, but that alendronate probably does not prevent non-vertebral fracture in women without these risk factors.[7] Furthermore, several bone biopsy studies suggest that after three years of bisphosphonate therapy, suppression of bone remodeling may damage bone and increase fracture risk.[14-17] A 2011 FDA review of all long-term RCTs of bisphosphonates found inconclusive evidence that continuing bisphosphonate therapy beyond five years reduces fracture risk regardless of initial BMD.[8, 18] The small size of the RCTs prevented the FDA review from examining many subgroups and, in particular, the FDA review included only 334 RCT participants over the age of 70 years who had used bisphosphonates for more than five years.[18] Thus, due to the small number of RCT participants, the FDA has called for more research on long-term bisphosphonate use in specific subgroups.[8]

Research is needed in larger populations of older women to evaluate the association of long-term bisphosphonate therapy with fracture risk among older women. In 2008-9, over 17,000 participants of the Women's Health Initiative (WHI), a longitudinal cohort study of postmenopausal women, reported current bisphosphonate use with a wide range of duration patterns from less than two years to over 10 years. Additionally, the WHI collected information on fractures annually. Thus, we investigated the use of long-term bisphosphonate therapy compared with short-term bisphosphonate therapy in relation to fracture using data from the WHI.

METHODS

Study Population

The WHI is an ongoing longitudinal research study with primary aims to develop strategies that reduce incidence of heart disease, cancer, and bone fracture in postmenopausal women. Between 1993 and 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 a study of estrogen hormone therapy (HT), a study of HT with progestin, a study of dietary modification, and a study of calcium and vitamin D supplementation. The RCTs of HT with and without progestin ended early in 2002 and 2004, respectively, after findings of significant harms; and the other WHI RCTs and the OS ended in 2005.[19] A subset of RCT and OS participants continued participation in the WHI Extension Studies beginning in 2005 (n=115,407). In 2008-9, 97,448 participants completed a current medication inventory, which was administered by mailed questionnaire to all active WHI participants. The WHI study design and methods have been described in detail elsewhere.[20-22]

In the subset of current bisphosphonate users who reported bisphosphonate use for two years or more at the 2008-9 medication inventory, had follow-up data thereafter, and had a 5-year hip fracture risk of 1.5% or greater, we analyzed the association of duration of

bisphosphonate use with fracture. We analyzed the association of longer duration of use (3-5, 6-9, 10+ years) with incident site-specific fracture (hip, wrist/forearm, and clinical vertebral) and with any clinical fracture, using shorter duration of use (2 years) as the referent group. We identified women with a predicted 5-year risk of hip fracture of 1.5% or greater using a risk prediction algorithm developed and validated in the WHI.[23] We excluded women who ever reported use of calcitonin, selective estrogen reuptake modulators, parathyroid hormone, and aromatase inhibitors, medications that affect bone metabolism (n=1,801). We also excluded women who discontinued and resumed bisphosphonate use prior to the medication inventory (n=1,000). Further, we excluded women who used HT within five years before the 2008-9 medication inventory (n=260). After exclusions, there were 5,137 women included in the analysis of duration of bisphosphonate use in relation to fracture.

Exposure Ascertainment

Duration of bisphosphonate use was self-reported on the 2008-9 medication inventory.[24] The mailed medication inventory form instructed participants to gather all current medication prescriptions and to use information from the prescription labels. Participants wrote the drug name, strength, and type (e.g., capsule, inhaler, etc.), and provided the duration of use (< 1 month, 1-12 months, and number of years).

Covariates

Covariates were selected *a priori* based on literature review to include factors that are associated with access to healthcare, the use of bisphosphonates, and the risk of fracture. Participants self-reported age, race, education level, fracture, physical function, general health rating (excellent, very good, good, fair, poor),[25] severe memory impairment (Alzheimer's disease or dementia), recreational physical activity, diabetes mellitus treated with shots or medication, oral corticosteroid use ($\geq$ 3 months), parental hip fracture, Parkinson's disease diagnosis,

alcohol use (> 2 servings/day), smoking status, and rheumatoid arthritis diagnosis. Current medication use and body mass index (BMI [kg/m^2]) were collected at clinical exams at years 0, 3, 6, and 9 for RCT participants and at years 0 and 3 for OS participants. For OS participants, medication use was also collected by self-report in study years 4-8. Cancer diagnosis was self-reported and, then confirmed by medical record review.[22] Physical function score was calculated from the RAND 36-Item Health Survey, with higher numbers indicating better physical function.[26] Recreational physical activity was assessed by self-report on a validated study questionnaire[27] and categorized in metabolic equivalent-hours per week.[28] This analysis used the most recent value collected at or before the 2008-9 medication inventory for all characteristics except for history of medication use. For history of use of medications, we used all measurements collected at or before the 2008-9 medication inventory.

Outcome Ascertainment

Outcomes of interest for this analysis were incident hip, clinical vertebral, and wrist/forearm fracture, and first clinical fracture at any site after the medication inventory. Outcomes were ascertained by self-report on a form administered annually during all years of follow-up, which asked women to report the first lifetime occurrence for site-specific fractures that occurred since completion of the previous form.[22] Thus, a woman could report multiple clinical fractures, but reported only the first fracture for a specific fracture site. The specific date of fracture was collected by self-report for all hip and femur fractures for all participants. For other fractures, the fracture date was recorded as the date of completion of the form. Additionally, the date of hip and femur fractures was adjudicated by medical record review for all participants through 2010 and for all previous HT RCT participant, and all African American and Hispanic participants (20% of participants) after 2010. Per the WHI protocol, site-specific clinical fracture excluded fractures of the finger, toe, jaw, nose, face, skull, rib, sternum, and cervical spine.

Statistical Analysis

Descriptive Analysis

We described the 5,137 bisphosphonate users included in the fracture analysis grouped by duration of use (2, 3-5, 6-9, and 10+ years). Comparison of descriptive statistics between groups was made using ANOVA and the chi-square test.

Statistical Analysis of Fracture Incidence

Participants contributed follow-up time from the date of the 2008-9 medication inventory until the occurrence of fracture, death, loss-to-follow-up, or end of study follow-up in 2013-14.[22] We presented the fracture incidence per 1,000 person-years for each outcome type during the entire follow-up period. Association between duration of bisphosphonate use and fracture was estimated using multivariate Cox proportional hazards survival models that compared 3-5, 6-9, and 10 or more years of bisphosphonate use with two years of use (reference group). There was one model for each site-specific incident fracture outcome type (hip, wrist/forearm, and clinical vertebral fracture) and one model for any clinical fracture. Models for site-specific incident fracture excluded women who reported an incident fracture for that site prior to the start of follow-up. The models were adjusted *a priori* for age, race, education level, BMI, physical function, general health rating, severe memory impairment diagnosis, recreational physical activity, treated diabetes mellitus, oral corticosteroid use, estrogen use within 6-10 years before medication inventory, parental hip fracture, Parkinson's disease diagnosis, smoking status, cancer diagnosis, and rheumatoid arthritis diagnosis. All models were stratified by a history of fracture at any site after age 54 years before the medication inventory. Subjects with missing covariate data were excluded from multivariate models (n=143; 2.8% of subjects). All statistical tests were two-tailed (α=0.05) and performed in Stata version 13.

Additional Analyses

Because some cancers and cancer treatments increase fracture risk,[29] we conducted a sensitivity analyses limited to women with no history of cancer before the medication inventory (n=4,379).[22] To create a more homogeneous study sample, we performed a sensitivity analysis limited to women who reported having had a clinical fracture after age 54 and before the date of the medication inventory (n=2,791). To explore fracture risk in nonusers of bisphosphonates, we conducted an analysis including the 26,813 nonusers of bisphosphonates who otherwise would have met the eligibility criteria for the primary analysis. All additional analyses were adjusted for the same covariates as described for the primary analysis and were stratified by history of fracture, except for the analysis limited to women with a history of fracture.

RESULTS

Descriptive characteristics

Characteristics of all 97,448 women who completed the 2008-9 medication inventory form are described in Supplemental Table 1.1. Among the 5,137 women in the analysis, 655 (13%) had used bisphosphonates for two years, 1,747 (34%) for 3-5 years, 1,034 (20%) for 6-9 years, and 1,701 (33%) for 10 or more years (Table 1.1). For all groups, the average age was approximately 81 years and 97% were over 70 years of age. Having a college degree or higher educational attainment was more common among women with longer duration of bisphosphonate use. On average, BMI was lower and diabetes was less common among women with 6-9 or 10 or more years of bisphosphonate use than among women with 2 or 3-5 years of use. Physical function score, recreational physical activity, and general health were higher among women with 6-9 or 10 or more years of bisphosphonate use than among women with 2 or 3-5 years of use. Estrogen use within the 6-10 years before the 2008-9 medication inventory was least common among women with 10 or more years of bisphosphonate use.

Other characteristics including history of fracture after age 54 did not significantly differ between groups.

Fracture Outcomes

The 5,137 women in the fracture analysis were followed for an average of 3.7 (SD: 1.2) years. During all years of follow-up, there were 128 hip fractures, 159 wrist/forearm fractures, 236 clinical vertebral fractures, and 1,318 clinical fractures (Table 1.2). The unadjusted fracture rate per 1,000 person-years was highest for the 10 or more years of bisphosphonate use group for all fracture outcome types except for clinical vertebral fracture. The two years of bisphosphonate use group had the lowest unadjusted fracture rate for all fracture outcome types except for wrist/forearm fracture.

In the primary multivariate-adjusted survival analysis, 10 or more years of bisphosphonate use was associated with increased risk of any clinical fracture compared with two years of use (HR: 1.29 [95% CI: 1.06-1.56]). Although the associations for 10 or more years were not statistically significant for any site-specific fracture, the hazard ratios were increased for hip and clinical vertebral fracture (HR: 1.67 [95% CI: 0.83-3.37] and HR: 1.62 [0.98-2.68]). There was no significant association of 3-5 years or 6-9 years of bisphosphonate use with fracture outcomes compared with two years of use.

In sensitivity analyses limited to women with no history of cancer and limited to women with a history of fracture after age 54, 10 or more years of bisphosphonate use remained associated with increased risk of any clinical fracture (HR: 1.35 [95% CI: 1.10-1.66]; Table 1.3 and HR: 1.28 [95% CI: 1.00-1.64]; Table 1.4). There were no other significant associations of longer duration of bisphosphonate use with fracture in the sensitivity analyses. In the analysis that included nonusers as an exposure group, nonusers had the lowest unadjusted fracture rate for all fracture outcome types except hip fracture, but nonuse of bisphosphonates was not

significantly associated with any fracture outcome compared with two years of use (Supplemental Table 1.2).

DISCUSSION

In our analysis of long-term bisphosphonate use and fracture, after multivariate adjustment, 10 or more years of bisphosphonate use was associated with higher risk of any clinical fracture compared with two years of use. This association remained significant in sensitivity analyses limited to women without a history of cancer and limited to women with a history of fracture after age 54 before the medication inventory. We could not detect a significant association of 10 or more years of bisphosphonate use with the risk of site-specific fractures, but the point estimates for the risks were increased by 60-70% for incident hip and clinical vertebral fracture suggesting the possibility of an elevated risk. We found no association between 3-5 or 6-9 years of bisphosphonate use and any fracture outcome, compared with two years of use.

Our findings add to a body of research that has raised questions about the benefit of long-term bisphosphonate use. All bisphosphonates suppress bone remodeling and bone biopsy studies suggest that extended bone remodeling suppression ($\geq$ 3 years) is associated with deterioration of the bone microarchitecture including decreased bone micro-hardness and microscopic cracks in bone that may increase susceptibility to fracture.[14-17] The FDA and the American Society for Bone and Mineral Research have concluded that long-term bisphosphonate use increases risk of atypical femoral fractures.[6,30-32] Furthermore, an FDA review of all long-term RCTs of bisphosphonates found inconclusive evidence that long-term bisphosphonate use decreases overall fracture risk compared to placebo.[6] Thus, in 2011, the FDA recommended that bisphosphonate users be routinely evaluated for symptoms of atypical fracture and for the appropriateness of continued bisphosphonate therapy, particularly during treatment beyond five years. [6]

To date, there are few studies of fracture that compare longer duration of bisphosphonate use with shorter duration of use among older women. Ours is the first to examine 10 or more years of bisphosphonate use compared with short-term use in a multivariate-adjusted analysis. In an open-label 2-year extension of a 5-year RCT of risedronate among 164 women aged 69 years on average, Mellstrom et al. compared 6-7 years of bisphosphonate use with 1-2 years of use and found no association between duration of bisphosphonate use and fracture risk.[33] Our findings for bisphosphonate use less than 10 years were similar to those of Mellstrom et al. The 2011 FDA review of all RCTs of long-term bisphosphonate use also noted that the proportion of older women who experienced a fracture was similar during earlier (0-3) and later (4-5, 6-9, 10+) years of bisphosphonate use among 1,626 women over age 70.[6] Our overall findings from a much larger cohort differ from the FDA findings for women with 10 or more years of use. However, the longer duration of use category in the FDA comparison of fractures by duration of exposure was 10-11 years, while the category of longest duration of use in our study was 10-15 years. Additionally, the older age and greater racial and ethnic diversity of our larger cohort may have revealed potential harms that could not be identified in a smaller less diverse group of older women.

Even though our study included 1,701 women with 10 or more years of bisphosphonate use and adjusted for participant characteristics, our findings should be interpreted with caution due to potential limitations of our analysis. Specifically, women with 10 or more years of bisphosphonate use may have been at increased risk of fracture from characteristics, such as low BMD at initiation of treatment, that our analysis did not account for. However, the FDA review found that BMD at initiation of treatment was not associated with fracture outcomes during long-term bisphosphonate use.[6]

Our finding that the risk of hip and vertebral fracture appeared to be elevated while the risk of wrist/forearm fracture was not elevated warrants more investigation. Differences in risk by fracture site could be explained by the unique etiology of site-specific incident fracture. Incident

wrist/forearm fracture, for instance, occurs at an earlier age on average than hip or clinical vertebral fracture.[34] Our analysis only examined incident site-specific fracture; before the start of follow-up, a greater percentage of women in this analysis had had an incident wrist/forearm fracture than had had a hip or clinical vertebral fracture. Thus, more women were excluded from the site-specific analysis for wrist/forearm fracture.

There are several additional limitations to this study. Only a subset of fractures was confirmed by medical record review, the study lacked information on subclinical morphometric vertebral fractures, and medication use data was self-reported. However, a validity study of self-reported fracture found good to excellent validity of self-reported fracture in the WHI,[35] and a validity study of the 2008-9 medication inventory found near perfect agreement of self-reported medication use with pharmacy records for four chronically used medications, including bisphosphonates.[36] Additionally, our study lacked information about adherence to bisphosphonates during the follow-up period and did not account for dosage or frequency of bisphosphonate use.

There are several strengths of this analysis. The large population based sample included older long-term bisphosphonate users with an average age of 81 years. Whereas the 2011 FDA review included information on only 334 women over the age of 70 who had used bisphosphonates for over five years, our study included 2,644 older women who had used bisphosphonates for over five years.[6] Our study also included more women with 10 or more years of bisphosphonate use than any previous study. Additionally, the WHI collected information on numerous factors, which allowed statistical adjustment for many participant characteristics that are predictive of fracture risk. Although this was an observational study, participant characteristics were very similar for each exposure group.

CONCLUSIONS

Among older women, 10 or more years of bisphosphonate use was associated with increased risk of any clinical fracture compared with two years of use, but duration of bisphosphonate use was not significantly associated with increased site-specific fracture. Our study was limited by a lack of information about BMD and bisphosphonate adherence. Thus, the findings should be interpreted with caution and confirmatory studies should be conducted in large population samples with information on BMD and medication adherence.

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Table 1.1: Characteristics of 5,137 post-menopausal women with ≥ 1.5% 5-year hip fracture risk categorized by duration of bisphosphonate use at 2008-9 medication inventory

Characteristic	Years of Bisphosphonate Use at 2008-9 Medication Inventory								*P-Value*
	2 Y (n=655)		3-5 Y (n=1,747)		6-9 Y (n=1,034)		10+ Y (n=1,701)		
	No. % or Mean ± SD								
Bisphosphonate use (y)	2.0 ± 0		4.1 ± 0.9		7.3 ± 1.0		11.1 ± 1.4		
Age (y)	81.2 ± 4.5		81.2 ± 4.4		81.1 ± 4.5		81.1 ± 4.4		0.08
Age > 70 years	629	*96.0*	1,687	*96.6*	1,000	*96.7*	1,644	*96.6*	0.06
White/Caucasian	607	*92.7*	1,639	*93.8*	986	*95.4*	1,609	*94.6*	0.11
Education									0.01
< High school diploma/GED	24	*3.7*	51	*2.9*	21	*2.0*	36	*2.1*	
High school diploma/GED	110	*16.8*	300	*17.2*	164	*15.9*	263	*15.5*	
School after high school	244	*37.3*	630	*36.1*	357	*34.5*	555	*32.6*	
College degree or higher	273	*41.7*	762	*43.6*	488	*47.2*	838	*49.3*	
Prior fracture after age 54 years	353	*53.9*	947	*54.2*	545	*52.7*	946	*55.6*	0.52
Parental hip fracture	108	*16.5*	312	*17.9*	211	*20.4*	330	*19.4*	0.17
Rheumatoid arthritis diagnosis	54	*8.2*	142	*8.1*	84	*8.1*	129	*7.6*	0.82
Corticosteroid use ≥ 3 months	30	*4.6*	73	*4.2*	53	*5.1*	73	*4.3*	0.67
Alcohol > 2 servings/day	21	*3.2*	45	*2.6*	30	*2.9*	46	*2.7*	0.86
Current smoker	32	*4.9*	83	*4.8*	45	*4.4*	61	*3.6*	0.31
BMI (kg/m^2)	26.7 ± 4.9		26.1 ± 5.0		25.3 ± 4.5		25.2 ± 4.5		<0.01
Physical function score	67.1 ± 26.3		70 ± 25.2		72.6 ± 23.7		71.8 ± 23.8		<0.01
Recreational physical activity[a]	12.0 ± 13.6		12.6 ± 12.3		14.0 ± 13.8		13.5 ± 13.2		0.03
General health rating:									<0.01
Fair or poor	89	*13.6*	189	*10.8*	90	*8.7*	144	*8.5*	
Good	262	*40.0*	735	*42.1*	374	*36.2*	622	*36.6*	
Very good or excellent	304	*46.4*	823	*47.1*	570	*55.1*	935	*55.0*	
Treated diabetes mellitus	76	*11.6*	163	*9.3*	83	*8.0*	132	*7.8*	0.02
Severe memory impairment	17	*2.6*	53	*3.0*	16	*1.5*	36	*2.1*	0.07
Estrogen used 6-10 y before	332	*50.7*	874	*50.0*	512	*49.5*	757	*44.5*	<0.01
Cancer diagnosis	97	*14.8*	258	*14.8*	143	*13.8*	260	*15.3*	0.78
Parkinson's disease diagnosis	4	*0.6*	18	*1.0*	11	*1.1*	16	*0.9*	0.79

[a]Recreational physical activity was categorized in metabolic equivalent-hours per week.

Table 1.2: Among 5,137 postmenopausal women with a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio (HR), and 95% confidence interval (CI) of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[b]
		Hip Fracture		
2 y	618	11	6.4	1.00
3-5 y	1,671	38	8.0	1.11 (0.54-2.28)
6-9 y	990	21	7.3	1.33 (0.61-2.93)
10+ y	1,648	58	12.2	1.67 (0.83-3.37)
		Wrist/Forearm Fracture		
2 y	512	20	14.2	1.00
3-5 y	1,375	53	13.9	0.99 (0.57-1.72)
6-9 y	789	29	12.8	0.99 (0.55-1.79)
10+ y	1,280	57	15.6	1.19 (0.69-2.06)
		Clinical Vertebral Fracture		
2 y	599	22	13.2	1.00
3-5 y	1,622	77	17.0	1.21 (0.73-2.02)
6-9 y	980	53	18.7	1.34 (0.79-2.29)
10+ y	1,571	84	18.7	1.62 (0.98-2.68)
		Any Clinical Fracture		
2 y	655	145	86.8	1.00
3-5 y	1,747	419	92.0	1.03 (0.85-1.25)
6-9 y	1,034	255	92.0	1.04 (0.85-1.29)
10+ y	1,701	499	112.2	1.29 (1.06-1.56)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of medication inventory to end of study in 2013-14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, oral corticosteroid use ≥ 3 months, estrogen use during 6-10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol > 2 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis and stratified by history of fracture after age 54.

Table 1.3: Among 4,379 postmenopausal women with no history of cancer and a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio (HR), and 95% confidence interval (CI) of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[b]
		Hip Fracture		
2 y	527	9	6.1	1.00
3-5 y	1,425	30	7.4	1.23 (0.54-2.80)
6-9 y	851	19	7.7	1.59 (0.66-3.79)
10+ y	1,398	50	12.3	1.98 (0.90-4.35)
		Wrist/Forearm Fracture		
2 y	438	16	13.3	1.00
3-5 y	1,171	46	14.0	1.02 (0.55-1.89)
6-9 y	681	25	12.8	1.14 (0.59-2.21)
10+ y	1,092	49	15.6	1.30 (0.70-2.40)
		Clinical Vertebral Fracture		
2 y	513	19	13.3	1.00
3-5 y	1,376	61	15.7	1.24 (0.70-2.19)
6-9 y	847	44	17.9	1.49 (0.83-2.68)
10+ y	1,336	65	16.9	1.64 (0.94-2.86)
		Any Clinical Fracture		
2 y	558	123	86.0	1.00
3-5 y	1,489	351	89.2	1.07 (0.87-1.33)
6-9 y	222	222	93.1	1.12 (0.89-1.40)
10+ y	416	416	110.0	1.35 (1.10-1.66)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of medication inventory to end of study in 2013-14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, oral corticosteroid use ≥ 3 months, estrogen use during 6-10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol > 2 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis and stratified by history of fracture after age 54.

Table 1.4: Among 2,791 postmenopausal women with a history of fracture after age 54 before the 2008-9 medication inventory and a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio (HR), and 95% confidence interval (CI) of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[b]
		Hip Fracture		
2 y	316	8	9.0	1.00
3-5 y	871	23	9.4	0.63 (0.27-1.49)
6-9 y	501	12	8.1	0.70 (0.27-1.78)
10+ y	893	32	12.4	0.88 (0.39-2.01)
		Wrist/Forearm Fracture		
2 y	224	14	22.9	1.00
3-5 y	624	26	15.5	0.74 (0.36-1.54)
6-9 y	343	14	14.2	0.74 (0.34-1.63)
10+ y	575	32	19.6	1.02 (0.51-2.05)
		Clinical Vertebral Fracture		
2 y	297	14	16.8	1.00
3-5 y	822	50	22.1	1.18 (0.61-2.26)
6-9 y	491	35	24.7	1.53 (0.78-3.01)
10+ y	816	47	20.3	1.41 (0.73-2.70)
		Any Clinical Fracture		
2 y	353	87	86.8	1.00
3-5 y	947	256	92.0	1.09 (0.85-1.41)
6-9 y	545	156	92.0	1.11 (0.85-1.46)
10+ y	946	300	112.2	1.28 (1.00-1.64)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of medication inventory to end of study in 2013-14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, oral corticosteroid use ≥ 3 months, estrogen use during 6-10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol > 2 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis.

Supplemental Table 1.1: Characteristics of 97,448 postmenopausal women categorized by bisphosphonate use at 2008-9 medication inventory and by 5-year hip fracture risk

	5-y Hip Fracture Risk < 1.5% (n=43,854)				5-y Hip Fracture Risk ≥ 1.5% (n=53,594)			
	Current Bisphosphonate Use				Current Bisphosphonate Use			
	Nonuser (n=37,633)		User (n=6,221)		Nonuser (n=42,730)		User (n=10,864)	
Characteristic	No. % or Mean ± SD				No. % or Mean ± SD			
Age (y)	70.1 ± 3.9		70.0 ± 3.8		79.7 ± 5.1		79.6 ± 5.0	
Age > 70 years	17,946	*47.7*	2,892	*46.5*	41,538	*97.2*	10,556	*97.2*
White/Caucasian	29,735	*79.0*	4,933	*79.3*	40,131	*93.9*	10,245	*94.3*
Education								
< High school diploma/GED	1,084	*2.9*	126	*2.0*	1,587	*3.7*	266	*2.4*
High school diploma/GED	5,139	*13.7*	777	*12.5*	7,667	*17.9*	1,793	*16.5*
School after high school	13,655	*36.3*	2,005	*32.2*	16,162	*37.8*	3,711	*34.2*
College degree or higher	17,454	*46.4*	3,274	*52.6*	17,062	*39.9*	5,043	*46.4*
Prior fracture after age 54 y	6,421	*17.1*	1,388	*22.3*	19,867	*46.5*	6,013	*55.3*
Parental hip fracture	3,035	*8.1*	637	*10.2*	6,988	*16.4*	2,056	*18.9*
Rheumatoid arthritis	3,044	*8.1*	431	*6.9*	3,950	*9.2*	938	*8.6*
Corticosteroid use ≥ 3 months	203	*0.5*	49	*0.8*	1,453	*3.4*	484	*4.5*
Current smoker	833	*2.2*	118	*1.9*	2,109	*4.9*	432	*4.0*
Alcohol > 2 servings/day	1,039	*2.8*	171	*2.7*	1,150	*2.7*	268	*2.5*
BMI (kg/m^2)	29.3 ± 6.2		26.7 ± 5.4		27.5 ± 5.4		25.7 ± 4.8	
Physical function score	81.2 ± 20.8		84.7 ± 18.4		65.9 ± 26.8		69.7 ± 25.2	
Recreational physical activity[a]	15.2 ± 14.9		16.5 ± 15.3		12.2 ± 13.5		13.2 ± 13.5	
General health rating:								
Fair or poor	1,360	*3.6*	142	*2.3*	6,541	*15.3*	1,232	*11.3*
Good	11,009	*29.3*	1,518	*24.4*	17,698	*41.4*	4,318	*39.7*
Very good or excellent	25,207	*67.0*	4,546	*73.1*	18,451	*43.2*	5,309	*48.9*
Treated diabetes mellitus	3,188	*8.5*	295	*4.7*	3,188	*7.5*	295	*2.7*
Severe memory impairment	485	*1.3*	67	*1.1*	1,740	*4.1*	363	*3.3*
Parkinson's disease	279	*0.7*	50	*0.8*	451	*1.1*	116	*1.1*
Cancer diagnosis	5,846	*15.5*	1,036	*16.7*	8,022	*18.8*	2,070	*19.1*
Ever used bisphosphonates	3,988	*10.6*	6,221	*100*	8,436	*19.7*	10,864	*100*
Ever used SERMs	3,766	*10.0*	938	*15.1*	4,938	*11.6*	1,606	*14.8*
Ever used calcitonin	514	*1.4*	238	*3.8*	1,641	*3.8*	624	*5.7*
Ever used estrogens	28,279	*75.1*	4,841	*77.8*	18,588	*43.5*	7,332	*67.5*

[a]Recreational physical activity was categorized in metabolic equivalent-hours per week.

Supplemental Table 1.2: Among 31,953 postmenopausal women, including nonusers of bisphosphonates, with a 5-year risk of hip fracture ≥ 1.5%, fracture incidence, hazard ratio (HR), and 95% confidence interval (CI) of hip, clinical vertebral, wrist/forearm, and any clinical fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[b]
		Hip Fracture		
2 y	618	11	6.4	1.00
3-5 y	1,671	38	8.0	1.23 (0.62-2.42)
6-9 y	990	21	7.3	1.32 (0.63-2.76)
10+ y	1,648	58	12.2	1.76 (0.92-3.38)
Nonuser	26,136	563	7.8	1.27 (0.70-2.32)
		Wrist/Forearm Fracture		
2 y	512	20	14.2	1.00
3-5 y	1,375	53	13.9	0.88 (0.52-1.49)
6-9 y	789	29	12.8	0.79 (0.44-1.42)
10+ y	1,280	57	15.6	1.00 (0.59-1.70)
Nonuser	22,383	573	9.4	0.66 (0.42-1.04)
		Clinical Vertebral Fracture		
2 y	599	22	13.2	1.00
3-5 y	1,622	77	17.0	1.03 (0.63-1.71)
6-9 y	980	53	18.7	1.11 (0.66-1.87)
10+ y	1,571	84	18.7	1.37 (0.84-2.25)
Nonuser	25,877	716	10.1	0.84 (0.53-1.31)
		Any Clinical Fracture		
2 y	655	145	86.8	1.00
3-5 y	1,747	419	92.0	1.00 (0.83-1.22)
6-9 y	1,034	255	92.0	1.01 (0.82-1.24)
10+ y	1,701	499	112.2	1.23 (1.02-1.48)
Nonuser	26,816	5,018	72.7	0.86 (0.73-1.02)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of medication inventory to end of study in 2013-14. Estimates are from Cox proportional hazards models adjusted for age, race, education level, BMI, physical function score, general health rating, recreational physical activity, treated diabetes mellitus, severe memory impairment, oral corticosteroid use ≥ 3 months, estrogen use during 6-10 years prior to medication inventory, parental hip fracture, smoking status, Parkinson's disease diagnosis, alcohol > 2 servings/day, rheumatoid arthritis diagnosis, and cancer diagnosis and stratified by history of fracture after age 54.

Chapter 2:

Long-term Bisphosphonate Use in Relation to Fracture Risk in Postmenopausal Women with Breast Cancer

Long-term Bisphosphonate Use in Relation to Fracture Risk in Postmenopausal Women with Breast Cancer

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Manuscript length: 3,020

Abstract length: 272

ABSTRACT

BACKGROUND: Evidence is inconclusive about whether long-term bisphosphonate therapy (>3-5 years) reduces or increases overall fracture risk. Further, there is little research on this topic among postmenopausal women with breast cancer, who may be at increased fracture risk because of their cancer and its treatment. We studied the association of long-term bisphosphonate use with fracture, compared with short-term use, among postmenopausal women with breast cancer.

METHODS: This analysis included 902 postmenopausal women with breast cancer enrolled in the Women's Health Initiative who reported current bisphosphonate use of two years duration or more on a medication inventory administered in 2008-9. The outcome of any clinical fracture was ascertained by self-report on an annual study form and a subset of fractures was adjudicated by medical record review. The association between duration of bisphosphonate use and fracture was estimated using multivariate Cox proportional hazards survival models that compared 4-7 years and eight or more years of bisphosphonate use with 2-3 years of use (reference group).

RESULTS: Women were 76 years of age on average and were followed for an average of 3.7 (SD: 1.1) years. There were 144 clinical fractures. In multivariate-adjusted analysis, eight or more years of bisphosphonate use was associated with increased risk of fracture compared with 2-3 years of use (HR: 1.65 [1.06-2.58]). There was no significant association of 4-7 years of bisphosphonate use with fracture.

CONCLUSIONS: Bisphosphonate use of eight or more years was associated with increased risk of any clinical fracture compared with 2-3 years of use. Our findings raise concern about the

safety of long-term bisphosphonate use and warrant confirmatory studies in large population-based cohorts with additional clinical data.

INTRODUCTION

The risks of breast cancer and osteoporotic fracture both increase with older 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] Due 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 alone, and 90% of women with breast cancer survive at least five 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, increase bone mineral density (BMD) by inhibiting bone resorption in the bone remodeling process.[5-9] A Cochrane Collaboration meta-analysis of 11 randomized clinical trials (RCTs) of alendronate, the most commonly prescribed bisphosphonate, concluded that 1-4 years of therapy may prevent fractures in women with low BMD (T-score < -2.5 SD) or with a vertebral fracture at commencement of treatment, but that alendronate probably does not prevent non-vertebral fracture in women with BMD closer to normal or without a prior vertebral fracture.[10] A Food and Drug Administration (FDA) meta-analysis of all RCTs of long-term bisphosphonate use (> 3-5 years) found inconclusive evidence that long-term bisphosphonate use reduces or increases fracture risk in women with low or closer to normal BMD.[11] Additionally, evidence of harms from bisphosphonate use led to an FDA recommendation in 2011, that long-term bisphosphonate users be routinely evaluated for the appropriateness of continued therapy.[11-14] The small sample sizes in the available data prevented the FDA from examining many subgroups, and the FDA called for more research to study long-term bisphosphonate use in populations with unique fracture risk.[11] Specifically, there is a lack of information about long-term bisphosphonate use in postmenopausal women with breast cancer.[10-12,15]

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 selective estrogen reuptake modulators (SERMs) and aromatase inhibitors, both of which affect fracture risk.[4,5,16,17] SERMs prevent breast cancer recurrence by blocking estrogen from binding with estrogen receptors and SERMs have an estrogenic effect in bone, leading to lower fracture risk.[18,19] Aromatase inhibitors prevent recurrence of hormone-receptor positive breast cancers by inhibiting the conversion of androgen to estrogen, but also deprive bone of estrogen, which increases fracture risk.[5,20]

To date, the association of long-term bisphosphonate use with fracture has not been studied in this high-risk population.[21] In 2008-9, 21% of 5,689 postmenopausal Women's Health Initiative (WHI) participants with breast cancer reported current use of bisphosphonates. The WHI collected fracture data annually before and after the medication inventory. 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. 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 a study of hormone therapy (HT) with estrogen, a study of HT with estrogen and progestin, a study of dietary modification, and a study of calcium and vitamin D supplementation. The RCTs of HT with progestin and without progestin ended early in 2002 and 2004, respectively, after findings of significant harms; and the other WHI RCTs and the OS ended in 2005.[22] Beginning in 2005, a subset of RCT and OS participants (n=115,407) continued participation in the WHI Extension Studies. In WHI, breast cancer was identified by self-report on a health events form, administered at least annually, and confirmed by physician review of medical records.[23] The

WHI study design and methods have been described in detail elsewhere.[23-25] In 2008-09, the WHI administered a mailed current medication inventory form to all active WHI participants, and mailed a breast health form, which asked about history of endocrine therapy for breast cancer, to all active WHI participants with a breast cancer diagnosis made during WHI enrollment. A total of 5,689 women completed both forms.

In the subset of women who completed both forms and reported current bisphosphonate use of 2 years or more, we analyzed the association of longer duration of use (4-7, 8+ years) with fracture, using shorter duration of use (2-3 years) as the referent group. We excluded one woman who had used parathyroid hormone, a medication that affects bone metabolism. Additionally, we excluded 22 women who had stopped and then resumed bisphosphonate use prior to the 2008-9 medication inventory. After exclusions, 902 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 2008-9 medication inventory.[26] The mailed medication inventory form instructed participants to gather all current medication prescriptions and to record information from the prescription labels. Participants wrote the drug name, strength, and type (capsule, tablet, etc.), and then reported the duration of use (< 1 month, 1-12 months, or number of years).

Covariates

Covariates were selected *a priori* based on literature review to include factors that are associated with bisphosphonate use and 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),[27] parental hip fracture, smoking status, and rheumatoid arthritis diagnosis. Recreational physical

activity was assessed by self-report on a validated study questionnaire[28] and categorized in metabolic equivalents (MET)-hours per week.[29] Medication use and body mass index (BMI [kg/m^2]) were collected at clinical exams 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 3-9, SERM use was collected at years 6, 7, and 8, and calcitonin use was collected at years 6 and 9 after enrollment. For HT RCT participants, estrogen and calcitonin use was collected at annual clinic visits in all study years and SERM use was also collected annually in years 2005-8. Duration of ever-use of aromatase inhibitors and SERMs was collected for all RCT and OS participants on the 2008-9 breast health form. Breast cancer diagnoses were confirmed and tumor characteristics (invasive tumor behavior, estrogen receptor status, and diagnosis date) were obtained from medical record review. 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, 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.[23] Additionally, a subset of fractures was confirmed by review of medical records. 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 902 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+ years). Comparison of descriptive statistics between groups was made using ANOVA and the chi-square test.

Statistical Analysis of Fracture Incidence

Participants contributed follow-up time from the date of completing the medication inventory in 2008-9 until the occurrence of fracture, death, loss-to-follow-up, or end of study follow-up in 2013-14, whichever occurred first.[23] 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 4-7 and eight or more years of bisphosphonate use with 2-3 years of use (reference group). Model 1 estimated hazard ratios adjusted *a priori* for age and race. Model 2 estimated hazard ratios adjusted *a priori* for characteristics associated with both bisphosphonate use and fracture risk: age, race, BMI, parental hip fracture, smoking status, rheumatoid arthritis, glucocorticoid use $\geq$ 3 months, diabetes mellitus treated with pills or shots, recreational physical activity, general health rating, SERM use (ever/never), aromatase inhibitor use (ever/never), calcitonin use (use within 10 years before medication inventory), and estrogen use (use within 10 years 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 SERM use and duration of bisphosphonate use with aromatase inhibitors use. 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, 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

To examine the association of each additional year of bisphosphonate use with fracture, we modeled bisphosphonate use as a continuous variable (years of use). We presented the results of this analysis as the predicted hazard ratio associated with a 5-year increase in duration of bisphosphonate use, which is equivalent to the interquartile range of duration of bisphosphonate use. To examine fracture risk among a more homogenous group of women who may be at a high fracture risk, we conducted a subgroup analysis limited to women who had a predicted 5-year risk of hip fracture of 1.5% or greater (n=607). Predicted 5-year risk of hip fracture was calculated using a fracture risk prediction algorithm developed and validated in the WHI.[30] To examine fracture risk in nonusers of bisphosphonates, we conducted an analysis including the 3,763 nonusers who otherwise would have met the eligibility criteria for the primary analysis. Additional analyses were adjusted for the same variables as the three primary models.

RESULTS

Descriptive characteristics

Characteristics of all 5,689 women who completed the medication inventory and breast health form are described in Supplemental Table 2.1. We observed a change over time in endocrine therapy use by WHI participants with breast cancer. SERM use decreased while

aromatase inhibitor use increased between 1993 and 2009; by seven years prior to the 2008-9 breast health form, aromatase inhibitor use surpassed SERM use (Supplemental Figure 2.1).

Among the 902 women in the fracture analysis, 282 (31%) had used bisphosphonates for 2-3 years, 326 (36%) for 4-7 years, and 294 (33%) for eight or more years or more (Table 2.1). White race was most common among women who had used bisphosphonates for 4-7 years and least common among women who had used bisphosphonates for 2-3 years. Among women with eight 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 did not significantly differ 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 144 clinical fractures (Table 2.2). Women with eight or more years of bisphosphonates use had the highest unadjusted fracture rate (76.6 per 1,000 person-years) and women 2-3 years of use had the lowest (46.7); the rate was intermediate among women with 4-7 years of use (52.5). 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, and variables significantly associated with fracture, eight or more years of bisphosphonate use was associated with increased risk of any clinical fracture (HR: 1.65 [95% CI: 1.06-2.58] and HR: 1.66 [95% CI: 1.08-2.54]). Bisphosphonate use of 4-7 years of was not associated with fracture compared with 2-3 years of use in any multivariate-adjusted model.

In the sensitivity analysis that modeled bisphosphonate exposure as a continuous variable, a five-year increase in bisphosphonate use was associated with a 27% (95% CI: 1.00-1.61) increase in fracture risk in Model 3 that adjusted for significant variables and a subset of *a priori* variables; the hazard ratio was elevated, but not statistically significant in Model 2 that

adjusted for all *a priori* variables (HR: 1.26 [95% CI: 0.99-1.63]; Table 2.3). In the analysis limited to 592 women with a high fracture risk as defined by a 5-year hip fracture risk of 1.5% or greater, fracture risk was elevated, but not significant for eight or more years of bisphosphonate use was compared with 2-3 years of use (HR: 1.64 [95% CI: 0.95-2.81]; Table 2.4). In the additional analysis that examined fractures among nonusers of bisphosphonates, nonusers had the lowest fracture rate (38.0 per 1,000 person-years), but nonuse of bisphosphonates was not significantly associated with fracture risk compared to 2-3 years of use (HR: 0.85 [0.60-1.19]; Supplemental Table 2.2).

DISCUSSION

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

In 2011, based on findings of harms and lack of evidence for efficacy after an FDA review of all RCTs of long-term bisphosphonate use, the FDA recommended that long-term bisphosphonate users be routinely evaluated for the appropriateness of continued therapy.[11, 12] The 2011 FDA review noted that unadjusted fracture rates were similar during earlier and later periods of bisphosphonate use.[11, 12] However, the FDA did not examine differences in fracture risk by duration of bisphosphonate exposure in many subgroups, and called for more research

in specific populations.[11, 12] There are few studies of long-term bisphosphonate use compared to short-term use in the general population, and this is the first study of this type among postmenopausal women with breast cancer.[11, 12, 31] Mellstrom et al. in an open-label 2-year extension of an RCT of risedronate found no association with fracture for 6-7 years of bisphosphonate use compared to 1-2 years of use among women without breast cancer.[31] Our findings in women with breast cancer for bisphosphonate exposure of less than eight years are similar to those of Mellstrom et al., but Mellstrom et al. did not examine bisphosphonate use beyond seven years. Our findings of increased fracture risk during eight or more years of use suggest the need for larger, more comprehensive studies of long-term bisphosphonate exposure that can account for additional factors such as BMD and bisphosphonate adherence and dosage, which may further explain the relationship between long-term bisphosphonate use and fracture risk.

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 SERM therapy to prevent recurrence of hormone receptor positive cancer.[32, 33] 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 SERMs are beneficial to bone[18, 19] and aromatase inhibitors are detrimental to bone,[5, 20] our findings suggest that eight or more years of bisphosphonate use is associated with increased fracture risk irrespective of history of SERM or aromatase inhibitor use.

Our findings should be interpreted with caution, though, because of study limitations. Only a subset of fractures was confirmed by medical record review, medication use was self-reported, and our analysis did not account for bisphosphonate adherence or dosage. However, a validity study of self-reported fracture found good to excellent validity of self-reported fracture

in the WHI[34] and a validity study of the 2008-9 medication inventory found near perfect agreement between self-reported duration of current medication use and pharmacy records for four chronically used medications, including bisphosphonates.[35] Additionally, 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 US, though, over 90% of women diagnosed with breast cancer survive for five years or longer.[3] 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. Additionally, the WHI collected information on numerous factors, which allowed statistical adjustment for many participant characteristics that are 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 characteristics associated with fracture risk, longer duration of bisphosphonate use was associated with increased risk of clinical fracture compared with shorter duration of use. Findings from this observational study should be interpreted with caution and further study is needed. Pending the results of studies in larger cohorts with information on BMD and medication adherence, 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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Table 2.1: Characteristics of 902 postmenopausal bisphosphonate users with breast cancer categorized by years of bisphosphonate use at 2008-9 medication inventory

Charactertistic	Duration of Bisphosphonate Use						*P-value*
	2-3 Years (n=282)		4-7 Years (n=326)		8+ Years (n=294)		
	No. *%* or Mean ± SD						
Bisphosponate use (y)	2.5 ± 0.5		5.2 ± 1.0		10.3 ± 1.8		
Age (y)	76.0 ± 6.2		76.3 ± 6.4		76.9 ± 6.5		*0.22*
White/Caucasian	246	*87.2*	307	*94.2*	266	*90.5*	*0.02*
Education							*0.37*
≤ High school diploma or GED	32	*11.3*	52	*16.0*	42	*14.3*	
Some education after high school	102	*36.2*	91	*27.9*	86	*29.3*	
College/post-graduate/professional	145	*51.4*	182	*55.8*	163	*55.4*	
History of fracture after age 54 years	111	*39.4*	132	*40.5*	125	*42.5*	*0.74*
Parent had hip fracture	53	*18.8*	53	*16.3*	44	*15.0*	*0.44*
Rheumatoid arthritis	25	*8.9*	29	*8.9*	21	*7.1*	*0.68*
Glucocorticoids ≥ 3 months	13	*4.6*	8	*2.5*	7	*2.4*	*0.21*
Current smoker	14	*5.0*	15	*4.6*	3	*1.0*	*0.02*
Body mass index (kg/m^2)	26.7 ± 4.8		26.5 ± 4.9		25.4 ± 4.4		*<0.01*
Diabetes mellitus treated with pills or shots	22	*7.8*	26	*8.0*	24	*8.2*	*0.99*
Recreational physical activity[a]	13.0 ± 12.8		13.6 ± 13.8		13.3 ± 12.4		*0.88*
General health rating:							*0.41*
Fair or poor	22	*7.8*	36	*11.0*	24	*8.2*	
Good	118	*41.8*	113	*34.7*	100	*34.0*	
Very good or excellent	143	*50.7*	177	*54.3*	170	*57.8*	
Invasive breast cancer tumor behavior	237	*84.0*	279	*85.6*	237	*80.6*	*0.24*
Breast cancer tumor estrogen receptor positive	207	*73.4*	244	*74.8*	212	*72.1*	*0.74*
Years from breast cancer diagnosis to medication inventory	7.3 ± 3.4		7.6 ± 3.3		8.0 ± 3.4		*0.04*
Ever used SERMs	161	*57.1*	190	*58.3*	168	*57.1*	*0.94*
Ever used aromatase inhibitors	147	*52.1*	177	*54.3*	119	*40.5*	*<0.01*
Estrogen use ≤ 10 y before medication inventory	127	*45.0*	138	*42.3*	125	*42.5*	*0.76*
Calcitonin use ≤ 10 y before medication inventory	7	*2.5*	11	*3.4*	14	*4.8*	*0.33*

[a]Recreational physical activity was categorized in metabolic equivalent-hours per week.

Table 2.2: Among 902 postmenopausal bisphosphonate users with breast cancer, fracture incidence, adjusted hazard rate (HR), and 95% confidence interval (CI) of fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		Model 1: Adjusted for Age and Race	Model 2: Adjusted for *a Priori* Variables	Model 3: Adjusted for Age, Race, Endrocrine Therapy, and Significant Variables
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[bc]	HR (95% CI)[bd]	HR (95% CI)[be]
2-3 y	282	*37*	46.7	1.00	1.00	1.00
4-7 y	326	*47*	52.5	1.18 (0.77-1.83)	1.20 (0.76-1.87)	1.23 (0.79-1.91)
8+ y	294	*60*	76.6	1.46 (0.96-2.21)	1.65 (1.06-2.58)	1.66 (1.08-2.54)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of 2008-9 medication inventory to end of study in 2013-14; [c]Model 1: Cox proportional hazards model adjusted for age and race; [d]Model 2: Cox proportional hazards model adjusted for SERM use, aromatase inhibitor use, age, race, parental hip fracture, BMI, smoking, rheumatoid arthritis, glucocorticoid use $\geq$ 3 months, calcitonin use, estrogen use, 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 SERM use, and history of aromatase inhibitor use and stratified by history of fracture after age 54.

Table 2.3: Among 902 postmenopausal bisphosphonate users with breast cancer, fracture incidence, adjusted hazard rate (HR), and 95% confidence interval (CI) of fracture associated with a 5 year increase in duration of bisphosphonate use*

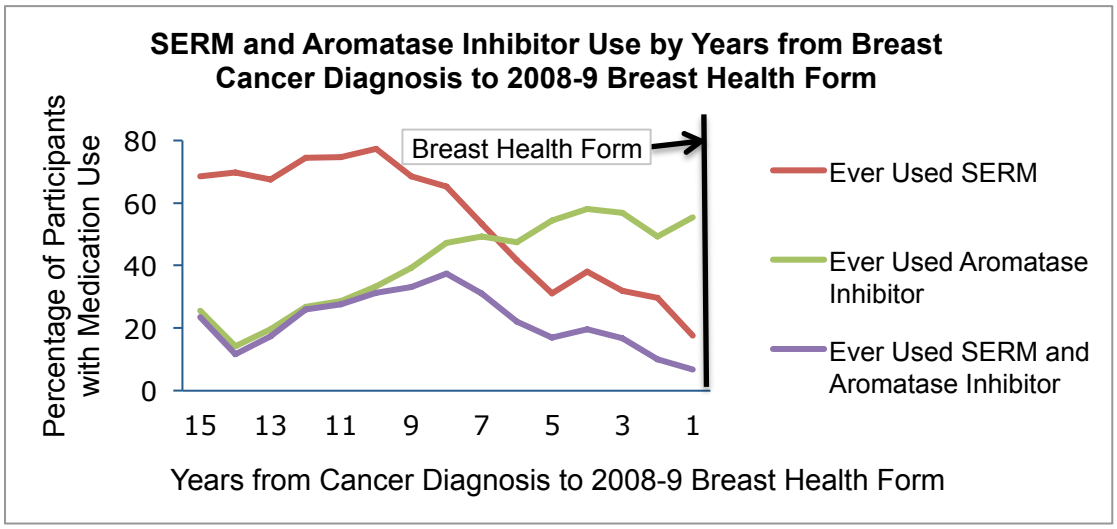
Exposure	Subjects (No.)	Fractures		Model 1: Adjusted for Age and Race	Model 2: Adjusted for *a Priori* Variables	Model 3: Adjusted for Age, Race, Endrocrine Therapy, and Significant Variables
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[bc]	HR (95% CI)[bd]	HR (95% CI)[be]
Bisphosphonate use (5 year increase)	902	*144*	58.3	1.20 (0.95-1.52)	1.26 (0.99-1.63)	1.27 (1.00-1.61)

*5 years is equivalent to the interquartile range; [a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of 2008-9 medication inventory to end of study in 2013-14; [c]Model 1: Cox proportional hazards model adjusted for age and race; [d]Model 2: Cox proportional hazards model adjusted for SERM use, aromatase inhibitor use, age, race, parental hip fracture, BMI, smoking, rheumatoid arthritis, glucocorticoid use $\geq$ 3 months, calcitonin use, estrogen use, 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 SERM use, and history of aromatase inhibitor use and stratified by history of fracture after age 54.

Table 2.4: Among 592 postmenopausal bisphosphonate users with breast cancer and high fracture risk*, fracture incidence, adjusted hazard rate (HR), and 95% confidence interval (CI) of fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		Model 1: Adjusted for Age and Race	Model 2: Adjusted for *a Priori* Variables	Model 3: Adjusted for Age, Race, Endrocrine Therapy, and Significant Variables
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[bc]	HR (95% CI)[bd]	HR (95% CI)[be]
2-3 y	178	*22*	45.3	1.00	1.00	1.00
4-7 y	215	*34*	57.4	1.25 (0.73-2.15)	1.20 (0.67-2.10)	1.28 (0.74-2.21)
8+ y	199	*43*	81.1	1.47 (0.87-2.48)	1.59 (0.91-2.79)	1.64 (0.95-2.81)

[*]High fracture risk defined by a 5-year risk of hip fracture $\geq$ 1.5%; [a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of 2008-9 medication inventory to end of study in 2013-14; [c]Model 1: Cox proportional hazards model adjusted for age and race; [d]Model 2: Cox proportional hazards model adjusted for SERM use, aromatase inhibitor use, age, race, parental hip fracture, BMI, smoking, rheumatoid arthritis, glucocorticoid use $\geq$ 3 months, calcitonin use, estrogen use, diabetes mellitus treated with shots or pills, recreational physical activity, and general health rating and stratfied 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 SERM use, and history of aromatase inhibitor use and stratfied by history of fracture after age 54.



Supplemental Figure 2.1: SERM and Aromatase inhibitor use among 5,689 postmenopausal women by the number of years from breast cancer diagnosis to the completion of the 2008-9 breast health form

Supplemental Table 2.1: Characteristics of 5,689 postmenopausal women with breast cancer categorized by bisphosphonate use at 2008-9 medication inventory and by type of endocrine therapy used for breast cancer

Charactertistic	Bisphosphonate Use in 2008-9				Ever Used Endocrine Therapy for Breast Cancer							
	Not Current User (n=4,490)		Current User (n=1,199)		Never used (n=1,534)		SERM Only (n=1,737)		Aromatase Inhibitor Only (n=1,032)		SERM + Aromatase Inhibitor (n=1,386)	
	No. % or Mean ± SD											
Age (y)	75.4 ± 6.4		76.3 ± 6.5		76.4 ± 6.9		76.1 ± 6.4		74.9 ± 6.1		74.6 ± 6.1	
White/Caucasian	4,002	*89.1*	1,082	*90.2*	1,361	*88.7*	1,576	*90.7*	905	*87.7*	1,242	*89.6*
Education												
≤ High school diploma or GED	718	*16.0*	173	*14.4*	254	*16.6*	279	*16.1*	163	*15.8*	195	*14.1*
Some education after high school	1,606	*35.8*	369	*30.8*	550	*35.9*	603	*34.7*	353	*34.2*	469	*33.8*
College/post-graduate/professional	2,142	*47.7*	650	*54.2*	722	*47.1*	844	*48.6*	511	*49.5*	715	*51.6*
History of fracture after age 54 years	1,467	*32.7*	487	*40.6*	537	*35.0*	585	*33.7*	358	*34.7*	474	*34.2*
Parent had hip fracture	551	*12.3*	200	*16.7*	216	*14.1*	237	*13.6*	134	*13.0*	164	*11.8*
Rheumatoid arthritis	360	*8.0*	99	*8.3*	138	*9.0*	124	*7.1*	86	*8.3*	111	*8.0*
Glucocorticoids ≥ 3 months	78	*1.7*	37	*3.1*	43	*2.8*	34	*2.0*	13	*1.3*	25	*1.8*
Current smoker	148	*3.3*	41	*3.4*	54	*3.5*	50	*2.9*	47	*4.6*	38	*2.7*
Body mass index (kg/m^2)	28.5 ± 5.8		26.4 ± 4.8		28.1 ± 5.8		27.4 ± 5.4		29.0 ± 6.0		28.2 ± 5.7	
Diabetes mellitus treated with pills or shots	614	*13.7*	103	*8.6*	201	*13.1*	203	*11.7*	140	*13.6*	173	*12.5*
Recreational physical activity[a]	13.0 ± 13.3		13.3 ± 13.3		12.9 ± 13.3		12.9 ± 13.1		12.7 ± 13.3		13.7 ± 13.5	
General health rating:												
Fair or poor	464	*10.3*	114	*9.5*	736	*48.0*	167	*9.6*	117	*11.3*	117	*8.4*
Good	1,893	*42.2*	465	*38.8*	621	*40.5*	705	*40.6*	454	*44.0*	578	*41.7*
Very good or excellent	2,133	*47.5*	620	*51.7*	177	*11.5*	865	*49.8*	461	*44.7*	691	*49.9*
Invasive breast cancer tumor behavior	3,566	*79.4*	990	*82.6*	987	*64.3*	1,240	*71.4*	998	*96.7*	1,331	*96.0*
Breast cancer tumor estrogen receptor positive	3,192	*71.1*	876	*73.1*	678	*44.2*	1,176	*67.7*	965	*93.5*	1,249	*90.1*
Years from breast cancer diagnosis to medication inventory	7.6 ± 3.5		7.5 ± 3.5		7.4 ± 3.6		9.0 ± 3.3		4.6 ± 2.3		8.1 ± 3.0	
Ever used bisphosphonates	723	*16.1*	1,199	*100*	455	*29.7*	614	*35.3*	351	*34.0*	502	*36.2*
Bisphosphonate use at medication inventory												
< 5 y	-	*0.0*	661	*55.1*	150	*9.8*	183	*10.5*	156	*15.1*	172	*12.4*
≥ 5 y	-	*0.0*	538	*44.9*	127	*8.3*	159	*9.2*	96	*9.3*	156	*11.3*
Ever used SERMs	2,453	*54.6*	670	*55.9*	-	*0.0*	1,737	*100*	-	*0.0*	1,386	*100*
Ever used aromatase inhibitors	1,838	*40.9*	580	*48.4*	-	*0.0*	-	*0.0*	1,032	*100*	1,386	*100*
Estrogen use ≤ 10 y before medication inventory	1,929	*43.0*	529	*44.1*	611	*39.8*	636	*36.6*	554	*53.7*	657	*47.4*
Calcitonin use ≤ 10 y before medication inventory	117	*2.6*	42	*3.5*	35	*2.3*	63	*3.6*	18	*1.7*	43	*3.1*

[a]Recreational physical activity was categorized in metabolic equivalent-hours per week.

Supplemental Table 2.2: Among 4,665 postmenopausal women with breast cancer, including nonusers of bisphosphonates, fracture incidence, adjusted hazard rate (HR), and 95% confidence interval (CI) of fracture by duration of bisphosphonate use at 2008-9 medication inventory

Duration of Bisphosphonate Use	Subjects (No.)	Fractures		Model 1: Adjusted for Age and Race	Model 2: Adjusted for *a Priori* Variables	Model 3: Adjusted for Age, Race, Endrocrine Therapy, and Significant Variables
		No.[a]	Incidence per 1,000 Person-years	HR (95% CI)[bc]	HR (95% CI)[bd]	HR (95% CI)[be]
2-3 y	282	*37*	46.7	1.00	1.00	1.00
4-7 y	326	*47*	52.5	1.17 (0.76-1.80)	1.16 (0.75-1.79)	1.19 (0.77-1.84)
8+ y	294	*60*	76.6	1.46 (0.96-2.18)	1.51 (1.00-2.30)	1.58 (1.04-2.39)
Nonusers	3,763	*399*	38.0	0.86 (0.61-1.20)	0.85 (0.60-1.19)	0.86 (0.61-1.21)

[a]Number of fractures during all follow-up years; [b]Follow-up period is from completion date of 2008-9 medication inventory to end of study in 2013-14; [c]Model 1: Cox proportional hazards model adjusted for age and race; [d]Model 2: Cox proportional hazards model adjusted for SERM use, aromatase inhibitor use, age, race, parental hip fracture, BMI, smoking, rheumatoid arthritis, glucocorticoid use $\geq$ 3 months, calcitonin use, estrogen use, diabetes mellitus treated with shots or pills, recreational physical activity, and general health rating and stratfied 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 SERM use, and history of aromatase inhibitor use and stratfied by history of fracture after age 54.

Chapter 3:

Validity of Self-reported Medication Use Compared with Pharmacy Records in a Cohort of Older Women: Findings from the Women's Health Initiative

Validity of Self-reported Medication Use Compared with Pharmacy Records in a Cohort of Older Women: Findings from the Women's Health Initiative

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Manuscript length: 2,000

Abstract length: 250

ABSTRACT

BACKGROUND: Observational studies that use medication exposure data rely upon accurate measurement of medication use. In most validity studies, self-reported medication use is collected with interviewer-administered forms or participants are asked about specific medications. We assessed the validity of medication use collected via a mailed medication inventory among older women.

METHODS: Participants were 223 Women's Health Initiative participants who were members of a health delivery system with an electronic pharmacy database. In 2008-9, participants completed a mailed medication inventory. Self-reported medication use was compared to pharmacy records for statins, calcium channel blockers, beta blockers, and bisphosphonates. We assessed sensitivity, specificity, and positive predictive value for current medication use. We assessed agreement on duration of use (<2, 2, 3, 4, and ≥5 years) using a weighted kappa statistic.

RESULTS: The mean age of participants was 75. Statins, beta blockers, and calcium channel blockers were each self-reported by over 15% of women, and bisphosphonates by 4.5%. Compared with pharmacy records, sensitivity, specificity, and positive predictive value for self-reported statin, beta blocker, and calcium channel blocker use were all 95% or greater. The sensitivity and positive predictive value for bisphosphonate use were 80%, and specificity was 90%. The kappa statistic for duration of use ranged from 0.87 (95% CI: 0.92-0.98) for beta blockers to 0.96 (95% CI: 0.92-0.98) for statins.

CONCLUSIONS: Compared with pharmacy records, self-reported current medication use and duration of use collected via mailed medication inventory in this population of older women had near perfect agreement for four chronically-used medication classes.

INTRODUCTION

Medication use is commonly assessed by self-report in research studies, but its accuracy is limited by participant recall error.[1, 2] Inaccurate self-reported data can lead to exposure misclassification and, thereby, to less reliable study findings. Validity studies can estimate misclassification in self-reported data and help determine whether study results may be biased. Pharmacy and medical records are often used as a "gold standard" for validity studies of self-reported medication use, and pharmacy records may be more complete than medical records.[1, 2] Increased age is associated with diminished accuracy of self-reported events,[1, 2] which makes validity studies among older women an important research topic.

Existing validity studies demonstrate good agreement between self-reported medication use and pharmacy or medical records among older women, but most studies used interviewer-administered forms or asked about specific medications.[1, 3-8] In particular, the accuracy of statin and antihypertensive medications collected via interviewer-administrated forms compared with pharmacy records has been established among older women,[3] but their accuracy via self-administered mailed forms has not been studied. Additionally, good accuracy of self-reported bisphosphonate use compared with pharmacy records was found among chronic glucocorticoid users, but it has not been studied in a general population of older women.[9]

The accuracy of data from self-administered mailed forms may differ from the accuracy of interviewer-administered forms and forms that query about specific medications. Thus, we conducted a validity study to compare self-reported medication use collected via a mailed medication inventory with pharmacy records among older Women's Health Initiative (WHI) participants for four classes of chronically-used medications: statins, calcium channel blockers, beta blockers, and bisphosphonates.

METHODS

Women's Health Initiative

The WHI is an ongoing longitudinal research study with primary aims to develop strategies that reduce disease in older women. Between 1993 and 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 a study of hormone therapy (HT) with estrogen, a study of HT with estrogen and progestin, a study of dietary modification, and a study of calcium and vitamin D supplementation. The RCT of HT with progestin ended early in 2002 and that of HT without progestin ended early in 2004 after findings of significant harms; and the other WHI RCTs and the OS ended in 2005.[10] Beginning in 2005, a subset of RCT and OS participants continued participation in the WHI Extension Studies (n=115,407). The WHI study design and methods have been described in detail.[11-13] In 2008-09, a current medication inventory was administered by mail to all active WHI participants.[14]

Group Health

Study subjects for the present study were WHI participants who were also Group Health (GH) enrollees for at least five years at the completion of the 2008-9 medication inventory. GH is an integrated healthcare delivery system that provides comprehensive health care to approximately 600,000 residents of Washington and Idaho. GH's electronic pharmacy database began in 1977 and has been used in numerous observational studies.[15] In a study of seniors who were enrollees of GH, 91% of enrollees with a drug benefit and 78% of enrollees without a drug benefit reported that they filled their prescriptions exclusively at GH-owned pharmacies.[16] In 2009, 84% of female GH enrollees age 65 and older had a drug benefit.

Study Participants and Recruitment

We identified 580 WHI participants who completed the 2008-9 medication inventory, were enrolled at the Seattle WHI clinic site, and reported having insurance through a health maintenance organization. Several Seattle health clinics offer health maintenance organization insurance. We asked women to respond only if they were GH enrollees. We mailed letters to these women asking if they were members of GH and if so, asking permission to use existing WHI self-report data and GH pharmacy records for the validity study. A total of 278 (48%) consented to participate, 130 (22%) responded that they were not GH enrollees, and 172 (30%) did not respond. Of the 278 women who consented, 223 were actually GH enrollees for at least five years at the 2008-9 medication inventory date and were eligible for the study. For these 223 women, we analyzed self-reported medication use compared with GH pharmacy records for four classes of chronically-used medications: statins, calcium channel blockers, beta blockers, and bisphosphonates.

Exposure Classification

In WHI, duration of medication exposure was self-reported on the 2008-9 medication inventory which was mailed to participants, self-administered, and returned to WHI by mail. Instructions on the medication inventory indicated that telephone assistance was available if needed, but only one of the 223 validity study participants completed the form by telephone. Current medication use was defined by the answer to the question, “Are you currently taking any medications that require a prescription from a doctor or health care provider?” The form instructed participants who answered “Yes” to gather all of their current prescription medications. The form included one example prescription label with a completed entry. Participants wrote the name, strength, type (tablet, capsule, etc.), and duration of use (<1 month, 1-12 months, continuous number of years) for each prescription medication. Medications were categorized to medication class using Medi-Span®, a pharmaceutical reference database.

We defined women as users of a medication class if they reported a medication in that class. We categorized self-reported duration of use from the medication inventory into groups (< 2, 2, 3, 4, and ≥ 5 years).

The reference date for medication exposure was the date the participant completed the 2008-9 WHI medication inventory. For this analysis, we used GH pharmacy records for five years before the reference date through sixty days after the reference date. From the GH data, we defined the duration of medication use as the reference date minus the date of the first pharmacy prescription during a period of continuous use that included the reference date. We defined a period of use as continuous if there was at least one prescription for a medication class during a sixty-day period after the run out date of the last prescription. We calculated the run out date as the prescription date plus the number of days of medication use supplied in the prescription. We defined a woman as a true current user of a medication class if the period of continuous use for that medication class included the reference date. We categorized duration of use into groups (< 2, 2, 3, 4, and ≥ 5 years).

Covariates

Self-reported characteristics of interest included age, race, education level, income level, marital status, and general health rating.[11,17] We used the most recent value collected in WHI on or before the medication inventory date.

Statistical Analysis

We described the characteristics of validity study participants and WHI participants not enrolled in the validity study. Accuracy of self-reported medication use reported on the 2008-9 medication inventory was examined using pharmacy records as the gold standard for four medication classes (statins, calcium channel blockers, beta blockers, and bisphosphonates). We assessed sensitivity (proportion of positives in the pharmacy records that were also reported

on the medication inventory), specificity (proportion of negatives in the pharmacy records that were also reported as negatives on the medication inventory), and positive predictive value (PPV [proportion of positives reported by the medication inventory that were verified by pharmacy records]) for each medication class. We assessed the accuracy of self-reported duration of medication use (< 2, 2, 3, 4, and ≥ 5 years) using the weighted kappa statistic. The kappa statistic measures inter-rater agreement beyond agreement expected by chance alone, and the weighted kappa statistic gives partial credit for close agreement between individual answers in two sets of ordered categorical variables.[18-20] Confidence intervals for the kappa statistic were bias-adjusted using 1,000 naïve bootstrap repetitions.[21-23] Women missing duration of use information ranged from 0 to 6 women for each medication class, and these women were excluded from the kappa statistic for that medication class. We also conducted a logistic regression analysis to assess participant characteristics as predictors of accuracy of self-reported data. For each medication class, two multivariate logistic regression models were conducted; one to examine age, education level, marital status, and general health rating "fair" or "poor" as predictors of disagreement of self-reported medication use with pharmacy records, and one to examine age, education level, and marital status as predictors of disagreement of duration of self-reported medication use with duration from pharmacy records. All statistical tests were two-tailed (α=0.05) and conducted with Stata Statistical Software version 13.

RESULTS

Descriptive Characteristics

Validity study participants (n=223) were older, more likely to be white, and had higher educational attainment compared with WHI participants not in the validity study (n=97,225; Table 3.1). Self-reported bisphosphonate use was less common among validity study participants.

Accuracy of Self-reported Medication Use

Self-reported current medication use was over 15% for statins, beta blockers, and calcium channel blockers and was 4.5% for bisphosphonates. The sensitivity, specificity, and PPV were all 95% or greater for statins, beta blockers, and calcium channel blockers. For bisphosphonates, the sensitivity and PPV were 80% and the specificity was 99%. The weighted kappa statistic comparing self-reported duration of medication use with true duration of use was almost perfect for all four medication classes and ranged from 0.87 to 0.96. In the multivariate logistic regression analysis, none of the participant characteristics were independently predictive of accuracy of self-reported medication use or self-reported duration of medication use for any medication class.

DISCUSSION

Our study among 223 older WHI participants suggests that a mailed medication inventory is a very good source of medication exposure data for chronically used medications. Compared with pharmacy records, we found near perfect sensitivity for self-reported use of statins, beta blockers, and calcium channel blockers and 80% sensitivity for bisphosphonates. Specificity and PPV of self-reported medication use and the kappa statistic for self-reported duration of medication use were near perfect for all four drug classes.

Our results are similar to those of Boudreau et al., who used an interviewer-administered form that prompted for specific medications and found near perfect agreement between self-reported data and pharmacy records for recent (within 6 months) statin and antihypertensive drug use among older members of GH.[3] Compared with Boudreau et al., current self-reported medication use collected via a mailed medication inventory was as accurate as data collected by an interviewer. Using mailed study forms can provide substantial economic savings compared with interviewer-administered forms, especially for studies as large as the WHI, which

collected a mailed medication inventory form from over 97,000 women. It is notable that the WHI medication inventory asked participants to refer to their prescription labels while completing the form. This technique could be utilized in other studies that collect self-reported current medication use.

Advanced age has been associated with decreased accuracy of self-reported events,[2] and validity studies of self-reported medication use have found associations between older age and decreased recall accuracy of medication use.[1,9] Our study found no association between increased age and recall accuracy. However, our study had limited power to detect differences by age.

There are several limitations to our study. The study sample may not be representative of the general population of older women, because 95% of the subjects were white and 56% had a college degree or higher educational attainment. However, the demographic characteristics differed only slightly from WHI participants not enrolled in the validity study. Additionally, our findings should not be generalized to past medication use, infrequently used medications, or less socially acceptable medications. Furthermore, we had few bisphosphonate users, which may have limited the accuracy of estimates related to bisphosphonates. As with any validity study using pharmacy records, disagreement between self-reported medication use and pharmacy records may be due to subjects not taking a medication after filling a pharmacy prescription or subjects filling a prescription at a pharmacy other than the pharmacies included in the validity study.

CONCLUSIONS

In this population of older women, a mailed medication inventory appears to be a highly accurate means of assessing current use and duration of use of four classes of chronically-used medications. Our findings are important for epidemiologic research, because self-reported medication data from the WHI is used in numerous analyses of medication effects.

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Table 3.1: Characteristics of 223 WHI[a] validity study participants and 97,225 WHI participants not in validity study that completed the 2008-9 medication inventory

Characteristic	WHI Validity Study Participants (n=223)		Other WHI Study Participants (n=97,225)	
	No.	% or Mean ± SD	No.	% or Mean ± SD
Age (y)				
60-69	35	*15.7*	24,481	*25.2*
70-79	117	*52.5*	47,811	*49.2*
≥ 80	71	*31.8*	24,933	*25.6*
Race				
White/Caucasian	211	*94.6*	84,833	*87.3*
African American	4	*1.8*	6,198	*6.4*
Asian/Pacific Islander	4	*1.8*	2,066	*2.1*
Education				
≤ High school diploma/GED	26	*11.7*	18,413	*18.9*
School after high school	71	*31.8*	35,462	*36.5*
College degree or higher	124	*55.6*	42,709	*43.9*
Marital status		*0.0*		
Never married	5	*2.2*	3,970	*4.1*
Married/Mariage-like relationship	166	*74.4*	65,022	*66.9*
Divorced/separated/widowed	52	*23.3*	27,875	*28.7*
Annual income ($)				
< 20,000	13	*5.8*	10,810	*11.1*
20,000-34,999	43	*19.3*	20,556	*21.1*
35,000-49,999	68	*30.5*	19,554	*20.1*
≥ 50,000	94	*42.2*	40,945	*42.1*
General health rating "fair" or "poor"	14	*6.3*	9,261	*9.5*
Prevalence of medication use self-reported on medication inventory				
Statin	80	*35.9*	38,764	*39.9*
Beta blocker	66	*29.6*	26,398	*27.2*
Calcium channel blocker	35	*15.7*	17,305	*17.8*
Bisphosphonate	10	*4.5*	17,075	*17.6*

[a]WHI, Women's Health Initiative.

Table 3.2: Accuracy of self-reported current medication use compared with pharmacy records for statins, beta blockers, calcium channel blockers, and bisphosphonates among 223 older postmenopausal women

	Accuracy of Self-report of Current Medication Use										Accuracy of Self-report of Duration of Current Medication Use	
					Sensitivity		Specificity		PPV[a]			
Medication Class	Self-report= yes, Pharmacy= yes (no.)	Self-report= yes, Pharmacy= no (no.)	Self-report= no, Pharmacy= yes (no.)	Self-report= no, Pharmacy= no (no.)	%	(95% CI[b])	%	(95% CI)	%	(95% CI)	Kappa Statistic[c]	(95% CI)
Statin	79	4	1	139	95	(88-99)	99	(96-100)	99	(93-100)	0.96	(0.92-0.98)
Beta blocker	65	2	1	155	97	(90-100)	99	(96-100)	98	(92-100)	0.87	(0.73-0.96)
Calcium channel blocker	35	0	0	188	100	(90-100)	100	(98-100)	100	(90-100)	0.89	(0.75-0.97)
Bisphosphonate	8	2	2	211	80	(44-97)	99	(97-100)	80	(44-97)	0.95	(0.67-1.00)

[a]PPV, positive predictive value; [b]CI, confidence interval; [c]Weighted bias-adjusted kappa statistic for duration of medication use (< 2, 2, 3, 4, ≥ 5 years); Participants with incomplete duration of use data were excluded from the kappa statistic for that medication class: 6 from statins, 6 from beta blockers, 3 from calcium channel blockers, and 0 from bisphosphonates.

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