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Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday

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Summary

Based upon interest in a bisphosphonate drug holiday, we evaluate the risk for hip fracture after bisphosphonate discontinuation. Among women compliant with bisphosphonates for ≥2 years, the risk of hip fracture was increased after discontinuation, although with higher compliance and a longer duration of preceding bisphosphonate therapy, this risk was attenuated.

Introduction—Recent data suggest that hip fracture risk was not significantly increased among women receiving 5 years of bisphosphonate therapy who were subsequently randomized to placebo. We studied older women compliant with bisphosphonates ≥2 years to evaluate the risk of hip fracture after bisphosphonate discontinuation.

Methods—Using administrative databases from a large U.S. healthcare organization, we identified women initiating bisphosphonate therapy compliant (Medication Possession Ratio, MPR ≥66%) for 2 years. We examined the rate of hip fracture among women who discontinued bisphosphonates versus those who remained on therapy.

Results—At 2 years, 9,063 women were eligible for analysis. Hip fracture incidence among women who discontinued bisphosphonates versus those who did not was 8.43 versus 4.67 per 1000 person years (p=0.016). The adjusted hazard ratio of hip fracture per 90 days following discontinuation was 1.2 (1.1–1.3). For women with higher compliance at 2 years (MPR ≥80%) or compliant for 3 years, there were no significant differences in risk associated with discontinuation.

Conclusions—The rate of hip fracture was increased among women compliant with bisphosphonate therapy for 2 years who subsequently discontinued, suggesting that discontinuation is not advisable under these conditions. This association was attenuated with higher compliance and a longer duration of previous bisphosphonate therapy.

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Keywords

Adherence; Bisphosphonates; Compliance; Discontinuation; Fracture

Introduction

Bisphosphonates are the medications most commonly used for the treatment of osteoporosis. Oral bisphosphonates were originally approved in a once-daily formulation. However, recognition of the long skeletal retention of the currently available bisphosphonates coupled with concerns about adherence with daily therapy led to less frequently-dosed but bioequivalent formulations. Current bisphosphonate dosing regimens include once-weekly (alendronate or risedronate), once or twice monthly (ibandronate and risedronate), and every three monthly (intravenous ibandronate). A once-yearly intravenous formulation (zoledronic acid) has also been approved by the US Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis. The long retention time of bisphosphonates in bone where inhibitory effects on osteoclasts may persist for months to years after drug discontinuation have led some to suggest a 'drug holiday', during which time patients intentionally discontinue medication but would still be protected from increased bone turnover and fracture. Indeed, a recent randomized controlled trial of 1099 women who received alendronate for a mean of five years showed that the risk of hip fracture was similar for the next five years among women who were randomized to placebo versus active treatment [1]. Results from a post hoc subgroup analysis of that study showed that this finding was true only for those women whose BMD at the end of five years was not in the osteoporotic range; hip fracture risk was increased among the individuals in the discontinuation group that had BMD in the osteoporotic range at the end of the five years. The extent to which these results can be generalized to persons with a prior bisphosphonate treatment duration of less than 5 years is unclear. Some studies have demonstrated that bone turnover markers increase at approximately 1 year after discontinuation [2,3], but the relationship between this observation and a possible increase in fracture rate is unclear. Finally, safety concerns related to possible over-suppression of bone turnover with increasing duration of bisphosphonate therapy [4] is another reason for which at least temporary drug discontinuation might be a desirable option.

As for many asymptomatic chronic diseases, long-term compliance with bisphosphonate therapy is poor for persons with postmenopausal osteoporosis (PMO) and glucocorticoid induced osteoporosis (GIOP) [5,6]. The persistent benefits of bisphosphonates can only be expected among individuals who were compliant with therapy, and patients may switch bisphosphonate formulations or discontinue temporarily but restart at a later time [7]. In light of these issues, we evaluated the effect of bisphosphonate discontinuation on the risk of hip fracture after a period of bisphosphonate treatment lasting at least two years. To do this, we used data from a large cohort of patients enrolled in a U.S. health care organization who were previously compliant with bisphosphonate therapy and used a dynamic definition of compliance that accounted for temporary discontinuation and bisphosphonate switching.

Methods

Study cohort

After institutional review board approval, we used the administrative claims of a large U.S. health care organization covering over 25 million people throughout the U.S. to identify a cohort of new bisphosphonate users. The cohort included women ages 60 to 78 years of age who had medical and pharmacy benefits, who were new users of alendronate or risedronate from January 1998 to July 2005, who continued bisphosphonate therapy for at least two years, and who did not have a claim for hip fracture, malignancy, HIV disease, or Paget's disease of

bone before initiating bisphosphonate therapy. To identify new bisphosphonate users, we required at least a six month-period without any bisphosphonate prescription. The date of the first filled bisphosphonate prescription after this 6-month period defined the user's index date. We restricted the cohort to women between age 60 and 78 at the beginning of the study because randomized controlled trials have shown the greatest benefit of bisphosphonates on the risk of hip fracture among older women. Also, age is a potentially strong confounder of the relation between discontinuation of bisphosphonates and fracture, and our HIPPA-compliant de-identified dataset did not contain data that would allow us to compute the exact age for cohort members older than 78. We used data from the six months prior to the index date to determine baseline demographics, comorbidities, and health services utilization. We also examined use of other screening services such as mammography to allow for adjustment for 'healthy behaviors' that are typically unmeasured in claims data.

Compliant subcohort

One of our goals was to investigate the association between bisphosphonate discontinuation and hip fracture among persons who had been compliant with bisphosphonate therapy for at least two years. We quantified compliance using the medication possession ratio (MPR), defined as the amount of bisphosphonate prescribed divided by the calendar time since the index date. Switching to another bisphosphonate formulation, either an alternate dosing frequency or a different drug, was considered no differently than remaining on the original bisphosphonate. We defined compliance as an MPR 66–100% at two years [8]. Because some investigators have adopted a definition of adherence requiring MPR 80–100% [9], we separately considered that threshold as well.

Discontinuation of bisphosphonate therapy and occurrence of hip fractures

We considered two measures of discontinuation of bisphosphonate therapy: 1) discontinuation for any length of time and 2) days since discontinuation (length of discontinuation). Discontinuation was determined using prescription data from the pharmacy database and was evaluated at 15-day intervals as a time-dependent variable. To identify hip fractures we used International Disease Classification, 9th version (ICD-9) codes for this condition [10].

Statistical analysis

We computed person-days on therapy and off therapy, beginning at entry into follow-up (2 years after initiating bisphosphonate therapy) and ending on the date of the first hip fracture, date of a filled prescription for a medication known to impact bone turnover (i.e., systemic estrogens, teriparatide, raloxifene, calcitonin), disenrollment from the health plan, or the end of the study. We first evaluated the crude incidence rate of hip fracture among those having discontinued (for any length of time) versus those remaining on bisphosphonate. We examined incident fracture rates for groups characterized by MPR 66–100% and MPR 80–100%, and by whether the patient had received at least two or three years of preceding bisphosphonate therapy. Incidence rate differences were computed, by comparing patients who remained on drug compared to those who discontinued. Although of interest, the sample sizes available in our data were inadequately powered to compare non-overlapping groups of patients with MPR 66–79% compared to 80–100%. In order to have a reference for hip fracture rate in an untreated but similar population, we computed incidence rates of hip fracture among persons with MPR<50% at two and three years as an approximation. This threshold was based on previous work showing that hip fracture rates appear to plateau among non-compliant persons with MPR<50% [9].

We also utilized Cox proportional hazards models to evaluate the relation between days since discontinuation and hip fracture. Time since discontinuation was initially examined as a continuous variable. We also examined the effect of time since discontinuation within discrete

time intervals. For these intervals, we considered 0–9 months and greater than 9 months since discontinuation. Factors hypothesized to potentially confound the exposure-outcome relationship were included based on clinical interest and their ability to modify the exposure-outcome relationship. Age within the 60–78 year range was assessed as a continuous variable, and a quadratic age term was added to evaluate whether the effect of age on hip fracture was exponential. In order to evaluate the appropriateness of the proportional hazards assumption, we examined interaction terms between observation time and baseline MPR. Violation of the proportionality assumption would be identified if the interaction term was statistically significant. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Sensitivity analyses

To ensure that our results were not dependent on the specific intervals of time since discontinuation specified for the main analysis (0–9, >9), we evaluated discontinuation intervals of 0–6, 6–12, and > 12 months since discontinuation. As part of a second sensitivity analysis, we used restriction to evaluate the possibility that women with a prior physician diagnosis of osteoporosis or a non-vertebral, non-hip fracture might have a different baseline risk for hip fracture; women that met neither of these two criteria were excluded. Finally, because of potential misclassification of whether a hip fracture actually occurred when using claims data, we performed a third sensitivity analysis that restricted outcome events to those where a physician submitted an evaluation and management (E/M) claim for hip fracture. This excluded, for example, claims where surgery was performed with a diagnosis code of hip fracture but no physician E/M claim was ever submitted.

Results

The demographic characteristics, comorbidities, and health services utilization of the 9,063 women initiating bisphosphonates that were compliant at 2 years and eligible for this discontinuation analysis are shown in Table 1. Approximately half of these women had a medical claim for osteoporosis in the six months prior to beginning bisphosphonate therapy, and approximately two-thirds underwent dual x-ray absorptiometry (DXA) testing during this period. Sixty percent (60%) of the women initiated bisphosphonate therapy with weekly alendronate, and approximately 20% initiated therapy with weekly risedronate. Observation time among these compliant women (48% of the original cohort) began at two years.

Table 2 displays the number and incidence rate of hip fracture among women who did and did not discontinue bisphosphonates, stratified by compliance (MPR < 50%, MPR 66–100% and MPR 80–100%) at two and three years. For both compliant groups of women, the incidence rate of hip fracture while on bisphosphonates was lower than while off bisphosphonates, although the incidence rate difference between being off and on-drug was significant only for the women with MPR 66–100% at two years. Trends suggested that there was a decreasing incidence rate gradient as baseline MPR and duration of preceding bisphosphonate therapy increased, although because these groups of women partially overlapped, direct comparisons were not possible. Compared to a non-adherent population with MPR<50% at 2 and 3 years (used to approximate a relatively untreated population), the incidence of hip fracture was lower in all compliant groups. Compared to the women with MPR<50%, the incidence rate differences for all other groups were significant for women who remained on bisphosphonate therapy. They were significant even for those off drug if they had taken bisphosphonates for 2 years with MPR≥80% (p=0.04). Although the corresponding incident rate difference was not statistically significant off drug for women that had taken bisphosphonates for 3 years with MPR≥80%, the number of fractures in this group was small and their hip fracture incidence rate (6.34 per 1,000 person years) was similar to the larger group adherent for 2 years (6.12 per 1,000 person years).

In crude and multivariable adjusted Cox proportional hazards models, the interaction term between observation time and baseline MPR was not significant, indicating that the proportional hazards assumption was not violated. Table 3 shows that the association between time since discontinuation and hip fracture was significant in both crude and adjusted models only for women with MPR 66–100% at two years. As further described in Table 3, for MPR 80–100% at two years and for a three year treatment period, time since discontinuation was not significantly associated with hip fracture.

With the consideration that the relationship between time since discontinuation and fracture may not be linear, we also examined time since discontinuation in discrete intervals (0–9 months vs. >9 months) in separate models shown in Table 4. Within these discrete intervals, time since discontinuation was significantly associated with an increased hazard ratio of hip fracture after 9 months in the analysis of women with MPR 66–100% at two years. Hazard ratio estimates from models assuming higher baseline MPR and longer duration of treatment were somewhat attenuated compared to women with MPR 66–100% at 2 years, although confidence intervals were wide.

Results from our three sensitivity analyses that varied the length of the discontinuation intervals, restricted the population to those with an osteoporosis diagnosis or a prior non-hip fracture, and varied the hip fracture outcome ICD-9 codes, confirmed our primary results and are not shown.

Discussion

Among women previously compliant with bisphosphonate therapy for at least two years, we found that the incidence rate of subsequent hip fracture was significantly lower than for a non-compliant population. Although we observed a relatively small number of hip fracture events in our primary analysis (n=71), which limited our ability to determine exactly when the rate of hip fracture increased, discontinuation of bisphosphonate for up to approximately 1 year did not appear to be associated with a significantly increased rate of hip fracture. Among women with baseline MPR 66–100% at two years (yielding the largest group of hip fractures), discontinuation of one year or longer was associated with a two to threefold increased relative risk of hip fracture after adjusting for a number of important covariates of interest including age, baseline health services utilization, and medical comorbidities. We also observed that with greater amounts of compliance (e.g., MPR 80–100%) and a longer duration of preceding bisphosphonate therapy, the incidence rate of hip fracture among persons having ceased bisphosphonate therapy was numerically lower than for women somewhat less compliant and having received a shorter prior course of therapy. However, they never reached the nadir in fracture rate achieved by women who remained on bisphosphonates.

The Fracture Intervention Long Term Extension (FLEX) trial evaluated 1099 women who had been treated with alendronate for approximately 5 years (78% of them who remained current users of study medication) and randomized them to placebo versus ongoing treatment with alendronate. Over the next five years, there were no significant differences in the incidence of hip fracture between those randomized to placebo versus active treatment in the intent-to-treat population. However, results from a subgroup analysis showed that those with osteoporotic BMD at the end of the five year initial treatment period had an increased rate of non-vertebral fractures after discontinuation, and those with non-osteoporotic BMD did not. In our study, we found that women in our study who were compliant with MPR 66–100% for 2 years had a significantly increased rate of hip fracture after discontinuation. We also found that women with higher baseline compliance (e.g., MPR≥80%) and those receiving bisphosphonates for at least three years did not have a significantly increased rate of fracture after discontinuation. This may reflect a biologic phenomenon whereby greater cumulative bisphosphonate exposure

provides greater fracture protection. Unfortunately, our data source did not permit us to stratify subjects by BMD at the time of discontinuation.

Our results have high relevance to clinical practice since many women have a repeat bone mineral density (BMD) test at 2–3 years after starting bisphosphonate therapy, and the possibility of discontinuation may be considered. Our data suggest that this may be reasonably safe with respect to the risk for hip fracture for at least one year. For women who are compliant for longer periods of time, an even longer period of discontinuation may also be safe, although our data were limited to examine longer discontinuation intervals. However, if discontinuation is advised, the practicalities of when to resume therapy are problematic and potentially arbitrary. Longitudinal changes in BMD likely will be too minor to provide much near-term guidance. Bone turnover markers, although theoretically more useful, are not widely available or adequately reimbursed in most clinical settings. Moreover, there may be medico-legal implications if a patient has a fracture after bisphosphonates have been intentionally discontinued.

The strengths of our study include a large cohort of patients receiving care in routine clinical settings. The incidence rates of hip fracture that we observed are similar to those from RCTs and a large observational study that used similar methods to ours [11]. Our large sample size permitted us to examine women compliant for two and three years using dynamic definitions of compliance based on MPRs that have been previously shown to be beneficial using bone mineral density (BMD) and fracture endpoints [8,9]. Additionally, we evaluated discontinuation in several different ways and reached similar conclusions about associations between bisphosphonate cessation and fractures.

Our results must be interpreted in light of our study design. Perhaps most importantly, patients were not randomized to discontinue bisphosphonate therapy, and the reasons for discontinuation were unknown. It is possible that physicians recommended that patients discontinue based on their perceived low risk for future fracture. However, our results show that discontinuation was not associated with a lower hip fracture rate, as might be expected if predominantly low-risk patients were recommended to discontinue. Moreover, separate analyses of high risk patients (defined as those having a medical diagnosis for osteoporosis or a claim for a recent non-hip fracture) yielded results similar to those for the overall groups of subjects. Finally, we recognize that women who are non-adherent with any therapy are likely different in many ways than women adherent to therapy, and claims data captures only a few of these potential confounders. However, our restriction of the study population to only women that were adherent for at least two or three years should attenuate this concern, given their history of prior adherence.

Despite having more hip fractures in our primary analysis (n=71) than occurred in the recent FLEX trial (n=33 hip fractures), our results were likely underpowered to evaluate the risk of discontinuation in small, discrete increments of time after discontinuation and in the subcohort of women with high adherence for at least 3 years (n=28 hip fractures). This observation is illustrated in the relatively wide confidence intervals shown in Tables 3 and 4. Additionally, we acknowledge the potential misclassification of the exact time that patients discontinue given our use of pharmacy data that informs us only when medications were filled but not actual medication-taking behavior. However, it is unlikely that this misclassification extended beyond a few months, and we have previously shown high concordance between pharmacy data and actual medication taking behavior for osteoporosis medications [12]. Additionally, we acknowledge that insurance claims for a hip fracture may misclassify actual events. However, in contrast to some other types of fracture such as vertebral fracture, misclassification of hip fracture in claims data has been previously shown to be uncommon [10]. Moreover, we conducted a sensitivity analysis restricting outcomes to those with physician E/M (i.e., office

visit) claims, which likely increased the specificity of our outcome definition and the corresponding positive predictive value of claims for hip fracture events. Finally, we recognize that the various bisphosphonates may have different skeletal retention times [13], and the relative near-term safety of drug discontinuation may differ between them. Unfortunately, despite our large sample size, the number of hip fractures that occurred among patients meeting our inclusion criteria were too small to be able to examine individual differences between the bisphosphonates. However, among the oral bisphosphonates represented in our study, most patients were treated with alendronate, which appears to have the longer skeletal retention time of the two bisphosphonates that we studied. Assuming that longer skeletal retention allows for a longer duration of fracture risk reduction after bisphosphonate discontinuation, our results therefore may reflect a 'best-case-scenario' with respect to the relative safety of discontinuation. Finally, we evaluated only hip fractures and not other types of fractures. We chose this endpoint because we have previously demonstrated a high rate of misclassification of incident vertebral fractures in administrative claims data [14], and the magnitude of benefit of bisphosphonate therapy to reduce non-hip, non-vertebral fractures is smaller than for hip fractures; thus, significant differences in fracture rates would likely be more difficult to detect.

We conclude that the risk for hip fracture among women that have previously been compliant with bisphosphonates for two years but whom subsequently discontinue use is increased. However, this risk appears to be attenuated with greater amounts of compliance and longer durations of preceding bisphosphonate therapy. With respect to the timing of this risk increases, our results indicate that this increase in risk appears to begin after approximately one year following discontinuation. This estimate may be overly conservative for women with very high compliance or treated with bisphosphonates for longer periods of time. Although an intentional drug holiday for up to this length of time may be safe, the practicalities of this approach may still outweigh potential benefits.

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Table 1

Demographic, comorbidity, and health services utilization of women compliant 2 years after beginning bisphosphonate therapy (n= 9,063)

	N	%
Demographics		
Age		
60–64	4510	50
65–74	2927	32
75–78	1626	18
Fracture in the 2 years prior to the start of the study period		
Wrist/Forearm	168	2
Clinical vertebral	170	2
Non-hip, non-vertebral (including wrist/forearm)*	346	4
Selected comorbidities**		
Osteoporosis diagnosis (excludes osteopenia)	4583	51
Diabetes	553	6
Rheumatoid arthritis	213	2
Hyperlipidemia	2953	33
Tobacco use	80	1
Hyperthyroidism	145	2
Charlson comorbidity index***	0	0–10
Prior use of selected medications* (any use)		
Systemic estrogen	2416	27
Raloxifene	239	3
Nasal calcitonin	271	3
Systemic glucocorticoids	563	6
Health services utilization**		
Outpatient visits, number****	2.0	1,4
Any hospitalization (yes/no)	390	4
Receipt of bone mineral density test (yes/no)	5766	64
Receipt of other screening tests (yes/no)		
Mammography	3320	37
Colonoscopy	504	6
Fecal occult blood test	2269	25
Flexible sigmoidscopy	87	1
Initial bisphosphonate prescribed		
Alendronate weekly	5376	59
Alendronate daily	1598	18
Risedronate weekly	1759	19
Risedronate daily	330	4

* Includes wrist/forearm, clavicle, humerus, leg, and pelvis

** Assessed in the 6 months prior to first bisphosphonate use

*** The Charlson comorbidity index reflects the total sum of medical comorbidities for each person. Data presented as median and ranges

**** Data shown are presented as median and inter-quartile range

Table 2

Incidence rates of hip fracture among women variably compliant with bisphosphonate therapy for two or three years

a. Two years of prior bisphosphonate therapy				
MPR<50% N=8878 women	MPR≥66% N=9063 women		MPR≥80% N=7505 women	
N, person-years	N, person-years	N, person-years	N, person-years	N, person-years
Rate off BP	Rate off BP	Rate on BP	Rate off BP	Rate on BP
	P value**	P value**	P value**	P value**
117, 11185	25, 2966	46, 9850	13, 2124	41, 8489
10.46	8.43*	4.67*	6.12	4.83
Referent	P=0.33**	P<0.0001**	P=0.04**	P<0.0001**
b. Three years of prior bisphosphonate therapy				
MPR < 50%, N=5385 women	MPR≥66%, N=4556 women		MPR≥80%, N=3715 women	
N, person-years	N, person-years	N, person-years	N, person-years	N, person-years
Rate off BP	Rate off BP	Rate on BP	Rate off BP	Rate on BP
	P value**	P value**	P value**	P value**
58, 5697	8, 1125	20, 4175	5, 789	18, 3523
10.18	7.11	4.79	6.34	5.11
Referent	P=0.34**	P=0.003**	P=0.30**	P=0.009**

BP=bisphosphonate; MPR=medication possession ratio at end of 2 or 3 year eligibility period (defines study baseline) Hip fracture rates expressed per 1,000 person years

* rates are significantly different at p=0.016 between persons on and off-drug within this MPR group but are not significantly different for the other three rate comparisons

** p value compares fracture rate in this column to fracture rate among women with MPR<50% in the same row

Table 3

Hazard ratios for associations between bisphosphonate discontinuation and hip fracture risk by baseline Medication Possession Ratio (MPR)-continuous time since discontinuation

Duration of time and level of adherence	MPR 66–100% at 2 years	MPR 80–100% at 2 years	MPR 66–100% at 3 years	MPR 80–100% at 3 years
Cohort size (n)	9063	7505	4556	3715
Hip fractures (n)*	71	54	28	23
Crude results				
Duration of time since discontinuation**	1.2 (1.1–1.3)	1.1 (1.0–1.3)	1.1 (0.9–1.5)	1.1 (0.8–1.5)
Adjusted results***				
Duration of time since discontinuation**	1.2 (1.1–1.3)	1.1 (0.9–1.2)	1.1 (0.9–1.4)	1.1 (0.8–1.5)

* Number of fractures on and off therapy is shown in Table 2

** Number of days since discontinuation expressed as a continuous variable, per 90 days

*** Models adjusted for age, Charlson comorbidity index, and number of outpatient visits. Additional covariates evaluated but not independently significant included prior hospitalization, recent non-hip fracture, screening behaviors (e.g., receipt of bone mineral density testing, screening mammography, prostate specific antigen testing, fecal occult blood testing, or screening colonoscopy), and past estrogen use

Table 4

Hazard ratios for associations between bisphosphonate discontinuation and hip fracture risk by baseline Medication Possession Ratio (MPR)—discrete time since discontinuation

Duration of time and level of adherence	MPR 66–100% at 2 years	MPR 80–100% at 2 years	MPR 66–100% at 3 years	MPR 80–100% at 3 years
Cohort size (n)	9063	7505	4556	3715
Hip fractures (n)*	71	54	28	23
Crude results				
Duration of time since discontinuation				
0–9 months	1.1 (0.6–2.1)	0.9 (0.4–1.9)	1.1 (0.4–2.8)	0.8 (0.3–2.9)
>9 months	4.2 (2.1–8.4)	2.3 (0.9–5.8)	3.3 (0.9–12.2)	2.5 (0.5–11.7)
Adjusted results**				
Duration of time since discontinuation				
0–9 months	1.0 (0.5–1.9)	0.8 (0.3–1.7)	0.9 (0.3–2.5)	0.7 (0.2–2.4)
>9 months	3.1 (1.5–6.1)	1.8 (0.7–4.5)	2.7 (0.7–9.8)	2.0 (0.4–9.3)

* number of fractures on and off therapy is shown in Table 2

** Models adjusted for age, Charlson comorbidity index, and number of outpatient visits. Additional covariates evaluated but not independently significant included prior hospitalization, recent non-hip fracture, screening behaviors (e.g., receipt of bone mineral density testing, screening mammography, prostate specific antigen testing, fecal occult blood testing, or screening colonoscopy), and past estrogen use